Official Title: Attain Stability Quad™ Clinical Study

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Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	Attain Stability™ Quad Clinical Study
Study Product Name	Attain Stability™ Quad MRI SureScan Left Ventricular Lead (Model 4798)
Sponsor/Local Sponsor	**Sponsor:** Medtronic, Inc. Cardiac Rhythm and Heart Failure Clinical Research 8200 Coral Sea Street NE Mounds View, MN 55112 U.S.A. 1-800-328-2518 **Local Sponsors:** Canada Medtronic of Canada 99 Hereford Street Brampton, ON, L6Y 0R3 Canada +1-905-460-3800 Europe, Middle East, Africa (EMEA)Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands +31-43-35-66-566 Hong Kong Medtronic Hong Kong Medical Ltd. 1104-11, 11/F, Tower 1, The Gateway, Harbour City, Kowloon, Hong Kong SAR, China +852-2919-1300 Malaysia Medtronic International Ltd (Malaysia) B-23-1 Level 23, The Ascent, Paradigm No 1 Jalan SS7/26A Kelena Jaya 46301 PetalingJaya Selangor Malaysia +603 7883 8000
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1. Sponsor Contact

Medtronic, Inc. is sponsoring the Attain Stability Quad Clinical Study. Regional contact information is provided below. This information may be subject to change during the course of the Attain Stability Quad Clinical Study. Periodic updates to study contact information will be sent to sites as needed.

Table 1: Study Sponsor Contact Information

Study Contacts	
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2. CROs/Core Laboratories

This information may be subject to change during the course of the Attain Stability Quad Clinical Study. Periodic updates to study contact information will be sent to sites as needed.

Table 2: CRO and Core Laboratory Information

Contact Information	Role
Cognizant Technology Solutions 500 Frank W. Burr Blvd. Teaneck, NJ 07666 United States Direct Phone: (201) 801-0233 Direct Fax: (201) 801-0243	Review of electronic case report forms and management of discrepancies

3. Version History

Version	Summary of Changes	Author(s)/Title
1.0	○ Initial Release	Melissa Thalin, Principal Clinical Research Specialist Rinie Peters, Associate Clinical Research Specialist Ann Vacca, Principal Customer Specialist Shelby Li, Senior Principal Statistician Joao Monteiro, Senior Statistician

4. Investigator Statement

Investigators will be provided with a separate investigator agreement to document their obligation and commitment with respect to study conduct.

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8. Glossary

Table 3: Glossary of Terms

Term	Definition
2090	Medtronic CareLink Programmer with the application software installed.
2290	Medtronic Analyzer
Medtronic Attain Stability Quad MRI SureScan (Model 4798) LV Lead	The quadripolar LV lead being studied (investigational in the United States/Canada, commercially available in EMEA, Hong Kong, and Malaysia).
Active Fixation Helix	A non-electrically active side helix, positioned between the LV 3 and LV 4 electrodes that will allow fixation of the Attain Stability Quad MRI SureScan (Model 4798) LV Lead in the cardiac vein.
ADE	Adverse Device Effect
AE	Adverse Event
Ag	Silver
CABG	Coronary Artery Bypass Graft

Term	Definition
CAD	Coronary Artery Disease
CDF	Cumulative Distribution Function
CEC	Clinical Events Committee
CIP	Clinical Investigation Protocol
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy: Established pacing therapy for patients with heart failure
CRT-D	Cardiac Resynchronization Therapy - Defibrillator
CRT-P	Cardiac Resynchronization Therapy - Pacemaker
CS	Coronary Sinus
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency
DEKRA	Deutscher Kraftfahrzeug-Überwachungs-Verein (German Motor Vehicle Inspections Association)
DMC	Data Monitoring Committee
EC	Ethics Committee
EMEA	Europe, the Middle East, and Africa
eCRF	Electronic Case Report Form
MEC/IRB/HREB/Ethics Board	Ethics Committee
FAL	Foreseeable Adverse Event List
FDA	Food and Drug Administration
Fr	French
GCP	Good Clinical Practice

Term	Definition
HF	Heart Failure
HTN	Hypertension
IC	Informed Consent
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IDE	Investigation Device Exemption
Ir	Iridium
IRB	Institutional Review Board
LAR	Legally Authorized Representative
LBBB	Left Bundle Branch Block
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MCRD	Monolithic Controlled Release Device which is located on the Attain Stability Quad MRI SureScan LV Lead (Model 4798) electrodes which elutes steroid to reduce inflammatory response within the cardiac vein.
Mechanical Stop	A component on the Attain Stability Quad MRI SureScan (Model 4798) LV Lead located at the base of the helix to prevent wedging of endothelial tissue in the helix and to prevent tissue ingrowth.
MedDRA	Medical Dictionary for Regulatory Activities
OC	Oracle Clinical (database management system)
OTW	Over-the-wire
PCT	Pacing Capture Threshold
PHD	Pre-Hospital Discharge means the point at which a subject has been released from the hospital post implant procedure.

Term	Definition
PMA	Premarket Approval
PNS	Phrenic Nerve Stimulation
POR	Power On Reset
Pt	Platinum
PTCA	Percutaneous Transluminal Coronary Angioplasty
QOL	Quality of Life
RA	Right Atrial
RRT	Recommended Replacement Time
RV	Right Ventricular
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SDN	Software Distribution Network
TÜV	Technischer Überwachungsverein (German safety validation organization)
UADE	Unanticipated Adverse Device Effect
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

9. Synopsis

Title	Attain Stability™ Quad Clinical Study
Product Name	Attain Stability™ Quad MRI SureScan Left Ventricular Lead (Model 4798)
Sponsor	Medtronic, Inc. Cardiac Rhythm and Heart Failure Clinical Research 8200 Coral Sea Street NE Mounds View, MN 55112 U.S.A. 1-800-328-2518
Local Sponsor	Canada Medtronic of Canada 99 Hereford Street Brampton, ON, L6Y 0R3 Canada +1-905-460-3800 EMEA Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands +31-43-35-66-566 Hong Kong Medtronic Hong Kong Medical Ltd. 1104-11, 11/F, Tower 1, The Gateway, Harbour City, Kowloon, Hong Kong SAR, China +852-2919-1300 Malaysia Medtronic International Ltd (Malaysia) B-23-1 Level 23, The Ascent, Paradigm, No 1 Jalan SS7/26A Kelena Jaya 46301 Petaling Jaya Selangor Malaysia +603 7883 8000
Indication under investigation	All subjects included in the study will be implanted with a Medtronic market released de novo CRT-P or CRT-D device, compatible market released Medtroinc RA and Medtronic RV leads and an Attain Stability QuadSureScan LV lead (Model 4798). For subjects enrolled who are receiving an upgrade to a CRT system, existing non-Medtronic RV and/or existing non-Medtronic RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used.

	Given the vast similarities between the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the Attain Performa family of leads, the proposed indications for use are the same. The indications are as follows: The Attain Stability Quad MRI SureScan 4798 steroid-eluting, quadripolar electrode, IS4 transvenous lead is indicated for chronic pacing in the left ventricle via the cardiac vein, when used with a compatible Medtronic Cardiac Resynchronization Therapy (CRT) System. Extended bipolar pacing is available using this lead in combination with a compatible market approved CRT-P or CRT-D system and RV lead.
Investigation Purpose	The Attain Stability Quad Clinical Study is a prospective, non-randomized, multi-site, Investigational Device Exemption (IDE) interventional clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV lead (Model 4798). This study will not be considered investigational in geographies with CE Mark of the Attain Stability Quadripolar LV lead (4798). However, data collected from all study subjects will be represented in the final report and the PMA Supplement (PMA-S) to the Model 4196 Original PMA.
Product Status	The Attain Stability Quad Clinical Study will be conducted using a research system composed of an approved CRT-D or CRT-P System. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is an active fixation quadripolar LV lead based on the Attain Performa lead family models (4298, 4398, and 4598). The lead incorporates an active fixation helix similar to the Attain Stability bipolar LV lead (Model 20066/4796) which is designed to allow an implanter more options in lead location. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered investigational in geographies where the product is not available commercially and will be labeled for clinical use only. These geographies include but are not limited to the US and Canada. Investigational Attain Stability Quad Leads will be distributed to a site only when Medtronic has received all required documentation (including but not limited to Ethic Committee approval, a signed Clinical Trial Agreement and documentation of training) and has notified the site of site readiness. Distribution of the investigational product to study sites will be managed by Medtronic and can only be

	ordered by Medtronic personnel. Site with these clinically labeled Attain Stability Quad MRI SureScan LV Leads (Model 4798) will track disposition upon receipt or return of the lead but also upon implant or explant of the lead. Disposition logs will be available within the electronic data management system and shall be maintained at each site in all geographies to track investigational product information. For geographies where the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is not considered investigational, commercially approved devices will be used. Sites that use commercially available Attain Stability Quad MRI SureScan LV Leads (Model 4798) will track device disposition upon implant or explant on the lead CRFs. The Medtronic approved CRT-P or CRT-D devices will be programmed and interrogated using a Medtronic CareLink (2090) programmer. Medtronic may incorporate additional programmers as they receive regulatory approval. The CareLink Monitor Model 2490C is an external monitor that is indicated for use in the transfer of patient and device data from implanted Medtronic devices. The CareLink Monitor Model 2490C interrogates implanted devices and temporarily stores these data, collaborates with the appropriate Medtronic server to confirm the establishment of an Internet connection with server, performs any required file translation functions necessary for data transfer, executes data file transfer, and collaborates with the appropriate Medtronic server to confirm data file transfer through the Internet connection with the server. The CareLink Monitor 2490C is not a programmer and cannot be used to program implanted device parameters. CareLink monitors are not a substitute for appropriate medical attention in the event of an emergency and should only be used as directed by a physician. Approved Medtronic CRT-P and CRT-D devices used in this study qualify for use with the Medtronic CareLink Monitor and Medtronic CareLink Network. Medtronic may incorporate additional home monitors as they receive regulatory approval. Medtronic's commercially available Model 2290 Analyzer must be available at each center during the implant

	procedure to determine acceptable electrical parameters. Medtronic may incorporate additional analyzers as they receive regulatory approval.
Primary Objective(s)	**<u>Primary Safety Objective: Lead complication-free rate at 6 months</u>** The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered safe if the probability of subjects free of Model 4798 lead-related complications at 6 months post-implant is greater than 87% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 87%). The study primary safety endpoint is Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complications through 6 months post implant. All reported system and procedure-related AEs will be reviewed by an event review committee for LV lead relatedness and severity (complication vs observation, refer to 17.1.2 for defintions). **<u>Primary Efficacy Objectives: Lead pacing capture thresholds at 6 months</u>** To demonstrate the effectiveness of the Attain Stability Quad MRI SureScan LV lead (Model 4798) the study will evaluate the likelihood that there are at least two programmable vectors for each patient post implant. The effectiveness of this lead will be evaluated based on two primary efficacy objectives. More specifically, both primary efficacy objectives must be met simultaneously. **<u>Primary Efficacy Objective #1</u>** The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet the objective if the proportion of subjects with at least one LV lead pacing vector having a pacing capture threshold less than or equal to 2.5 V at 0.5ms pulse width at 6 months post-implant is greater than 80% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 80%). The endpoint for the primary efficacy objective is whether or not there is at least one Model 4798 LV lead pacing vector with pacing capture voltage thresholds less than or equal to 2.5V. This endpoint will be measured at the 6-month post implant follow-up visit.

	Primary Efficacy Objective #2 The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet the objective if the proportion of subjects with at least one additional LV lead pacing vector having a pacing capture threshold less than or equal to 4.0 V at 0.5ms pulse width at 6 months post-implant is greater than 80% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 80%). The co-primary efficacy endpoint is whether or not a second Model 4798 lead configuration has a pacing capture threshold less than or equal to 4V, excluding the pacing vector that is already counted to the primary efficacy endpoint #1. This endpoint will be measured at 6-month post implant follow-up visit.

Secondary

Objective(s)	The secondary objectives are descriptive in nature and are intended to provide additional information about the Attain Stability Quad Model 4798 LV lead. There will be no established performance requirements for these secondary objectives.
	
	o Implant procedure related information: success rate, implant related times
	  o Endpoints will include implant success rate and procedure durations.
	o 6-month reliability: post implant lead failure modes (i.e. complication rate)
	  o Endpoint is Model 4798 lead related complications.
	o Electrical measurements (PCT and Impedance) at follow-ups
	  o Endpoints are the electrical measurements are pacing capture thresholds and impedance values for the four extended bipolar configurations, i.e. LV1 to RVCoil, LV2 to RV Coil, LV3 to RV Coil and LV4 to RV Coil (refer to 15.8.2.3 for the testing procedure requirements)

Study Design	The Attain Stability Quad Clinical Study is a prospective, non-randomized, multi-site, global, Investigational Device Exemption (IDE) interventional clinical study. The

	purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV lead (Model 4798) in patients indicated for a de novo LV lead implant. This will be assessed through primary safety and primary efficacy endpoints. All subjects included in the study will be implanted with a Medtronic market released CRT-P or CRT-D device and an Attain Stability Quad MRI SureScan LV Lead (Model 4798). For de novo CRT systems, compatible market released Medtronic RA and Medtronic RV leads will be required. For subjects enrolled who are receiving an upgrade to a CRT system, existing non-Medtronic RV and/or existing non-Medtronic RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used. Up to 471 subjects will be enrolled into the study and up to 471 Attain Stability Quad MRI SureScan LV Leads (Model 4798) implanted, to ensure a minimum effective sample size of 400 Model 4798 leads implanted with 6 months post implant follow up visits (assuming 15% attrition). For the secondary endpoint of individual lead failure modes, Bayesian methods utilizing data from up to 37 historical patients will be used. All other objectives will be analyzed using only patients enrolled in this study. After a successful implant, threshold testing will occur to show one LV vector with pacing capture threshold (PCT) ≤ 2.5 V @ 0.5ms and with sufficient safety margin was programmed. Subjects will then be followed at implant, three months, six months and every six months thereafter until FDA approval is obtained or until study closure, whichever comes first. The study duration is expected to be approximately 19 months. This represents 13 months for subject enrollment and 6 months for subject follow-up for the last subject enrolled. Subjects are anticipated to be in the study for on average 12 months. The first enrollment is projected to occur in May 2017.
Sample Size	Up to 471 subjects will be enrolled into the study, to ensure a minimum effective sample size of 400 Model 4798 leads implanted with 6 months post implant follow up visits (assuming 15% attrition) at up to 50 sites worldwide.
Inclusion/Exclusion Criteria	**Inclusion Criteria:** • Patient meets CRT implant criteria as determined by local regulatory and/or hospital policy

	• Patient (or legally authorized representative) has signed and dated the study-specific Consent Form • Patient is 18 years of age or older, or is of legal age to give informed consent per local and national law • Patient is expected to remain available for follow-up visits **Exclusion Criteria:** • Patient has had a previous unsuccessful LV lead implant attempt • Patient has an existing epicardial LV lead • Patient is currently implanted with a recalled (i.e. market-withdrawn, recalled or safety alert) RA and/or RV lead • Patient has known coronary venous vasculature that is inadequate for lead placement • Patient has unstable angina pectoris or has had an acute myocardial infarction (MI) within the past 30 days • Patient has had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the past 90 days • Patient has contraindications for standard transvenous cardiac pacing (e.g., mechanical right heart valve) • Patient has had a heart transplant (patients waiting for heart transplants are allowed in the study) • Patient has known renal insufficiency that would prevent them from receiving an occlusive venogram during the implant procedure • Patient is contraindicated for <1mg dexamethasone acetate • Patient is enrolled in any concurrent drug and/or device study that may confound the results of this study • Patient has a terminal illness and is not expected to survive more than six months • Patient meets exclusion criteria required by local law (e.g. age, pregnancy, breast feeding, etc.) • Patient is unable to tolerate an urgent thoracotomy
Study Procedures and Assessments	Clinical data will be collected at the study milestones: at enrollment, baseline, implant/PHD, 3M, 6M, thereafter every occurring 6M and study exit visits:

	Enrollment/Baseline: ○ Subject Informed Consent ○ Inclusion/Exclusion criteria verified ○ Subject demographics ○ Cardiovascular medications ○ Cardiovascular medical history ○ NYHA classification ○ Patient Global Assessment ○ Kansas City Cardiomyopathy Questionnaire (KCCQ) **Implant:** ○ Occlusive venogram with pre-determined target vessel location identified ○ System and procedure information ○ Analyzer PCT data collection post lead fixation and prior to connecting the leads to the CRT-P/D device: 1) Following guidewire/stylet has been pulled back prozimal to the helix and electrodes 2) Post slitting the cannulation catheter PHD CRT System Testing and Programming using the implanted CRT-P or CRT-D device and the device programmer: <u>Lead Impedance</u> ○ Collect LV Lead Impedances using Vector Express on all vectors ○ Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil or the final programmed vector ○ Retain printouts for any manually tested vector at the site <u>Pacing Capture Thresholds (PCT)</u> ○ Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors ○ NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) ○ Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil or the final programmed vector

	○ Retain printouts for any manually tested vector at the site Phrenic Nerve Stimulation (PNS) ○ Test for presence of PNS at 8.0V at 0.5ms on final programmed vector ○ NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms ○ NOTE: PNS observed during this testing will not be considered an AE Other Data Collection ○ Rationale for selecting specific LV lead pacing vector for final programming ○ Final device interrogation/save-to-media ○ AE Assessment ○ Study deviations ○ Device deficiencies **3 Month (remote or in office visit):** Lead Impedance ○ Perform a manual LV Lead Impedance Test for the final programmed vector ○ Retain printouts for any manually tested vector at the site Pacing Capture Thresholds (PCT) ○ Perform PCTs at 0.5ms pulse width on the final programmed vector ○ NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) ○ Perform a manual PCT test at 0.5ms pulse width on the final programmed vector ○ Retain printouts for any manually tested vector at the site Phrenic Nerve Stimulation (PNS) (in office visit only) ○ Test for presence of PNS at 8.0V at 0.5ms on final programmed vector ○ NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms ○ NOTE: PNS observed during this testing will not be considered an AE Other Data Collection ○ NYHA classification ○ Patient Global Assessment ○ Rationale for selecting specific LV lead pacing vectorfor final programming ○ Final device interrogation/save-to-media

	○ AE Assessment ○ Study deviations ○ Device deficiencies **6 Month:** <u>Lead Impedance</u> ○ Collect LV Lead Impedances using Vector Express on all vectors ○ Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil or the final programmed vector ○ Retain printouts for any manually tested vector at the site <u>Pacing Capture Thresholds (PCT)</u> ○ Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors ○ NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) ○ Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil or the final programmed vector ○ Retain printouts for any manually tested vector at the site <u>Phrenic Nerve Stimulation (PNS)</u> ○ Test for presence of PNS at 8.0V at 0.5ms on vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil ○ Test for presence of PNS at 8.0V at 0.5ms on final programmed vector ○ NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms ○ NOTE: PNS observed during this testing will not be considered an AE <u>Other Data Collection</u> ○ NYHA classification ○ Patient Global Assessment ○ Kansas City Cardiomyopathy Questionnaire (KCCQ) ○ Rationale for selecting specific LV lead pacing vector for final programming ○ Final device interrogation/save-to-media

	○ AE Assessment ○ Study deviations ○ Device deficiencies **12 Month:** <u>Lead Impedance</u> ○ Collect LV Lead Impedances using Vector Express on all vectors ○ Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil or the final programmed vector ○ Retain printouts for any manually tested vector at the site <u>Pacing Capture Thresholds (PCT)</u> ○ Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors ○ NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) ○ Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil or the final programmed vector ○ Retain printouts for any manually tested vector at the site <u>Phrenic Nerve Stimulation (PNS)</u> ○ Test for presence of PNS at 8.0V at 0.5ms on final programmed vector ○ NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms ○ NOTE: PNS observed during this testing will not be considered an AE <u>Other Data Collection</u> ○ NYHA classification ○ Patient Global Assessment ○ Kansas City Cardiomyopathy Questionnaire (KCCQ) ○ Rationale for selecting specific LV lead pacing vector for final programming ○ Final device interrogation/save-to-media ○ AE Assessment ○ Study deviations ○ Device deficiencies

	Recurring 6 Month follow-ups (remote or inoffice visit): Lead Impedance o Perform a manual LV Lead Impedance Test for the final programmed vector o Retain printouts for any manually tested vector at the site Pacing Capture Thresholds (PCT) o Perform PCTs at 0.5ms pulse width on the final programmed vector o NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) o Perform a manual PCT test at 0.5ms pulse width on the final programmed vector o Retain printouts for any manually tested vector at the site Phrenic Nerve Stimulation (PNS) (in office visit only) o Test for presence of PNS at 8.0V at 0.5ms on final programmed vector o NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms o NOTE: PNS observed during this testing will not be considered an AE Other Data Collection o NYHA classification o Patient Global Assessment o Rationale for selecting specific LV lead pacing vectorfor final programming o Final device interrogation/save-to-media o AE Assessment o Study deviations o Device deficiencies **Study Exit:** o Report the reason for exit o Final Interrogation file (or Carelink transmissions)- for exits occuring priorto the 6 month visit) o Study Deviations o AEs and Device Deficiencies
Safety Assessments	Adverse Event and Device Deficiency handling in the Attain Stability Quad Clinical Study is ISO 14155:2011 compliant for all participating geographies with the exception (to Section 17 of the ISO standard) that only

	those AEs which are related to the subject's system, procedure, accessory, or are cardiovascular-related, and all Serious AEs, will be collected. This ensures any AEs which could potentially be relevant will be collected. Reporting of these events to Medtronic will occur on an Adverse Event (AE) Form, including date of AE, treatment, resolution, assessment of both the seriousness of the AE and the relatedness to the investigational device or procedure. Each AE must be recorded on a separate AE eCRF. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened.
Statistics	The primary objective will be analyzed using the time-to-first event Kaplan-Meier survival analysis method. A minimum number of subjects who have completed their 6 months post-implant visits will be required. Time 0 will be the day a subject undergoes the implant procedure of a Attain Stability Quad MRI SureScan LV Lead (Model 4798), which will be independent of success status of this implant procedure. Event date is the onset date of a subject's first complication that is related to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) according to CEC adjudication. Subjects who undergo an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt and do not experience any LV lead related complications, will be censored at the time of their last known exposure to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) for the survival analysis. For any lost-to-follow up subject, the last contact date will be used as the censor date. The 1-sided 97.5% confidence limit lower bound for the survival probability at 6 months (183 days) will be calculated using the log-log survival function approach (Kalbfleisch and Prentice 2002).

10. Introduction

10.1. Background

Several clinical trials (including MIRCLE[1], MIRACLE-ICD[2], CONTAK-CD[3], MUSTIC[4], PATH-CHF[5], COMPANION[6], MADIT CRT[7], and CARE-HF[8]) have demonstrated the benefit of cardiac resynchronization therapy (CRT) among patients with moderate to severe heart failure (HF) with a prolonged QRS duration and depressed Left Ventricular (LV) function.

Approximately 5.7 million people in the United States (US) are living with HF[9]. Heart Failure may be a chronic condition which causes the heart to not pump oxygenated blood efficiently through the body due

to stiffening of the heart muscle. Heart Failure may affect one or both sides of the heart. It is most often caused by coronary artery disease (CAD) or uncontrolled hypertension (HTN). Patients who suffer from HF experience a variety of different symptoms including most often fatigue, cough, and shortness of breath, swollen feet (edema) and weight gain.

Heart Failure is treated with medications and sometimes cardiac devices (i.e. pacemaker or defibrillator with CRT). Medications work to relieve symptoms and reverse the effects of HF. Cardiac Resynchronization Therapy devices treat HF by synchronizing the left and right ventricles of the heart which improves the heart's ability to pump oxygenated blood to the body.[10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21]

Cardiac Resynchronization Therapy devices are made up of 4 main components; the can or battery, a Right Atrial (RA) lead, a Right Ventricular (RV) lead, and a Left Ventricular (LV) lead.

The LV lead specifically is important at maintaining ventricular synchrony. In 2014, Medtronic released the Attain® Performa™ family of LV leads (models 4298, 4398 and 4598). The three different shapes of these leads (double canted, straight, and S-shaped) were designed to enable the lead to be passively fixed within different anatomies of coronary vessels. In addition, the 4 strategically placed electrodes on the lead were designed to offer 16 different electrical vector programming configurations.

Medtronic also released the Attain Stability bipolar LV lead (Model 20066/4796) (CE Mark approved in September 30, 2013) in Europe. This lead has a side helix which enables it to be actively fixated to the vessel wall. The active fixation is an advantageous component in vessels that are wide or have short take-offs. The next generation of LV lead is known as the Attain Stability™ Quad MRI SureScan LV lead (Model 4798). This is a quadripolar lead similar to its Attain Performa predecessor leads and has a side helix for active fixation like the Attain Stability bipolar lead.

10.2. Purpose

The Attain Stability Quad Clinical Study is a prospective, non-randomized, multi-site, Investigational Device Exemption (IDE), interventional clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability™ Quad MRI SureScan LV Lead (Model 4798). This study will not be considered investigational in geographies with CE Mark of the Attain Stability™ Quad MRI SureScan LV lead (Model 4798). However, data collected from all study subjects will be represented in the final clinical report and the PMA Supplement (PMA-S) to the Attain Ability Model 4196 Original PMA (P080006, approved April 7, 2009).

Subjects successfully implanted with the Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be followed at implant, three months, six months and every six months thereafter until FDA approval is obtained or until study closure, whichever comes first.

11. Objectives and Endpoints

11.1. Objectives

11.1.1. Primary Objective(s)

Primary Safety Objective: Lead complication-free rate at 6 months

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered safe if the probability of subjects free of Model 4798 lead-related complications at 6 months post-implant is greater than 87% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 87%).

Primary Efficacy Objectives: Lead pacing capture thresholds at 6 months

To demonstrate the effectiveness of the Attain Stability Quad MRI SureScan LV Lead (Model 4798), the study will evaluate the likelihood that there are at least two programmable vectors for each patient post implant. The effectiveness of this lead will be evaluated based on two primary efficacy objectives. More specifically, both primary efficacy objectives must be met simultaneously.

Primary Efficacy Objective #1

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet this objective if the proportion of subjects with at least one LV lead pacing vector having a pacing capture threshold less than or equal to 2.5 V at 0.5 ms pulse width at 6 months post-implant is greater than 80% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 80%).

Primary Efficacy Objective #2

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet this objective if the proportion of subjects with at least one additional (or second) LV lead pacing vector having a pacing capture threshold less than or equal to 4.0 V at 0.5 ms pulse width at 6 months post-implant is greater than 80% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 80%).

11.1.2. Secondary Objective(s)

The secondary objectives are descriptive in nature and are intended to provide additional information about the Attain Stability Quad MRI SureScan LV Lead (Model 4798). There will be no established performance requirements for these secondary objectives.

- To summarize implant procedure related information: success rate, implant related times
- To estimate 6-month reliability: post implant lead failure modes (i.e. complication rate)
- To estimate electrical measurement values (Pacing Capture Thresholds (PCTs) and Lead Impedance) at 6 months post-implant

11.2. Endpoints

11.2.1 Primary Endpoints

Primary Safety Endpoint

The study primary safety endpoint is Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complications through 6 months post implant. All reported system and procedure-related AEs will be reviewed by an event review committee for LV lead relatedness and severity (complication vs observation, refer to 17.1.2 for defintions).

Primary Efficacy Endpoint #1

The Model 4798 LV lead has sixteen (16) programmable pacing configurations. The endpoint for the primary efficacy objective is whether or not there is at least one Model 4798 LV lead pacing vector with pacing capture voltage thresholds less than or equal to 2.5V. This endpoint will be measured at the 6-month post implant follow-up visit.

Primary Efficacy Endpoint #2

The co-primary efficacy endpoint is whether or not a second Model 4798 lead configuration has a pacing capture threshold less than or equal to 4V, excluding the pacing vector that is already counted to the primary efficacy endpoint #1. This endpoint will be measured at 6-month post implant follow-up visit.

11.2.2 Secondary Endpoints

To summarize implant procedure related information

Implant procedure related endpoints will include implant success rate and procedure durations.

To estimate 6-month reliability

The Model 4798 LV lead 6-month reliability endpoint is Model 4798 lead related complications.

To estimate electrical measurement values (Pacing Capture Thresholds (PCTs) and Lead Impedance) at 6 months post-implant

The electrical measurements are pacing capture thresholds and impedance values for the four extended bipolar configurations, i.e. LV1 to RVCoil, LV2 to RV Coil, LV3 to RV Coil and LV4 to RV Coil (refer to 15.8.2.3 for the testing procedure requirements).

12. Study Design

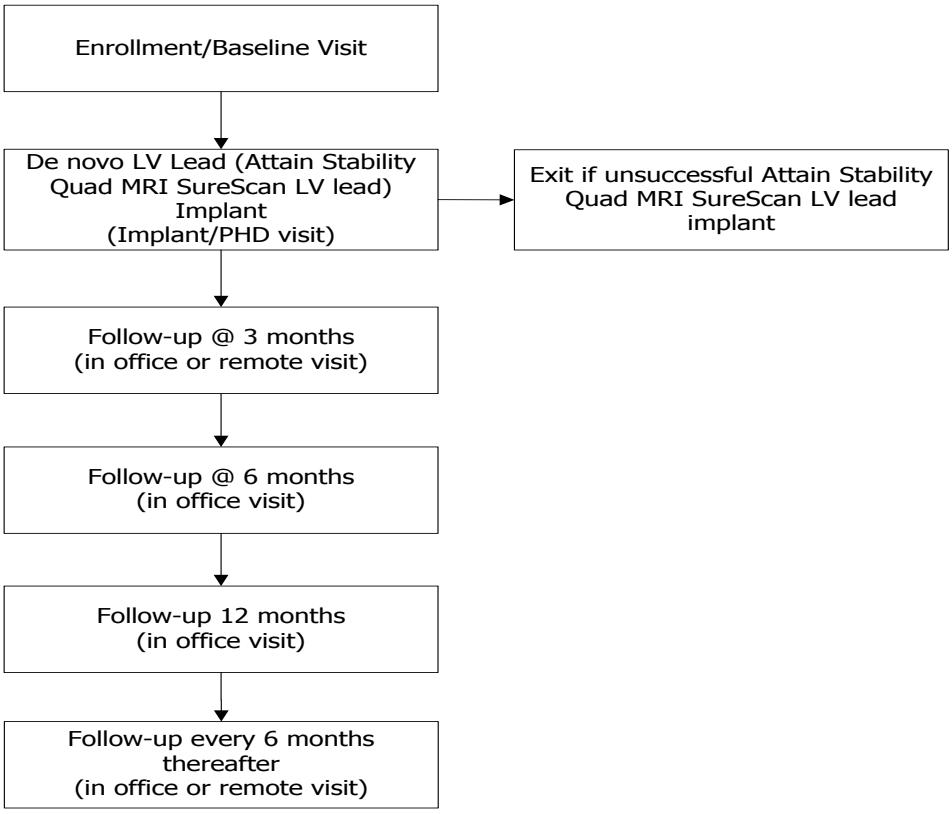
The Attain Stability Quad Clinical Study is a prospective, non-randomized, multi-site, Investigational Device Exemption (IDE), interventional clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) in patients indicated for a de novo LV lead implant. This will be assessed through a primary safety and primary efficacy endpoints.

All subjects included in the study will be implanted with a Medtronic market released CRT-P or CRT-D device and an Attain Stability Quad MRI SureScan LV Lead (Model 4798). For de novo CRT systems, compatible market released Medtronic RA and Medtronic RV leads will be required. For subjects enrolled who are receiving an upgrade to a CRT system, existing non-Medtronic RV and/or existing non-Medtronic RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used.

Up to 471 subjects will be enrolled into the study and up to 471 Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted, to ensure a minimum effective sample size of 400 Model 4798 leads implanted with 6 months post implant follow up visits (assuming 15% attrition). For the secondary endpoint of individual lead failure modes, Bayesian methods utilizing data from up to 37 historical patients will be used. All other objectives will be analyzed using only patients enrolled in this study. After a successful implant, threshold testing will occur to show one LV vector with pacing capture threshold (PCT) ≤ 2.5 V @ 0.5ms and with sufficient safety margin was programmed. Subjects will then be followed at implant, three months, six months and every six months thereafter until FDA approval is obtained or until study closure, whichever comes first.

The study will look to collect the following information: demographics, medical history, standard physical, NYHA class, implanted device information, pacing capture thresholds, device interrogations or save-to-media, medications, adverse events , system modifications, device deficiencies, and exit information. See Figure 1 and Section 15 for further detail on study procedures and data collection as well as time-points for data collection.

Figure 1: Study Visits



The study is expected to be conducted at up to 50 sites worldwide. Participating geographies are expected to include, but are not limited to: the United States, Canada, EMEA, Malaysia, and Hong Kong. To ensure a widespread distribution of data and to minimize site bias in the study results, the maximum number of subjects allowed at a single site is 50 subjects.

12.1. Duration

The study duration is expected to be approximately 19 months. This represents 13 months for subject enrollment and 6 months for subject follow-up for the last subject enrolled. Subjects are anticipated to be in the study for on average 12 months. The first enrollment is projected to occur in May 2017. Subjects will complete visits at enrollment/baseline, implant, 3 months, 6 months, and then every 6 months thereafter. Subjects will not be replaced with newly enrolled subjects upon early exit. As described in Section 19, the sample size accounts for attrition.

12.2. Rationale

Upon market release, this Attain Stability Quad MRI SureScan LV Lead (Model 4798) will provide physicians an alternative option to actively fixate the lead utilizing a side helix feature to achieve stability. The Attain Stability Quad Clinical Study is designed to demonstrate that the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is safe and effective. See Section 19 for further background information and evaluation of clinical data. See Section 10 for further background on the study design.

12.3. Study Oversight

The study will utilize a Steering Committee (SC). The SC is responsible for the scientific content of the study and for providing input for the execution of the study. Members of the SC may be study site investigators. The purpose of the SC is to provide unbiased opinions and expertise to the Attain Stability Quad Clinical Study design and process. The SC will support the execution of the Attain Stability Quad Clinical Study and provide guidance, feedback and direction to the clinical study. The SC is comprised of the members as indicated in Table 4 below.

Table 4: Steering Committee Members

Committee Member	Contact information
George H. Crossley III, MD Steering Committee Co-Chair	Electrophysiology Fellowship Program Director Vanderbilt University Medical Center 1211 Medical Center Drive Nashville, TN 37232 United States (615) 322-5000 george.crossley@vanderbilt.edu
Kevin P. Jackson, MD Steering Committee Co-Chair	Electrophysiologist Duke Cardiology of Raleigh Medical Office Building 6 3320 Wake Forest Road 2nd Floor, Suite 200 Raleigh, NC 27609 United States (919) 862-5100 k.j@duke.edu
Dr. Maria Grazia Bongiorni	Electrophysiologist University Hospital of Pisa Lungarno Antonio Pacinotti 43, 56126 Pisa PI Italia +39 050 221 2111 m.g.bongiorni@med.unipi.it
Prof. Svein Faerestrand	Electrophysiologist University of Bergen Jonas Liesvei 65 Bergen, Norway 5021 +47 55 97 67 04 svein.faerestrand@helse-bergen.no
Dr. Axel Kloppe	Electrophysiologist Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil GmbH, Bürkle-de-la-Camp-Platz 1, 44789 Bochum, Germany +49 234 3026050 axel.kloppe@bergmannsheil.de

Melissa Kong, MD	Electrophysiologist Silicon Valley Cardiology 1300 Stockbridge Ave Redwood City, CA 94061 United States (650) 363-5262 mhkong1@gmail.com
Raymond Yee, MD	Electrophysiologist London Health Sciences Centre 339 Windemere Road London, ON N6A 5A5 Canada (519) 663-3671 ryee@uwo.ca
Francois Philippon, MD	Electrophysiologist Institut Universitaire de Cardiologie et de Pneumologie de Quebec 2725 Chemin Ste-Foy Quebec G1V 4G5 Canada (418) 656-8711 francois.philippon@fmed.ulaval.ca

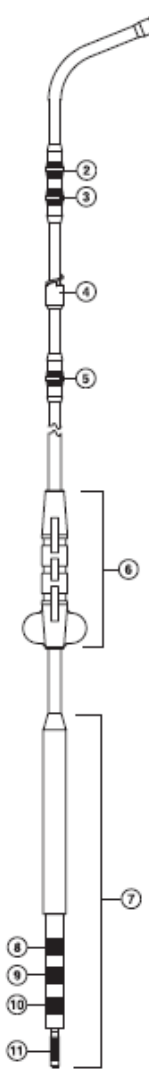
The study will also utilize a Clinical Events Committee (CEC) who will be responsible for adjudicating adverse events and deaths, including procedure and/or system-related complications. Further details for the CEC are provided in Section 18.1.

13. Product Description

13.1. General

The Medtronic Attain Stability Quad MRI SureScan (Model 4798) is a steroid-eluting, quadripolar electrode, transvenous, over-the-wire (OTW), IS4-LLLL compatible, active fixation, cardiac vein pacing LV lead. This lead is similar to the Attain Performa family of quadripolar leads (Models 4298, 4398, and 4598) but also has a side helix for active fixation which is similar to the Attain Stability bipolar lead (Model 20066/4796) (available outside of the United States). Figure 2 is a drawing of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) illustrating the specifications and location of the four electrodes in comparison to the side helix.

Figure 2: Attain Stability Quad MRI SureScan LV Lead (Model 4798) Specifications Drawing



[1] Electrode LV1 (the distal electrode): nominally 5.8 mm^2 geometric pacing surface area
[2] Electrode LV2: nominally 5.8 mm^2 geometric pacing surface area
[3] Electrode LV3: nominally 5.8 mm^2 geometric pacing surface area
[4] Helix assembly
[5] Electrode LV4 (the proximal electrode): nominally 5.8 mm^2 geometric pacing surface area
[6] Anchoring sleeve
[7] IS4 connector
[8] Contact LV4
[9] Contact LV3
[10] Contact LV2
[11] Contact LV1

Table 5 provides compares of the Attain Performa family of leads design features to the Attain Stability Quad MRI SureScan LV Lead (Model 4798).

Table 5: Comparison of Medtronic Quadripolar LV Leads

	Attain Performa			Attain Stability Quad
Design Feature	Model 4298	Model 4398	Model 4598	Model 4798
Shape	Double Canted	Straight	S-Shaped	Single Canted
Implant Method	Guide wire, stylet, or hybrid guide wire via Medtronic Delivery System	Same as 4298	Same as 4298	Guide wire, stylet, or hybrid guide wire via Medtronic Delivery System and active fixation
Delivery System Inner Diameter	≥ 5.7 Fr ID	Same as 4298	Same as 4298	Same as 4298
Lead Body Diameter	5.3 Fr proximal/3.9 Fr distal	Same as 4298	Same as 4298	4.4 Fr proximal/3.9 Fr distal
Lead Body Conductor	Single Quadfilar Coil (Multiconductor)	Same as 4298	Same as 4298	Same as 4298
Conductor Material	Ag core-low Titanium MP35Ncoil	Same as 4298	Same as 4298	Same as 4298
Insulation (Outer/Inner)	Polyurethane 55D SI-PI	Same as 4298	Same as 4298	Same as 4298
Polarity	Selectable Quad-electrode	Same as 4298	Same as 4298	Same as 4298
Electrode Material	PT/Ir* alloy with TiN coating	Same as 4298	Same as 4298	Same as 4298
Fixation Helix Material	N/A	N/A	N/A	Pt/Ir** alloy
Electrode Spacing	21mm/ 1.3mm/ 21mm	Same as 4298	Same as 4298	Same as 4298
Surface Area per	5.8	Same as 4298	Same as 4298	Same as 4298

Electrode (mm^2)				
Steroid and Dose / MCRD	Dexamethasone acetate Each (4) Ring 72µg	Same as 4298	Same as 4298	Same as 4298
Total Target Dose	288 µg/lead	Same as 4298	Same as 4298	Same as 4298

*90/10 Platinum Iridium
**80/20 Platinum Iridium

Similar to the Attain Performa family of leads, the Attain Stability Quad MRI SureScan LV Lead (Model 4798) contains 4 electrodes with surface area of 5.8 mm^2 per electrode and is designed to function as cathodes or anodes, depending on how the device LV pacing vector is programmed:

- electrode LV1, the distal electrode, positioned near the distal tip of the lead
- electrode LV2, positioned 21 mm proximal to electrode LV1
- electrode LV3, positioned 1.3 mm proximal to electrode LV2
- electrode LV4, the proximal electrode, positioned 21 mm proximal to electrode LV3

The electrode spacing on the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is identical to the approved Attain Performa family of leads. This includes a non-uniform electrode spacing consisting of a reduced electrode spacing configuration (LV2-LV3) that alters the size of the electric field that is generated when stimulating the heart tissue. This close electrode spacing is designed to reduce the likelihood of stimulating the phrenic nerve while still allowing for optimal lead placement and acceptable pacing capture thresholds.

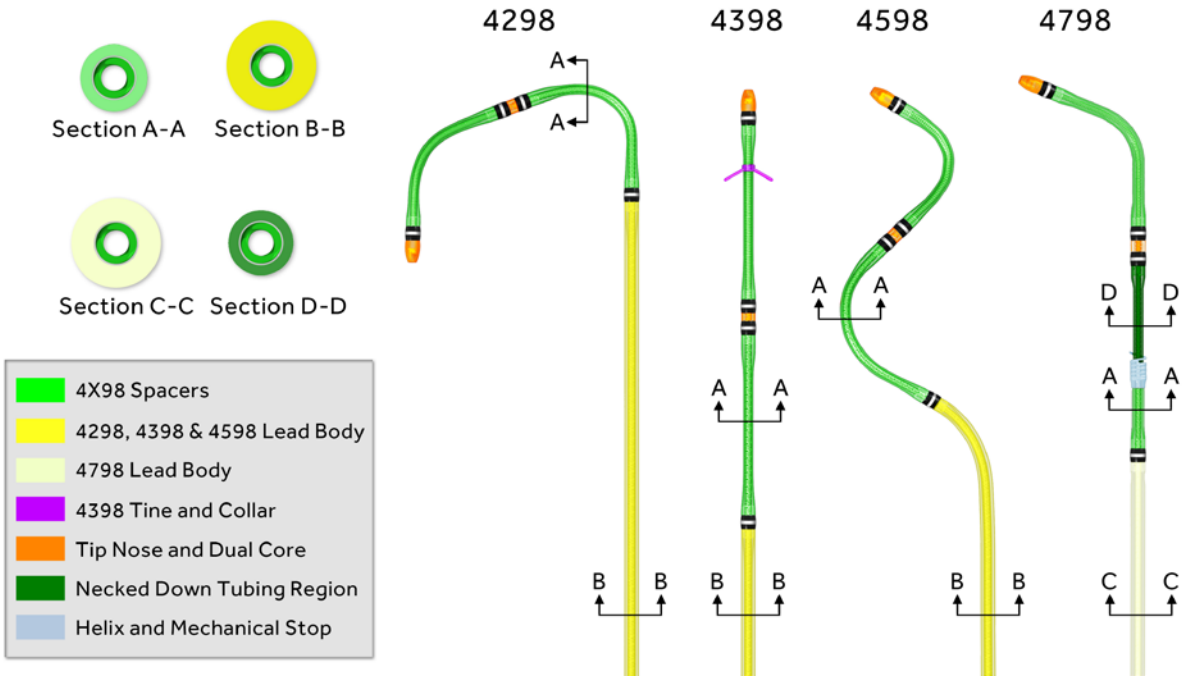
Similar to Attain Performa, each electrode contains a Monolithic Controlled Release Device (MCRD) for elution of steroid to reduce inflammatory response within the cardiac vein. The MCRDs contain a combined-total target dosage of 288 µg of dexamethasone acetate steroid. The target dose of the steroid is 72 µg at each MCRD. Upon exposure to body fluids, the steroid elutes from the MCRDs. The steroid suppresses the inflammatory response that is believed to cause threshold rise typically associated with implanted pacing electrodes.

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) has the same lead body conductor (Single Quadfilar Coil (Multiconductor), conductor material (Ag core-low Titanium MP35N coil), insulation (outer/inner) (Polyurethane 55D SI-PI), and requires a similar delivery system inner diameter as the Attain Performa family of leads (≥ 5.7 Fr ID).

Unlike the Attain Performa family of leads, the Attain Stability Quad MRI SureScan LV Lead (Model 4798) has a slightly smaller lead body diameter. The lead body diameter of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is 4.4 Fr proximal (compared to 5.3 Fr on the Attain Performa family of leads) and 3.9 French distal (same as Attain Performa family of leads). This slightly smaller lead body tubing diameter is designed to enhance torquability and steerability to facilitate adherence of the side helix in the target location.

Figure 3 is a visual comparison between the Attain Perform leads and the Attain Stability Quad MRI SureScan LV Lead (Model 4798) illustrating the similar electrode location but different lead body diameter.

Figure 3: Comparison of Attain Performa Leads and the Attain Stability Lead Model 4798



A detailed comparison of the Attain Stability bipolar lead (Model 4796) and Attain Stability Quad lead (Model 4798) is presented in Table 6.

Table 6: Comparison of Medtronic Attain Stability Bipolar and Quadripolar LV Leads

	Attain Stability	Attain Stability Quad
Design Feature	Model 4796/20066	Model 4798
Shape	Single Canted	Same as 4796/20066
Implant Method	Guide wire, Stylet, or hybrid guide wire via Medtronic Delivery System and active fixation	Same as 4796/20066
Delivery System Inner Diameter	≥ 5.7 Fr ID	Same as 4796/20066
Lead body diameter	3.9 Fr proximal / 3.4 Fr distal	4.4 Fr proximal /3.9 Fr distal
Lead Body Conductor	Single 2 Filar Coil (Multiconductor)	Single Quadfilar Coil (Multiconductor)
Conductor Material	Ag core-low Titanium MP35N coil	Same as 4796/20066

	Attain Stability	Attain Stability Quad
Design Feature	Model 4796/20066	Model 4798
Shape	Single Canted	Same as 4796/20066
Insulation (Outer/Inner)	Polyurethane 55D SI-PI	Same as 4796/20066
Polarity	bipolar	Selectable Quad-electrode
Electrode Material	Pt/Ir* alloy with TiN coating	Same as 4796/20066
Fixation Helix Material	Pt/Ir** alloy	Same as 4796/20066
Electrode Spacing	21 mm	21mm / 1.3mm / 21mm
Surface Area per electrode (mm^2)	5.8	Same as 4796/20066
Steroid and Dose / MCRD	Dexamethasone acetate Tip 160µg , Ring 72µg	Dexamethasone acetate Each (4) Ring 72µg
Total Target Dose	232µg/lead	288 µg/lead
Molded Tip Seal	Silicone (with steroid), pierced hole	Silicone (without steroid), cross-cut hole
Fixation Method	Helix	Same as 4796/20066
Connector	IS-1 B1	IS4-LLLL
Length (cm)	88 cm only	78 and 88 cm

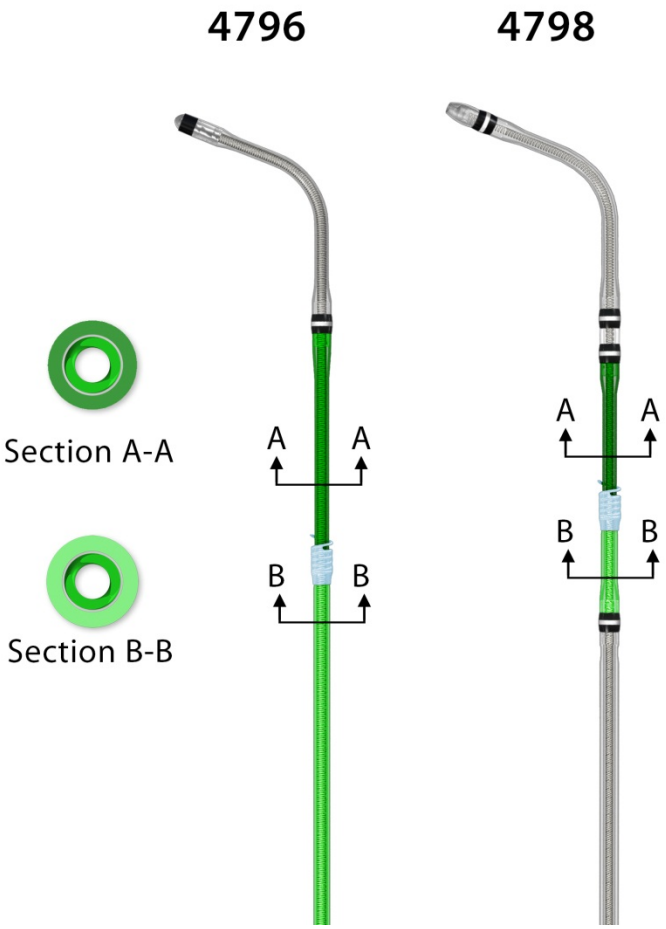
*90/10 Platinum Iridium
**80/20 Platinum Iridium

The non-electrically active side fixation helix component is similar to the Attain Stability Bipolar LV lead (Model 20066/4796) and is designed to enable active fixation in the cardiac vein. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) side helix is positioned between the LV3 and LV4 electrode; specifically 10 mm proximal from the LV3 electrode (see Figure 2).

A mechanical stop component is located at the base of the helix to prevent wedging of the endothelial tissue in the helix and to prevent tissue ingrowth. The helix component is platinum (Pt) iridium (Ir) alloy (Pt/Ir 80/20). This same Pt/Ir material is also used in the market released right ventricular active fixation lead Models 5076, 3830, and 4076. Both the helix and mechanical stop components are identical to those used on the CE Mark approved Medtronic Attain Stability model 20066/4796 active fixation lead and are shown in Figure 4.

The Model 4798 lead has one distal curve/cant. This distal curve geometry (angle) is identical to the Attain Performa model 4298, as well as Attain Ability models 4196 and 4296 most distal cant. The single distal cant is also identical to the CE Mark approved model 20066/4796 active fixation lead (Figure 4). The purpose of the distal cant is to provide physicians the ability to "steer" the distal tip of the lead when navigating difficult vein anatomy or acute vasculature angulation by rotating the lead (counterclockwise) and aligning the distal tip towards the desired direction. The distal cant for the Model 4798 lead is not intended, or necessary, to provide any fixation of the implanted lead as any retention force from the cant would be negligible compared to the stability provided by the properly implanted and verified fixated helix.

Figure 4: Attain Stability Bipolar (Model 20066/4796) & Attain Stability Quad MRI SureScan (Model 4798) Active Fixation Leads



The Attain Stability Quad Clinical Study will be conducted to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) in combination with CRT system components mentioned in Table 7.

Table 7: Study Component Information

Component	US/Canada	EMEA/Hong Kong/Malaysia
Attain Stability Quad MRI SureScan LV Lead (Model	Investigational	Market-released

4798)		
Medtronic CRT-P or Medtronic CRT-D (with VectorExpress capabilities)	Market-released	Market-released
Medtronic RV lead (non-Medtronic and non-recalled/non-market withdrawaled/non-safety alerted lead acceptable for upgrades)	Market-released	Market-released
Medtronic RA lead (optional) (non-Medtronic and non-recalled/non-market withdrawn/non-safety alerted lead acceptable for upgraded systems)	Market-released	Market-released

Given the similarities between the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the Attain Performa family of leads, the proposed indications for use are the same. The indications are as follows:

Proposed Indication Statement for Use for the Attain Stability Quad Lead:

The Attain Stability Quad MRI SureScan 4798 steroid-eluting, quadripolar electrode, IS4 transvenous lead is indicated for chronic pacing in the left ventricle via the cardiac vein, when used with a compatible Medtronic Cardiac Resynchronization Therapy (CRT) System. Extended bipolar pacing is available using this lead in combination with a compatible market approved CRT-D system and RV lead.

Market-Released Right Atrial Lead

Commercially available Medtronic RA lead models with an IS-1 connector are required when an RA lead is implanted with de novo CRT systems. An RA lead is not required to be implanted in circumstances determined appropriate per physician's medical assessment. Medtronic commercially available RA leads with an IS-1 connector are recommended but compatible non-Medtronic leads are permissible in enrolled patients receving a CRT system upgrades.

Medtronic Market-Released Right Ventricular Lead

Commercially available Medtronic RV defibrillation leads with a DF4 connector are required for de novo CRT systems. Medtronic RV defibrillation leads with DF1 connectors may be incorporated in the study as DF1-compatible CRT-P and CRT-D devices are made available for the study. A non-Medtronic RV lead is permissible in enrolled patients receving a CRT system upgrades.

13.2. Manufacturer

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is manufactured by Medtronic, Inc.

13.3. Packaging

Packaging and labeling for all market approved system components can be found with each package insert. Manuals can be found on http://manuals.medtronic.com. For CE Marked devices the labeling is in the appropriate local language.

For investigational products in the US and Canada, the language of labeling and clinical manuals will be in English and/or local language where it is required. Investigational products will be clearly labeled e.g. "exclusively for clinical investigation."

In Canada, each investigational device will be labelled with the statements "Investigational Device"; "To be Used by Qualified Investigators Only"; "Instrument de recherche" and "Réservé uniquement à l'usage de chercheurs compétents".

13.4. Intended Population

In the Attain Stability Quad Clinical Study, the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is to be used in subjects where a de novo LV lead is indicated. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is intended to be used in conjunction with a market released Medtronic CRT-P or CRT-D device, a Medtronic (for de novo CRT implants) RV lead, and a Medtronic (for de novo CRT implants) RA lead (optional).

A complete SureScan system is required for use in the MRI environment. Before performing an MRI scan, refer to the SureScan MRI technical manual for MRI-specific warnings and precautions.

13.5. Equipment

All commercially available equipment will be used according to their approved intended use.

Medtronic CareLink (2090) Programmer

The Medtronic approved CRT-P or CRT-D devices will programmed and interrogated using a Medtronic CareLink (2090) programmer. Medtronic may incorporate additional programmers as they receive regulatory approval.

Medtronic CareLink Home Monitor 2490C and Network

The CareLink Monitor Model 2490C is an external monitor that is indicated for use in the transfer of patient and device data from implanted Medtronic devices. The CareLink Monitor Model 2490C interrogates implanted devices and temporarily stores these data, collaborates with the appropriate Medtronic server to confirm the establishment of an Internet connection with server, performs any required file translation functions necessary for data transfer, executes data file transfer, and collaborates with the appropriate Medtronic server to confirm data file transfer through the Internet connection with the server. The CareLink Monitor 2490C is not a programmer and cannot be used to program implanted device parameters. CareLink monitors are not a substitute for appropriate medical attention in the event of an emergency and should only be used as directed by a physician. Approved Medtronic CRT-P and CRT-D devices used in this study qualify for use with the Medtronic CareLink Monitor and Medtronic CareLink Network. Medtronic may incorporate additional home monitors as they receive regulatory approval.

Pacing System Analyzer

Medtronic's commercially available Model 2290 Analyzer must be available at each center during the implant procedure to determine acceptable electrical parameters. Medtronic may incorporate additional analyzers as they receive regulatory approval.

13.6. Product Use

See Section 13 Product Description.

13.7. Product Receipt, Tracking, and Accountability

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered investigational in geographies where the product is not available commercially and will be labeled for clinical use only. These geographies include but are not limited to the US and Canada. Investigational Attain Stability Quad Leads will be distributed to a site only when Medtronic has received all required documentation (including but not limited to Ethic Committee approval, a signed Clinical Trial Agreement and documentation of training) and has notified the site of site readiness.

Distribution of the investigational product to study sites will be managed by Medtronic and investigational products can only be ordered by Medtronic personnel. Site with these clinically labeled Attain Stability Quad MRI SureScan LV Lead (Model 4798) will track disposition upon receipt or return of the lead but also upon implant or explant of the lead. Disposition logs will be available within the electronic data management system and shall be maintained at each site in all geographies to track investigational product information. The logs should be updated when an investigational product is received, opened, implanted explanted, disposed of or returned to Medtronic. The logs will track the following investigational lead data (but are not limited to) model and serial numbers of devices delivered to the site, subject IDs of the subjects, implanted, received dates of devices, implant/used dates, explant dates, returned-to-sponsor dates and reasons, initials of all persons who received, used or disposed each device, and method of disposal. Medtronic will perform periodic reconciliation of investigational product to ensure traceability.

For geographies where the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is not considered investigational, commercially approved devices will be used. Sites that use commercially available Attain Stability Quad MRI SureScan LV Lead (Model 4798) will track device disposition upon implant or explant of the lead on the CRFs.

13.8. Product Storage

All investigational products must be stored in a secure location at the site. It is the responsibility of the investigator to correctly handle, store and track the investigational products. Further details may be found in the Clinical Manual or User Manual (dependent on each geography's commercial release of the product).

13.9. Product Return

All explanted, open but unused, and defective products (devices or leads, etc.) should be returned to Medtronic for analysis whenever possible and when permissible by local laws and regulations. If the products are explanted but not returned, a justification is required to be reported on the appropriate case report form(s) or disposition log(s) (note that this is not considered a study deviation). In geographies where the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is considered investigational, the

Disposition Log must be updated in the event of an explant. To receive a Returned Product Mailer Kit, please contact your local Medtronic field personnel or representative. All unused investigational products must be returned to Medtronic upon study closure at the site.

14. Selection of Subjects

14.1. Study Population

Patients of both genders that are 18 years of age and older (or of legal age to give informed consent per local and national law) that are indicated for a de novo LV lead implantation and who meet all inclusion and no exclusion criteria are eligible for an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt. There will be no control group for this study.

14.2. Subject Enrollment

Patients who meet all of the inclusion and none of the exclusion criteria (see sections 14.3 and 14.4) are eligible to be enrolled in this study. Upon signing and dating the Informed Consent Form (ICF), the patient is considered a subject enrolled in the study.

14.3. Inclusion Criteria

- Patient meets CRT implant criteria as determined by local regulatory and/or hospital policy
- Patient (or legally authorized representative) has signed and dated the study-specific Informed Consent Form
- Patient is 18 years of age or older, or is of legal age to give informed consent per local and national law
- Patient is expected to remain available for follow-up visits

14.4. Exclusion Criteria

- Patient has had a previous unsuccessful LV lead implant attempt
- Patient has an existing epicardial LV lead
- Patient is currently implanted with a recalled (i.e. market-withdrawn, recalled or safety alert) RA and/or RV lead
- Patient has known coronary venous vasculature that is inadequate for lead placement
- Patient has unstable angina pectoris or has had an acute myocardial infarction (MI) within the past 30 days
- Patient has had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the past 90 days
- Patient has contraindications for standard transvenous cardiac pacing (e.g., mechanical right heart valve)
- Patient has had a heart transplant (patients waiting for heart transplants are allowed in the study)
- Patient has known renal insufficiency that would prevent them from receiving an occlusive venogram during the implant procedure
- Patient is contraindicated for <1mg dexamethasone acetate
- Patient is enrolled in any concurrent drug and/or device study that may confound the results of this study
- Patient has a terminal illness and is not expected to survive more than six months
- Patient meets exclusion criteria required by local law (e.g. age, pregnancy, breast feeding, etc.)
- Patient is unable to tolerate an urgent thoracotomy

14.5. Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Subjects will be evaluated at baseline to confirm eligibility for enrollment with defined inclusion/exclusion criteria
- Subject demographics and medical history will be collected at baseline and differences that may affect primary endpoints will be identified
- To ensure widespread distribution of data between sites, the maximum number of subjects allowed per site is 50
- All implanters in the study will be experienced in the implant of CRT-P and/or CRT-D systems
- Data collection requirements and study procedures will be standardized across all sites and geographies

- All study site personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials, and required to follow the CIP
- Per the specifications in the Monitoring Plan, monitoring visits will be conducted for adherence to the CIP and to verify the CRF data against source data
- Pre-defined statistical methods specified in the CIP and the Statistical Analysis Plan (SAP) will be followed
- The SC members will not have influence on the treatment decisions by study site investigators during the trial
- An independent and blinded CEC will regularly review and adjudicate reported adverse events and deaths (per Section 18.1)
- Registration of the trial on ClinicalTrials.gov and the publication plan will ensure that study results will be reported
- All study investigators are required to meet 21 CFR Part 54, Financial Disclosure by Clinical Investigators, to identify potential bias due to financial interest in the outcome of the study

In summary, potential sources of bias that may be encountered in this Attain Stability Quad Clinical Study have been considered and minimized by careful study design.

15. Study Procedures

Prior to performing study related procedures, all sites must have Ethics Committee (EC) and associated regulatory authority approval if applicable (e.g., Competent Authority approval) as well as documentation from Medtronic of site readiness.

Medtronic representatives may perform the following activities at the study sites during the study, if appropriately trained and under supervision of the Principal Investigator:

- Study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support at all visits (e.g. programming of the CRT-P or CRT-D device according to study requirements, performing device interrogations/save-to-media, etc.), but no CRF data entry shall be performed by Medtronic personnel
- Monitoring activities

15.1. Study Personnel Requirements

Site personnel training and delegation will be completed prior to participation in the Attain Stability Quad Clinical Study. The site personnel training consists of required training topics (CIP, Informed Consent Form, CRFs, regulations). Members of the study site team will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study.

All Principal Investigators shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Be qualified practitioners and experienced in the diagnosis, management, and treatment of HF subjects with CRT devices
- Be experienced in the field of application and trained in the use of the Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- Disclose potential conflicts of interest, including financial that interfere with the conduct of the clinical investigation or interpretation of results
- Be knowledgeable with the method of obtaining an informed consent

In addition, the Principal Investigator shall be able to demonstrate that the proposed investigational site:

- Has an experienced CRT implanter who is experienced and trained in the handling/implanting of CRT-P and/or CRT-D devices
- Has the required number of eligible subjects needed within the agreed recruitment period
- Has one or more qualified investigators, a qualified investigation site team and adequate facilities for the foreseen duration of the clinical investigation

15.2. Site Activation

During the activation process (prior to subject enrollment), Medtronic will train site personnel on the CIP, the implant procedure, relevant standards and regulations, informed consent process, and on data collection and reporting tools. If new members join the study site team, they will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study. For new members, local Ethics Committee notification requirements must be met, as well as Medtronic requirements noted on the training and delegation form.

A Clinical Trial Agreement (CTA) shall be entered into effect by Medtronic, the participating investigation site and/or the principal clinical investigator at each investigational site as per local legal requirements, and returned, fully executed, to Medtronic prior to the commencement of any study activities. Financial aspects of conducting and reporting a study will be specified in the agreement. By signing and dating the agreement the investigator indicates approval of the CIP.

Prior to performing study related activities, all sites must have Ethics Committee approval, as applicable for that geography.

All local and regional regulatory requirements will be fulfilled prior to site activation and enrollment of subjects into the study. Each study site must have written documentation from Medtronic of site and investigator readiness before beginning any study-related activities. Requirements for activation vary by geography, and may include, but are not limited to the following:

- Written documentation of Ethics Committee approval of the current version of the CIP and ICF, subject materials (e.g. Global Assessment and KCCQ), and voting list (as required by local law)
- Regulatory authority approval or notification (as required per local law)
- Fully executed CTA on file with the sponsor
- Financial Disclosure (for Principal Investigators and Co-Investigators)
- Current Curriculum Vitae (CV) (signed and dated as required by local law) of investigators and key members (as required by local law) of the investigation site team on file with the sponsor
- Documentation of delegated tasks

- Documentation of study site personnel training

Additional requirements imposed by the Ethics Committee and regulatory authority shall be followed, if applicable.

Medtronic will provide each study site with documentation of study site readiness; this letter must be sent prior to subject enrollment.

15.3. Equipment Requirements

The following equipment must be available at each site to support study activities:

- Medtronic 2090 programmer (or latest market released Medtronic programmer)
- Attain Stability Quad MRI SureScan LV Lead (Model 4798) (either clinically labeled product or commercial released product located at the site or carried to the implant by the Medtronic representative)
- Computer with high speed internet access using a web browser compatible with the electronic data management system for electronic database entry

The equipment necessary for the assessment for the study is the Medtronic 2090 programmer. The maintenance and calibration of the programmers used for this study will be assessed outside of this clinical study. Sites are responsible for maintaining and calibrating non-programmer equipment used in the course of this study in accordance with established site practice. Records should be kept and able to be provided upon request by the Sponsor or regulatory agency. For sites located in EMEA, programmer calibration and maintenance will be performed by the Medtronic office in Heerlen, The Netherlands. In Germany, the calibration of the programmers are under the responsibility of the hospitals and this calibration will be done mainly by DEKRA or TÜV.

15.4. Schedule of Events

Clinical data will be collected at the study milestones detailed in Table 8. Data will be collected via electronic case report forms (eCRFs), programmer print-outs, and interrogation files. Post-implant follow-ups apply only to those subjects in whom an Attain Stability Quad MRI SureScan LV Lead (Model 4798) was successfully implanted or an implant was attempted. Subject visits will occur at enrollment, baseline, implant/pre-hospital discharge (PHD), 3 months post-implant, 6 months post-implant, and every 6 months thereafter until PMA approval of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted or study termination, whichever comes first. Medtronic personnel may assist study personnel during implant and study visits.

Table 8: Data Collection and Study Procedure Requirements at Subject Visits

STUDY PROCEDURE	Enrollment /Baseline	Implant /PHD	3 months post-implant (remote or inoffice visit)	6 months post-implant (inoffice visit)	12 months post-implant (inoffice visit)	Recurring 6 month follow-ups (remote or inoffice visit)	Exit
Subject Informed Consent	✓						
Inclusion / Exclusion criteria verified	✓						
Subject demographics	✓						
Cardiovascular medications	✓						
Cardiovascular medical history	✓						
NYHA classification	✓		✓	✓	✓	✓	
Patient Global Assessment	✓		✓	✓	✓		
Kansas City Cardiomyopathy Questionnaire (KCCQ)	✓			✓	✓		
Occlusive venogram with pre-determined pacing location identified		✓					
System and procedure information		✓					
Lead Impedance (all 16 vectors)		✓	✓ (final programmed vector only)	✓	✓	✓ (final programmed vector only)	
Pacing Capture Thresholds (all 16 vectors)		✓	✓ (final programmed vector only)	✓	✓	✓ (final programmed vector only)	
Phrenic Nerve Stimulation (final programmed vector)		✓	✓ (inoffice visit only)	✓	✓		
Phrenic Nerve Stimulation (vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil)				✓			
Rationale for selecting specific LV lead pacing vector for final programming		✓	✓	✓	✓		
Final device interrogation/save-to-media		✓	✓ (CareLink transmission is acceptable for remote visits)	✓	✓	✓	✓ (required only if subject exits prior to 6 months post-implant visit; CareLink transmission is acceptable)
AE Assessment		✓	✓	✓	✓	✓	✓
Exit Subject							✓
Adverse Events (incl. AE with outcome of death)	As they occur						
Device Deficiencies							
System Modifications							
Study Deviations							
CareLink Transmissions (optional)							

Table 9 below specifies permitted time windows for the required subject visits. Subject visit target dates and windows for each follow-up will be made available to the study site. Should a subject miss a visit or the visit falls outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits. Data analyses will include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation.

Table 9: Visit Windows

Visit	Window
Implant	0-30 days since Baseline Assessment
	(days since implant)
Pre-hospital discharge	0-7
3-month	76 - 106
6-month	183 - 213
12-month	350 - 380
18-month	518 - 578
24-month	701 - 761

15.5. Subject Consent

Informed consent (IC) is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate (ISO 14155:2011). This process includes obtaining IC and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (data protection authorization; i.e. HIPAA in the US) as required by law. Informed Consent Forms are required to be approved by the study site's Institutional Review Board (IRB) or Ethics Committee (EC) and Medtronic, and signed and dated by the subject and the Principal Investigator. A subject may only consent after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate.

Prior to enrolling subjects, each site must have documented IRB/EC approval of the IC Form (ICF) and the data protection authorization as required by law. Any changes to a previously approved ICF throughout the course of the study must be reviewed and approved by Medtronic and the IRB/EC reviewing the application before being used to consent or re-consent a study subject. The document(s) must be controlled (i.e. versioned and dated) to ensure it is clear which version(s) was approved by Medtronic and the IRB/EC. All important new information should be provided in written form to new and existing subjects throughout the study. If relevant, all affected subjects must be asked to confirm their continuing IC in writing.

Prior to initiation of any study-specific procedures, IC must be obtained from the subject (or legally authorized representative). Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize sites to submit subject information to the study sponsor. The IC process must be conducted by the principal investigator or an authorized designee, and the ICF and data protection authorization, as required by law, must be given to the subject in a language he/she is able to read and understand.

The process of obtaining informed consent shall:

- Ensure that the principal investigator or an authorized designee conducts the IC process.
- Include all aspects of the Attain Stability Quad Clinical Study that are relevant to the subject's decision to participate throughout the clinical study.
- Avoid any coercion or undue improper influence on, or inducement of the subject to participate.
- Not waive or appear to waive the subject's legal rights.
- Ensure the ICF and data protection authorization, as required by law, are given to the subject in a non-technical language the subject is able to read and understand.
- Provide ample time and opportunity for the subject to read and understand the ICF to inquire about details of the study, and to consider participation. All questions about the study should be answered to the satisfaction of the subject.
- Include a personally dated signature of the subject acknowledging that their participation in the study is voluntary.
- Include a personally dated signature by the principal investigator or authorized designee responsible for conducting the IC process, as required by local law.
- Include any other locally required signatories, such as witnesses, as indicated by country-specific legislations.
- Provide the subject with a copy of the ICF, the data protection authorization, as required by law, and any other written information, signed and dated if required by local law.
- Ensure subjects are notified of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study.

If IC is obtained the same day the subject begins participating in study-related procedures, it must be documented that consent was obtained prior to participation in any study-related procedures. It is best practice for the IC process to be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write, witnessed (impartial third party) IC will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the ICF. Informed consent shall be obtained through a supervised oral process. An independent witness must be present throughout the process. The ICF and any other information must be read aloud and explained to the prospective subject, if allowed by local law. The witness signs and personally dates the ICF, attesting that the information was accurately explained and that informed consent was freely given. The subject should "make his mark" (sign or otherwise physically mark the document so as to indicate consent) on the ICF as well. The ICF should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

The original of the signed ICF must be filed in the hospital/clinical chart and/or with the subject's study documents. A second signed original or a copy should be given to the subject for their records (if applicable).

The ICF and data protection authorization, as required by law, must be available for monitoring, auditing and regulatory inspections.

Geography specific ICF Templates will be provided under separate cover.

15.6. Enrollment

The point of enrollment is defined as the time at which a patient has signed and dated the ICF. The date the subject signed (or legally authorized representative) the ICF and data protection authorization, as required by law, must be documented in the subject's medical records. At that point, the patient is considered a subject in the study, a study subject ID number will be assigned, and the subject must be followed for the duration of the study unless the subject exits the study prior to study closure. Each investigational center will be responsible for maintaining subject identification records (e.g. subject identification log) according to ISO 14155.

Enrollment will occur on the same day as the baseline visit. Once IC is obtained, report AEs/deaths, study deviations and subject exits as they occur. To accurately track subject enrollment, Medtronic should be notified of the enrollment as soon as possible after a patient has signed the ICF.

15.7. Baseline

The baseline visit can be a stand-alone visit or can occur on the same day as, but not later than, the implant visit. The following procedures will be completed/data will be collected at the baseline visit:

- Subject Informed Consent
- Inclusion/Exclusion criteria verified
- Subject demographics
- Cardiovascular medications
- Cardiovascular medical history
- NYHA classification
- Patient Global Assessment

Kansas City Cardiomyopathy Questionnaire (KCCQ) Cardiovascular medications include ACE inhibitors, ARBs, antiarrhythmic, anti-coagulants, antithrombotics, and antiplatelet, antihypertensive, antilipidemics (statins), beta blockers, calcium channel blockers, diuretics, digitalis, inotropes, nitrates, digoxin, and vasodilators.

If implant does not occur within 30 days of enrollment, verification of all inclusion and all exclusion criteria must be repeated before an implant attempt.

15.8. Implant/PHD

Information collected at Implant/PHD will include data from the day of the implant procedure until released from the hospital. The implant CRF will be used to collect data at implant. Implantation of the CRT device and right heart leads should be performed according to the Instruction for Use (IFU) in geographies where the devices are commercially available.

Any Medtronic commercially released right atrial (RA) and any Medtronic commercially released right ventricular (RV) lead may be implanted. Existing non-Medtronic RV and/or RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used in enrolled who are receiving an upgrade to

a CRT system. The right-heart leads should be implanted according to the labeling provided with the applicable lead.

The implanted system device must include a Medtronic commercially released CRT device which can be programmed to utilize all electrodes, allowing upgrades from implantable pulse generators (IPGs) and implantable cardioverter defibrillators (ICDs). Device and lead requirements are as follows:

- Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- For de novo CRT implants, any Medtronic commercially released transvenous (active or passive fixation) RA pacing lead (unless medical justification to exclude this lead) and any Medtronic commercially released transvenous (active or passive fixation) RV lead
- For upgrades to a CRT system, existing non-Medtronic RV and/or non-Medtronic RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used in enrolled who are receiving an upgrade to a CRT system
- Medtronic commercially released CRT devices that measure discrete LV electrical values from all four electrodes (i.e. Vector Express)

15.8.1. Final System Configuration

For information on the requirements for the implanted system refer to Section 13. The system is successfully implanted when the Medtronic CRT device is successfully connected to the RA, RV and the LV lead (except if a medical condition such as chronic atrial fibrillation excludes the need for an RA lead). The configuration of the successfully implanted system components will be collected. This will include the serial number of each implanted component (CRT-D or CRT-P device, and leads), and the location of lead placement.

15.8.2. Implant Procedure

Implantation of the CRT device and cardiac leads must be performed by a trained clinical study investigator and according to the manufacturer's instructions for use. It is recommended to use Medtronic catheters that are compatible with the Attain Stability Quad MRI SureScan LV Lead (Model 4798) (e.g., > 7 Fr) during the implant for gaining access to the coronary sinus (CS).

For complete information regarding the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the implant procedure, reference the Clinical Manual in the US and Canada or the Instructions for Intended Use (Technical Manual in EMEA, Hong Kong, and Malaysia). These documents are located under a separate cover.

15.8.2.1. Venogram

An occlusive venogram is required for venous visualization of the subject's coronary vasculature and will be used to pre-determine a target implant vessel prior to placing the Attain Stability Quad MRI SureScan LV Lead (Model 4798). Once the pre-determined target vessel site is determined, a venous image will be collected. A copy of the venous image will be submitted to Medtronic and kept on file at the center.

15.8.2.2. Implanting the LV lead

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be implanted according to the implant instructions found within the lead packaging. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) can be positioned with the aid of a guide wire (0.36 mm to 0.46 mm or 0.014 inches to 0.018 inches in diameter), stylet, an inner catheter, or an inner catheter plus hybrid guide wire. If a stylet is

used for lead positioning, only use the stylets packaged with the lead or in a stylet kit (downsized knob). Always use a stylet that is 3 cm shorter than the lead length listed on the IS4 connector label. Other stylets may extend beyond the lead tip causing injury or perforation of the cardiac vein or heart. If using a Medtronic integrated valve system (e.g. SureValve), rotate the helix counterclockwise to allow safe passage of the helix when inserting the lead into the delivery system to prevent the side helix from inadvertently attaching to the valve. Rust stylets are not recommended with this lead due to the risk of conductor coil/insulation perforation.

Follow the Attain Stability Quad MRI SureScan LV Lead (Model 4798) package insert carefully for fixating the side helix to the vein. Consider using a J-shaped stylet if fixation is unsuccessful. An overview of the key implanting tips includes:

- Rotate the lead counterclockwise when inserting the lead through the SureValve to prevent the helix from attaching to the valve
- Refrain from wedging the lead into the vessel so that the lead can easily rotate during fixation allowing torque to transfer from the proximal end to the distal end of the lead
- To fixate the side helix in the desired location, rotate the lead clockwise with the guidewire inserted in the lead which will provide extra stiffness to the lead
- Ensure the guidewire is removed to allow for lead pliability to visualize and confirm lead fixation during the Push Test and the Pull Test
- To reposition the lead, insert the guidewire and rotate the lead counterclockwise without applying tension to the lead to unfixate

Information on surgical data, such as tool use, and implant times, etc. will be collected during the implant procedure.

In an event that one Attain Stability Quad MRI SureScan LV Lead (Model 4798) is determined to be not suitable for a patient after the initial lead insertion; the implanting physician must assess the onset of any potential AEs. A second Attain Stability Quad MRI SureScan LV Lead (Model 4798) may only be introduced upon confirmation that no system-related AEs resulted from the first Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt. Any LV lead related AE observed during the initial LV lead attempt prohibits an attempt of a second Attain Stability Quad MRI SureScan LV Lead (Model 4798).

If the subject does not have a successful Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant at the conclusion of the initial implant procedure, the subject should be followed until procedure or system related AEs are resolved or are unresolved with no further actions planned, whichever occurs later.

If an attempt to implant the Attain Stability Quad MRI SureScan LV Lead (Model 4798) does not occur, or if the Model 4798 LV lead cannot be implanted, the reasons why the lead was not attempted or attempted but not implanted must be documented on the Implant and Study Exit CRF. See additional definitions below.

No Attain Stability Quad MRI SureScan LV Lead (Model 4798) Attempted (lead not inserted into the body)

An Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt is defined as any time a Model 4798 lead is introduced into the body. Subjects that do not have an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempted will be exited from the study following their implant procedure unless another Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt is scheduled. Adverse events, device deficiencies and deviations must be documented before the subject is exited.

Attain Stability Quad MRI SureScan LV Lead (Model 4798) Attempted but Not Implanted

An Attain Stability Quad MRI SureScan LV Lead (Model 4798) that is inserted into the body that is not successfully placed will be considered an unsuccessful Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt. Note: An unsuccessful implant itself is not considered an AE. Adverse Events occurring during an unsuccessful implant (e.g. dissection, perforation) will be recorded and classified. Subjects with an unsuccessful Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt will be followed until procedure or system related AEs have been resolved or are deemed unresolvable with no further action planned.

15.8.2.3. CRT System Testing and Programming During Implant

Prior to connecting the leads to the CRT can, initial electrical measurements will be taken using the Analyzer (Model 2290 or market released equivalent) to confirm adequate pacing thresholds (PCTs) prior to closing the pocket per the center's standard testing method. These PCTs will be collected on the same vector, at two timepoints once the lead is fixated and prior to connecting the leads to the can using the Analyzer. The timepoints are as follows;

1.) Prior to slitting the cannulation catheter - Collect the first PCT using the Analyzer after the lead is fixated and the guidewire/stylet has been pulled back proximal to the helix and electrodes.

2.) Post slitting the cannulation catheter – Collect the second PCT using the Anlyzer after the lead is fixated and following slitting of the cannulation catheter.

These PCT measurements will be collected on the CRF. This data will only be collected if an Attain Stability Quad MRI SureScan LV Lead (Model 4798) is successfully placed.

Pacing voltage thresholds are measured to determine whether the underlying myocardium will respond effectively to pacing and to evaluate lead stability in the cardiac vein. It is required to perform LV pacing threshold measurements during implant using the pacing threshold test at a 0.5ms pulse width. It is recommended to begin at 2.5 Volts and decrease amplitude after at least 3 pulses until capture is lost. If there is no capture at 2.5 V; stop the test and repeat at a higher voltage using the 0.5ms pulse width. The lowest amplitude where capture consistently occurs is the pacing threshold value. Collect data using the Analyzer (Model 2290 or market released equivalent).

It is recommended that physicians locate a final LV pacing site that can be captured using less than or equal to 2.5 V at 0.5ms, R-wave sensing of at least 4.0 mV, and does not cause diaphragmatic stimulation at 10V at 0.5ms. For additional details regarding the left ventricular leads and implant tools, refer to the respective technical manuals provided with each product.

Individual patient venous anatomies as well as pathologies present in the left ventricular myocardium are factors that will influence LV lead placement. Therefore, the best cardiac vein lead electrode location to stimulate the LV may vary for each patient.

15.8.2.4. Final Lead Placement Data Collection

Following fixation and once the final position of the lead is determined, collect a venous image of the final placement of the lead. A copy of the venous image will be submitted to Medtronic and kept on file at the center.

15.8.2.5. Pre-Hospital Discharge CRT System Testing and Programming

The following electrical testing will be performed using the implanted CRT-P or CRT-D device and the device programmer once the leads are connected to the CRT-P or CRT-D and pre-hospital discharge:

Lead Impedance

- Collect LV Lead Impedances using Vector Express on all vectors
- Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil or the final programmed vector
- Retain printouts for any manually tested vector at the site

Pacing Capture Thresholds (PCT)

- Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil or the final programmed vector
- Retain printouts for any manually tested vector at the site

Phrenic Nerve Stimulation (PNS)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

Other data collected prior to hospital discharge following the implant includes;

- Rationale for selecting specific LV lead pacing vector for final programming
- Final device interrogation/save-to-media
- AE Assessment
- Study deviations
- Device deficiencies

15.9. 3 Months Post-Implant (remote or in office visit)

The 3 month scheduled follow-ups may be done remotely or inoffice. For remote visits, CareLink transmissions may substitute device interrogations. The following procedures will be completed and data will be collected at the 3 month Follow-up visit;

Lead Impedance

- Perform a manual LV Lead Impedance Test the final programmed vector
- Retain printouts for any manually tested vector at the site

Pacing Capture Thresholds (PCT)

- Perform PCTs at 0.5ms pulse width on the final programmed vector
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Perform a manual PCT test at 0.5ms pulse width on the final programmed vector
- Retain printouts for any manually tested vector at the site

Phrenic Nerve Stimulation (PNS) (in office visit only)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

- NYHA classification
- Patient Global Assessment
- Rationale for selecting specific LV lead pacing vector for final programming
- Final device interrogation/save-to-media
- AE Assessment
- Study deviations
- Device deficiencies

15.10. 6 Months Post-Implant (in office visit)

The following procedures will be completed and data will be collected during the 6 month in office Follow-up visit.

Lead Impedance

- Collect LV Lead Impedances using Vector Express on all vectors
- Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil or the final programmed vector
- Retain printouts for any manually tested vector at the site

Pacing Capture Thresholds (PCT)

- Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil or the final programmed vector
- Retain printouts for any manually tested vector at the site

Phrenic Nerve Stimulation (PNS)

- Test for presence of PNS at 8.0V at 0.5ms on vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil
- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If at any tested vector PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

- NYHA classification
- Patient Global Assessment
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Rationale for selecting specific LV lead pacing vector for final programming
- Final device interrogation/save-to-media
- AE Assessment
- Study deviations
- Device deficiencies

15.11. 12 Months Post-Implant (in office visit)

The following procedures will be completed and data will be collected during the 12 month in office Follow-up visit.

Lead Impedance

- Collect LV Lead Impedances using Vector Express on all vectors
- Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil or the final programmed vector
- Retain printouts for any manually tested vector at the site

Pacing Capture Thresholds (PCT)

- Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil or the final programmed vector
- Retain printouts for any manually tested vector at the site

Phrenic Nerve Stimulation (PNS)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

- NYHA classification
- Patient Global Assessment
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Rationale for selecting specific LV lead pacing vector for final programming
- Final device interrogation/save-to-media
- AE Assessment
- Study deviations
- Device deficiencies

15.12. Recurring 6 Month Follow-ups

After the 12 Month Follow-Up visit, subjects will be seen every 6 months. These scheduled follow-ups are considered "Recurring 6 month follow-up visits". These scheduled follow-ups may be done remotely or inoffice. For remote visits, CareLink transmissions may substitute device interrogations. The following procedures will be completed during these visits:

Lead Impedance

- Perform a manual LV Lead Impedance Test for the final programmed vector
- Retain printouts for any manually tested vector at the site

Pacing Capture Thresholds (PCT)

- Perform PCTs at 0.5ms pulse width on the final programmed vector
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Perform a manual PCT test at 0.5ms pulse width on the final programmed vector
- Retain printouts for any manually tested vector at the site

Phrenic Nerve Stimulation (PNS) (in office visit only)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

- NYHA classification
- Rationale for selecting specific LV lead pacing vector for final programming
- Final device interrogation/save-to-media
- AE Assessment
- Study deviations
- Device deficiencies

15.13. Device Interrogation/Save-to-Media

For the implant and follow-up visits, a final "Interrogate All" device interrogation file (.pdd) must be obtained and saved in a digital format (Save-to-Media). Store one copy of the save-to-media at the site and send a copy to Medtronic. Do not clear device data.

A device interrogation (final "Interrogate All") and Save-to-Media should also be completed at the time of study exit (prior to 6 month visit), a system modification (initial and final "Interrogate All"), and in the case of a death (where possible).

15.14. System Modifications

A system modification will be reported in the event the device and/or leads require invasive modification (e.g. generator or lead explant, generator or lead replacement, lead repositioning, etc.). In the event of a system modification, regardless of outcome of the modification, subjects should remain in the study when possible and the follow-up visit schedule for the subject will remain unchanged. For a system modification the following information/activities are required to be collected:

- Modification or replace/explant date
- Reason for modification
- Information on device or lead modified
- Information on any replacement device(s)
- Final device interrogation/save-to-media
- Study deviations
- AEs and device deficiencies (as applicable)

It is recommended that all explanted Medtronic products (device, leads, etc.) are returned to Medtronic for analysis per local process and when permissible by local laws and regulations.

In the event that subject has a re-attempt after a previous unsuccessful system modification, the subsequent attempt(s) must be reported via CRF as separate system modifications.

Attain Stability Quad MRI SureScan LV Lead (Model 4798) repositioned or replaced with another Attain Stability Quad MRI SureScan LV Lead (Model 4798)

If the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is repositioned or replaced, the following LV lead electrical tests and data collection must be completed:

Lead Impedance

- Collect LV Lead Impedances using Vector Express on all vectors
- Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil or the final programmed vector
- NOTE: Retain printouts for any manually tested vector at the site

Pacing Capture Thresholds (PCT)

- Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil, LV2 to RVcoil, LV3 to RVcoil, LV4 to RVcoil or the final programmed vector
- NOTE: Retain printouts for any manually tested vector at the site

Phrenic Nerve Stimulation (PNS)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

- Record the reason why the final configuration was selected for final programming
- Record any programming changes to the LV lead apart from the LV lead pacing vector since the last visit and provide rationale for the change(s)

Attain Stability Quad MRI SureScan LV Lead (Model 4798) capped or explanted without replacement with another Attain Stability Quad MRI SureScan LV Lead (Model 4798)

If the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is capped or explanted without replacement while the subject is in the study, subjects will continue to be followed per their original follow-up schedule for safety monitoring until study closure. LV lead electrical testing and interrogation files will not be required at follow-ups for subjects without the full protocol required system implanted.

Explant of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the Medtronic CRT-P or CRT-D device without replacement with another Attain Stability Quad MRI SureScan LV Lead (Model 4798) and Medtronic CRT-P or CRT-D device

Subjects who have their Attain Stability Quad MRI SureScan LV Lead (Model 4798) and Medtronic CRT-P or CRT-D device explanted without replacement during a system modification procedure should be exited from the study as soon as all system related and/or system modification procedure related AEs are resolved. If no system or procedure related AEs are present at the conclusion of such a system modification procedure, the subject should be exited immediately.

Medtronic CRT-P or CRT-D device explanted without replacement, Attain Stability Quad MRI SureScan LV Lead (Model 4798) remains implanted

If the Medtronic CRT-P or CRT-D device is explanted and a replacement device will be implanted, all attempts should be made to replace with another Medtronic CRT-P or CRT-D device. In the event that an explanted Medtronic CRT-P or CRT-D device cannot be replaced with a new Medtronic CRT-P or CRT-D device, subjects who still have an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted will continued to be followed for safety monitoring in person per their original follow-up schedule until study closure. Events related to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) should be reported. Left ventricular lead electrical testing will not be required at follow-ups for subjects without the full protocol required system implanted. In an event that a second Attain Stability Quad MRI SureScan LV Lead (Model 4798) was implanted as a result of an Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complication, the subject will be followed for safety, however the second implanted Attain Stability Quad MRI SureScan LV Lead (Model 4798) will not be included for the analyses of study objectives except reportable system related adverse events.

15.15. Study Exit

Study Exit is defined as the moment when a subject officially stops participating in the study. Date and reason for subject exit must be reported to Medtronic at the earliest opportunity.

Subjects will be exited from the study for any of the following situations:

- Study completed
- Subject lost to follow-up
- Subject did not meet eligibility criteria and was not yet implanted with an Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- Subject did not have a successful implant and no attempt at re-implant is made
- Subject did not provide consent or data protection authorization, as required by law
- Subject chooses to exit (i.e. revokes consent)
- Investigator withdraws subject

Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing system- and procedure-related AEs are resolved, unresolved with no further actions planned, or 30 days post the 6 month visit, whichever occurs first. Following exit, subjects will continue to receive standard medical care. There will be no further required study-related follow-up visits for these subjects. All data through the time of the subject's exit will be available for data analyses.

If possible, the following procedures should be performed / data collected at the exit visit:

- Report the reason for exit
- Final interrogation file (or CareLink transmission) for exits occurring prior to the 6 month visit
- Study deviations
- AEs and device deficiencies (as applicable)

After subjects are exited from the study they should receive standard medical care and should be managed and followed per physician discretion.

15.15.1. Study Completed

All subjects will be followed until FDA Pre-Market Approval (PMA) of the Attain Stability Quad MRI SureScan LV Lead (Model 4798). Medtronic will notify sites when the study is complete. Upon exiting subjects, if the current follow-up visit and exit visit are combined, then both the follow-up CRF and a Study Exit CRF need to be completed but only one device interrogation/save-to-media needs to be completed and collected. If AEs are unresolved at time of exit, it should be noted on the AE CRF that the AE is unresolved at time of study exit.

15.15.2. Lost to Follow-up

In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be recorded. In addition, follow the regulations set forth by the governing IRB or EC.

15.15.3. Study Exit Upon Sponsor Request

A subject must be exited from the study if the sponsor suspends study enrollment and a subject has signed the ICF but no implant attempt of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) has occurred (see Section 15.8.2.2).

15.16. Subject Withdrawal or Discontinuation

15.16.1. Subject Chooses to Exit (i.e. revokes consent)

A subject can withdraw from the study at any time. If the subject wishes to exit from the study (i.e. the subject revokes consent), the site is required to document the reason for exit on the Exit CRF. In addition, study sites shall follow the regulations set forth by the governing Ethics Committee. For countries following ISO 14155, permission may be requested to follow up with the patient outside of the study due to withdrawal based on problems related to the investigational feature safety or performance. If possible, the following data should be collected prior to subject withdrawal:

- Report the reason for subject withdrawal
- Final device interrogation/save-to-media
- Study deviations
- AEs and device deficiencies (as applicable)

15.16.2. Investigator Withdraws Subject

No subjects should be withdrawn by investigators unless compelling medical justification is present. It is recommended investigators discuss any withdrawals with the study sponsor prior to exiting subjects. If

an Investigator withdrawal is necessary, the following data should be collected prior to subject withdrawal if possible:

- Report the reason for subject withdrawal
- Final device interrogation/save-to-media
- Study deviations
- AEs and device deficiencies (as applicable)

The following are reasons for investigator-initiated subject withdrawal;

Medical Necessity

A subject may be exited from the study if an investigator feels it is necessary to withdraw the subject from the study due to a medical condition or other reason. In such cases, the subject will be notified and provided an explanation regarding the reasons for the study exit.

Explant of Medtronic CRT-P or CRT-D Device and Attain Stability Quad MRI SureScan LV Lead (Model 4798)

Subjects in which the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the Medtronic CRT-P or CRT-D device are explanted without replacement (i.e., subject no longer has a Medtronic CRT-P or CRT-D device and an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted) shall be exited from the study (refer to Section 15.8.2.2). Subjects exposed to an Attain Stability Quad MRI SureScan LV Lead (Model 4798) through a lead attempt must be followed through at least one month or until all implant related AEs (system-, and/or procedure-related) have resolved or are unresolved with no further actions planned. Subjects who have either an Attain Stability Quad MRI SureScan LV Lead (Model 4798) (active or not active) or a Medtronic CRT-P or CRT-D device implanted will continued to be followed for safety until study completion.

Attain Stability Quad MRI SureScan LV Lead (Model 4798) Not Implanted

Subjects that are not anticipated to have an implant attempt (e.g. do not meet inclusion/exclusion criteria) must be exited from the study. Subjects that have a CRT system implant attempt, but who do not have an Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempted (See Section 15.8.2.2 for definition) will be exited from the study following their procedure unless an Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt is scheduled. If this attempt is more than 30 days from the baseline assessment, verification of the baseline data must be completed prior to a subsequent implant attempt.

Subjects with an unsuccessful Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt will be followed at pre hospital discharge and one month unless there are ongoing implant related AEs (system- and/or procedure related), in which case they will be followed beyond one month until the implant related (i.e., system-, and/or procedure related) AEs have been resolved or are considered unresolved with no further actions planned. The subjects may be followed via a clinic visit or by phone contact. In geographies where the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is market-released, subjects will be exited from the study after the assessment of implant procedure or CRT system related AEs if the initial attempt of one Attain Stability Quad MRI SureScan LV Lead (Model 4798) model was unsuccessful. The subject may undergo implant attempts with any market released LV lead that provides the best benefit to the patient, but data collection on these subsequent attempts will not be required as these subjects will be considered exited from the study.

15.17. Assessment of Efficacy

The primary efficacy objective is based on the pacing capture threshold data collected as discussed in Section 19.1.

15.18. Assessment of Safety

The primary safety objective is based on the Adverse Event data collected. Further information on the collection of Adverse Events is discussed in Section 17.1.1.

15.19. Recording Data

The study will collect data using Oracle Clinical, an electronic data management system for clinical studies. Sites will enter data onto CRFs within the Oracle Clinical database.

Data reported on the CRFs shall be derived from source documents, which may include worksheets, patient medical records, programmer printouts and device interrogation/save-to-media files. These source documents must be created and maintained by the investigational site team. Further detail on data management is provided in Section 21.2.

15.20. Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan or the Clinical Trial Agreement.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. In all geographies, prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported to Medtronic regardless of whether they are medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The deviation must be recorded in Oracle Clinical with an explanation for the deviations. In the occurrence of a corrupted device interrogation/save-to-media file, Medtronic will request a deviation to document that a readable device interrogation/save-to-media file is unavailable.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB/EC as well as Medtronic as soon as possible but no later than five (5) working days, or according to local requirements. Reporting of all other study deviations should comply with IRB/EC policies and/or local laws and deviations must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, and terminate the study). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic may provide site-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

16. Risks and Benefits

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of the product, from the research and development phase through the study phase and market release. The risk analysis process for the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is being performed in accordance with ISO 14971, and will ensure that the level of risk has been reduced as low as possible and is acceptable prior to starting the Attain Stability Quad Clinical Study.

Potential Risks

Standard risks associated with the medical device used in this study, an analysis of Adverse Device Effects and a history of modification or recall of device under investigation or equivalent devices are listed in the Instruction for Use Manual or Clinical Manual.

The potential adverse events (listed in alphabetical order) related to the use of transvenous leads inlcude, but are not limited to, the following conditions:

- Air embolism
- Avulsion or other damage to the endocardium, valve, or vein (particularly in fragile hearts)
- Cardiac dissection or perforation
- Cardiac tamponade
- Coronary sinus dissection
- Death
- Endocarditis or pericarditis
- Erosion through the skin
- Extracardiac muscle or nerve stimulation
- Fibrillation or other arrhythmias
- Heart Block
- Heart wall or vein wall rupture
- Hematoma/seroma
- Infection
- Lead conductor fracture or insulation failure
- Lead dislodgement
- Myocardial irritability
- Myopotential sensing
- Pericardial effusion or rub
- Pneumothorax
- Rejection phenomena (local tissue reaction, fibrotic tissue formation)
- Threshold elevation or exit block
- Thrombosis
- Thrombotic embolism

Additional potential adverse events related to the lead and the programmed paramenters include, but are not limited to, the following:

Table 10: Additional adverse events related to the lead and programmed parameters

Potential adverse event	Indicator of potential adverse event	Corrective actions to consider
Lead dislodgement[i]	Intermittent or continuous loss of capture or LV EGM signal integrity (including sensing)[i]	Reprogram the LV pacing polarity. Reposition the lead.
Lead dislodgement[i]	Intermittent or continuous oversensing	Reprogram the LV pacing polarity. Reposition the lead.
Lead conductor fracture	Intermittent or continuous loss of capture or LV EGM signal integrity (including sensing)[i]	Replace the lead. Reprogram the LV pacing polarity.
Lead conductor insulation failure	Intermittent or continuous loss of capture or LV EGM signal integrity (including sensing)[i]	Replace the lead. Reprogram the LV pacing polarity.
Threshold elevation or exit block	Loss of capture[i]	Adjust the implantable device output. Reprogram the LV pacing polarity. Replace or reposition the lead.

[I] Transient loss of capture or LV EGM signal integrity (including sensing) may occur following surgery until lead stabilization takes place. If stabilization does not occur, lead dislodgement may be suspected.

Implant techniques that may damage the lead include, but are not limited to, the following techniques:

Table 11: Implant Techniques that may damage the lead

Implant techniques that may damage the lead	Possible effects on the lead	Corrective action to consider
Forcing the lead through the introducer/delivery system	Electrode, conductor coil, or insulation damage	Replace the lead.
Use of too medial of an approach with venous introducer resulting in clavicle and first rib binding	Conductor coil fracture, insulation damage	Replace the lead.
Using too stiff a stylet	Conductor coil/insulation perforation	Replace the lead.
Puncturing the periosteum or tendon when using subclavian introducer approach resulting in binding	Conductor coil fracture, insulation damage	Replace the lead.
Advancing the lead through the non-coronary central access veins without the stylet or guide wire fully inserted	Tip distortion or insulation perforation	Replace the lead.
Inserting the proximal end of the guide wire through the lead tip seal without using the guide wire insertion tool	Lead tip seal damage or conductor coil/insulation damage	Replace the lead.

Subjects who are pregnant may be at increased risk (e.g., radiation exposure, and other unforeseen risk to the fetus), and are excluded from participation in the study. If a subject becomes pregnant during the study, she must notify the physician immediately. The subject will remain in the study for intention to treat analysis, but the investigator will avoid any procedures that may be determined harmful.

There may be other discomforts and risks related to the CRT-P or CRT-D device, the Attain Stability Quad MRI SureScan LV Lead (Model 4798), and/or this study that are not foreseen at this time. Interactions with concomitant medical treatment are not expected.

The adverse event collection requirements in this study will ensure that risks associated with the study device and the Attain Stability Quad MRI SureScan LV Lead (Model 4798) are adequately monitored.

16.2. Risk Minimization

Medtronic has minimized the risks to the subject by the following:

- Performing required laboratory and pre-clinical testing prior to the Attain Stability Quad Clinical Study; this information is available under separate cover in the RPI with the FDA IDE submission and the CER with the CE-Mark
- Implementing quality control measures into development and production processes
- Providing guidelines for subject selection and evaluation, and subject inclusion and exclusion criteria
- Providing adequate instructions via the Attain Stability Quad MRI SureScan LV Lead (Model 4798) User Manual, training, and labeling

- Selecting implanters that have demonstrated previous experience with implanting CRT-P or CRT-D devices and specifically LV leads
- Selecting investigators that have demonstrated previous experience with the programming, interrogating, and monitoring of CRT-P or CRT-D devices
- After enrollment in the Attain Stability Quad Clinical Study, at each protocol required follow-up, the investigator must interrogate the study device to verify appropriate study device function and to evaluate the subject's health and assess for any AEs

16.3. Potential Benefits

The potential benefits of having the Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted are similar to other LV leads currently available to the public. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is expected to increase lead stability and reduce the need for patients to undergo an additional procedure to replace a dislodged/displaced lead. Due to the active fixation helix, it may be possible to place the lead in veins of various sizes. There is a possibility that the Attain Stability Quad MRI SureScan LV Lead (Model 4798) may offer no additional benefit over similar LV leads. The information gained from this study could result in the improved management of other CRT patients.

16.4. Risk-Benefit Rationale

The risk-benefit analysis has shown that there are no major additional risks associated with the Attain Stability Quad MRI SureScan LV Lead (Model 4798), other than those associated with the implant, while benefits to the patient are possible. Any residual risk associated with this study is considered low and acceptable.

17. Adverse Event Assessments

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Medtronic has established procedures in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information. This study is conducted in accordance with these procedures and regulations.

Data collected in this study may be used in support of global regulatory approvals. Since the safety reporting requirements and classification systems vary for each regulatory agency, requirements from all geographies are taken into account for the collection and reporting of safety information. Adverse Events and Device Deficiencies will be reported in all geographies.

17.1. Adverse Event and Device Deficiency Assessment

17.1.1. Adverse Events

Adverse Event definitions are provided in Table 12. The following AEs will be collected throughout the study duration, starting at the time the informed consent form is signed:

- All procedure related AEs
- All system related AEs
- All accessory related AEs
- All cardiovascular related AEs
- All Serious Adverse Events (SAEs), regardless of relatedness

Reporting of these events to Medtronic will occur on an AE Form, including date of AE, treatment, resolution, assessment of both the seriousness of the AE and the relatedness to the investigational device or procedure. Each AE must be recorded on a separate AE eCRF. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. In addition, AEs impacting users or other persons, Non-subject Adverse Events, (reportable per ISO 14155) will be collected.

In all geographies, Unavoidable AEs, listed in Table 12, need not be reported unless the AE worsens or is present outside the stated timeframe post-implant.

For AEs that require immediate reporting (see Table 14), initial reporting may be done by contacting the study sponsor per the sponsor contact information. The original completed AE CRF must be submitted to Medtronic as soon as possible.

Any medication, whether cardiovascular or not, associated with the treatment of an AE must be reported. Medication changes that are not related to adverse events will not be collected.

Subject deaths are also required to be reported. Refer to Section 17.4 for Subject Death collection and reporting requirements.

17.1.2. Device Deficiencies

Device deficiency (DD) information will be collected throughout the study and reported to Medtronic. Note that DDs that result in an Adverse Device Effect (ADE) to the subject should be captured as an AE only. Device Deficiencies that did not lead to an AE but could have led to a Serious Adverse Device Effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting (see Table 14). For DDs that require immediate reporting, initial reporting may be done by contacting the study sponsor per the sponsor contact information.

17.1.3. Event Updates and Resolution

For any changes in status of a previously reported AE (i.e. change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE form. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject dies or exits the study, or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to their 6 month visit, all efforts should be made to continue following the subject until all unresolved system or procedure related adverse events, as classified by the investigator, are resolved or unresolved with no further actions planned.

At the time of study exit, all collected AEs with an outcome of ”Unresolved” must be reviewed and an update to the original AE must be reported. At a minimum, if there are no changes to the description, relatedness, test and procedures or actions taken, the outcome must be updated to reflect “Unresolved at time of study exit”.

17.2. Definitions/Classifications

Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system, and includes but is not restricted to: the CRT-P or CRT-D device, the RA, RV or LV leads, the programmer, and implant tools.

Table 12: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. (ISO 14155:2011, 3.2)
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. (ISO 14155:2011, 3.1)
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors and inadequate labeling (ISO 14155:2011, 3.15)
Relatedness	
Procedure Related	An Adverse Event that is directly related to the implantation or surgical modification of the system. NOTE: In general, this excludes events that are inherent to any surgical procedure (e.g. anesthesia complications) as well as indirect subsequent consequences of the procedure (e.g. reaction to pain medication).

System Related (includes all implantable components and features, associated introduction tools, operational and installed software and programmers as defined in the Clinical Investigation Plan)	An adverse event that results from the presence or performance of any component of the system. Device-related: An adverse event that results from the presence or performance (intended or otherwise) of the device. RA lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the RA lead. RV lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the RV lead. LV lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the LV lead. a) LV Lead Fixation-related: An adverse event that results from the presence or performance of the side-helix.
Accessory Related	Programmer Related: An adverse event that results from the presence or performance (intended or otherwise) of the programmer Implant tool-related: An adverse event that results from the presence or performance (intended or otherwise) of the implant tool.
Cardiovascular Related	An Adverse Event relating to the heart and the blood vessels or the circulation (e.g. Atrial Fibrillation, Myocardial Infarction, stroke, perivascular disease)
Heart Failure Related	An adverse event related to worsening heart failure signs and symptoms such as hypervolemic and hypovolemic status requiring the administration, alteration, adjustment or augmentation of HF therapy (diuretics, inotropes and/or vasodilators etc.) or the utilization of ultrafiltration devices.
MRI Related	An adverse event which is caused by the interaction between the pacing system and the MRI system that occurs during the MRI procedure and up through the one-month post-MRI/waiting period follow-up visit.

Not Related	Relationship to the device or procedures can be excluded when: ▪ The event is not a known side effect of the product category the device belongs to or of similar devices and procedures; ▪ The event has no temporal relationship with the use of the device or the procedures; ▪ The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; ▪ The discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure) do not impact the serious event; ▪ The event involves a body-site or an organ not expected to be affected by the device or procedure; ▪ The serious event can be attributed to another cause (e.g., an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors); ▪ The event does not depend on a false result given by the device used for diagnosis (when applicable); ▪ Harms to the subject are not clearly due to use error; ▪ In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

Causal Relationship	The event is associated with the device or study procedures beyond reasonable doubt when: ▪ The event is a known side effect of the product category the device belongs to or of similar devices and procedures; ▪ The event has a temporal relationship with device use/application or procedures; ▪ The event involves a body-site or organ that the device or procedures are applied to or the device or procedures have an effect on; ▪ The serious event follows a known response pattern to the medical device (if the response pattern is previously known); ▪ The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure) impact on the serious event (when clinically feasible); ▪ Other possible causes (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug, or treatment) have been adequately ruled out; ▪ Harm to the subject is due to error in use; ▪ The event depends on a false result given by the device used for diagnosis (when applicable); ▪ In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Seriousness	
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. (ISO 14155:2011, 3.37)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011, 3.36)

Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. (ISO 14155:2011, 3.42)
Complication	An adverse event that includes the following is considered a complication: • Results in death, • Involves any termination of significant device function, or • Requires an invasive intervention Non-invasive (21 CFR 812.3 (k)): when applied to a diagnostic device or procedure, means one that does not by design or intention: Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os *Note* (FDA): Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive. *** Only system or procedure related AEs will be classified as complication or observation
Observation	Any Adverse Event that is not a complication. *** Only system or procedure related AEs will be classified as complication or observation
Other	

<table>
<tr><td>Unavoidable Adverse Event</td><td>An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator's opinion, including, but not limited to:
<table>
<tr><th>Event Description</th><th>Timeframe (hours) from the Surgical Procedure</th></tr>
<tr><td>Anesthesia related nausea / vomiting</td><td>24</td></tr>
<tr><td>Low-grade fever (<100°F or 37.8°C)</td><td>48</td></tr>
<tr><td>Pocket site / Incisional pain</td><td>72</td></tr>
<tr><td>Mild to moderate bruising / ecchymosis</td><td>168</td></tr>
<tr><td>Sleep problems (insomnia)</td><td>72</td></tr>
<tr><td>Back pain related to laying on table</td><td>72</td></tr>
<tr><td>Shoulder pain/discomfort/stiffness related to shoulder immobilization during procedure</td><td>72</td></tr>
</table></td></tr>
</table>

17.3. Reporting of Adverse Events

17.3.1. Adverse Events and Device Deficiency Classification

All reported AEs and DDs will be reviewed by a Medtronic representative. Adverse Events will be classified according to the definitions provided.

Upon receipt of AEs at Medtronic, a Medtronic representative will review the AE/DD for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize the Medical Dictionary for Regulatory Activities (MedDRA), to assign a MedDRA term for each AE based on the information provided by the investigator.

Regulatory reporting of AEs and DDs that could have led to an SADE will be completed according to local regulatory requirements. Refer to Table 14 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the investigator to abide by any additional AE reporting requirements stipulated by the IRB/EC responsible for oversight of the study.

APPENDIX 1 contains the Foreseeable Adverse Event List (FAL), which is a list of adverse events related to the system or procedure that have been observed in previous studies and may be experienced by subjects. This list may help to assess if an AE is unanticipated in nature.

For emergency contact regarding a UADE, SAE and/or SADE, contact a Attain Stability Quad Clinical Study representative immediately (refer to the study contact list provided in the site's study documents binder/investigator site file or refer to the Sponsor Contact Information section provided in the CIP).

Adverse Events and Deaths will be classified according to the standard definitions as outlined below:

Table 13: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters

Relatedness	Investigator	Device, RA Lead, RV Lead, LV Lead, Implant Tool(s), Programmer, Procedure, Cardiovascular, Heart Failure, MRI
	Sponsor	Device, RA Lead, RV Lead, LV Lead, Implant Tool(s), Programmer, Procedure
Seriousness	Investigator	SAE
	Sponsor	SAE, UADE/USADE, Device Deficiency with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

An independent Clinical Events Committee (CEC) will review and adjudicate, at a minimum, all events classified by the investigator or Medtronic as procedure or system related to determine relatedness and complication or observation classifications. In addition, the CEC will also review and adjudicate all Adverse Events resulting in death.

17.3.2. Adverse Events and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and device deficiencies will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator to abide by the adverse event reporting requirements stipulated by local law and the site's IRB/EC.

Table 14: Reporting Requirements

Serious Adverse Events (SAEs)	
Investigator submit to:	
Medtronic	**Canada:** Investigators are required to report SAEs to the sponsor immediately except for those SAEs that the protocol or other document (e.g. Investigator's Brochure (IB)) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. Medical Devices Regulations, sections 59-61. *A guidance for "immediately" is within 72 hours of the investigator becoming aware of the event; Report to sponsor, without unjustified delay ISO 14155:2011, sec 9.8.b).* **EMEA:** Immediately after the investigator first learns of the event or new information in relation with an already reported event. **All geographies:** Report to the sponsor, without unjustified delay, all serious adverse events.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.

Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Adverse Device Effects (ADEs),	
Investigator submit to:	
Medtronic	**EMEA:** Immediately after the investigator first learns of the event or new information in relation with an already reported event. **All geographies:** Submit in a timely manner after the investigator first learns of the effect.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Serious Adverse Device Effects (SADEs), Unanticipated Adverse Device Effects (UADEs), Unanticipated Serious Adverse Device Effects (USADEs),	
Investigator submit to:	
Medtronic	**US:** Submit as soon as possible, but no later than within 10 working days after the investigator first learns of the event. (21 CFR 812.150(a)(1)) **Canada:** SADEs on the patient, the user or any other person must be reported to the Sponsor within 72 hours after it comes to the attention of the qualified investigator. It is recommended for the investigator to report safety events as soon as possible but no longer than 15 calendar days." **All geographies:** Immediately after the investigator learns of the event or of new information in relation to an already reported event.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement
Ethics Committee	**All geographies:** Submit to Ethics Committees per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Investigators	**All geographies:** Submit per local reporting requirement.
All other reportable Adverse Events	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the event.

Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Device Deficiencies with SADE potential	
Investigator submit to:	
Medtronic	**Canada:** DDs that have resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person or could do so were it to reoccur must be reported to the Sponsor within 72 hours after it comes to the attention of the qualified investigator **EMEA:** Immediately after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency. **All other geographies:** Submit or report as required per local reporting requirements.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the deficiency.
Regulatory authorities	**Canada:** any DD that: a. has resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person; These must be reported by Medtronic to the Regulator within 10 days from the date Medtronic becomes aware. or b. could do so were it to reoccur. These must be reported by Medtronic to the Regulator within 30 days from the date Medtronic becomes aware. **All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.

17.4. Subject Death

17.4.1. Death Data Collection

All subject deaths must be reported by the investigator to Medtronic on an AE form (AE with outcome of death) as soon as possible after the investigator first learns of the death. In case of death, there should be one SAE with the outcome of death reported.

In the event of a subject's death, it is recommended that the implanted system be explanted and returned to Medtronic for analysis whenever possible per local process. Local laws and procedures must be followed where applicable.

System Interrogation Data Recommendations:

- After the subject has died but prior to explant, it is strongly recommended that the system be interrogated and a full summary interrogation (Interrogate All) performed when possible, and saved in a digital format (Save-to-Media). Store one copy of the save-to-media at the site and send a copy to Medtronic.
- Make the device interrogation/save-to-media file before any programming to prevent overwriting information in the device's memory and/or distinguishing between events detected during versus before the explant procedure.
- Recommend obtaining the exact date and time of death as lower temperatures after death can cause ERI and other "event flags" to be stored in the device memory.

If the system is not interrogated, an explanation must be entered on the AE form. For ICD systems, the ventricular tachycardia (VT) and ventricular fibrillation (VF) detection capabilities must be disabled to avoid inadvertent shocks. If any system component is returned to Medtronic, internal return product reporting systems may be used to gather additional information about the returned device/component.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic Attain Stability Quad Clinical Study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records should be sent to the Medtronic Attain Stability Quad Clinical Study team, if available. If an autopsy is conducted, the autopsy report should also be sent to the Medtronic Attain Stability Quad Clinical Study team if available and allowed by state/local law. When the death occurs at a remote site, it is the investigative site's responsibility to attempt retrieval of information about the death. Additionally, device disposition information should be updated. In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to system and/or procedure
- Device interrogation and Save-to-Media (if available)
- Device disposition information
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and allowed by state/local law)

17.4.2. Death Classification and Reporting

Sufficient information will be required in order to properly classify the subject's death. The Investigator shall classify each subject death per the following definitions:

Cardiac Death: A death directly related to the electrical or mechanical dysfunction of the heart.

Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be

determined, SCD will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.

Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.

Non-cardiac Death: A death not classified as a cardiac death.

Unknown Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

Table 15: Subject Death Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-cardiac, Unknown

The Clinical Events Committee will review all deaths and provide a final adjudication of the death classification.

Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements.

17.5. Product Complaint Reporting

Product complaint reporting and vigilance reporting are applicable and AEs related to any market-released device during the study must be reported. The reporting of product complaints is not part of the Attain Stability Quad Clinical Study and should be done in addition to the AE reporting requirements. Refer to local regulations for reporting requirements.

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

- Abuse: Abnormal use (definition acc. #4.1 of Meddev 2.12-1 rev8)
- Misuse: Use error (definition acc. #4.20 of Meddev 2.12-1 rev8)

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the regulatory authorities (e.g. Competent Authority) as applicable for the following incidents immediately upon learning of them:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
    - Life-threatening illness or injury
    - Permanent impairment of a body function or permanent damage to a body structure

- A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

18. Data Review Committees

18.1. Clinical Events Committee

The study will utilize a Clinical Events Committee (CEC). At regular intervals, an independent CEC will review events and adjudicate at a minimum all system, and procedure-related events. Additionally, the CEC will provide an adjudication of the death classification for all reported deaths.

The CEC will consist of a minimum of three (3) non-Medtronic-employed physicians that are not participating investigators for the study, including a CEC chairperson.

Medtronic personnel may facilitate and participate in CEC meetings but will be non-voting members.

For AEs and deaths reviewed by the CEC, Medtronic will provide the CEC with the Investigator's description and classification and supportive documentation (when available). The CEC is responsible for reviewing the Investigator's assessment and supportive documentation (when available), reviewing applicable definitions, and determining final classifications for all adjudication parameters. For AEs, classification includes system/procedure relatedness and complication or observation. Additionally, the CEC will provide an adjudication for all reported deaths, including system/procedure relatedness and cardiac relatedness.

If the CEC disagrees with the investigator's classification of the event, the difference will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the CRF documenting the AE will be updated accordingly.

If the investigator does not agree with the CEC's adjudication classification, both determinations will be provided within the final report; however the CEC's adjudication will be used for data analysis. The disagreement will also be included in reporting to ethics committees and regulatory authorities, if required.

18.2. Data Monitoring Committee

A Data Monitoring Committee (DMC) will not be utilized for this study considering:

- An independent CEC will be formed to adjudicate at minimum all system and procedure related events and all deaths.
- This study does not meet FDA's recommended criteria (Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees) for when a study should use a DMC, primarily because the study is not evaluating the effectiveness of a treatment intended to prolong life or reduce the risk of a major adverse health outcome.
- As a result of risk analysis and mitigation efforts as outlined in Section 16, any residual risk associated with this study is considered low and acceptable.
- The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is a modification of the currently market approved Attain Performa lead Models 4298, 4398, and 4598 is a modification of the currently market approved Model 4396 LV lead. The Attain Stability Quad lead Model 4798 has a similar electrode spacing as the Attain Performa lead Models 4298, 4398, and 4598.
- Study will be conducted under FDA oversight via an investigational device exemption (IDE).

19. Statistical Design and Methods

This section presents statistical considerations for the study design and provides a high-level description of planned analysis and reporting. More details will be given in a separate Statistical Analysis Plan (SAP) that will be completed before data freeze for the primary objective analysis. Any deviation to the pre-specified statistical analyses will be noted in the study report. The analysis of the study objectives will be completed when the sample size requirements (see Table 18) for all the study primary and secondary objectives are met. An interim analysis will be conducted when 360 subjects are enrolled in the study. This interim analysis is specifically designed for one of the secondary objectives (details in Section 19.2.2).

19.1. Primary Objectives

19.1.1. Primary Safety Objective

Objective

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered safe if the probability of subjects free of Model 4798 lead-related complications at 6 months post-implant is greater than 87% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 87%).

Hypothesis:
H_0: $S_{(6\text{-month})} \leq 87\%$
H_1: $S_{(6\text{-month})} > 87\%$

where $S_{6\text{-month}}$ is the probability that a subject remains free from Model 4798 lead related complications through 6 months since implant.

Endpoint Justification

The study primary safety endpoint is Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complications. All reported system and procedure-related AEs will be reviewed by an event review committee for LV lead relatedness and severity (see Section 18.1).

Lead related complication free survival probability to evaluate lead safety performance is widely accepted across cardiac device manufacturers and in the medical literature. Current already market-released Quadripolar LV lead 6-month safety performance is summarized in Table 16. The population

performance of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is expected to be similar to the Medtronic Attain Performa Model 4298 lead.

Table 16: Safety Performance of Market Released Quadripolar Lead

	Medtronic Attain Performa	St. Jude Medical Quartet[22]	Boston Scientific ACUITY X4[23]
6-month LV Lead Complication Free Survival Probability Estimate	Model 4298 (Canted): 96.0% Model 4398 (Straight): 98.8% Model 4598 (S-shape): 96.2%	96% at 3 months	Straight: 96.5% Spiral: 98.5%

Statistical Analysis Methods

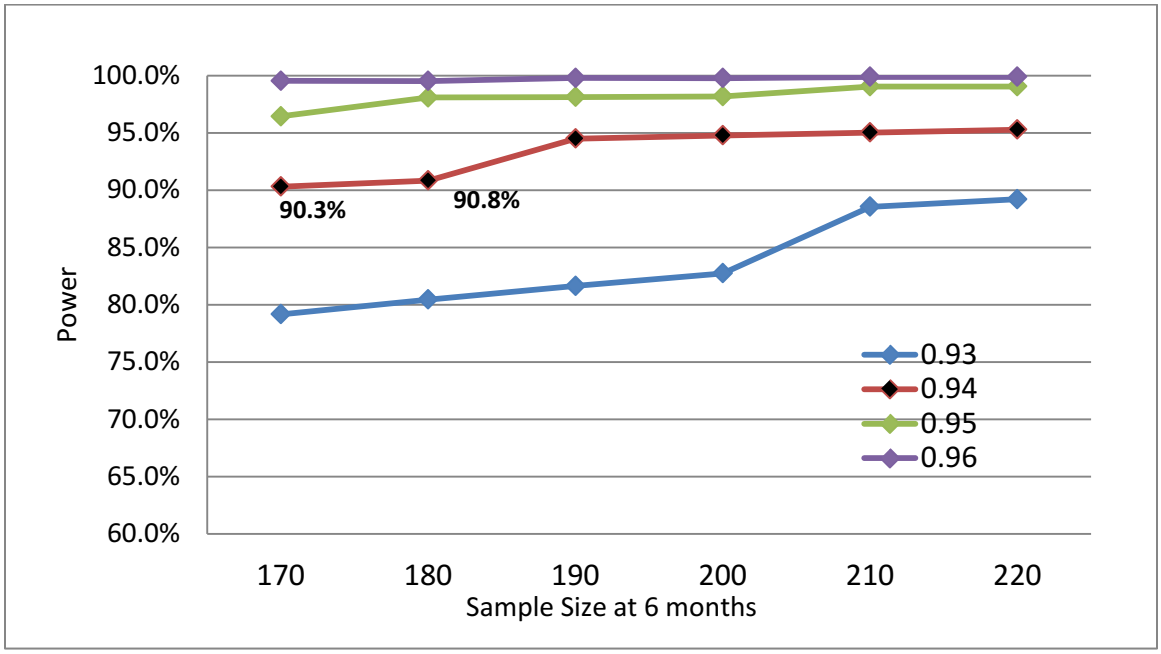
The primary objective will be analyzed using the time-to-first event Kaplan-Meier survival analysis method. A minimum number of subjects who have completed their 6-month post-implant visit will be required. Time 0 will be the day a subject undergoes the implant procedure of a Attain Stability Quad MRI SureScan LV Lead (Model 4798), which will be independent of success status of this implant procedure. Event date is the onset date of a subject's first complication that is related to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) according to CEC adjudication. Subjects who undergo an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt and do not experience any LV lead related complications, will be censored at the time of their last known exposure to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) for the survival analysis. For any lost-to-follow up subject, the last contact date will be used as the censor date. The 1-sided 97.5% confidence limit lower bound for the survival probability at 6 months (183 days) will be calculated using the log-log survival function approach (Kalbfleisch and Prentice 2002).

Sample Size Consideration

The primary safety objective performance criterion is set to be identical to Medtronic's Attain Performa Clinical Study (IDE Number: G120213). Therefore, the sample size calculation assumptions are derived based on the Model 4298 lead study results. The Attain Performa Model 4298 lead reported a 6-month complication free survival probably of 96.0%, with 97.5% Confidence Lower Limit of 94.3% (PMA-s clinical report).

The binomial calculation (Z-test) is used for initial sample size estimation. In order to preserve the overall study power, a type II error less than 10% was used for the sample size calculation. A sample size of 170 subjects completing their 6-month visit achieves greater than 90% power to detect a difference of 7% using the one-sided binomial test. The target significance level is 0.025. These results assume that the population proportion under the null hypothesis is 87% with an expected value of 94% (Figure 5). To account for 15% attrition, the enrollment size for this objective is 200.

Figure 5: Primary Safety Objective Sample Size Consideration by Difference Performance Assumption



Determination of Patients / Data for Analysis

All consented subjects who undergo an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt will be included in the analysis cohort. If a patient experiences multiple Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant procedures during the study, the analysis cohort will only consider the first procedure. In the event multiple complications occur, the survival analysis endpoint is reached when the first Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complication occurs.

19.1.2. Primary Efficacy Objective #1

Objective

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet the first primary efficacy objective if the proportion of subjects with at least one Attain Stability Quad MRI SureScan LV Lead (Model 4798) pacing vector having a pacing capture threshold (PCT) less than or equal to 2.5 V at 0.5ms pulse width at 6 months post-implant is greater than 80% (i.e., the lower bound of the one-sided 97.5% confidence interval must be greater than 80%).

Hypothesis
H_0: $P1_{6\text{-month}} \leq 80\%$
H_A: $P1_{6\text{-month}} > 80\%$,

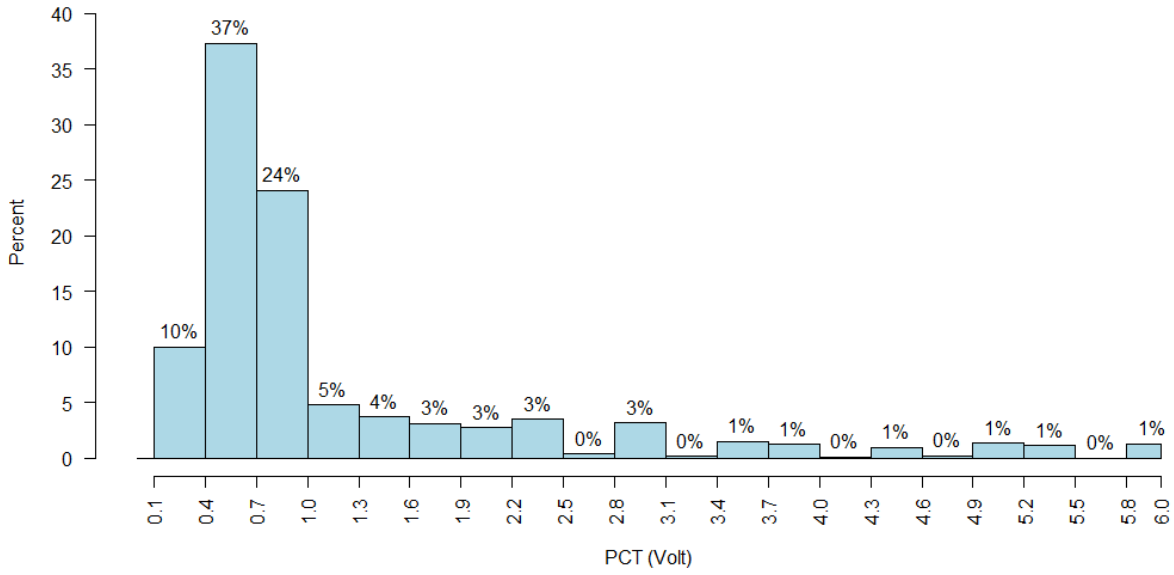
where $P1_{6\text{-month}}$ is the proportion of subjects with pacing voltage thresholds ≤ 2.5V at 0.5ms (with absence of PNS at this threshold) at 6 months follow-up visit post-implant for at least one LV lead pacing vector.

Endpoint Justification

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is equipped with the identical four electrodes to the Attain Performa LV leads. At the same time, the unique fixation mechanism may cause

the distal end of the lead (tip) to be implanted away from the apical region of the heart, and therefore the PCT may be slightly higher than the values observed in other Quadripolar LV leads. Therefore, we simulated the lead pacing threshold values based on the Attain Performa IDE study data, but excluding the PCT values collected at the most distal electrode. The simulation estimated that 89% of the subjects will achieve this endpoint (Figure 6).

Figure 6: Simulated PCT Distribution



Statistical Analysis Methods

All subjects with valid pacing thresholds measured at the 6 month follow-up visit will be included in this analysis. The proportion of subjects having at least one LV lead pacing vector with voltage thresholds less than or equal to 2.5V will be calculated. The lower bound of the 1-sided 97.5% Confidence Interval will be calculated using the Exact binomial method. Any subject in which no valid pacing threshold value is measured or who has an unable-to-capture result via all LV lead pacing vectors will be reviewed and adjudicated for a possible lead related AE but will not be included for this evaluation if the occurrence is deemed to be a system related event (e.g. lead dislodgement). However, this event may be counted against the safety primary endpoint based on the CEC's final classification.

Sample Size

The primary efficacy endpoint will be analyzed using the Exact binomial method. In order to preserve the overall study power, a type II error less than 10% was used for the sample size calculation. A sample size of 145 subjects achieves 91% power to detect a difference of 0.1 using a one-sided binomial test at a target significance level of 0.025. These results assume that the population proportion under the null hypothesis is 80%, with an expected proportion of 90%.

Determination of Patients / Data for Analysis

All subjects enrolled into this study satisfying the following conditions will be included in this analysis:

- Successfully implanted with a Medtronic Quad CRT-P or CRT-D device and Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- Completed 6-month follow-up visit
- Initially implanted Attain Stability Quad MRI SureScan LV Lead (Model 4798) is active at the 6–month follow-up visit
- At least one available and valid pacing threshold at the 6-month follow-up visit

19.1.3. Primary Efficacy Objective # 2

Objective

The Attain Stability Quad lead will meet the second primary efficacy objective if the proportion of subjects with at least one additional (or second) LV lead pacing vector having a pacing capture threshold less than or equal to 4.0 V at 0.5ms pulse width at 6 months post-implant is greater than 80% (i.e., the one-sided 97.5% lower confidence bound must be greater than 80%).

Hypothesis
H_0: $P2_{6\text{-month}} \leq 80\%$
H_A: $P2_{6\text{-month}} > 80\%$,

where $P2_{6\text{-month}}$ is the proportion of subjects with at least one additional LV lead pacing vector with pacing voltage thresholds ≤ 4.0V at 0.5ms at 6 months post-implant follow-up visit.

Endpoint Justification

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) has 16 LV programmable pacing vectors . Subjects may have the pacing configuration programmed or reprogrammed at each clinic visit. A pacing threshold of 4.0 V will allow an adequate safety margin for programming LV pacing output. The maximum pacing amplitude of the CRT-P or CRT-D devices capable of programming pacing output to any LV lead pacing vector is 8.0V. In actual clinical practice, a less than 3V safety margin is used for the programmed LV lead pacing output in 99% of the patients.

Statistical Analysis Methods

The efficacy endpoint #2 will be analyzed using the Exact binomial method. The proportion of subjects with at least 2 LV lead pacing vectors having voltage thresholds less than or equal to 4.0V at 0.5ms will be calculated. The lower bound of the 1-sided 97.5% Confidence Interval will be calculated using the Exact binomial method. Any subject in which no valid pacing threshold values are measured or with an Unable-to-capture result via all LV lead pacing vectors will be reviewed and adjudicated for possible lead related complications, and therefore may be counted against the study safety endpoint. However, it will be counted as a failure if there is not any additional LV lead pacing vectors (excluding the vector that is already include for the efficacy endpoint #1) are unable to capture with no lead related events reported.

Sample Size

The Attain Performa Model 4298 LV lead observed 97.7% subjects who were able to obtain a non-programmed pacing vector with PCT less than or equal to 4 volts. A sample size of 50 subjects completing the 6 month visit achieves 98% power to detect a difference of 0.18 using a one-sided binomial test at a target significance level of 0.025. These results assume that the population proportion under the null hypothesis is 80%, with the expected proportion of 97%.

Determination of Patients / Data for Analysis

All subjects enrolled into this study satisfying the following conditions will be included in this analysis:

- Successfully implanted with a Medtronic Quad CRT-P or CRT-D device and Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- Completed 6-month follow-up visit
- Initially implanted Attain Stability Quad MRI SureScan LV Lead (Model 4798) lead is active at the 6–month follow-up visit
- At least one available and valid pacing threshold at the 6-month follow-up visit. In the event a subject failed to provide more than one valid pacing threshold value, that subject will be considered as not having at least one additional LV lead pacing with PCT ≤ 4.0V at 0.5ms at 6 months post-implant follow-up visit

19.2. Secondary Objectives

19.2.1. Secondary Objective # 1

Objective - Implant procedure related information: success rate, implant related times

The Attain Stability Quad LV lead implant success rate will be estimated as the number of subjects with Attain Stability Quad MRI SureScan LV Lead (Model 4798) successfully implanted divided by the total number of subjects who had a Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt. A 2-sided 95% Confidence Interval will be calculated using the Exact Binomial method.

The distribution of implant related times will be summarized through statistical summaries such as mean, standard deviation, minimum, median and maximum. Only subjects with the Attain Stability Quad MRI SureScan LV Lead (Model 4798) successfully implanted will be included in this calculation. The total implant time is defined as time from initial incision to final skin closure. Fluoroscopy time is defined as the total time the fluoroscope is imaging. Cannulation time is defined as the time from insertion of the first CS cannulation catheter to the first successful CS cannulation. Successful lead placement time is defined as the time from lead insertion of the successfully placed lead to the time when the lead is placed in its first acceptable pacing location.

19.2.2. Secondary Objective # 2

Objective - 6-month reliability: post implant lead failure modes

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is a composite of two existing market released Medtronic products. The helix fixation is identical to the Attain Stability LV Lead Model 20066/4796 (market released outside of the US). The remainder of the lead is similar to the Attain Performa LV Lead Model 4298, released worldwide.

Historical datasets will be used as informative priors for lead related complications. More specifically, analysis of all complications related to fixation (helix performance) will use data from the Attain Stability (Model 20066/4796) research study, conducted outside of the US. Analysis of all other lead related complications will use data from the Attain Performa clinical study, conducted globally. Credible intervals will be constructed for each individual failure mode within the two groups.

Historical Data (for secondary endpoints only)

- Fixation-related LV lead complications - Data from the 37 patients who completed 6-month follow up with a successfully implanted 20066 lead in the Attain Stability study will be used as an informative prior.
- All other LV lead-related complications - Data from the 401 patients who completed 6-month follow up in the Attain Performa 4298 study will be used as an informative prior.

These historical datasets will be downweighted such that their effective sample size will not exceed the 9% of the total sample size (i.e at most 37 subjects at 6 months).

Statistical Analysis Methods

The weighted historical data will be incorporated using the power prior method[24]. The weight of the historical data will be adjusted using a loss function[25], which scales from 0 to 1 according to the similarity of the historical and observed data. This loss function adjusts the amount of weight the prior receives. The comparison between historical and observed data will be performed twice, once for each group of complications (fixation-related and all other). The objective of using a loss function with the power prior method is to reduce the influence of an informative prior in the parameter estimation, when the historical data does not agree with the current study data.

If analysis of failure rate shows a high level of agreement between historical and current study data or there is better performance for Attain Stability Quad MRI SureScan LV Lead (Model 4798) compared to historical data, the historical data will be weighted at or near a maximum level (9% of total effective sample size). If the Attain Stability Quad MRI SureScan LV Lead (Model 4798) performs worse than historical data, the historical data will receive very little or zero weight. Note that there will be two loss function weights, one for fixation-related complications and one for all other complications. Credible interval calculations will be done separately for individual failure modes within the two groups of complications (fixation and all other).

Denote by θ_c and θ_h the probabilities of lead complication for the current and historical studies respectively. The posterior distributions of θ_c and θ_h respectively, both with minimally informative priors are:

$$\theta_c = beta(y_c + 1, n_c - y_c + 1)$$
$$\theta_h = beta(y_h + 1, n_h - y_h + 1)$$

These posterior distributions are then stochastically compared using a posterior Bayesian p-value[26] as:

$$p = P(\theta_c \leq \theta_h)$$

The desired characteristics for the loss function are:

1. For $p \geq \sim 0.5$, there is a high level of agreement between current and historical data, therefore the loss function should allow a_0 to be close to 1, allowing for full weight of historical data.

2. Conversely, for $p < \sim 0.5$, there begins to be evidence of disagreement between current and historical data, and a_0 should start to down-weight the prior, i.e. a_0 approaches zero as p approaches zero.

The Weibull cumulative distribution function (CDF) meets these criteria:

$$a_0 = 1 - e^{-(p*5)^2}$$

Note that for the case where the number of samples in the prior is different than the effective number, a scaling factor will be applied, where n_h is the desired effective number of prior samples and N_h is the actual number of prior samples:

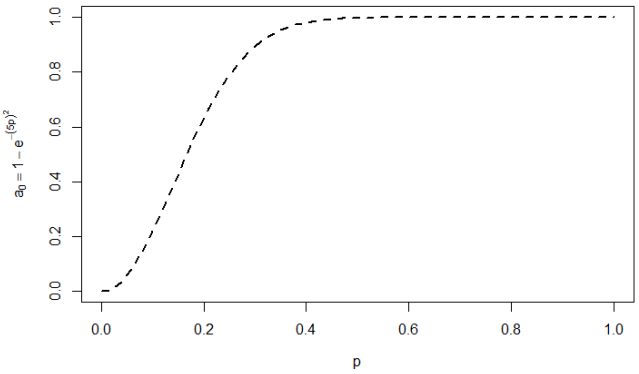
$$a_0 = \frac{n_h}{N_h}\left[1 - e^{-(p*5)^2}\right]$$

Sample values are listed in Table 17 below and illustrated in Figure 7. The comparison between current and historical data will be performed for all LV lead fixation related complications using Attain Stability (Model 20066) historical data and for all other LV lead related complications using Attain Performa historical data.

Table 17: Prior weight from Attain Stability (Model 20066) and prior weight from Attain Performa as a function of the posterior Bayesian p-value (p)

	Prior weight from Attain Stability (Model 20066)	Prior weight from Attain Performa
$\boldsymbol{p}$	$a_0 = 1 - e^{-(p*5)^2}$	$a_0 = \frac{37}{401}\left[1 - e^{-(p*5)^2}\right]$
0.01	0.002	0.000
0.05	0.061	0.006
0.1	0.221	0.020
0.2	0.632	0.058
0.5	0.998	0.092

Figure 7: Loss Function $a_0 = 1 - e^{-(p*5)^2}$

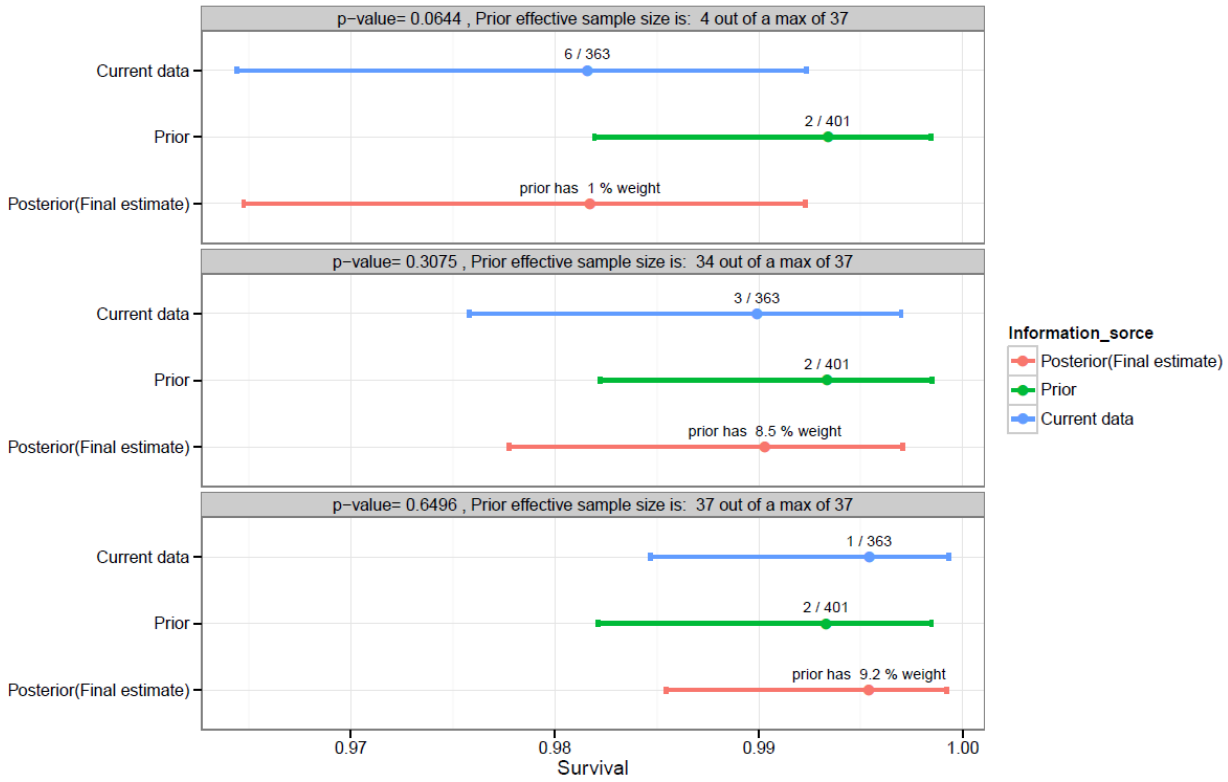


Note that the loss function proposed here does not reduce the strength of the prior when the current study outperforms the historical data. This implementation of the loss function is only concerned with negative impacts to patients, i.e. it penalizes an optimistic prior while not penalizing a pessimistic prior.

Also, note that this function is selected for the shape of the CDF rather than due to conventional statistical properties of the Weibull distribution.

Figure 8 illustrates the effect of the power prior coupled with the loss function. The figure shows credible intervals in scenarios where the prior is optimistic (better performance than current study), in agreement (similar performance to the current study), and pessimistic (worse performance than the clinical study). Note that the prior data source in Figure 8 is the Attain Performa study, with 401 patients. As will be discussed later, these data are scaled to represent a maximum of 37 patients (i.e. 9% weight).

Figure 8: Credible Intervals for Scenarios of Agreement Between Historical and Current Data



The prior data set in Figure 8 has 401 samples. However, the maximum effective historical data sample size is $n_h = 37$, for a maximum weight of 9%. Therefore, the prior will be scaled by a factor of (37/401). As an example, illustrated in the middle panel above, if the effective sample size is 34 out of 37, the prior has received 89% of the maximum weight, or 8.5%.

The panels in Figure 8 can be interpreted as follows:

- Top panel: The current data shows lower performance than the prior. The loss function produces a substantial penalty resulting in almost no weight to the prior (1%). The posterior (final estimate) is essentially the same as the current study.
- Middle panel: The current data is very similar to the prior. The loss function penalty is small, resulting in a prior weight of 8.5% (recall that the maximum weight is 9.2%). Because the agreement is good, the posterior(final estimate) is similar to both the prior and current study.
- Bottom panel: The current data is very similar, with slightly better performance than the prior. The loss function produces a weight very close to the maximum of 9.2%. The posterior (final estimate) is a balance between the prior and current study.

Sample Size

A Bayesian adaptive design is set up to enroll patients until a sufficient sample size is achieved to have high probability of meeting the required effective sample size of $n_e = 400$. The number of enrolled patients in the study may vary from 363 to 400 subjects due to the adaptations to the trial. This study follows methods from Berry, et.al.[27]

The interim analysis will take place after 360 subjects have been enrolled into the study.

The Adaptive Bayesian sample size algorithm will stop or continue enrollment accordingly to the following:

1.) If the predictive probability of $n_e \geq 400$ is larger than 80% then enrollment will stop.
2.) If the predictive probability of $n_e \geq 400$ is less than 80%, enroll sufficient additional patients to make the probability of $n_e \geq 400$ at least 80%.

At the time of the interim analysis, some patients will not have completed the full evaluation period. A longitudinal model will be employed to enable final observations to be imputed for those subjects with incomplete information.

There are 3 types of subjects at a given interim analysis:

1.) Subjects that have complete data
2.) Subjects that have partial data (censored value at a particular time)
3.) Subjects that have no information (subjects that have not been enrolled)

Predictive probabilities for types 2 and 3 will have to be computed. The predictive probability model that will be used is a piecewise exponential. This will allow the final outcomes for the subjects who have not had an event and have not completed 6 month follow up to be simulated.

Note this Bayesian approach to borrow information from historical datasets will only be used for the secondary objective #2.

19.2.3. Secondary Objective # 3

Objective – Electrical measurements (PCT and Impedance) at follow-ups

Pacing Capture Threshold (PCT) and impedance data will be collected using VectorExpress™. Pacing vector changes will be monitored for all implanted patients at follow-up visits.

Summary statistics for PCT and impedance at each time point (i.e. Implant, 6 months, etc.). The distribution of the electrical measurements at the final programmed pacing vector will be presented as n, mean, standard deviation, minimum, median and maximum. In the event of a replacement of a Medtronic Quad CRT-P or CRT-D device and/or the implanted LV lead, only measurements from the

Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted at the initial implant procedure will be included in the analysis cohort for this objective.

19.3. Additional Analysis

19.3.1. Poolability Analysis

Additional analysis will be conducted to summarize study primary objectives by patient characteristics, such as gender, age group, race and study site geography. The purpose of the poolability analysis is to identify if there is any clinical meaningful difference in a subgroup of patients. These analyses will not be statistically powered, and there is no pre-specified statistical significance level for these analyses.

19.3.2. Sensitivity Analysis

All subjects enrolled into this study and successfully implanted with a Medtronic Quad CRT-P or CRT-D device and Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be included in the primary efficacy analysis datasets (efficacy objectives #1 and #2). Sensitivity analysis such as the Tipping Point method or similar will be conducted to investigate the influence of subjects who were successfully implanted with the required system however missed a 6 month post implant follow-up test(s) (due to reasons such as missing in-office visit, subject exit, death and/or the initial implanted lead was deactivated). For this purpose, all subjects with successful implant who do not meet analysis cohort requirements, will be considered as the worst case scenario (i.e. failure to meet the efficacy endpoints).The results will be submitted as part of the clinical reports.

19.3.3. Additional Data Collection

Heart failure clinical outcomes will be assessed. The measurements, including NYHA classification, death, heart failure related hospitalization, heart failure related study exits and subject self-reported global assessment for each subject will be obtained at 6 months post-implant. Summary statistics will be provided.

19.3.3. Overall Study Sample Size Requirements

The sample size requirement at 6-months for each of the study objectives is displayed in Table 18. The first row does not account for attrition, while the second row is inflated by 15% attrition. The sample size for Secondary Objective #2 assumes the conservative case that the interim look results in, no borrowing of historical data. Therefore, the overall sample size for the study is 471.

Table 18: Required Sample Size by Study Objective

	Primary Safety Objective	Primary Efficacy Objective #1	Primary Efficacy Objective #2	Secondary Objective #1	Secondary Objective #2 (post-implant failure modes)	Secondary Objective #3	Overall
Number needed at 6-months	170	145	50	NA	400	NA	400
Number of enrollments	200	171	59	NA	471	NA	471

20. Ethics

20.1. Statement(s) of Compliance

This study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). Good Clinical Practice includes review and approval by an independent IRB/EC before initiating a study, continuing review of an ongoing study by an IRB/EC, and obtaining and documenting the freely given IC of a subject before initiating the study.

The clinical investigation shall not begin until all required approvals and documents from the IRB/EC and a regulatory authority, if needed, have been received. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

The Attain Stability Quad Clinical Study was designed to reflect the GCP principles outlined in ISO 14155:2011 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In accordance with ISO 14155:2011, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation. Adverse Event and Device Deficiency handling in the Attain Stability Quad Clinical Study is ISO 14155:2011 compliant for all participating geographies with the exception that only those AEs which are related to the subject's system, procedure, accessory, or are cardiovascular-related, and all Serious AEs, will be collected. This ensures any AEs which could potentially be relevant will be collected. The scope and duration of the Attain Stability Quad Clinical Study would make collection of all AEs to be a significant burden for investigators and investigative sites. Therefore, only a subset of AEs will be collected in this study, including any that could be potentially relevant.

The principles of the Declaration of Helsinki have been implemented through the IC process, IRB/EC approval, study training, clinical trial registration, pre-clinical testing, risk-benefit assessment and publication policy.

Ultimately, all sites in all geographies will follow and comply with:

- Principles of Declaration of Helsinki
- 21 CFR Part 11 (Electronic Records, Electronic Signatures) (per local law)
- 21 CFR Part 54 (Financial Disclosure by Clinical Investigators)
- The Clinical Trial Agreement
- The procedures described within this CIP
- Local Ethics Board Requirements

In addition to the regulatory requirements outlined above, the study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. These include but are not limited to:

- In the United States, the study will be conducted under an FDA IDE in compliance with 21 CFR Parts:
  - 50: Protection of Human Subjects
  - 56: Institutional Review Boards
  - 812: Investigational Device Exemptions
- In Canada, SOR/98-282, Section 59-88 will be followed and Mandatory Problem Reporting 59(1), 59(2), 60 (1)).
- In EMEA the study will be conducted in compliance with the Active Implantable Medical Device Directive (AIMDD) and Declaration of Helsinki version 2013.
- In Hong Kong and Malaysia, the study will be conducted in compliance with the Declaration of Helsinki version 2013.
- In EMEA, an IB is not required for this study as it is a post market study

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act FDAAA and Declaration of Helsinki on http://clinicaltrials.gov (PL 110-85, section 810(a)). In addition, the study may be registered in local regulatory databases where required by local law.

Approval of the CIP and CIP amendments is required from the following groups prior to any study procedures at a study site:

- Medtronic
- Principal Investigators (where required by local law/regulations)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent medical ethics committee or institutional review board.

Similarly, approval of subsequent revisions to the CIP is required at each study site from the above mentioned groups prior to implementation of the revised CIP at the site.

21. Study Administration

21.1. Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this Attain Stability Quad Clinical Study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the CTA, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the Subject IC, Data Protection Authorization (where applicable) and CTA. The principal investigator should also be available during monitoring visits.

Monitoring for the study, including site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

Monitoring visits may be conducted periodically to assess site study progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to IRB/EC approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs. Monitors review site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to site personnel. Monitors may work with study personnel to determine appropriate corrective action

recommendations and to identify trends within the study or at a particular site. Regulatory documents may be reviewed at each study site.

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of adverse events, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation.

21.2. Data Management

Data will be collected using Oracle Clinical, an electronic data management system for clinical studies. CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

Only authorized persons can complete CRFs. CRFs shall be signed by the Principle Investigator. The Principle Investigator can delegate the CRF sign off task to Sub-Investigators only. Delegation of authority will be specified on the appropriate documentation.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to make it anonymous, for instance, where the subject's name cannot be removed from the data carrier.

Procedures in the CIP require source documentation. Source documentation will be maintained at the site. Source documents, which may include worksheets, patient medical records, programmer printouts and device interrogation files, must be created and maintained by the investigational site team. For source documentation, the investigational site study team must sign and date any copies or printouts of original source documents with a statement that this is a complete and true reproduction of the original source document.

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. The CRF may be considered source for the following data collection elements recorded directly on the CRFs:

- Enrollment Notification
    - Site assigned patient reference
- Baseline
    - Administrative information
- Adverse Event eCRF
    - Date study site became aware of event
    - Relatedness of adverse event
- Device Deficiency eCRF
    - Date study site became aware of event
- Subject Death
    - Date study site became aware of death
    - Relatedness of death
- System Modification
    - Justification for explanted product not being returned to Medtronic
- Deviations

    - Reason for deviation
- Investigational product Disposition Log
    - Date the Investigational Attain Stability Quad lead was implanted/explanted

Even when the CRF may be considered as source, an alternate method of source documentation is always strongly encouraged.

Save-to-media data collected at office visits will be sent to Medtronic. Upon receipt, device data will be maintained within a Medtronic device database and retrieved for analysis and reporting.

21.3. Direct Access to Source Data/Documents

The sponsor or a regulatory authority may audit or inspect the study site to evaluate the conduct of the study. The clinical investigator(s)/institution(s) shall allow study related monitoring, audits, IRB/EC review and regulatory inspection.

21.4. Confidentiality

All records and other information about subjects participating in this study will be treated as confidential.

21.5. CIP Amendments

Approval of subsequent revisions to the CIP is required at each study site from the following groups prior to implementation of the revised CIP at the site:

- Medtronic
- Principal Investigators (where required by local law)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent medical ethics committee or institutional review board.

If a CIP amendment occurs, site personnel will need to be re-trained as necessary, and will need to submit any changes to their IRB/EC as required by the committee. Protocol amendments will also be reported to and approved by the FDA, or regulatory authority.

21.6. Warranty/Insurance Information

21.6.1. Warranty

Warranty information is provided in the product packaging for the commercially released CRT-P or CRT-D devices and leads, and additional copies are available upon request.

21.6.2. Insurance (EMEA)

Medtronic Bakken Research Center B.V. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the EC and/or Competent Authority (CA).

21.6.3. Insurance (Canada)

Medtronic of Canada is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate general liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a General Liability insurance statement/certificate will be provided to the Ethics Committee.

21.6.4. Insurance (Malaysia)

Medtronic International Ltd. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

21.6.5. Insurance (Hong Kong)

Medtronic Hong Kong Medical Ltd. Ltd. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

21.7. Record Retention

21.7.1. Investigator Records

The investigator is responsible for the preparation and retention of the records including, but not limited to, those cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (e.g., the study binder provided to the investigator) or Subject Study Binder. Case Report Forms must be maintained and signed electronically by an investigator within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law/regulation or hospital administration requires) after product approval. Measures shall be taken to avoid loss or premature destruction.

- All correspondence between the IRB/EC, sponsor, monitor, regulatory authority and/or the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
    - Signed and dated informed consent form, in accordance with local requirements
    - Observations of adverse events/adverse device effects/device deficiencies
    - Medical history
    - Baseline, Implant and follow-up data (if applicable)
    - Documentation of the dates and rationale for any deviation from the protocol
- Electronically signed and dated eCRFs and a blank set of CRFs where required by local law
- All approved versions of the CIP, IC
- Fully executed Clinical Trial Agreement
- Ethics Committee approval documentation. Written information that the investigator or other study staff, when member of the Ethics Committee, did not participate in the approval process.

Approval documentation must include the Ethics Board composition, where required per local law.
- Regulatory authority notification, correspondence and approval, where required per local law.
- List of investigation sites: This list is not yet final at the time of CIP development. The list will be provided under separate cover and will be maintained by the sponsor.
- Financial disclosure (investigators)
- Enrollment Log (for sites following ISO 14155)
- For sites where the Attain Stability Quad lead is considered investigational, device disposition logs containing Model and serial numbers of devices implanted, subject IDs of the subjects implanted, implant/used dates, explant dates, returned-to-sponsor dates and reasons and method of disposal/destruction
- Current curriculum vitae (signed and dated in EMEA only) of principal investigators and key members of investigation site team (as required by local law)
- Documentation of delegated tasks
- Study training records for investigation site team
- Assurance certificates (EMEA, Hong Kong, and Malaysia)
- Any other records that FDA and local regulatory agencies require to be maintained (e.g. Ethics Committee Roster, study equipment calibration information)
- Final Study Report including the statistical analysis

21.7.2. Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all CRFs, AEs and ADEs (reported per the country-specific collection requirements), DDs, deaths, crossovers and any deviations from the CIP. If any action is taken by an IRB/EC with respect to this Attain Stability Quad Clinical Study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Investigator reporting requirements for safety data are listed in Section 17.3).

Table 19: Investigator Reports Applicable for All Geographies per Medtronic Requirements

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing Ethics Committee of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and Ethics Committee	Any deviation from the clinical investigation plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Failure to obtain informed consent	Sponsor and Ethics Committee	Informed consent shall be obtained in writing and documented before a subject is enrolled into the Attain Stability Quad Clinical Study
Final Report	Ethics Committee and Relevant Authorities	This report must be submitted within 3 months of study completion or termination.

21.7.3. Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records that includes, but is not limited to:

- All correspondence which pertains to the Attain Stability Quad Clinical Study
- Executed Clinical Trial Agreement
- Financial disclosures (investigators)
- Current curriculum vitae (signed and dated in EMEA only) of principal investigators and key members of investigation site team (as required by local law)
- Device Disposition Logs containing Model and serial numbers of devices implanted, subject IDs of the subjects implanted, implant/used dates, explant dates, returned-to-sponsor dates and reasons and method of disposal/destruction
- Electronically signed and dated eCRFs
- All approved informed consent templates, and other information provided to the subjects and advertisements, including translations
- Copies of all Ethics Committee approval letters and relevant Ethics Committee correspondence and Ethics Committee voting list/roster/letter of assurance
- List of names, addresses, and professional position of the clinical investigators and coordinating clinical, if appointed.
- Names and addresses of the institutions in which the Attain Stability Quad Clinical Study will be conducted: This list is not yet final at the time of CIP development. The list will be provided under separate cover and will be maintained by the sponsor.
- Regulatory authorities correspondence, notification and approval as required by national legislation
- Insurance certificates (EMEA, Hong Kong, and Malaysia)
- Names/contact addresses of monitors
- Monitoring reports (interim monitoring visit reports, follow-up letters and close-out visit reports)
- Site qualification visit reports
- Statistical analyses and underlying supporting data
- Final report of the Attain Stability Quad Clinical Study
- The approved Clinical Investigation Plan and study related reports, and revisions
- Documentation of delegated tasks
- Study training records for site personnel and Medtronic personnel involved in the study
- Sample of CRFs
- Any other records that local regulatory agencies require to be maintained

21.7.4. Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of reviewing Ethics Committee, regulatory agency or FDA, provide accurate, complete and current information about any aspect of the Attain Stability Quad Clinical Study. Safety data Medtronic reporting requirements are listed in Section 17.3).

Table 20: Sponsor Reports for Canada

Report	Submit to	Description/Constraints

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, Ethics Committee, Relevant authorities, and Head of the Institution	Provide prompt notification of termination or suspension and reason(s).
Recall and device disposition	Investigators, Ethics Committee	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices.
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically.

Table 21: Sponsor Reports for EMEA, Malaysia, Hong Kong

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, Ethics Committee, Relevant authorities and Head of the Institution	Provide prompt notification of termination or suspension and reason(s) per local law. *(ISO 14155:2011)*
Withdrawal of Ethics Committee approval	Investigators, Ethics Committee and relevant authorities	Investigators and other Ethics Committees will be notified only if required by local laws or by the Ethics Committee.
Withdrawal of CA approval	Investigators, Ethics Committee, and relevant authorities	Investigators, Ethics Committees and relevant authorities will be notified only if required by local laws or by the Ethics Committee.
Progress Reports	Ethics Committee and regulatory authorities	This will be submitted to the Ethics Committee and regulatory authorities only if required by local law.
Final report	Investigators, Ethics Committee, and Regulatory authorities upon request	• The investigator shall have the opportunity to review and comment on the final report. • If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). • The signature of the principal Investigator in each site should be obtained.
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. *(ISO 14155:2011)* Site specific study deviations will be submitted to investigators periodically.

Table 22: Sponsor Reports for the United States

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Investigators, Ethics Committee, FDA, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(2))*
Withdrawal of FDA approval	Investigators, Ethics Committee, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(3))*
Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. *(21 CFR 812.150(b)(4))*
Progress Reports	Ethics Committee and FDA	Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(5), 812.36(f)*
Recall and device disposition	Investigators, Head of Institution, Ethics Committee, relevant authorities, and FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6))*
Failure to obtain informed consent	FDA	Investigator's report will be submitted to FDA within five working days of notification. *(21 CFR 812.150(b)(8))*
Final report	Investigators, Ethics Committee, Regulatory authorities upon request, and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and IRBs/MECs within six months after completion or termination of this study. *(21 CFR 812.150(b)(7))*
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically.
Other	IRB, FDA	Accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(b)(10))*

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in secured file cabinets at Medtronic during the course of this study. After closure of the study Medtronic will archive records and reports as required by applicable regulations.

21.8. Publication and Use of Information

Publications from the Attain Stability Quad Clinical Study will be handled according to Medtronic Policies and Standard Operating Procedures and as indicated in the CTA.

21.8.1. Publication Committee

The Attain Stability Quad Clinical Study will utilize a Publication Committee which will include the Steering Committee members as well as Medtronic personnel. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to:

- Manage elements addressed in the publication plan as outlined in this section
- Develop the final Publication Plan under separate cover
- Execute the Publication Plan
- Oversee the publication of primary, secondary and ancillary study results
- Review and prioritize publication proposals
- Provide input on publication content, and
- Determine authorship

In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan. Membership in the Publication Committee does not guarantee authorship. The committee will meet as needed.

21.8.2. Management of Primary, Secondary, and Ancillary Publications

The Publication Committee reviews, prioritizes and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary/ancillary objectives, respectively, as specified in the Clinical Investigation Plan. An ancillary publication is any publication that does not address the study objectives identified in the Clinical Investigation Plan. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this Attain Stability Quad Clinical Study and clinicians not participating in this Attain Stability Quad Clinical Study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual site data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

21.8.3. Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE), Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Medtronic personnel, must at a minimum meet all of the conditions below:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published

Decisions regarding authorship and contributor-ship will be made by the publication committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the

authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All investigators not listed as co-authors will be acknowledged as the "Medtronic Attain Stability Quad Clinical Study Investigators" and will be individually listed according to the guidelines of the applicable scientific journal when possible. Any other contributors will be acknowledged by name with their specific contribution indicated.

21.8.4. Transparency

Transparency of study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to all investigators, IRB/ECs and Competent Authorities of participating countries when required by local law
- Registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- Submitting for publication the primary study results after the study ends
- Disclosing conflicts of interest (e.g. financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- Making an individual sites study data accessible to the corresponding investigator after the completion of the study, if requested

21.9. Suspension or Early Termination

21.9.1. Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or regulatory authority, whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing IRB/EC oversight is required until the overall study closure process is complete. Upon study closure, subjects should be managed and followed per physician discretion.

21.9.2. Early Termination or Suspension

Early Termination of the Study is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single site. Study Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single site. In the event the whole study or a single site is terminated, subjects will be exited.

Study-Wide Termination or Suspension

Possible reasons for considering study suspension or termination of the study include but are not limited to:

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)

- Technical issues during the manufacturing process

Investigator/Site Termination or Suspension

Possible reasons for clinical investigator or site termination or suspension include but are not limited to:

- Failure to obtain initial IRB/EC approval or annual renewal of the study
- Persistent non-compliance to the clinical investigation (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment
- Noncompliance to regulations and the terms of the CTA (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.)
- Institutional Review Board/Ethics Committee suspension of the site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

21.9.3. Procedures for Termination or Suspension

Medtronic-Initiated and Regulatory Authority-Initiated

- Medtronic will promptly inform the clinical investigators of the (early) termination or suspension and the reasons and inform the regulatory authority(s) where required
- In the case of study termination or suspension for reasons other than a temporary IRB/EC approval lapse, the investigator will promptly inform the IRB/EC
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

Investigator-Initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the IRB/EC
- The investigator will promptly inform the regulatory authorities (for regions following ISO only)
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

Institutional Review Board Ethics Committee-Initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with IRB/EC policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)

- The investigator will promptly inform the subjects, and/or the personal physician of the subjects, with the rationale for the study termination or suspension
- The investigator will promptly inform the regulatory authorities (for regions following ISO 14155 only)

22. Appendices

APPENDIX 1: Foreseeable Adverse Event List

The information provided in this section pertains to foreseeable AEs that may be observed in study subjects and may collectively assist in identifying those events that are unexpected in nature. The foreseeable adverse events information consists of three parts: (1) listing of potential adverse events associated with implantation of CRT system and transvenous leads, (2) rates of AEs reported from previous Medtronic studies evaluating CRT systems and transvenous leads, and (3) AEs rates reported in published literature for procedures similar to the CRT system implant procedure. This information will be used in combination with device labeling, current event reporting information, and other published data to assess for an unexpected occurrence.

The implantation of the study device, CRT-P or CRT-D, involves surgery, therefore, standard AEs associated with a surgical procedure may be experienced (e.g. anesthesia complications, injury, infections, bleeding, exacerbation of pre-existing conditions, healing complications, etc.). The focus of this section is to specifically address in more detail, those events that are foreseeable due to the use, performance, and/or presence of the system under investigation.

Additional potential risks associated with the implantation of the CRT system and the Attain Stability Quad MRI SureScan LV Lead (Model 4798), as well as risk minimization are discussed within Section 16.

Treatment required for procedure and/or system related adverse events that are experienced may include medication, device reprogramming, device modification (e.g. repositioning, surgical abandonment, surgical removal), or other surgical and medical remedies. The AEs associated with the use of transvenous leads, pacing and defibrillation systems include, but are not limited to, the following:

Table 23: Listing of Potential Adverse Events Associated with System Implant

- acceleration of tachyarrhythmias (caused by device)
- air embolism
- bleeding
- body rejection phenomena, including local tissue reaction
- cardiac dissection
- cardiac perforation
- cardiac tamponade
- chronic nerve damage
- constrictive pericarditis
- death
- device migration
- endocarditis
- erosion
- excessive fibrotic tissue growth
- extrusion
- fibrillation or other arrhythmias
- fluid accumulation
- formation of hematomas/seromas or cysts
- heart block
- heart wall or vein wall rupture
- hemothorax
- infection
- keloid formation
- lead abrasion and discontinuity
- lead migration/dislodgment
- complications and mortality due to inability to deliver appropriate and intended therapy
- muscle and/or nerve stimulation
- myocardial damage
- myocardial irritability
- myopotential sensing
- pericardial effusion
- pericardial rub
- pneumothorax
- poor connection of the lead to the device, which may lead to oversensing, undersensing, or a loss of therapy
- stroke
- threshold elevation
- thrombotic embolism
- thrombosis
- tissue necrosis
- valve damage (particularly in fragile hearts)
- venous occlusion
- venous perforation

An additional potential AE associated with the use of transvenous left ventricular pacing leads is coronary sinus dissection.

Additional potential AEs associated with the use of ICD systems include, but are not limited to, the following events:

- inappropriate shocks
- potential mortality due to inability to defibrillate
- shunting current or insulating myocardium during defibrillation

Patients susceptible to frequent shocks despite medical management could develop psychological intolerance to an ICD system that might include the following conditions:

- dependency
- depression
- fear of premature battery depletion
- fear of shocking while conscious
- fear that shocking capability may be lost
- imagined shocking (phantom shock)

Adverse Events Reported in Previous Medtronic Studies

The listing below provides an example of reported system and procedure related AEs in recent Medtronic studies. This table includes a summary of combined system or procedure related AEs as reported in the Concerto-AT, Insync III US, 4194, 4195, 4196, 4396, Adaptive CRT, and Attain Performa studies along with their incidence. The observed rate is based on the study populations that included a total of 3,246 subjects. In total, there were 1749 system or procedure related events. This includes both serious and non-serious events. The rate is calculated as number of subjects that experience the event, not accounting for duration of follow-up.

Table 24: System or procedure-related adverse events from previous clinical studies

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Abdominal pain	1	1	0.03%	(0.00%, 0.17%)
Acidosis	1	1	0.03%	(0.00%, 0.17%)
Acute respiratory failure	4	4	0.12%	(0.03%, 0.32%)
Adverse drug reaction	1	1	0.03%	(0.00%, 0.17%)
Air embolism	1	1	0.03%	(0.00%, 0.17%)
Alcohol withdrawal syndrome	1	1	0.03%	(0.00%, 0.17%)
Alpha haemolytic streptococcal infection	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Anaemia	7	7	0.22%	(0.09%, 0.44%)
Anaemia postoperative	1	1	0.03%	(0.00%, 0.17%)
Anaphylactic shock	1	1	0.03%	(0.00%, 0.17%)
Anticoagulation drug level below therapeutic	1	1	0.03%	(0.00%, 0.17%)
Anxiety	3	3	0.09%	(0.02%, 0.27%)
Application site rash	2	2	0.06%	(0.01%, 0.22%)
Arterial haemorrhage	1	1	0.03%	(0.00%, 0.17%)
Arteriovenous fistula	1	1	0.03%	(0.00%, 0.17%)
Arteriovenous fistula operation	1	1	0.03%	(0.00%, 0.17%)
Arthralgia	1	1	0.03%	(0.00%, 0.17%)
Arthritis bacterial	1	1	0.03%	(0.00%, 0.17%)
Ascites	1	1	0.03%	(0.00%, 0.17%)
Atelectasis	2	2	0.06%	(0.01%, 0.22%)
Atrial fibrillation	19	19	0.59%	(0.35%, 0.91%)
Atrial flutter	4	4	0.12%	(0.03%, 0.32%)
Atrial tachycardia	5	4	0.12%	(0.03%, 0.32%)
Atrioventricular block	16	16	0.49%	(0.28%, 0.80%)
Back pain	3	3	0.09%	(0.02%, 0.27%)
Bacteraemia	1	1	0.03%	(0.00%, 0.17%)
Cardiac arrest	8	8	0.25%	(0.11%, 0.49%)
Cardiac failure	46	43	1.32%	(0.96%, 1.78%)
Cardiac failure chronic	5	5	0.15%	(0.05%, 0.36%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Cardiac pacemaker battery replacement	1	1	0.03%	(0.00%, 0.17%)
Cardiac perforation	8	8	0.25%	(0.11%, 0.49%)
Cardiac sarcoidosis	1	1	0.03%	(0.00%, 0.17%)
Cardiac tamponade	3	3	0.09%	(0.02%, 0.27%)
Cardiac vein dissection	38	37	1.14%	(0.80%, 1.57%)
Cardiac vein perforation	5	5	0.15%	(0.05%, 0.36%)
Cardiogenic shock	3	3	0.09%	(0.02%, 0.27%)
Cardiomyopathy	1	1	0.03%	(0.00%, 0.17%)
Cardiovascular disorder	1	1	0.03%	(0.00%, 0.17%)
Cellulitis	2	2	0.06%	(0.01%, 0.22%)
Cerebral infarction	1	1	0.03%	(0.00%, 0.17%)
Cerebrovascular accident	3	3	0.09%	(0.02%, 0.27%)
Chest discomfort	4	4	0.12%	(0.03%, 0.32%)
Chest pain	8	8	0.25%	(0.11%, 0.49%)
Chronic obstructive pulmonary disease	3	3	0.09%	(0.02%, 0.27%)
Circulatory collapse	1	1	0.03%	(0.00%, 0.17%)
Colitis	1	1	0.03%	(0.00%, 0.17%)
Complication of device insertion	1	1	0.03%	(0.00%, 0.17%)
Complication of device removal	4	4	0.12%	(0.03%, 0.32%)
Constipation	1	1	0.03%	(0.00%, 0.17%)
Contusion	2	2	0.06%	(0.01%, 0.22%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Cough	1	1	0.03%	(0.00%, 0.17%)
Cystitis	1	1	0.03%	(0.00%, 0.17%)
Decubitus ulcer	1	1	0.03%	(0.00%, 0.17%)
Deep vein thrombosis	14	14	0.43%	(0.24%, 0.72%)
Dehydration	1	1	0.03%	(0.00%, 0.17%)
Delirium	1	1	0.03%	(0.00%, 0.17%)
Device alarm issue	1	1	0.03%	(0.00%, 0.17%)
Device battery issue	1	1	0.03%	(0.00%, 0.17%)
Device capturing issue	30	29	0.89%	(0.60%, 1.28%)
Device computer issue	19	19	0.59%	(0.35%, 0.91%)
Device connection issue	19	19	0.59%	(0.35%, 0.91%)
Device damage	1	1	0.03%	(0.00%, 0.17%)
Device dislocation	125	107	3.30%	(2.71%, 3.97%)
Device electrical impedance issue	12	12	0.37%	(0.19%, 0.64%)
Device extrusion	2	1	0.03%	(0.00%, 0.17%)
Device failure	1	1	0.03%	(0.00%, 0.17%)
Device lead damage	13	13	0.40%	(0.21%, 0.68%)
Device lead issue	1	1	0.03%	(0.00%, 0.17%)
Device misuse	9	9	0.28%	(0.13%, 0.53%)
Device pacing issue	69	67	2.06%	(1.60%, 2.61%)
Device psychogenic complication	7	7	0.22%	(0.09%, 0.44%)
Device related infection	3	3	0.09%	(0.02%, 0.27%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Device signal detection issue	2	2	0.06%	(0.01%, 0.22%)
Device stimulation issue	443	349	10.75%	(9.71%, 11.87%)
Diabetes	1	1	0.03%	(0.00%, 0.17%)
Diarrhea	1	1	0.03%	(0.00%, 0.17%)
Dizziness	1	1	0.03%	(0.00%, 0.17%)
Dressler's syndrome	1	1	0.03%	(0.00%, 0.17%)
Drug hypersensitivity	3	3	0.09%	(0.02%, 0.27%)
Dysarthria	1	1	0.03%	(0.00%, 0.17%)
Dyspnoea	2	2	0.06%	(0.01%, 0.22%)
Dyspnoea exertional	1	1	0.03%	(0.00%, 0.17%)
Dyspnoea paroxysmal nocturnal	1	1	0.03%	(0.00%, 0.17%)
Ecchymosis	2	2	0.06%	(0.01%, 0.22%)
Electromagnetic interference	1	1	0.03%	(0.00%, 0.17%)
Endocarditis	1	1	0.03%	(0.00%, 0.17%)
Endocarditis staphylococcal	1	1	0.03%	(0.00%, 0.17%)
Erythema multiforme	1	1	0.03%	(0.00%, 0.17%)
Fatigue	5	5	0.15%	(0.05%, 0.36%)
Fluid overload	1	1	0.03%	(0.00%, 0.17%)
Gastroenteritis	1	1	0.03%	(0.00%, 0.17%)
Gastrointestinal haemorrhage	1	1	0.03%	(0.00%, 0.17%)
Haematoma	2	2	0.06%	(0.01%, 0.22%)
Haematuria	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Haemoptysis	2	2	0.06%	(0.01%, 0.22%)
Haemothorax	4	4	0.12%	(0.03%, 0.32%)
Hot flush	1	1	0.03%	(0.00%, 0.17%)
Hydrothorax	1	1	0.03%	(0.00%, 0.17%)
Hyperglycaemia	1	1	0.03%	(0.00%, 0.17%)
Hyperkalaemia	4	4	0.12%	(0.03%, 0.32%)
Hypersensitivity	1	1	0.03%	(0.00%, 0.17%)
Hypertension	1	1	0.03%	(0.00%, 0.17%)
Hyponatraemia	2	2	0.06%	(0.01%, 0.22%)
Hypotension	20	20	0.62%	(0.38%, 0.95%)
Hypovolaemia	1	1	0.03%	(0.00%, 0.17%)
Ileus	1	1	0.03%	(0.00%, 0.17%)
Impaired healing	2	2	0.06%	(0.01%, 0.22%)
Implant site bruising	2	2	0.06%	(0.01%, 0.22%)
Implant site cellulitis	1	1	0.03%	(0.00%, 0.17%)
Implant site effusion	1	1	0.03%	(0.00%, 0.17%)
Implant site erosion	1	1	0.03%	(0.00%, 0.17%)
Implant site erythema	6	6	0.18%	(0.07%, 0.40%)
Implant site haematoma	98	96	2.96%	(2.40%, 3.60%)
Implant site haemorrhage	6	6	0.18%	(0.07%, 0.40%)
Implant site hypoaesthesia	1	1	0.03%	(0.00%, 0.17%)
Implant site infection	44	44	1.36%	(0.99%, 1.82%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Implant site inflammation	3	3	0.09%	(0.02%, 0.27%)
Implant site irritation	5	5	0.15%	(0.05%, 0.36%)
Implant site oedema	3	3	0.09%	(0.02%, 0.27%)
Implant site pain	72	64	1.97%	(1.52%, 2.51%)
Implant site rash	3	3	0.09%	(0.02%, 0.27%)
Implant site swelling	4	4	0.12%	(0.03%, 0.32%)
Implant site warmth	1	1	0.03%	(0.00%, 0.17%)
Incision site complication	1	1	0.03%	(0.00%, 0.17%)
Incision site haemorrhage	5	5	0.15%	(0.05%, 0.36%)
Incision site pain	4	4	0.12%	(0.03%, 0.32%)
Incisional drainage	1	1	0.03%	(0.00%, 0.17%)
Infection	2	2	0.06%	(0.01%, 0.22%)
Infusion site extravasation	1	1	0.03%	(0.00%, 0.17%)
Intracardiac thrombus	6	6	0.18%	(0.07%, 0.40%)
Lead dislodgement	33	30	0.92%	(0.62%, 1.32%)
Leukocytosis	2	2	0.06%	(0.01%, 0.22%)
Localized oedema	1	1	0.03%	(0.00%, 0.17%)
Mediastinal effusion	1	1	0.03%	(0.00%, 0.17%)
Medical device discomfort	3	3	0.09%	(0.02%, 0.27%)
Medical device site reaction	1	1	0.03%	(0.00%, 0.17%)
Monoparesis	1	1	0.03%	(0.00%, 0.17%)
Muscle spasms	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Muscle twitching	1	1	0.03%	(0.00%, 0.17%)
Musculoskeletal chest pain	2	2	0.06%	(0.01%, 0.22%)
Musculoskeletal pain	42	40	1.23%	(0.88%, 1.67%)
Musculoskeletal stiffness	1	1	0.03%	(0.00%, 0.17%)
Myocardial infarction	1	1	0.03%	(0.00%, 0.17%)
Nausea	1	1	0.03%	(0.00%, 0.17%)
Neck pain	1	1	0.03%	(0.00%, 0.17%)
Nephrosclerosis	1	1	0.03%	(0.00%, 0.17%)
Neuropathy peripheral	1	1	0.03%	(0.00%, 0.17%)
Nodal rhythm	2	2	0.06%	(0.01%, 0.22%)
Non-cardiac chest pain	1	1	0.03%	(0.00%, 0.17%)
Oedema peripheral	12	12	0.37%	(0.19%, 0.64%)
Oliguria	1	1	0.03%	(0.00%, 0.17%)
Operative haemorrhage	1	1	0.03%	(0.00%, 0.17%)
Orthostatic hypotension	2	2	0.06%	(0.01%, 0.22%)
Oversensing	34	33	1.02%	(0.70%, 1.42%)
Oxygen saturation decreased	1	1	0.03%	(0.00%, 0.17%)
Pacemaker generated arrhythmia	6	6	0.18%	(0.07%, 0.40%)
Pain	1	1	0.03%	(0.00%, 0.17%)
Pain in extremity	1	1	0.03%	(0.00%, 0.17%)
Palpitations	9	9	0.28%	(0.13%, 0.53%)
Paraesthesia	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Pericardial effusion	16	15	0.46%	(0.26%, 0.76%)
Pericarditis	4	4	0.12%	(0.03%, 0.32%)
Phantom shocks	4	3	0.09%	(0.02%, 0.27%)
Phlebitis	2	2	0.06%	(0.01%, 0.22%)
Pleural effusion	21	21	0.65%	(0.40%, 0.99%)
Pneumonia	9	9	0.28%	(0.13%, 0.53%)
Pneumothorax	43	43	1.32%	(0.96%, 1.78%)
Pocket erosion	4	4	0.12%	(0.03%, 0.32%)
Post procedural haemorrhage	2	2	0.06%	(0.01%, 0.22%)
Presyncope	3	3	0.09%	(0.02%, 0.27%)
Procedural haemorrhage	1	1	0.03%	(0.00%, 0.17%)
Procedural headache	2	2	0.06%	(0.01%, 0.22%)
Procedural pain	1	1	0.03%	(0.00%, 0.17%)
Pruritus	1	1	0.03%	(0.00%, 0.17%)
Pruritus generalized	1	1	0.03%	(0.00%, 0.17%)
Pulmonary embolism	1	1	0.03%	(0.00%, 0.17%)
Pulmonary oedema	3	3	0.09%	(0.02%, 0.27%)
Pulmonary sepsis	1	1	0.03%	(0.00%, 0.17%)
Pulseless electrical activity	2	2	0.06%	(0.01%, 0.22%)
Pyrexia	5	5	0.15%	(0.05%, 0.36%)
Rash	8	8	0.25%	(0.11%, 0.49%)
Rash generalized	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Renal failure	8	8	0.25%	(0.11%, 0.49%)
Renal failure acute	2	2	0.06%	(0.01%, 0.22%)
Renal impairment	1	1	0.03%	(0.00%, 0.17%)
Respiratory acidosis	1	1	0.03%	(0.00%, 0.17%)
Respiratory distress	1	1	0.03%	(0.00%, 0.17%)
Respiratory failure	1	1	0.03%	(0.00%, 0.17%)
Sepsis	3	3	0.09%	(0.02%, 0.27%)
Sepsis syndrome	1	1	0.03%	(0.00%, 0.17%)
Septic shock	4	4	0.12%	(0.03%, 0.32%)
Sinus arrest	1	1	0.03%	(0.00%, 0.17%)
Sinus bradycardia	1	1	0.03%	(0.00%, 0.17%)
Sinus tachycardia	2	2	0.06%	(0.01%, 0.22%)
Staphylococcal infection	2	2	0.06%	(0.01%, 0.22%)
Stitch abscess	1	1	0.03%	(0.00%, 0.17%)
Subclavian vein thrombosis	2	2	0.06%	(0.01%, 0.22%)
Subcutaneous emphysema	1	1	0.03%	(0.00%, 0.17%)
Subcutaneous haematoma	1	1	0.03%	(0.00%, 0.17%)
Sudden cardiac death	10	10	0.31%	(0.15%, 0.57%)
Superior vena cava stenosis	1	1	0.03%	(0.00%, 0.17%)
Supraventricular extrasystoles	1	1	0.03%	(0.00%, 0.17%)
Supraventricular tachycardia	2	2	0.06%	(0.01%, 0.22%)
Syncope	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Tachycardia	1	1	0.03%	(0.00%, 0.17%)
Thrombophlebitis	2	2	0.06%	(0.01%, 0.22%)
Thrombosis	8	8	0.25%	(0.11%, 0.49%)
Thrombotic stroke	1	1	0.03%	(0.00%, 0.17%)
Toxicity to various agents	1	1	0.03%	(0.00%, 0.17%)
Twiddler's syndrome	5	5	0.15%	(0.05%, 0.36%)
Undersensing	7	7	0.22%	(0.09%, 0.44%)
Urinary retention	2	2	0.06%	(0.01%, 0.22%)
Vena cava thrombosis	1	1	0.03%	(0.00%, 0.17%)
Venous occlusion	1	1	0.03%	(0.00%, 0.17%)
Ventricular dyssynchrony	1	1	0.03%	(0.00%, 0.17%)
Ventricular extrasystoles	2	2	0.06%	(0.01%, 0.22%)
Ventricular fibrillation	1	1	0.03%	(0.00%, 0.17%)
Ventricular tachycardia	11	11	0.34%	(0.17%, 0.61%)
Vomiting	3	3	0.09%	(0.02%, 0.27%)
Weaning failure	1	1	0.03%	(0.00%, 0.17%)
Weight decreased	1	1	0.03%	(0.00%, 0.17%)
Wound dehiscence	1	1	0.03%	(0.00%, 0.17%)

Adverse Events in Literature

The potential AEs associated with the implantation of CRT-P or CRT-D systems have been documented in various articles in medical scientific literature. A summary of those events and their published incidence are included below.

1. Ahsan SY, Saberwal B, Lambiase PD, Chaubey S, Segal OR, Gopalamurugan AB, McCready J, Rogers DP, Lowe MD, and Chow AWC. An 8-year single-centre experience of cardiac

resynchronization therapy: procedural success, early and late complications, and left ventricular lead performance. Europace 2013;15:711-717.

Retrospective data were analyzed for all acute and chronic complications occurring over 490 consecutive CRT device procedures in 402 patients, from 2000 through 2008. Associated complications were reported by timeframe.

Table 25: Complications reported in Ahsan et al.

Table 3 Early and late complications by complication type[a]

Complication type	Early (<90 days) (*n*)	Late (>90 days) (*n*)	Mean time to late complication (months)
Death	1	0	–
Pneumothorax	2	0	–
Phrenic nerve stimulation requiring revision	3	4	11.4 (±8)
Infection	7	7	14.9 (±11)
Noise on RV/RA lead	1	3	17.0 (±22)
Box migration	2	1	15.0
RV/RA/LV lead fracture	1	4	33.1
Lead erosion	3	0	–
RV/RA lead displacement	6	6	4.9 (±2)
Inability to implant LV lead	13	–	–
LV lead displacement	5	5	6.8 (±4)
Total	44 (9.4%)	30 (6.1%)	

[a]This table shows all early and late complications and the mean time to their occurrence.

2. Dickstein K, Bogale N, Priori S, Auricchio A, Cleland JG, Gitt A, Limbourg T, Linde C, van Veldhuisen DJ, Brugada J; Scientific Committee; National Coordinators. The European Cardiac Resynchronization Therapy Survey. European Heart Journal 2009; 30:2450–2460.

The primary aim of this survey was to describe current European practice associated with CRT implantations. A total of 140 centers from 13 European countries contributed data from consecutive patients successfully implanted with a CRT device with or without an ICD between November 2008 and June 2009. The total number of patients enrolled was 2438.

Table 26: Complications reported in Dickstein et al.

Event	Incidence (%)
Peri-procedural complications	10
Bleeding	1
Pocket haematoma	3
Pneumothorax	1
Pericardial tamponade	0.3
Coronary sinus dissection	1
Phrenic nerve pacing	2
Lead dislocation	3

Post–implantation device related complications	4
Lead displacement	2
Lead malfunction	0
Phrenic nerve stimulation	2

3. Kirkfeldt R.E., Johansen J.B., Nohr E.A., Jorgensen O.D., Nielsen J.C. Complications after cardiac implantable electronic device implantations: An analysis of a complete, nationwide cohort in Denmark. European Heart Journal 2014 35:18 1186-1194.

This was a population-based cohort study in all Danish patients who underwent a Cardiac Implantable Electronic Device (CIED) procedure from May 2010 to April 2011. The study population consisted of 5918 consecutive patients. Total of 562 patients (9.5%) experienced at least one complication.

Table 27: Complications reported by Kirkfeldt et al. shows cumulative incidence of complications at 6 months[a].

Table 27: Complications reported by Kirkfeldt et al.

Complication type	**All (n=5918)**	**New Implant (n=4335)**	**Generator replacement (n=1136)**	**Upgrade/Lead revision (n=427)**
Any complication	562 (9.5; 8.7–10.2)	432 (9.9; 9.0–10.8)	67 (5.9; 4.5–7.3)	63 (14.8; 11.4–18.1)
Any major complication[b]	329 (5.6; 5.0–6.1)	253 (5.8; 5.1–6.5)	40 (3.5; 2.4–4.6)	36 (8.4; 5.8–11.1)
Any minor complication[c]	250 (4.2; 3.7–4.7)	189 (4.3; 3.7–4.9)	30 (2.6; 1.7–3.6)	31 (7.3; 4.8–9.7)
Major complications				
Lead related re-intervention	143 (2.4; 2.0–2.8)	120 (2.8; 2.3–3.2)	10 (0.9; 0.3–1.4)	13 (3.0; 1.4–4.7)
Infection	49 (0.8; 0.6–1.1)	24 (0.6; 0.3–0.8)	17 (1.5; 0.8–2.2)	8 (1.9; 0.6–3.2)
Local infection	22 (0.4; 0.2–0.5)	10 (0.2; 0.1–0.4)	8 (0.7; 0.2–1.1)	4 (1.0; 0.0–1.9)
Systemic infection/endocarditis	27 (0.5; 0.3–0.6)	14 (0.3; 0.2–0.5)	9 (0.8; 0.3–1.3)	4 (0.9; 0.0–1.9)
Pneumothorax requiring drainage	51 (0.9; 0.6–1.1)	45 (1.0; 0.7–1.3)	0	6 (1.4; 0.3–2.5)
Cardiac perforation	38 (0.6; 0.4–0.8)	35 (0.8; 0.5–1.1)	0	3 (0.7; 0.0–1.5)

Cardiac perforation (No intervention)	21 (0.4; 0.2–0.5)	18 (0.4; 0.2–0.6)	0	3 (0.7; 0.0–1.5)
Cardiac perforation (Intervention)	17 (0.3; 0.2–0.4)	17 (0.4; 0.2–0.6)	0	0
Pocket revision because of pain	25 (0.4; 0.3–0.6)	10 (0.2; 0.1–0.4)	9 (0.8; 0.3–1.3)	6 (1.4; 0.3–2.5)
Generator-lead interface problem with re-intervention	7 (0.1; 0.0–0.2)	3 (0.1; 0.0–0.1)	4 (0.4; 0.0–0.7)	0
Haematoma requiring re-intervention	10 (0.2; 0.1–0.3)	9 (0.2; 0.1–0.3)	1 (0.1; 0.0–0.3)	0
Other[d]	16 (0.3; 0.1–0.4)	16 (0.4; 0.2–0.5)	0	0
Minor complications				
Haematoma[e]	138 (2.3; 1.9–2.7)	104 (2.4; 1.9–2.8)	20 (1.8; 1.0–2.5)	14 (3.3; 1.6–5.0)
Wound infection treated with antibiotics	69 (1.2; 0.9–1.4)	47 (1.1; 0.8–1.4)	12 (1.0; 0.5–1.7)	10 (2.3; 0.9–3.8)
Pneumothorax conservatively treated	39 (0.7; 0.5–0.9)	32 (0.7; 0.5–1.0)	0	7 (1.6; 0.4–2.8)
Lead dislodgement without re-intervention	10 (0.2; 0.1–0.3)	9 (0.2; 0.1–0.3)	0	1 (0.2; 0.0–0.7)

[a]Reported as absolute frequencies and percentages with 95% CIs in parenthesis.

[b]All re-interventions were categorized as major complications due to their inherently higher risk of infections e.g. local CIED infections requiring re-intervention, systemic infections, pocket revisions etc.

[c]Minor complications included haematomas resulting in a prolonged hospital stay, hospital re-admissions, or additional out-patient visits, wound infections treated with antibiotics, pneumothorax conservatively treated, and lead dislodgements without re-intervention.

[d]Deep venous thrombosis (n=8), Twiddler's syndrome (n=3), wound revision (n=3), stroke (n=1), myocardial infarction (n=1)

[e]Resulting in prolonged hospital stay, hospital re-admission, or additional out-patient visit.

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Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	Attain Stability™ Quad Clinical Study
Study Product Name	Attain Stability™ Quad MRI SureScan Left Ventricular Lead (Model 4798)
Sponsor/Local Sponsor	**Sponsor:** Medtronic, Inc. Cardiac Rhythm and Heart Failure Clinical Research 8200 Coral Sea Street NE Mounds View, MN 55112 U.S.A. 1-800-328-2518 **Local Sponsors:** Canada Medtronic of Canada 99 Hereford Street Brampton, ON, L6Y 0R3 Canada +1-905-460-3800 Europe, Middle East, Africa (EMEA)Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands +31-43-35-66-566 Hong Kong Medtronic Hong Kong Medical Ltd. 1104-11, 11/F, Tower 1, The Gateway, Harbour City, Kowloon, Hong Kong SAR, China +852-2919-1300 Malaysia Medtronic International Ltd (Malaysia) B-23-1 Level 23, The Ascent, Paradigm No 1 Jalan SS7/26A Kelena Jaya 46301 PetalingJaya Selangor Malaysia +603 7883 8000
Document Version	Version 2.0; 13/JAN/2017

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1. Sponsor Contact

Medtronic, Inc. is sponsoring the Attain Stability Quad Clinical Study. Regional contact information is provided below. This information may be subject to change during the course of the Attain Stability Quad Clinical Study. Periodic updates to study contact information will be sent to sites as needed.

Table 1: Study Sponsor Contact Information

Study Contacts	
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2. CROs/Core Laboratories

This information may be subject to change during the course of the Attain Stability Quad Clinical Study. Periodic updates to study contact information will be sent to sites as needed.

Table 2: CRO and Core Laboratory Information

Contact Information	Role
Cognizant Technology Solutions 500 Frank W. Burr Blvd. Teaneck, NJ 07666 United States Direct Phone: (201) 801-0233 Direct Fax: (201) 801-0243	Review of electronic case report forms and management of discrepancies

3. Version History

Version	Summary of Changes	Author(s)/Title
1.0	○ Initial Release	Melissa Thalin, Principal Clinical Research Specialist Rinie Peters, Associate Clinical Research Specialist Ann Vacca, Principal Customer Specialist Shelby Li, Senior Principal Statistician Joao Monteiro, Senior Statistician
2.0	○ Added slitting information for Implant analyzer PCT at synopsis and table 8 ○ Remote visits: ▪ Changed wording to clarify required actions ▪ Removed manual PCT test ▪ Deleted rationale for final vector progammed ○ Recurring 6 mth FU: ▪ Removed PNS test ▪ Removed Patient Global Assessment ○ System Modification ▪ Reduced electrical testing requirements ○ Patient Global Assessment ▪ Added to Glossary ▪ Removed from Baseline and 3 month visits ○ Vectors ▪ Added additional 4 CRT-P vectors (LV to Can) throughout ○ Investigator Lead Handling Assessment ▪ Added to Implant visit ○ Adjusted # of participating centers ○ Updated exclusion criteria #2 ○ Updates to grammer, version ,and footers	Melissa Thalin, Principal Clinical Research Specialist Rinie Peters, Associate Clinical Research Specialist

4. Investigator Statement

Investigators will be provided with a separate investigator agreement to document their obligation and commitment with respect to study conduct.

5. Index

6. List of Tables

7. List of Figures

8. Glossary

Table 3: Glossary of Terms

Term	Definition
2090	Medtronic CareLink Programmer with the application software installed.
2290	Medtronic Analyzer
Medtronic Attain Stability Quad MRI SureScan (Model 4798) LV Lead	The quadripolar LV lead being studied (investigational in the United States/Canada, commercially available in EMEA, Hong Kong, and Malaysia).
Active Fixation Helix	A non-electrically active side helix, positioned between the LV 3 and LV 4 electrodes that will allow fixation of the Attain Stability Quad MRI SureScan (Model 4798) LV Lead in the cardiac vein.
ADE	Adverse Device Effect
AE	Adverse Event
Ag	Silver
CABG	Coronary Artery Bypass Graft

Term	Definition
CAD	Coronary Artery Disease
CDF	Cumulative Distribution Function
CEC	Clinical Events Committee
CIP	Clinical Investigation Protocol
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy: Established pacing therapy for patients with heart failure
CRT-D	Cardiac Resynchronization Therapy - Defibrillator
CRT-P	Cardiac Resynchronization Therapy - Pacemaker
CS	Coronary Sinus
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency
DEKRA	Deutscher Kraftfahrzeug-Überwachungs-Verein (German Motor Vehicle Inspections Association)
DMC	Data Monitoring Committee
EC	Ethics Committee
EMEA	Europe, the Middle East, and Africa
eCRF	Electronic Case Report Form
MEC/IRB/HREB/Ethics Board	Ethics Committee
FAL	Foreseeable Adverse Event List
FDA	Food and Drug Administration
Fr	French
GCP	Good Clinical Practice

Term	Definition
HF	Heart Failure
HTN	Hypertension
IC	Informed Consent
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IDE	Investigation Device Exemption
Ir	Iridium
IRB	Institutional Review Board
LAR	Legally Authorized Representative
LBBB	Left Bundle Branch Block
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MCRD	Monolithic Controlled Release Device which is located on the Attain Stability Quad MRI SureScan LV Lead (Model 4798) electrodes which elutes steroid to reduce inflammatory response within the cardiac vein.
Mechanical Stop	A component on the Attain Stability Quad MRI SureScan (Model 4798) LV Lead located at the base of the helix to prevent wedging of endothelial tissue in the helix and to prevent tissue ingrowth.
MedDRA	Medical Dictionary for Regulatory Activities
OC	Oracle Clinical (database management system)
OTW	Over-the-wire
PCT	Pacing Capture Threshold
Patient Global Assessment	Self-reported assessment to provide information on patient condition compared to previous heart failure status

Term	Definition
PHD	Pre-Hospital Discharge means the point at which a subject has been released from the hospital post implant procedure.
PMA	Premarket Approval
PNS	Phrenic Nerve Stimulation
POR	Power On Reset
Pt	Platinum
PTCA	Percutaneous Transluminal Coronary Angioplasty
QOL	Quality of Life
RA	Right Atrial
RRT	Recommended Replacement Time
RV	Right Ventricular
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SDN	Software Distribution Network
TÜV	Technischer Überwachungsverein (German safety validation organization)
UADE	Unanticipated Adverse Device Effect
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

9. Synopsis

Title	Attain Stability™ Quad Clinical Study
Product Name	Attain Stability™ Quad MRI SureScan Left Ventricular Lead (Model 4798)
Sponsor	Medtronic, Inc. Cardiac Rhythm and Heart Failure Clinical Research 8200 Coral Sea Street NE Mounds View, MN 55112 U.S.A. 1-800-328-2518
Local Sponsor	Canada Medtronic of Canada 99 Hereford Street Brampton, ON, L6Y 0R3 Canada +1-905-460-3800 EMEA Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands +31-43-35-66-566 Hong Kong Medtronic Hong Kong Medical Ltd. 1104-11, 11/F, Tower 1, The Gateway, Harbour City, Kowloon, Hong Kong SAR, China +852-2919-1300 Malaysia Medtronic International Ltd (Malaysia) B-23-1 Level 23, The Ascent, Paradigm, No 1 Jalan SS7/26A Kelena Jaya 46301 Petaling Jaya Selangor Malaysia +603 7883 8000
Indication under investigation	All subjects included in the study will be implanted with a Medtronic market released de novo CRT-P or CRT-D device, compatible market released Medtroinc RA and Medtronic RV leads and an Attain Stability QuadSureScan LV lead (Model 4798). For subjects enrolled who are receiving an upgrade to a CRT system, existing non-Medtronic RV and/or existing non-Medtronic RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used.

	Given the vast similarities between the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the Attain Performa family of leads, the proposed indications for use are the same. The indications are as follows: The Attain Stability Quad MRI SureScan 4798 steroid-eluting, quadripolar electrode, IS4 transvenous lead is indicated for chronic pacing in the left ventricle via the cardiac vein, when used with a compatible Medtronic Cardiac Resynchronization Therapy (CRT) system. Extended bipolar pacing is available using this lead in combination with a compatible market approved CRT-D system and RV defibrillation lead.
Investigation Purpose	The Attain Stability Quad Clinical Study is a prospective, non-randomized, multi-site, global, Investigational Device Exemption (IDE) interventional clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV lead (Model 4798). This study will not be considered investigational in geographies with CE Mark of the Attain Stability Quadripolar LV lead (4798). However, data collected from all study subjects will be represented in the final report and the PMA Supplement (PMA-S) to the Model 4196 Original PMA.
Product Status	The Attain Stability Quad Clinical Study will be conducted using a research system composed of an approved CRT-D or CRT-P System. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is an active fixation quadripolar LV lead based on the Attain Performa lead family models (4298, 4398, and 4598). The lead incorporates an active fixation helix similar to the Attain Stability bipolar LV lead (Model 20066/4796) which is designed to allow an implanter more options in lead location. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered investigational in geographies where the product is not available commercially and will be labeled for clinical use only. These geographies include but are not limited to the US and Canada. Investigational Attain Stability Quad Leads will be distributed to a site only when Medtronic has received all required documentation (including but not limited to Ethic Committee approval, a signed Clinical Trial Agreement and documentation of training) and has notified the site of site readiness. Distribution of the investigational product to study sites will be managed by Medtronic and can only be

	ordered by Medtronic personnel. Site with these clinically labeled Attain Stability Quad MRI SureScan LV Leads (Model 4798) will track disposition upon receipt or return of the lead but also upon implant or explant of the lead. Disposition logs will be available within the electronic data management system and shall be maintained at each site in all geographies to track investigational product information. For geographies where the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is not considered investigational, commercially approved devices will be used. Sites that use commercially available Attain Stability Quad MRI SureScan LV Leads (Model 4798) will track device disposition upon implant or explant on the lead CRFs. The Medtronic approved CRT-P or CRT-D devices will be programmed and interrogated using a Medtronic CareLink (2090) programmer. Medtronic may incorporate additional programmers as they receive regulatory approval. The CareLink Monitor Model 2490C is an external monitor that is indicated for use in the transfer of patient and device data from implanted Medtronic devices. The CareLink Monitor Model 2490C interrogates implanted devices and temporarily stores these data, collaborates with the appropriate Medtronic server to confirm the establishment of an Internet connection with server, performs any required file translation functions necessary for data transfer, executes data file transfer, and collaborates with the appropriate Medtronic server to confirm data file transfer through the Internet connection with the server. The CareLink Monitor 2490C is not a programmer and cannot be used to program implanted device parameters. CareLink monitors are not a substitute for appropriate medical attention in the event of an emergency and should only be used as directed by a physician. Approved Medtronic CRT-P and CRT-D devices used in this study qualify for use with the Medtronic CareLink Monitor and Medtronic CareLink Network. Medtronic may incorporate additional home monitors as they receive regulatory approval. Medtronic's commercially available Model 2290 Analyzer must be available at each center during the implant

	procedure to determine acceptable electrical parameters. Medtronic may incorporate additional analyzers as they receive regulatory approval.
Primary Objective(s)	**<u>Primary Safety Objective: Lead complication-free rate at 6 months</u>** The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered safe if the probability of subjects free of Model 4798 lead-related complications at 6 months post-implant is greater than 87% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 87%). The study primary safety endpoint is Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complications through 6 months post implant. All reported system and procedure-related AEs will be reviewed by an event review committee for LV lead relatedness and severity (complication vs observation, refer to 17.1.2 for defintions). **<u>Primary Efficacy Objectives: Lead pacing capture thresholds at 6 months</u>** To demonstrate the effectiveness of the Attain Stability Quad MRI SureScan LV lead (Model 4798) the study will evaluate the likelihood that there are at least two programmable vectors for each patient post implant. The effectiveness of this lead will be evaluated based on two primary efficacy objectives. More specifically, both primary efficacy objectives must be met simultaneously. **<u>Primary Efficacy Objective #1</u>** The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet the objective if the proportion of subjects with at least one LV lead pacing vector having a pacing capture threshold less than or equal to 2.5 V at 0.5ms pulse width at 6 months post-implant is greater than 80% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 80%). The endpoint for the primary efficacy objective is whether or not there is at least one Model 4798 LV lead pacing vector with pacing capture voltage thresholds less than or equal to 2.5V. This endpoint will be measured at the 6-month post implant follow-up visit.

	Primary Efficacy Objective #2 The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet the objective if the proportion of subjects with at least one additional LV lead pacing vector having a pacing capture threshold less than or equal to 4.0 V at 0.5ms pulse width at 6 months post-implant is greater than 80% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 80%). The co-primary efficacy endpoint is whether or not a second Model 4798 lead configuration has a pacing capture threshold less than or equal to 4V, excluding the pacing vector that is already counted to the primary efficacy endpoint #1. This endpoint will be measured at 6-month post implant follow-up visit.

Secondary

Objective(s)	The secondary objectives are descriptive in nature and are intended to provide additional information about the Attain Stability Quad Model 4798 LV lead. There will be no established performance requirements for these secondary objectives. o Implant procedure related information: success rate, implant related times o Endpoints will include implant success rate and procedure durations. o 6-month reliability: post implant lead failure modes (i.e. complication rate) o Endpoint is Model 4798 lead related complications. o Electrical measurements (PCT and Impedance) at follow-ups o Endpoints are the electrical measurements (pacing capture thresholds and impedance values) for the four extended bipolar (CRT-D) or unipolar (CRT-P) vectors, i.e. LV1 to RVCoil/Can, LV2 to RV Coil/Can, LV3 to RV Coil/Can and LV4 to RV Coil/Can (refer to 15.8.2.3 for the testing procedure requirements)

Study Design	The Attain Stability Quad Clinical Study is a prospective, non-randomized, multi-site, global, Investigational Device Exemption (IDE) interventional clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV lead (Model 4798) in patients indicated for a de novo LV lead implant. This will be assessed through primary safety and primary efficacy endpoints. All subjects included in the study will be implanted with a Medtronic market released de novo CRT-P or CRT-D device and an Attain Stability Quad MRI SureScan LV Lead (Model 4798). Compatible market released Medtronic RA and Medtronic RV leads will be required. For subjects enrolled who are receiving an upgrade to a CRT system, existing non-Medtronic RV and/or existing non-Medtronic RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used. Up to 471 subjects will be enrolled into the study and up to 471 Attain Stability Quad MRI SureScan LV Leads (Model 4798) implanted, to ensure a minimum effective sample size of 400 Model 4798 leads implanted with 6 months post implant follow up visits (assuming 15% attrition). For the secondary endpoint of individual lead failure modes, Bayesian methods utilizing data from up to 37 historical patients will be used. All other objectives will be analyzed using only patients enrolled in this study. After a successful implant, threshold testing will occur per protocol requirement. Subjects will then be followed at implant, three months, six months and every six months thereafter until FDA approval is obtained or until study closure, whichever comes first. The study duration is expected to be approximately 19 months. This represents 13 months for subject enrollment and 6 months for subject follow-up for the last subject enrolled. Subjects are anticipated to be in the study for on average 12 months. The first enrollment is projected to occur in May 2017.
Sample Size	Up to 471 subjects will be enrolled into the study, to ensure a minimum effective sample size of 400 Model 4798 leads implanted with 6 months post implant follow up visits (assuming 15% attrition) at up to 56 sites worldwide.
Inclusion/Exclusion Criteria	**Inclusion Criteria:** • Patient meets CRT implant criteria as determined

	by local regulatory and/or hospital policy • Patient (or legally authorized representative) has signed and dated the study-specific Consent Form • Patient is 18 years of age or older, or is of legal age to give informed consent per local and national law • Patient is expected to remain available for follow-up visits **Exclusion Criteria:** • Patient has had a previous unsuccessful LV lead implant attempt • Patient has a previous CRT system or LV lead implanted (for example, transvenous or epicardial) • Patient is currently implanted with a recalled (i.e. market-withdrawn, recalled or safety alert) RA and/or RV lead • Patient has known coronary venous vasculature that is inadequate for lead placement • Patient has unstable angina pectoris or has had an acute myocardial infarction (MI) within the past 30 days • Patient has had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the past 90 days • Patient has contraindications for standard transvenous cardiac pacing (e.g., mechanical right heart valve) • Patient has had a heart transplant (patients waiting for heart transplants are allowed in the study) • Patient has known renal insufficiency that would prevent them from receiving an occlusive venogram during the implant procedure • Patient is contraindicated for <1mg dexamethasone acetate • Patient is enrolled in any concurrent drug and/or device study that may confound the results of this study • Patient has a terminal illness and is not expected to survive more than six months • Patient meets exclusion criteria required by local law (e.g. age, pregnancy, breast feeding, etc.) • Patient is unable to tolerate an urgent thoracotomy
Study Procedures and Assessments	Clinical data will be collected at the study milestones: at enrollment, baseline, implant/PHD, 3M, 6M, thereafter

	every occurring 6M and study exit visits: **Enrollment/Baseline:** ○ Subject Informed Consent ○ Inclusion/Exclusion criteria verified ○ Subject demographics ○ Cardiovascular medications ○ Cardiovascular medical history ○ NYHA classification ○ Kansas City Cardiomyopathy Questionnaire (KCCQ) **Implant:** ○ Occlusive venogram with pre-determined target vessel location identified ○ Analyzer PCT data collection post lead fixation and prior to connecting the leads to the CRT-P/D device: 1. Pre-slitting the cannulation catheter and following guidewire/stylet has been pulled back proximal to the helix and electrodes 2. Post slitting the cannulation catheter ○ Investigator Lead Handling Assessment ○ System and procedure information PHD CRT System Testing and Programming using the implanted CRT-P or CRT-D device and the device programmer: <u>Lead Impedance</u> ○ Collect LV Lead Impedances using Vector Express on all vectors ○ Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site <u>Pacing Capture Thresholds (PCT)</u> ○ Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors ○ NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)

	○ Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site <u>Phrenic Nerve Stimulation (PNS)</u> ○ Test for presence of PNS at 8.0V at 0.5ms on final programmed vector ○ NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms ○ NOTE: PNS observed during this testing will not be considered an AE <u>Other Data Collection</u> ○ Rationale for selecting specific LV lead pacing vector for final programming ○ Final device interrogation/save-to-media ○ AE Assessment ○ Study deviations ○ Device deficiencies **3 Month (remote or in office visit):** <u>Lead Impedance</u> ○ Obtain LV Lead Impedance Test for the final programmed vector ○ Retain printouts at the site <u>Pacing Capture Thresholds (PCT)</u> ○ Obtain PCTs at 0.5ms pulse width on the final programmed vector ○ NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) ○ Retain printouts at the site <u>Phrenic Nerve Stimulation (PNS) (in office visit only)</u> ○ Test for presence of PNS at 8.0V at 0.5ms on final programmed vector ○ NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms ○ NOTE: PNS observed during this testing will not be considered an AE <u>Other Data Collection</u> ○ NYHA classification ○ Final device interrogation/save-to-media (or CareLink transmission) ○ AE Assessment

	○ Study deviations ○ Device deficiencies **6 Month:** <u>Lead Impedance</u> ○ Collect LV Lead Impedances using Vector Express on all vectors ○ Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site <u>Pacing Capture Thresholds (PCT)</u> ○ Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors ○ NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) ○ Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site <u>Phrenic Nerve Stimulation (PNS)</u> ○ Test for presence of PNS at 8.0V at 0.5ms on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can ○ Test for presence of PNS at 8.0V at 0.5ms on final programmed vector ○ NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms ○ NOTE: PNS observed during this testing will not be considered an AE <u>Other Data Collection</u> ○ NYHA classification ○ Patient Global Assessment ○ Kansas City Cardiomyopathy Questionnaire (KCCQ) ○ Rationale for selecting specific LV lead pacing vector for final programming ○ Final device interrogation/save-to-media

	○ AE Assessment ○ Study deviations ○ Device deficiencies **12 Month:** <u>Lead Impedance</u> ○ Collect LV Lead Impedances using Vector Express on all vectors ○ Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site <u>Pacing Capture Thresholds (PCT)</u> ○ Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors ○ NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) ○ Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site <u>Phrenic Nerve Stimulation (PNS)</u> ○ Test for presence of PNS at 8.0V at 0.5ms on final programmed vector ○ NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms ○ NOTE: PNS observed during this testing will not be considered an AE <u>Other Data Collection</u> ○ NYHA classification ○ Patient Global Assessment ○ Kansas City Cardiomyopathy Questionnaire (KCCQ) ○ Rationale for selecting specific LV lead pacing vector for final programming ○ Final device interrogation/save-to-media ○ AE Assessment ○ Study deviations ○ Device deficiencies

	Recurring 6 Month follow-ups (remote or inoffice visit): Lead Impedance o Obtain LV Lead Impedance Test for the final programmed vector o Retain printouts at the site Pacing Capture Thresholds (PCT) o Obtain PCTs at 0.5ms pulse width on the final programmed vector o NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) o Retain printouts at the site Other Data Collection o NYHA classification o Final device interrogation/save-to-media (or CareLink transmission) o AE Assessment o Study deviations o Device deficiencies **Study Exit:** o Report the reason for exit o Final Interrogation file (or Carelink transmissions) for exits occuring prior to the 6 month visit) o Study Deviations o AEs o Device Deficiencies
Safety Assessments	Adverse Event and Device Deficiency handling in the Attain Stability Quad Clinical Study is ISO 14155:2011 compliant for all participating geographies with the exception that only those AEs which are related to the subject's system, procedure, accessory, or are cardiovascular-related, heart failure-related, MRI-related, and all Serious AEs, will be collected (refer to Section 17 for AE assessment). This ensures any AEs which could potentially be relevant will be collected. Reporting of these events to Medtronic will occur on an Adverse Event (AE) Form, including date of AE, treatment, resolution, assessment of both the seriousness of the AE and the relatedness to the investigational device or procedure. Each AE must be recorded on a separate AE eCRF. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened.

Statistics	The primary objective will be analyzed using the time-to-first event Kaplan-Meier survival analysis method. A minimum number of subjects who have completed their 6 months post-implant visits will be required. Time 0 will be the day a subject undergoes the implant procedure of a Attain Stability Quad MRI SureScan LV Lead (Model 4798), which will be independent of success status of this implant procedure. Event date is the onset date of a subject's first complication that is related to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) according to CEC adjudication. Subjects who undergo an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt and do not experience any LV lead related complications, will be censored at the time of their last known exposure to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) for the survival analysis. For any lost-to-follow up subject, the last contact date will be used as the censor date. The 1-sided 97.5% confidence limit lower bound for the survival probability at 6 months (183 days) will be calculated using the log-log survival function approach (Kalbfleisch and Prentice 2002).

10. Introduction

10.1. Background

Several clinical trials (including MIRCLE[1], MIRACLE-ICD[2], CONTAK-CD[3], MUSTIC[4], PATH-CHF[5], COMPANION[6], MADIT CRT[7], and CARE-HF[8]) have demonstrated the benefit of cardiac resynchronization therapy (CRT) among patients with moderate to severe heart failure (HF) with a prolonged QRS duration and depressed Left Ventricular (LV) function.

Approximately 5.7 million people in the United States (US) are living with HF[9]. Heart Failure may be a chronic condition which causes the heart to not pump oxygenated blood efficiently through the body due to stiffening of the heart muscle. Heart Failure may affect one or both sides of the heart. It is most often caused by coronary artery disease (CAD) or uncontrolled hypertension (HTN). Patients who suffer from HF experience a variety of different symptoms including most often fatigue, cough, shortness of breath, swollen feet (edema) and weight gain.

Heart Failure is treated with medications and sometimes cardiac devices (i.e. pacemaker or defibrillator with CRT). Medications work to relieve symptoms and reverse the effects of HF. Cardiac Resynchronization Therapy devices treat HF by synchronizing the left and right ventricles of the heart which improves the heart's ability to pump oxygenated blood to the body.[10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21]

Cardiac Resynchronization Therapy devices are primarily made up of 4 main components; the can or battery, a Right Atrial (RA) lead, a Right Ventricular (RV) lead, and a Left Ventricular (LV) lead.

The LV lead specifically is important at maintaining ventricular synchrony. In 2014, Medtronic released the Attain® Performa™ family of LV leads (models 4298, 4398 and 4598). The three different shapes of these leads (double canted, straight, and S-shaped) were designed to enable the lead to be passively fixed within different anatomies of coronary vessels. In addition, the 4 strategically placed electrodes on the lead were designed to offer 16 different electrical vector programming configurations.

Medtronic also released the Attain Stability bipolar LV lead (Model 20066/4796) (CE Mark approved in September 30, 2013) in Europe. This lead has a side helix which enables it to be actively fixated to the vessel wall. The active fixation is an advantageous component in vessels that are wide or have short take-offs. The next generation of LV lead is known as the Attain Stability™ Quad MRI SureScan LV lead (Model 4798). This is a quadripolar lead similar to its Attain Performa predecessor leads and has a side helix for active fixation like the Attain Stability bipolar lead.

10.2. Purpose

The Attain Stability Quad Clinical Study is a prospective, non-randomized, multi-site, global, Investigational Device Exemption (IDE), interventional clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability™ Quad MRI SureScan LV Lead (Model 4798). This study will not be considered investigational in geographies with CE Mark of the Attain Stability™ Quad MRI SureScan LV lead (Model 4798). However, data collected from all study subjects will be represented in the final clinical report and the PMA Supplement (PMA-S) to the Attain Ability Model 4196 Original PMA (P080006, approved April 7, 2009). Subjects successfully implanted with the Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be followed at implant, three months, six months and every six months thereafter until FDA approval is obtained or until study closure, whichever comes first.

11. Objectives and Endpoints

11.1. Objectives

11.1.1. Primary Objective(s)

Primary Safety Objective: Lead complication-free rate at 6 months

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered safe if the probability of subjects free of Model 4798 lead-related complications at 6 months post-implant is greater than 87% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 87%).

Primary Efficacy Objectives: Lead pacing capture thresholds at 6 months

To demonstrate the effectiveness of the Attain Stability Quad MRI SureScan LV Lead (Model 4798), the study will evaluate the likelihood that there are at least two programmable vectors for each patient post implant. The effectiveness of this lead will be evaluated based on two primary efficacy objectives. More specifically, both primary efficacy objectives must be met simultaneously.

Primary Efficacy Objective #1

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet this objective if the proportion of subjects with at least one LV lead pacing vector having a pacing capture threshold less than or equal to 2.5 V at 0.5 ms pulse width at 6 months post-implant is greater than 80% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 80%).

Primary Efficacy Objective #2

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet this objective if the proportion of subjects with at least one additional (or second) LV lead pacing vector having a pacing capture threshold less than or equal to 4.0 V at 0.5 ms pulse width at 6 months post-implant is greater than 80% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 80%).

11.1.2. Secondary Objective(s)

The secondary objectives are descriptive in nature and are intended to provide additional information about the Attain Stability Quad MRI SureScan LV Lead (Model 4798). There will be no established performance requirements for these secondary objectives.

- To summarize implant procedure related information: success rate, implant related times
- To estimate 6-month reliability: post implant lead failure modes (i.e. complication rate)
- To estimate electrical measurement values (Pacing Capture Thresholds (PCTs) and Lead Impedance) at 6 months post-implant

11.2. Endpoints

11.2.1 Primary Endpoints

Primary Safety Endpoint

The study primary safety endpoint is Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complications through 6 months post implant. All reported system and procedure-related AEs will be reviewed by an event review committee for LV lead relatedness and severity (complication vs observation, refer to 17.1.2 for defintions).

Primary Efficacy Endpoint #1

The Model 4798 LV lead has sixteen (16) programmable pacing vectors. The endpoint for the primary efficacy objective is whether or not there is at least one Model 4798 LV lead pacing vector with pacing capture voltage thresholds less than or equal to 2.5V. This endpoint will be measured at the 6-month post implant follow-up visit.

Primary Efficacy Endpoint #2

The co-primary efficacy endpoint is whether or not a second Model 4798 lead configuration has a pacing capture threshold less than or equal to 4V, excluding the pacing vector that is already counted to the primary efficacy endpoint #1. This endpoint will be measured at 6-month post implant follow-up visit.

11.2.2 Secondary Endpoints

To summarize implant procedure related information

Implant procedure related endpoints will include implant success rate and procedure durations.

To estimate 6-month reliability

The Model 4798 LV lead 6-month reliability endpoint is Model 4798 lead related complications.

To estimate electrical measurement values (Pacing Capture Thresholds (PCTs) and Lead Impedance) at 6 months post-implant

The electrical measurements are pacing capture thresholds and impedance values for the four extended bipolar (CRT-D) vectors (i.e. LV1 to RVCoil, LV2 to RV Coil, LV3 to RV Coil, LV4 to RV Coil) or the unipolar (CRT-P) vectors (i.e. LV1 to Can, LV2 to Can, LV3 to Can, LV4 to Can) (refer to 15.8.2.3 for the testing procedure requirements).

12. Study Design

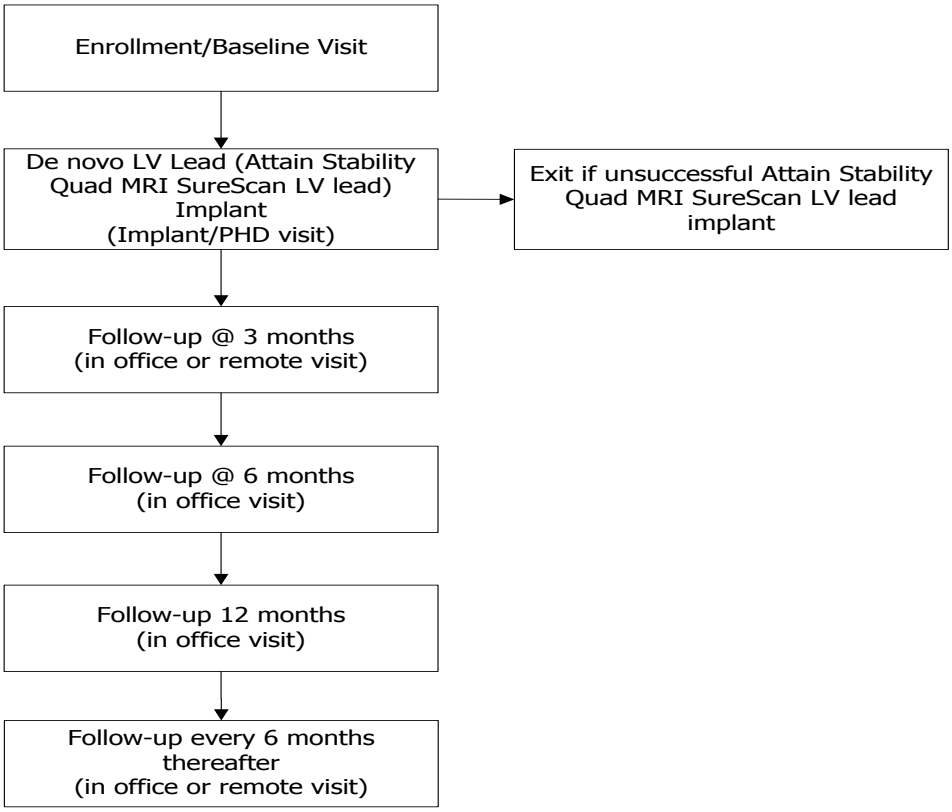
The Attain Stability Quad Clinical Study is a prospective, non-randomized, multi-site, global, Investigational Device Exemption (IDE), interventional clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) in patients indicated for a de novo LV lead implant. This will be assessed through a primary safety and primary efficacy endpoints.

All subjects included in the study will be implanted with a Medtronic market released de novo CRT-P or CRT-D device and an Attain Stability Quad MRI SureScan LV Lead (Model 4798). Compatible market released Medtronic RA and Medtronic RV leads will be required. For subjects enrolled who are receiving an upgrade to a CRT system, existing non-Medtronic RV and/or existing non-Medtronic RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used.

Up to 471 subjects will be enrolled into the study and up to 471 Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted, to ensure a minimum effective sample size of 400 Model 4798 leads implanted with 6 months post implant follow up visits (assuming 15% attrition). For the secondary endpoint of individual lead failure modes, Bayesian methods utilizing data from up to 37 historical patients will be used. All other objectives will be analyzed using only patients enrolled in this study. After a successful implant, threshold testing will occur to show one LV vector with pacing capture threshold (PCT) ≤ 2.5 V @ 0.5ms and with sufficient safety margin was programmed. Subjects will then be followed at implant, three months, six months and every six months thereafter until FDA approval is obtained or until study closure, whichever comes first.

See Figure 1 and Section 15 for further detail on study procedures and data collection as well as time-points for data collection.

Figure 1: Study Visits



The study is expected to be conducted at up to 56 sites worldwide. Participating geographies are expected to include, but are not limited to: the United States, Canada, EMEA, Malaysia, and Hong Kong. To ensure a widespread distribution of data and to minimize site bias in the study results, the maximum number of subjects allowed at a single site is 50 subjects.

12.1. Duration

The study duration is expected to be approximately 19 months. This represents 13 months for subject enrollment and 6 months for subject follow-up for the last subject enrolled. Subjects are anticipated to be in the study for on average 12 months. The first enrollment is projected to occur in May 2017. Subjects will complete visits at enrollment/baseline, implant, 3 months, 6 months, and then every 6 months thereafter. Subjects will not be replaced with newly enrolled subjects upon early exit. As described in Section 19, the sample size accounts for attrition.

12.2. Rationale

Upon market release, this Attain Stability Quad MRI SureScan LV Lead (Model 4798) will provide physicians an alternative option to actively fixate the lead utilizing a side helix feature to achieve stability. The Attain Stability Quad Clinical Study is designed to demonstrate that the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is safe and effective. See Section 19 for further background information and evaluation of clinical data. See Section 10 for further background on the study design.

12.3. Study Oversight

The study will utilize a Steering Committee (SC). The SC is responsible for the scientific content of the study and for providing input for the execution of the study. Members of the SC may be study site investigators. The purpose of the SC is to provide unbiased opinions and expertise to the Attain Stability Quad Clinical Study design and process. The SC will support the execution of the Attain Stability Quad Clinical Study and provide guidance, feedback and direction to the clinical study. The SC is comprised of the members as indicated in Table 4 below.

Table 4: Steering Committee Members

Committee Member	Contact information
George H. Crossley III, MD Steering Committee Co-Chair	Electrophysiology Fellowship Program Director Vanderbilt University Medical Center 1211 Medical Center Drive Nashville, TN 37232 United States (615) 322-5000 george.crossley@vanderbilt.edu
Kevin P. Jackson, MD Steering Committee Co-Chair	Electrophysiologist Duke Cardiology of Raleigh Medical Office Building 6 3320 Wake Forest Road 2nd Floor, Suite 200 Raleigh, NC 27609 United States (919) 862-5100 k.j@duke.edu
Dr. Maria Grazia Bongiorni	Electrophysiologist University Hospital of Pisa Lungarno Antonio Pacinotti 43, 56126 Pisa PI Italia +39 050 221 2111 m.g.bongiorni@med.unipi.it
Prof. Svein Faerestrand	Electrophysiologist University of Bergen Jonas Liesvei 65 Bergen, Norway 5021 +47 55 97 67 04 svein.faerestrand@helse-bergen.no
Dr. Axel Kloppe	Electrophysiologist Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil GmbH, Bürkle-de-la-Camp-Platz 1, 44789 Bochum, Germany +49 234 3026050 axel.kloppe@bergmannsheil.de

Melissa Kong, MD	Electrophysiologist Silicon Valley Cardiology 1300 Stockbridge Ave Redwood City, CA 94061 United States (650) 363-5262 mhkong1@gmail.com
Raymond Yee, MD	Electrophysiologist London Health Sciences Centre 339 Windemere Road London, ON N6A 5A5 Canada (519) 663-3671 ryee@uwo.ca
Francois Philippon, MD	Electrophysiologist Institut Universitaire de Cardiologie et de Pneumologie de Quebec 2725 Chemin Ste-Foy Quebec G1V 4G5 Canada (418) 656-8711 francois.philippon@fmed.ulaval.ca

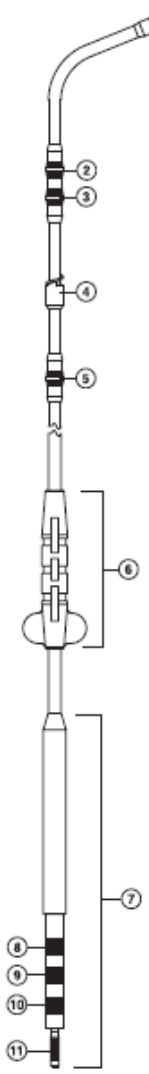
The study will also utilize a Clinical Events Committee (CEC) who will be responsible for adjudicating adverse events and deaths, including procedure and/or system-related complications. Further details for the CEC are provided in Section 18.1.

13. Product Description

13.1. General

The Medtronic Attain Stability Quad MRI SureScan (Model 4798) is a steroid-eluting, quadripolar electrode, transvenous, over-the-wire (OTW), IS4-LLLL compatible, active fixation, cardiac vein pacing LV lead. This lead is similar to the Attain Performa family of quadripolar leads (Models 4298, 4398, and 4598) but also has a side helix for active fixation which is similar to the Attain Stability bipolar lead (Model 20066/4796) (available outside of the United States). Figure 2 is a drawing of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) illustrating the specifications and location of the four electrodes in comparison to the side helix.

Figure 2: Attain Stability Quad MRI SureScan LV Lead (Model 4798) Specifications Drawing



[1] Electrode LV1 (the distal electrode): nominally 5.8 mm^2 geometric pacing surface area
[2] Electrode LV2: nominally 5.8 mm^2 geometric pacing surface area
[3] Electrode LV3: nominally 5.8 mm^2 geometric pacing surface area
[4] Helix assembly
[5] Electrode LV4 (the proximal electrode): nominally 5.8 mm^2 geometric pacing surface area
[6] Anchoring sleeve
[7] IS4 connector
[8] Contact LV4
[9] Contact LV3
[10] Contact LV2
[11] Contact LV1

Table 5 provides compares of the Attain Performa family of leads design features to the Attain Stability Quad MRI SureScan LV Lead (Model 4798).

Table 5: Comparison of Medtronic Quadripolar LV Leads

	Attain Performa			Attain Stability Quad
Design Feature	Model 4298	Model 4398	Model 4598	Model 4798
Shape	Double Canted	Straight	S-Shaped	Single Canted
Implant Method	Guide wire, stylet, or hybrid guide wire via Medtronic Delivery System	Same as 4298	Same as 4298	Guide wire, stylet, or hybrid guide wire via Medtronic Delivery System and active fixation
Delivery System Inner Diameter	≥ 5.7 Fr ID	Same as 4298	Same as 4298	Same as 4298
Lead Body Diameter	5.3 Fr proximal/3.9 Fr distal	Same as 4298	Same as 4298	4.4 Fr proximal/3.9 Fr distal
Lead Body Conductor	Single Quadfilar Coil (Multiconductor)	Same as 4298	Same as 4298	Same as 4298
Conductor Material	Ag core-low Titanium MP35Ncoil	Same as 4298	Same as 4298	Same as 4298
Insulation (Outer/Inner)	Polyurethane 55D SI-PI	Same as 4298	Same as 4298	Same as 4298
Polarity	Selectable Quad-electrode	Same as 4298	Same as 4298	Same as 4298
Electrode Material	PT/Ir* alloy with TiN coating	Same as 4298	Same as 4298	Same as 4298
Fixation Helix Material	N/A	N/A	N/A	Pt/Ir** alloy
Electrode Spacing	21mm/ 1.3mm/ 21mm	Same as 4298	Same as 4298	Same as 4298
Surface Area per	5.8	Same as 4298	Same as 4298	Same as 4298

Electrode (mm^2)				
Steroid and Dose / MCRD	Dexamethasone acetate Each (4) Ring 72µg	Same as 4298	Same as 4298	Same as 4298
Total Target Dose	288 µg/lead	Same as 4298	Same as 4298	Same as 4298

*90/10 Platinum Iridium
**80/20 Platinum Iridium

Similar to the Attain Performa family of leads, the Attain Stability Quad MRI SureScan LV Lead (Model 4798) contains 4 electrodes with surface area of 5.8 mm^2 per electrode and is designed to function as cathodes or anodes, depending on how the device LV pacing vector is programmed:

- electrode LV1, the distal electrode, positioned near the distal tip of the lead
- electrode LV2, positioned 21 mm proximal to electrode LV1
- electrode LV3, positioned 1.3 mm proximal to electrode LV2
- electrode LV4, the proximal electrode, positioned 21 mm proximal to electrode LV3

The electrode spacing on the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is identical to the approved Attain Performa family of leads. This includes a non-uniform electrode spacing consisting of a reduced electrode spacing configuration (LV2-LV3) that alters the size of the electric field that is generated when stimulating the heart tissue. This close electrode spacing is designed to reduce the likelihood of stimulating the phrenic nerve while still allowing for optimal lead placement and acceptable pacing capture thresholds.

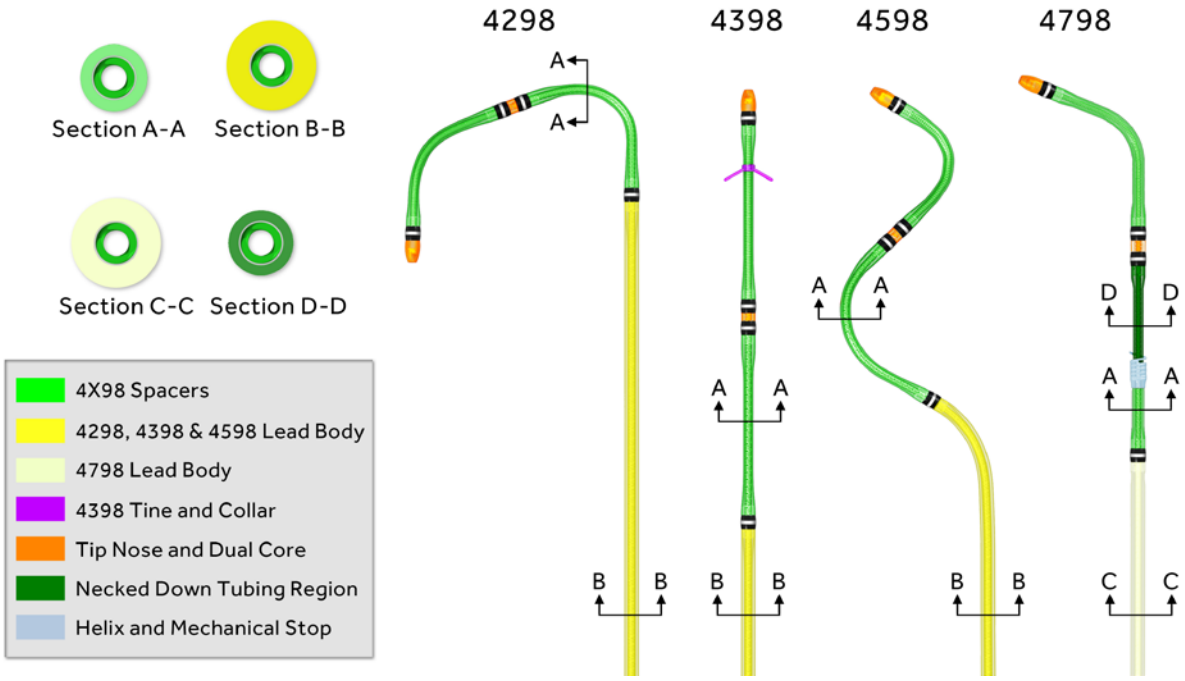
Similar to Attain Performa, each electrode contains a Monolithic Controlled Release Device (MCRD) for elution of steroid to reduce inflammatory response within the cardiac vein. The MCRDs contain a combined-total target dosage of 288 µg of dexamethasone acetate steroid. The target dose of the steroid is 72 µg at each MCRD. Upon exposure to body fluids, the steroid elutes from the MCRDs. The steroid suppresses the inflammatory response that is believed to cause threshold rise typically associated with implanted pacing electrodes.

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) has the same lead body conductor (Single Quadfilar Coil (Multiconductor), conductor material (Ag core-low Titanium MP35N coil), insulation (outer/inner) (Polyurethane 55D SI-PI), and requires a similar delivery system inner diameter as the Attain Performa family of leads (≥ 5.7 Fr ID).

Unlike the Attain Performa family of leads, the Attain Stability Quad MRI SureScan LV Lead (Model 4798) has a slightly smaller lead body diameter. The lead body diameter of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is 4.4 Fr proximal (compared to 5.3 Fr on the Attain Performa family of leads) and 3.9 French distal (same as Attain Performa family of leads). This slightly smaller lead body tubing diameter is designed to enhance torquability and steerability to facilitate adherence of the side helix in the target location.

Figure 3 is a visual comparison between the Attain Perform leads and the Attain Stability Quad MRI SureScan LV Lead (Model 4798) illustrating the similar electrode location but different lead body diameter.

Figure 3: Comparison of Attain Performa Leads and the Attain Stability Lead Model 4798



A detailed comparison of the Attain Stability bipolar lead (Model 4796) and Attain Stability Quad lead (Model 4798) is presented in Table 6.

Table 6: Comparison of Medtronic Attain Stability Bipolar and Quadripolar LV Leads

	Attain Stability	Attain Stability Quad
Design Feature	Model 4796/20066	Model 4798
Shape	Single Canted	Same as 4796/20066
Implant Method	Guide wire, Stylet, or hybrid guide wire via Medtronic Delivery System and active fixation	Same as 4796/20066
Delivery System Inner Diameter	≥ 5.7 Fr ID	Same as 4796/20066
Lead body diameter	3.9 Fr proximal / 3.4 Fr distal	4.4 Fr proximal /3.9 Fr distal
Lead Body Conductor	Single 2 Filar Coil (Multiconductor)	Single Quadfilar Coil (Multiconductor)
Conductor Material	Ag core-low Titanium MP35N coil	Same as 4796/20066

	Attain Stability	Attain Stability Quad
Design Feature	Model 4796/20066	Model 4798
Shape	Single Canted	Same as 4796/20066
Insulation (Outer/Inner)	Polyurethane 55D SI-PI	Same as 4796/20066
Polarity	bipolar	Selectable Quad-electrode
Electrode Material	Pt/Ir* alloy with TiN coating	Same as 4796/20066
Fixation Helix Material	Pt/Ir** alloy	Same as 4796/20066
Electrode Spacing	21 mm	21mm / 1.3mm / 21mm
Surface Area per electrode (mm^2)	5.8	Same as 4796/20066
Steroid and Dose / MCRD	Dexamethasone acetate Tip 160µg , Ring 72µg	Dexamethasone acetate Each (4) Ring 72µg
Total Target Dose	232µg/lead	288 µg/lead
Molded Tip Seal	Silicone (with steroid), pierced hole	Silicone (without steroid), cross-cut hole
Fixation Method	Helix	Same as 4796/20066
Connector	IS-1 B1	IS4-LLLL
Length (cm)	88 cm only	78 and 88 cm

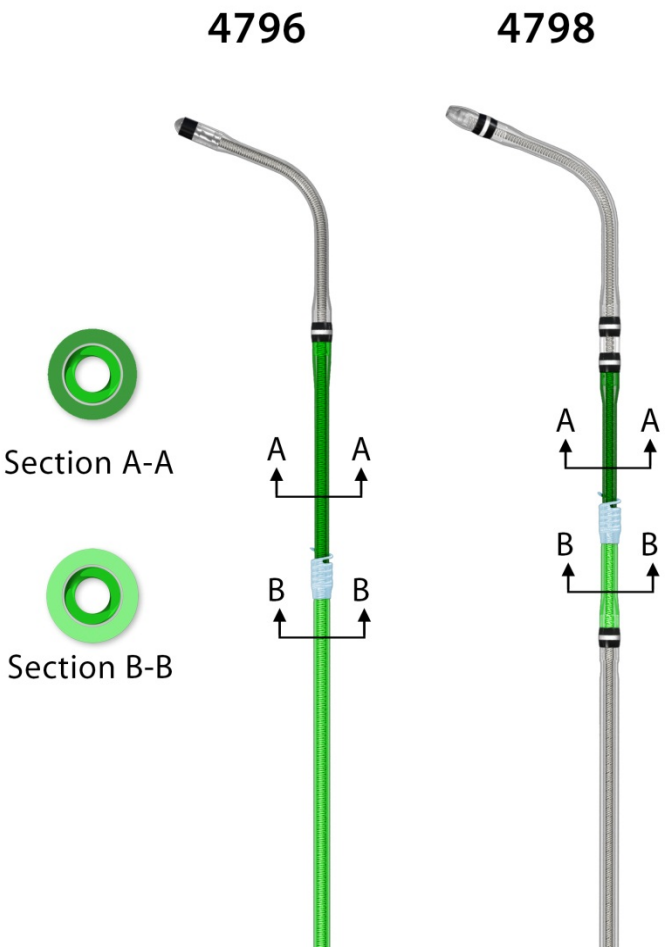
*90/10 Platinum Iridium
**80/20 Platinum Iridium

The non-electrically active side fixation helix component is similar to the Attain Stability Bipolar LV lead (Model 20066/4796) and is designed to enable active fixation in the cardiac vein. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) side helix is positioned between the LV3 and LV4 electrode; specifically 10 mm proximal from the LV3 electrode (see Figure 2).

A mechanical stop component is located at the base of the helix to prevent wedging of the endothelial tissue in the helix and to prevent tissue ingrowth. The helix component is platinum (Pt) iridium (Ir) alloy (Pt/Ir 80/20). This same Pt/Ir material is also used in the market released right ventricular active fixation lead Models 5076, 3830, and 4076. Both the helix and mechanical stop components are identical to those used on the CE Mark approved Medtronic Attain Stability model 20066/4796 active fixation lead and are shown in Figure 4.

The Model 4798 lead has one distal curve/cant. This distal curve geometry (angle) is identical to the Attain Performa model 4298, as well as Attain Ability models 4196 and 4296 most distal cant. The single distal cant is also identical to the CE Mark approved model 20066/4796 active fixation lead (Figure 4). The purpose of the distal cant is to provide physicians the ability to "steer" the distal tip of the lead when navigating difficult vein anatomy or acute vasculature angulation by rotating the lead (counterclockwise) and aligning the distal tip towards the desired direction. The distal cant for the Model 4798 lead is not intended, or necessary, to provide any fixation of the implanted lead as any retention force from the cant would be negligible compared to the stability provided by the properly implanted and verified fixated helix.

Figure 4: Attain Stability Bipolar (Model 20066/4796) & Attain Stability Quad MRI SureScan (Model 4798) Active Fixation Leads



The Attain Stability Quad Clinical Study will be conducted to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) in combination with CRT system components mentioned in Table 7.

Table 7: Study Component Information

Component	US/Canada	EMEA/Hong Kong/Malaysia
Attain Stability Quad MRI SureScan LV Lead (Model 4798)	Investigational	Market-released
Medtronic CRT-P or Medtronic CRT-D (with VectorExpress capabilities)	Market-released	Market-released
Medtronic RV lead (non-Medtronic and non-recalled/non-market withdrawaled/non-safety alerted lead acceptable for upgrades)	Market-released	Market-released
Medtronic RA lead (optional) (non-Medtronic and non-recalled/non-market withdrawn/non-safety alerted lead acceptable for upgraded systems)	Market-released	Market-released

Given the similarities between the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the Attain Performa family of leads, the proposed indications for use are the same. The indications are as follows:

Proposed Indication Statement for Use for the Attain Stability Quad Lead:

The Attain Stability Quad MRI SureScan 4798 steroid-eluting, quadripolar electrode, IS4 transvenous lead is indicated for chronic pacing in the left ventricle via the cardiac vein, when used with a compatible Medtronic Cardiac Resynchronization Therapy (CRT) System. Extended bipolar pacing is available using this lead in combination with a compatible market approved CRT-D system and RV lead.

Market-Released Right Atrial Lead

Commercially available Medtronic RA lead models with an IS-1 connector are required when an RA lead is implanted with de novo CRT systems. An RA lead is not required to be implanted in circumstances determined appropriate per physician's medical assessment. Medtronic commercially available RA leads with an IS-1 connector are recommended but compatible non-Medtronic leads are permissible in enrolled patients receving a CRT system upgrades.

Medtronic Market-Released Right Ventricular Lead

Commercially available Medtronic RV defibrillation leads with a DF4 connector are required for de novo CRT systems. Medtronic RV defibrillation leads with DF1 connectors may be incorporated in the study as DF1-compatible CRT-P and CRT-D devices are made available for the study. A non-Medtronic RV lead is permissible in enrolled patients receving a CRT system upgrades.

13.2. Manufacturer

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is manufactured by Medtronic, Inc.

13.3. Packaging

Packaging and labeling for all market approved system components can be found with each package insert. Manuals can be found on http://manuals.medtronic.com. For CE Marked devices the labeling is in the appropriate local language.

For investigational products (e.g. in the US and Canada), the language of labeling and clinical manuals will be in English and/or local language where it is required. Investigational products will be clearly labeled e.g. "exclusively for clinical investigation."

In Canada, each investigational device will be labelled with the statements "Investigational Device"; "To be Used by Qualified Investigators Only"; "Instrument de recherche" and "Réservé uniquement à l'usage de chercheurs compétents".

13.4. Intended Population

In the Attain Stability Quad Clinical Study, the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is to be used in subjects where a de novo LV lead is indicated. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is intended to be used in conjunction with a market released Medtronic CRT-P or CRT-D device, a Medtronic (for de novo CRT implants) RV lead, and a Medtronic (for de novo CRT implants) RA lead (optional).

A complete SureScan system is required for use in the MRI environment. Before performing an MRI scan, refer to the SureScan MRI technical manual for MRI-specific warnings and precautions.

13.5. Equipment

All commercially available equipment will be used according to their approved intended use.

Medtronic CareLink (2090) Programmer

The Medtronic approved CRT-P or CRT-D devices will be programmed and interrogated using a Medtronic CareLink (2090) programmer. Medtronic may incorporate additional programmers as they receive regulatory approval.

Medtronic CareLink Home Monitor 2490C and Network

The CareLink Monitor Model 2490C is an external monitor that is indicated for use in the transfer of patient and device data from implanted Medtronic devices. The CareLink Monitor Model 2490C interrogates implanted devices and temporarily stores these data, collaborates with the appropriate Medtronic server to confirm the establishment of an Internet connection with server, performs any required file translation functions necessary for data transfer, executes data file transfer, and collaborates with the appropriate Medtronic server to confirm data file transfer through the Internet connection with the server. The CareLink Monitor 2490C is not a programmer and cannot be used to program implanted device parameters. CareLink monitors are not a substitute for appropriate medical attention in the event of an emergency and should only be used as directed by a physician. Approved Medtronic CRT-P and CRT-D devices used in this study qualify for use with the Medtronic CareLink Monitor and Medtronic

CareLink Network. Medtronic may incorporate additional home monitors as they receive regulatory approval.

Pacing System Analyzer

Medtronic's commercially available Model 2290 Analyzer must be available at each center during the implant procedure to determine acceptable electrical parameters. Medtronic may incorporate additional analyzers as they receive regulatory approval.

13.6. Product Use

See Section 13 Product Description.

13.7. Product Receipt, Tracking, and Accountability

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered investigational in geographies where the product is not available commercially and will be labeled for clinical use only. These geographies include but are not limited to the US and Canada. Investigational Attain Stability Quad Leads will be distributed to a site only when Medtronic has received all required documentation (including but not limited to Ethic Committee approval, a signed Clinical Trial Agreement and documentation of training) and has notified the site of site readiness.

Distribution of the investigational product to study sites will be managed by Medtronic and investigational products can only be ordered by Medtronic personnel. Sites with these clinically labeled Attain Stability Quad MRI SureScan LV Leads (Model 4798) will track disposition upon receipt or return of the lead but also upon implant or explant of the lead. Disposition logs will be available within the electronic data management system and shall be maintained at each site in all geographies to track investigational product information. The logs should be updated when an investigational product is received, opened, implanted explanted, disposed of or returned to Medtronic. The logs will track the following investigational lead data (but are not limited to) model and serial numbers of devices delivered to the site, subject IDs of the subjects, implanted, received dates of devices, implant/used dates, explant dates, returned-to-sponsor dates and reasons, initials of all persons who received, used or disposed each device, and method of disposal. Medtronic will perform periodic reconciliation of investigational product to ensure traceability.

For geographies where the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is not considered investigational, commercially approved devices will be used. Sites that use commercially available Attain Stability Quad MRI SureScan LV Lead (Model 4798) will track device disposition upon implant or explant of the lead on the CRFs.

13.8. Product Storage

All investigational products must be stored in a secure location at the site. It is the responsibility of the investigator to correctly handle, store and track the investigational products. Further details may be found in the Clinical Manual or User Manual (dependent on each geography's commercial release of the product).

13.9. Product Return

All explanted, open but unused, and defective products (devices or leads, etc.) should be returned to Medtronic for analysis whenever possible and when permissible by local laws and regulations. If the products are explanted but not returned, a justification is required to be reported on the appropriate case report form(s) or disposition log(s) (note that this is not considered a study deviation). In geographies where the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is considered investigational, the Disposition Log must be updated in the event of an explant. To receive a Returned Product Mailer Kit, please contact your local Medtronic field personnel or representative. All unused investigational products must be returned to Medtronic upon study closure at the site.

14. Selection of Subjects

14.1. Study Population

Patients of both genders that are 18 years of age and older (or of legal age to give informed consent per local and national law) that are indicated for a de novo LV lead implantation and who meet all inclusion and no exclusion criteria are eligible for an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt. There will be no control group for this study.

14.2. Subject Enrollment

Patients who meet all of the inclusion and none of the exclusion criteria (see sections 14.3 and 14.4) are eligible to be enrolled in this study. Upon signing and dating the Informed Consent Form (ICF), the patient is considered a subject enrolled in the study.

14.3. Inclusion Criteria

- Patient meets CRT implant criteria as determined by local regulatory and/or hospital policy
- Patient (or legally authorized representative) has signed and dated the study-specific Informed Consent Form
- Patient is 18 years of age or older, or is of legal age to give informed consent per local and national law
- Patient is expected to remain available for follow-up visits

14.4. Exclusion Criteria

- Patient has had a previous unsuccessful LV lead implant attempt
- Patient has a previous CRT system or LV lead implanted (for example, transvenous or epicardial)
- Patient is currently implanted with a recalled (i.e. market-withdrawn, recalled or safety alert) RA and/or RV lead
- Patient has known coronary venous vasculature that is inadequate for lead placement
- Patient has unstable angina pectoris or has had an acute myocardial infarction (MI) within the past 30 days
- Patient has had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the past 90 days
- Patient has contraindications for standard transvenous cardiac pacing (e.g., mechanical right heart valve)
- Patient has had a heart transplant (patients waiting for heart transplants are allowed in the study)
- Patient has known renal insufficiency that would prevent them from receiving an occlusive venogram during the implant procedure
- Patient is contraindicated for <1mg dexamethasone acetate
- Patient is enrolled in any concurrent drug and/or device study that may confound the results of this study
- Patient has a terminal illness and is not expected to survive more than six months
- Patient meets exclusion criteria required by local law (e.g. age, pregnancy, breast feeding, etc.)
- Patient is unable to tolerate an urgent thoracotomy

14.5. Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Subjects will be evaluated at baseline to confirm eligibility for enrollment with defined inclusion/exclusion criteria
- Subject demographics and medical history will be collected at baseline and differences that may affect primary endpoints will be identified
- To ensure widespread distribution of data between sites, the maximum number of subjects allowed per site is 50
- All implanters in the study will be experienced in the implant of CRT-P and/or CRT-D systems
- Data collection requirements and study procedures will be standardized across all sites and geographies

- All study site personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials, and required to follow the CIP
- Per the specifications in the Monitoring Plan, monitoring visits will be conducted for adherence to the CIP and to verify the CRF data against source data
- Pre-defined statistical methods specified in the CIP and the Statistical Analysis Plan (SAP) will be followed
- The SC members will not have influence on the treatment decisions by study site investigators during the trial
- An independent and blinded CEC will regularly review and adjudicate reported adverse events and deaths (per Section 18.1)
- Registration of the trial on ClinicalTrials.gov and the publication plan will ensure that study results will be reported
- All study investigators are required to meet 21 CFR Part 54, Financial Disclosure by Clinical Investigators, to identify potential bias due to financial interest in the outcome of the study

In summary, potential sources of bias that may be encountered in this Attain Stability Quad Clinical Study have been considered and minimized by careful study design.

15. Study Procedures

Prior to performing study related procedures, all sites must have Ethics Committee (EC) and associated regulatory authority approval if applicable (e.g., Competent Authority approval) as well as documentation from Medtronic of site readiness.

Medtronic representatives may perform the following activities at the study sites during the study, if appropriately trained and under supervision of the Principal Investigator:

- Study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support at all visits (e.g. programming of the CRT-P or CRT-D device according to study requirements, performing device interrogations/save-to-media, etc.), but no CRF data entry shall be performed by Medtronic personnel
- Monitoring activities

15.1. Study Personnel Requirements

Site personnel training and delegation will be completed prior to participation in the Attain Stability Quad Clinical Study. The site personnel training consists of required training topics (CIP, Informed Consent Form, CRFs, regulations). Members of the study site team will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study.

All Principal Investigators shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Be qualified practitioners and experienced in the diagnosis, management, and treatment of HF subjects with CRT devices
- Be experienced in the field of application and trained in the use of the Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- Disclose potential conflicts of interest, including financial that interfere with the conduct of the clinical investigation or interpretation of results
- Be knowledgeable with the method of obtaining an informed consent

In addition, the Principal Investigator shall be able to demonstrate that the proposed investigational site:

- Has an experienced CRT implanter who is experienced and trained in the handling/implanting of CRT-P and/or CRT-D devices
- Has the required number of eligible subjects needed within the agreed recruitment period
- Has one or more qualified investigators, a qualified investigation site team and adequate facilities for the foreseen duration of the clinical investigation

15.2. Site Activation

During the activation process (prior to subject enrollment), Medtronic will train site personnel on the CIP, the implant procedure, relevant standards and regulations, informed consent process, and on data collection and reporting tools. If new members join the study site team, they will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study. For new members, local Ethics Committee notification requirements must be met, as well as Medtronic requirements noted on the training and delegation form.

A Clinical Trial Agreement (CTA) shall be entered into effect by Medtronic, the participating investigation site and/or the principal clinical investigator at each investigational site as per local legal requirements, and returned, fully executed, to Medtronic prior to the commencement of any study activities. Financial aspects of conducting and reporting a study will be specified in the agreement. By signing and dating the agreement the investigator indicates approval of the CIP.

Prior to performing study related activities, all sites must have Ethics Committee approval, as applicable for that geography.

All local and regional regulatory requirements will be fulfilled prior to site activation and enrollment of subjects into the study. Each study site must have written documentation from Medtronic of site and investigator readiness before beginning any study-related activities. Requirements for activation vary by geography, and may include, but are not limited to the following:

- Written documentation of Ethics Committee approval of the current version of the CIP and ICF, subject materials (e.g. Global Assessment and KCCQ), and voting list (as required by local law)
- Regulatory authority approval or notification (as required per local law)
- Fully executed CTA on file with the sponsor
- Financial Disclosure (for Principal Investigators and Co-Investigators)
- Current Curriculum Vitae (CV) (signed and dated as required by local law) of investigators and key members (as required by local law) of the investigation site team on file with the sponsor
- Documentation of delegated tasks

- Documentation of study site personnel training

Additional requirements imposed by the Ethics Committee and regulatory authority shall be followed, if applicable.

Medtronic will provide each study site with documentation of study site readiness; this letter must be sent prior to subject enrollment.

15.3. Equipment Requirements

The following equipment must be available at each site to support study activities:

- Medtronic 2290 Analyzer (or latest market released Medtronic analyzer)
- Medtronic 2090 programmer (or latest market released Medtronic programmer)
- Attain Stability Quad MRI SureScan LV Lead (Model 4798) (either clinically labeled product or commercial released product located at the site or carried to the implant by the Medtronic representative)
- Computer with high speed internet access using a web browser compatible with the electronic data management system for electronic database entry

The equipment necessary for the assessment for the study includes the Medtronic 2290 Analyzer and Medtronic 2090 programmer. The maintenance and calibration of the equipment used for this study will be assessed outside of this clinical study. Sites are responsible for maintaining and calibrating non-analyzer/programmer equipment used in the course of this study in accordance with established site practice or local regulation. Records should be kept and able to be provided upon request by the Sponsor or regulatory agency.

15.4. Schedule of Events

Clinical data will be collected at the study milestones detailed in Table 8. Data will be collected via electronic case report forms (eCRFs), still cine images, analyzer/programmer print-outs, and interrogation files. Post-implant follow-ups apply only to those subjects in whom an Attain Stability Quad MRI SureScan LV Lead (Model 4798) was successfully implanted or an implant was attempted. Subject visits will occur at enrollment, baseline, implant/pre-hospital discharge (PHD), 3 months post-implant, 6 months post-implant, and every 6 months thereafter until PMA approval of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted or study termination, whichever comes first. Medtronic personnel may assist study personnel during implant and study visits.

Table 8: Data Collection and Study Procedure Requirements at Subject Visits

STUDY PROCEDURE	Enrollment /Baseline	Implant/ PHD	3 months post-implant (remote or inoffice visit)	6 months post-implant (inoffice visit)	12 months post-implant (inoffice visit)	Recurring 6 month follow-ups (remote or inoffice visit)	Exit
Subject Informed Consent	✓						
Inclusion / Exclusion criteria verified	✓						
Subject demographics	✓						
Cardiovascular medications	✓						
Cardiovascular medical history	✓						
NYHA classification	✓		✓	✓	✓	✓	
Patient Global Assessment				✓	✓		
Kansas City Cardiomyopathy Questionnaire (KCCQ)	✓			✓	✓		
Occlusive venogram with pre-determined pacing location identified		✓					
Analyzer PCT data collection (pre and post slitting the cannulation catheter)		✓ (Implant)					
Investigator Lead Handling Assessment		✓ (Implant)					
System and procedure information		✓					
Lead Impedance (all 16 vectors)		✓	✓ (final programmed vector only)	✓	✓	✓ (final programmed vector only)	
Pacing Capture Thresholds (all 16 vectors)		✓	✓ (final programmed vector only)	✓	✓	✓ (final programmed vector only)	
Phrenic Nerve Stimulation (final programmed vector)		✓	✓ (inoffice visit only)	✓	✓		
Phrenic Nerve Stimulation (vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can)				✓			
Rationale for selecting specific LV lead pacing vector for final programming		✓		✓	✓		
Final device interrogation/save-to-media		✓	✓ (CareLink transmission is acceptable for remote visits)	✓	✓	✓ (CareLink transmission is acceptable for remote visits)	✓ (required only if subject exits prior to 6 months post-implant visit; CareLink transmission is acceptable)
AE Assessment		✓	✓	✓	✓	✓	✓
Exit Subject							✓
Adverse Events (incl. AE with outcome of death)	As they occur						
Device Deficiencies							
System Modifications							
Study Deviations							

Table 9 below specifies permitted time windows for the required subject visits. Subject visit target dates and windows for each follow-up will be made available to the study site. Should a subject miss a visit or the visit falls outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits. Data analyses will include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation.

Table 9: Visit Windows

Visit	Window
Implant	0-30 days since Baseline Assessment
	(days since implant)
Pre-hospital discharge	0-7
3-month	76 - 106
6-month	183 - 213
12-month	350 - 380
18-month	518 - 578
24-month	701 - 761

15.5. Subject Consent

Informed consent (IC) is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate (ISO 14155:2011). This process includes obtaining IC and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (data protection authorization; i.e. HIPAA in the US) as required by law. Informed Consent Forms are required to be approved by the study site's Institutional Review Board (IRB) or Ethics Committee (EC) and Medtronic, and signed and dated by the subject and the Principal Investigator. A subject may only consent after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate.

Prior to enrolling subjects, each site must have documented IRB/EC approval of the IC Form (ICF) and the data protection authorization as required by law. Any changes to a previously approved ICF throughout the course of the study must be reviewed and approved by Medtronic and the IRB/EC reviewing the application before being used to consent or re-consent a study subject. The document(s) must be controlled (i.e. versioned and dated) to ensure it is clear which version(s) was approved by Medtronic and the IRB/EC. All important new information should be provided in written form to new and existing subjects throughout the study. If relevant, all affected subjects must be asked to confirm their continuing IC in writing.

Prior to initiation of any study-specific procedures, IC must be obtained from the subject (or legally authorized representative). Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize sites to submit subject information to the study sponsor. The IC process must be conducted by the principal investigator or an authorized designee, and the ICF and data protection authorization, as required by law, must be given to the subject in a language he/she is able to read and understand.

The process of obtaining informed consent shall:

- Ensure that the principal investigator or an authorized designee conducts the IC process.
- Include all aspects of the Attain Stability Quad Clinical Study that are relevant to the subject's decision to participate throughout the clinical study.
- Avoid any coercion or undue improper influence on, or inducement of the subject to participate.
- Not waive or appear to waive the subject's legal rights.
- Ensure the ICF and data protection authorization, as required by law, are given to the subject in a non-technical language the subject is able to read and understand.
- Provide ample time and opportunity for the subject to read and understand the ICF to inquire about details of the study, and to consider participation. All questions about the study should be answered to the satisfaction of the subject.
- Include a personally dated signature of the subject acknowledging that their participation in the study is voluntary.
- Include a personally dated signature by the principal investigator or authorized designee responsible for conducting the IC process, as required by local law.
- Include any other locally required signatories, such as witnesses, as indicated by country-specific legislations.
- Provide the subject with a copy of the ICF, the data protection authorization, as required by law, and any other written information, signed and dated if required by local law.
- Ensure subjects are notified of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study.

If IC is obtained the same day the subject begins participating in study-related procedures, it must be documented that consent was obtained prior to participation in any study-related procedures. It is best practice for the IC process to be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write, witnessed (impartial third party) IC will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the ICF. Informed consent shall be obtained through a supervised oral process. An independent witness must be present throughout the process. The ICF and any other information must be read aloud and explained to the prospective subject, if allowed by local law. The witness signs and personally dates the ICF, attesting that the information was accurately explained and that informed consent was freely given. The subject should "make his mark" (sign or otherwise physically mark the document so as to indicate consent) on the ICF as well. The ICF should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

The original of the signed ICF must be filed in the hospital/clinical chart and/or with the subject's study documents. A second signed original or a copy should be given to the subject for their records (if applicable).

The ICF and data protection authorization, as required by law, must be available for monitoring, auditing and regulatory inspections.

Geography specific ICF Templates will be provided under separate cover.

15.6. Enrollment

The point of enrollment is defined as the time at which a patient has signed and dated the ICF. The date the subject signed (or legally authorized representative) the ICF and data protection authorization, as required by law, must be documented in the subject's medical records. At that point, the patient is considered a subject in the study, a study subject ID number will be assigned, and the subject must be followed for the duration of the study unless the subject exits the study prior to study closure. Each investigational center will be responsible for maintaining subject identification records (e.g. subject identification log) according to ISO 14155.

Enrollment will occur on the same day as the baseline visit. Once IC is obtained, report AEs/deaths, study deviations and subject exits as they occur. To accurately track subject enrollment, Medtronic should be notified of the enrollment as soon as possible after a patient has signed the ICF.

15.7. Baseline

The baseline visit can be a stand-alone visit or can occur on the same day as, but not later than, the implant visit. The following procedures will be completed/data will be collected at the baseline visit:

- Subject Informed Consent
- Inclusion/Exclusion criteria verified
- Subject demographics
- Cardiovascular medications
- Cardiovascular medical history
- NYHA classification
- Kansas City Cardiomyopathy Questionnaire (KCCQ)

Cardiovascular medications include ACE inhibitors, ARBs, antiarrhythmic, anti-coagulants, antithrombotics, and antiplatelet, antihypertensive, antilipidemics (statins), beta blockers, calcium channel blockers, diuretics, digitalis, inotropes, nitrates, digoxin, and vasodilators.

If implant does not occur within 30 days of enrollment, verification of all inclusion and all exclusion criteria must be repeated before an implant attempt.

15.8. Implant/PHD

Information collected at Implant/PHD will include data from the day of the implant procedure until released from the hospital. The implant CRF will be used to collect data at implant. Implantation of the CRT device and right heart leads should be performed according to the Instruction for Use (IFU) in geographies where the devices are commercially available.

Any Medtronic commercially released right atrial (RA) and any Medtronic commercially released right ventricular (RV) lead may be implanted. Existing non-Medtronic RV and/or RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used in enrolled who are receiving an upgrade to

a CRT system. The right-heart leads should be implanted according to the labeling provided with the applicable lead.

The implanted system device must include a Medtronic commercially released CRT device which can be programmed to utilize all electrodes, allowing upgrades from implantable pulse generators (IPGs) and implantable cardioverter defibrillators (ICDs). Device and lead requirements are as follows:

- Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- For de novo CRT implants, any Medtronic commercially released transvenous (active or passive fixation) RA pacing lead (unless medical justification to exclude this lead) and any Medtronic commercially released transvenous (active or passive fixation) RV lead
- For upgrades to a CRT system, existing non-Medtronic RV and/or non-Medtronic RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used in enrolled who are receiving an upgrade to a CRT system
- Medtronic commercially released CRT devices that measure discrete LV electrical values from all four electrodes (i.e. Vector Express)

15.8.1. Final System Configuration

For information on the requirements for the implanted system refer to Section 13. The system is successfully implanted when the Medtronic CRT device is successfully connected to the RA, RV and the LV lead (except if a medical condition such as chronic atrial fibrillation excludes the need for an RA lead). The configuration of the successfully implanted system components will be collected. This will include the serial number of each implanted component (CRT-D or CRT-P device, and leads), and the location of lead placement.

15.8.2. Implant Procedure

Implantation of the CRT device and cardiac leads must be performed by a trained clinical study investigator and according to the manufacturer's instructions for use. It is recommended to use Medtronic catheters that are compatible with the Attain Stability Quad MRI SureScan LV Lead (Model 4798) (e.g., > 7 Fr) during the implant for gaining access to the coronary sinus (CS).

For complete information regarding the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the implant procedure, reference the Clinical Manual in the US and Canada or the Instructions for Intended Use (Technical Manual in EMEA, Hong Kong, and Malaysia). These documents are located under a separate cover.

15.8.2.1. Venogram

An occlusive venogram is required for venous visualization of the subject's coronary vasculature and will be used to pre-determine a desired target pacing location prior to placing the Attain Stability Quad MRI SureScan LV Lead (Model 4798). Once the pre-determined target pacing location is determined, a venous image will be collected. A copy of the venous image will be submitted to Medtronic and kept on file at the center.

15.8.2.2. Implanting the LV lead

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be implanted according to the implant instructions found within the lead packaging. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) can be positioned with the aid of a guide wire (0.36 mm to 0.46 mm or 0.014 inches to 0.018

inches in diameter), stylet, an inner catheter, or an inner catheter plus hybrid guide wire. If a stylet is used for lead positioning, only use the stylets packaged with the lead or in a stylet kit (downsized knob). Always use a stylet that is 3 cm shorter than the lead length listed on the IS4 connector label. Other stylets may extend beyond the lead tip causing injury or perforation of the cardiac vein or heart. If using a Medtronic integrated valve system (e.g. SureValve), rotate the helix counterclockwise to allow safe passage of the helix when inserting the lead into the delivery system to prevent the side helix from inadvertently attaching to the valve. Rust stylets are not recommended with this lead due to the risk of conductor coil/insulation perforation.

Follow the Attain Stability Quad MRI SureScan LV Lead (Model 4798) package insert carefully for fixating the side helix to the vein. Consider using a J-shaped stylet if fixation is unsuccessful. An overview of the key implanting tips includes:

- Rotate the lead counterclockwise when inserting the lead through the SureValve to prevent the helix from attaching to the valve
- Refrain from wedging the lead into the vessel so that the lead can easily rotate during fixation allowing torque to transfer from the proximal end to the distal end of the lead
- To fixate the side helix in the desired location, rotate the lead clockwise with the guidewire inserted in the lead which will provide extra stiffness to the lead
- Ensure the guidewire is removed to allow for lead pliability to visualize and confirm lead fixation during the Push Test and the Pull Test
- To reposition the lead, insert the guidewire and rotate the lead counterclockwise without applying tension to the lead to unfixate

Information on surgical data, such as tool use, and implant times, etc. will be collected during the implant procedure.

In an event that one Attain Stability Quad MRI SureScan LV Lead (Model 4798) is determined to be not suitable for a patient after the initial lead insertion; the implanting physician must assess the onset of any potential AEs. A second Attain Stability Quad MRI SureScan LV Lead (Model 4798) may only be introduced upon confirmation that no system-related AEs resulted from the first Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt. Any LV lead related AE observed during the initial LV lead attempt prohibits an attempt of a second Attain Stability Quad MRI SureScan LV Lead (Model 4798).

If the subject does not have a successful Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant at the conclusion of the initial implant procedure, the subject should be followed until procedure or system related AEs are resolved or are unresolved with no further actions planned, whichever occurs later.

If an attempt to implant the Attain Stability Quad MRI SureScan LV Lead (Model 4798) does not occur, or if the Model 4798 LV lead cannot be implanted, the reasons why the lead was not attempted or attempted but not implanted must be documented on the Implant and Study Exit CRF. See additional definitions below.

No Attain Stability Quad MRI SureScan LV Lead (Model 4798) Attempted (lead not inserted into the body)

An Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt is defined as any time a Model 4798 lead is introduced into the body. Subjects that do not have an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempted will be exited from the study following their implant procedure

unless another Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt is scheduled. Adverse events, device deficiencies and deviations must be documented before the subject is exited.

Attain Stability Quad MRI SureScan LV Lead (Model 4798) Attempted but Not Implanted

An Attain Stability Quad MRI SureScan LV Lead (Model 4798) that is inserted into the body that is not successfully placed will be considered an unsuccessful Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt. Note: An unsuccessful implant itself is not considered an AE. Adverse Events occurring during an unsuccessful implant (e.g. dissection, perforation) will be recorded and classified. Subjects with an unsuccessful Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt will be followed until procedure or system related AEs have been resolved or are deemed unresolvable with no further action planned.

15.8.2.3. CRT System Testing and Programming During Implant

Prior to connecting the leads to the CRT can, initial electrical measurements will be taken using the Analyzer (Model 2290 or market released equivalent) to confirm adequate pacing thresholds (PCTs) prior to closing the pocket per the site's standard testing method. These PCTs will be collected on the same vector, at two timepoints once the lead is fixated and prior to connecting the leads to the can using the Analyzer. The timepoints are as follows;

1.) Prior to slitting the cannulation catheter – Collect the first PCT using the Analyzer after the lead is fixated and the guidewire/stylet has been pulled back proximal to the helix and electrodes.

2.) Post slitting the cannulation catheter – Collect the second PCT using the Anlyzer after the lead is fixated and following slitting of the cannulation catheter.

These PCT measurements will be collected on the CRF. This data will only be collected if an Attain Stability Quad MRI SureScan LV Lead (Model 4798) is successfully placed.

Pacing voltage thresholds are measured to determine whether the underlying myocardium will respond effectively to pacing and to evaluate lead stability in the cardiac vein. It is required to perform LV pacing threshold measurements during implant using the pacing threshold test at a 0.5ms pulse width. It is recommended to begin at 2.5 Volts and decrease amplitude after at least 3 pulses until capture is lost. If there is no capture at 2.5 V; stop the test and repeat at a higher voltage using the 0.5ms pulse width. The lowest amplitude where capture consistently occurs is the pacing threshold value. Collect data using the Analyzer (Model 2290 or market released equivalent).

It is recommended that physicians locate a final LV pacing site that can be captured using less than or equal to 2.5 V at 0.5ms, R-wave sensing of at least 4.0 mV, and does not cause diaphragmatic stimulation at 10V at 0.5ms. For additional details regarding the left ventricular leads and implant tools, refer to the respective technical manuals provided with each product.

Individual patient venous anatomies as well as pathologies present in the left ventricular myocardium are factors that will influence LV lead placement. Therefore, the best cardiac vein lead electrode location to stimulate the LV may vary for each patient.

15.8.2.4. Final Lead Placement Data Collection

Following fixation and once the final position of the lead is determined, collect a venous image of the final placement of the lead. A copy of the venous image will be submitted to Medtronic and kept on file at the center.

15.8.2.5. Pre-Hospital Discharge CRT System Testing and Programming

The following electrical testing will be performed using the implanted CRT-P or CRT-D device and the device programmer once the leads are connected to the CRT-P or CRT-D and pre-hospital discharge:

Lead Impedance

- Collect LV Lead Impedances using Vector Express on all vectors
- Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Phrenic Nerve Stimulation (PNS)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

Other data collected prior to hospital discharge following the implant includes;

- Rationale for selecting specific LV lead pacing vector for final programming
- Final device interrogation/save-to-media
- AE Assessment
- Study deviations
- Device deficiencies

15.9. 3 Months Post-Implant (remote or in office visit)

The 3 month scheduled follow-ups may be done remotely or inoffice. For remote visits, CareLink transmissions may substitute device interrogations. The following procedures will be completed and data will be collected at the 3 month Follow-up visit;

Lead Impedance

- Obtain LV Lead Impedance Test for the final programmed vector
- Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Obtain PCTs at 0.5ms pulse width on the final programmed vector
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Retain printouts at the site

Phrenic Nerve Stimulation (PNS) (in office visit only)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

- NYHA classification
- Final device interrogation/save-to-media (or CareLink transmission)
- AE Assessment
- Study deviations
- Device deficiencies

15.10. 6 Months Post-Implant (in office visit)

The following procedures will be completed and data will be collected during the 6 months in office Follow-up visit.

Lead Impedance

- Collect LV Lead Impedances using Vector Express on all vectors
- Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Phrenic Nerve Stimulation (PNS)

- Test for presence of PNS at 8.0V at 0.5ms on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can
- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If at any tested vector PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

- NYHA classification
- Patient Global Assessment
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Rationale for selecting specific LV lead pacing vector for final programming
- Final device interrogation/save-to-media
- AE Assessment
- Study deviations
- Device deficiencies

15.11. 12 Months Post-Implant (in office visit)

The following procedures will be completed and data will be collected during the 12 month in office Follow-up visit.

Lead Impedance

- Collect LV Lead Impedances using Vector Express on all vectors
- Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Phrenic Nerve Stimulation (PNS)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

- NYHA classification
- Patient Global Assessment
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Rationale for selecting specific LV lead pacing vector for final programming
- Final device interrogation/save-to-media
- AE Assessment
- Study deviations
- Device deficiencies

15.12. Recurring 6 Month Follow-ups (remote or inoffice visit)

After the 12 Month Follow-Up visit, subjects will be seen every 6 months. These scheduled follow-ups are considered "Recurring 6 month follow-up visits". These scheduled follow-ups may be done remotely or inoffice. For remote visits, CareLink transmissions may substitute device interrogations. The following procedures will be completed during these visits:

Lead Impedance

- Obtain LV Lead Impedance Test for the final programmed vector
- Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Obtain PCTs at 0.5ms pulse width on the final programmed vector
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Retain printouts at the site

Other Data Collection

- NYHA classification
- Final device interrogation/save-to-media (or CareLink transmission)
- AE Assessment
- Study deviations
- Device deficiencies

15.13. Device Interrogation/Save-to-Media

For the implant and follow-up visits, a final "Interrogate All" device interrogation file (.pdd) must be obtained and saved in a digital format (Save-to-Media). Store one copy of the save-to-media at the site and send a copy to Medtronic. Do not clear device data.

A device interrogation (final "Interrogate All") and Save-to-Media should also be completed at the time of study exit (prior to 6 month visit), a system modification (initial and final "Interrogate All"), and in the case of a death (where possible).

15.14. System Modifications

A system modification will be reported in the event the device and/or leads require invasive modification (e.g. generator or lead explant, generator or lead replacement, lead repositioning, etc.). In the event of a system modification, regardless of outcome of the modification, subjects should remain in the study

when possible and the follow-up visit schedule for the subject will remain unchanged. For a system modification the following information/activities are required to be collected:

- Modification or replace/explant date
- Reason for modification
- Information on device or lead modified
- Information on any replacement device(s)
- Final device interrogation/save-to-media
- Study deviations
- AEs and device deficiencies (as applicable)

It is recommended that all explanted Medtronic products (device, leads, etc.) are returned to Medtronic for analysis per local process and when permissible by local laws and regulations.

In the event that subject has a re-attempt after a previous unsuccessful system modification, the subsequent attempt(s) must be reported via CRF as separate system modifications.

Attain Stability Quad MRI SureScan LV Lead (Model 4798) repositioned or replaced with another Attain Stability Quad MRI SureScan LV Lead (Model 4798)

If the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is repositioned or replaced, the following LV lead electrical tests and data collection must be completed:

Lead Impedance

- Obtain LV Lead Impedance Test for the final programmed vector
- Perform a manual test for a missing value
- NOTE: Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Obtain a PCT at 0.5ms pulse width using Vector Express on the final programmed vector
- Perform a manual test for a missing value
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- NOTE: Retain printouts at the site

Phrenic Nerve Stimulation (PNS)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

- Record the reason why the final configuration was selected for final programming
- Record any programming changes to the LV lead apart from the LV lead pacing vector since the last visit and provide rationale for the change(s)

Attain Stability Quad MRI SureScan LV Lead (Model 4798) capped or explanted without replacement with another Attain Stability Quad MRI SureScan LV Lead (Model 4798)

If the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is capped or explanted without replacement while the subject is in the study, subjects will continue to be followed per their original follow-up schedule for safety monitoring until study closure. LV lead electrical testing and interrogation files will not be required at follow-ups for subjects without the full protocol required system implanted.

Explant of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the Medtronic CRT-P or CRT-D device without replacement with another Attain Stability Quad MRI SureScan LV Lead (Model 4798) and Medtronic CRT-P or CRT-D device

Subjects who have their Attain Stability Quad MRI SureScan LV Lead (Model 4798) and Medtronic CRT-P or CRT-D device explanted without replacement during a system modification procedure should be exited from the study as soon as all system related and/or system modification procedure related AEs are resolved. If no system or procedure related AEs are present at the conclusion of such a system modification procedure, the subject should be exited immediately.

Medtronic CRT-P or CRT-D device explanted without replacement, Attain Stability Quad MRI SureScan LV Lead (Model 4798) remains implanted

If the Medtronic CRT-P or CRT-D device is explanted and a replacement device will be implanted, all attempts should be made to replace with another Medtronic CRT-P or CRT-D device. In the event that an explanted Medtronic CRT-P or CRT-D device cannot be replaced with a new Medtronic CRT-P or CRT-D device, subjects who still have an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted will continued to be followed for safety monitoring in person per their original follow-up schedule until study closure. Events related to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) should be reported. Left ventricular lead electrical testing will not be required at follow-ups for subjects without the full protocol required system implanted. In an event that a second Attain Stability Quad MRI SureScan LV Lead (Model 4798) was implanted as a result of an Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complication, the subject will be followed for safety, however the second implanted Attain Stability Quad MRI SureScan LV Lead (Model 4798) will not be included for the analyses of study objectives except reportable system related adverse events.

15.15. Study Exit

Study Exit is defined as the moment when a subject officially stops participating in the study. Date and reason for subject exit must be reported to Medtronic at the earliest opportunity.

Subjects will be exited from the study for any of the following situations:

- Study completed
- Subject lost to follow-up
- Subject did not meet eligibility criteria and was not yet implanted with an Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- Subject did not have a successful implant and no attempt at re-implant is made
- Subject did not provide consent or data protection authorization, as required by law
- Subject chooses to exit (i.e. revokes consent)
- Investigator withdraws subject

Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing system- and procedure-related AEs are resolved, unresolved with no further actions planned, or 30 days post the 6 month visit, whichever occurs first. Following exit, subjects will continue to receive standard medical care. There will be no further required study-related follow-up visits for these subjects. All data through the time of the subject's exit will be available for data analyses.

If possible, the following procedures should be performed / data collected at the exit visit:

- Report the reason for exit
- Final interrogation file (or CareLink transmission) for exits occurring prior to the 6 month visit
- Study deviations
- AEs and device deficiencies (as applicable)

After subjects are exited from the study they should receive standard medical care and should be managed and followed per physician discretion.

15.15.1. Study Completed

All subjects will be followed until FDA Pre-Market Approval (PMA) of the Attain Stability Quad MRI SureScan LV Lead (Model 4798). Medtronic will notify sites when the study is complete. Upon exiting subjects, if the current follow-up visit and exit visit are combined, then both the follow-up CRF and a Study Exit CRF need to be completed but only one device interrogation/save-to-media needs to be completed and collected. If AEs are unresolved at time of exit, it should be noted on the AE CRF that the AE is unresolved at time of study exit.

15.15.2. Lost to Follow-up

In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be recorded. In addition, follow the regulations set forth by the governing IRB or EC.

15.15.3. Study Exit Upon Sponsor Request

A subject must be exited from the study if the sponsor suspends study enrollment and a subject has signed the ICF but no implant attempt of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) has occurred (see Section 15.8.2.2).

15.16. Subject Withdrawal or Discontinuation

15.16.1. Subject Chooses to Exit (i.e. revokes consent)

A subject can withdraw from the study at any time. If the subject wishes to exit from the study (i.e. the subject revokes consent), the site is required to document the reason for exit on the Exit CRF. In addition, study sites shall follow the regulations set forth by the governing Ethics Committee. For countries following ISO 14155, permission may be requested to follow up with the patient outside of the study due to withdrawal based on problems related to the investigational feature safety or performance. If possible, the following data should be collected prior to subject withdrawal:

- Report the reason for subject withdrawal
- Final device interrogation/save-to-media
- Study deviations
- AEs and device deficiencies (as applicable)

15.16.2. Investigator Withdraws Subject

No subjects should be withdrawn by investigators unless compelling medical justification is present. It is recommended investigators discuss any withdrawals with the study sponsor prior to exiting subjects. If

an Investigator withdrawal is necessary, the following data should be collected prior to subject withdrawal if possible:

- Report the reason for subject withdrawal
- Final device interrogation/save-to-media
- Study deviations
- AEs and device deficiencies (as applicable)

The following are reasons for investigator-initiated subject withdrawal;

Medical Necessity

A subject may be exited from the study if an investigator feels it is necessary to withdraw the subject from the study due to a medical condition or other reason. In such cases, the subject will be notified and provided an explanation regarding the reasons for the study exit.

Explant of Medtronic CRT-P or CRT-D Device and Attain Stability Quad MRI SureScan LV Lead (Model 4798)

Subjects in which the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the Medtronic CRT-P or CRT-D device are explanted without replacement (i.e., subject no longer has a Medtronic CRT-P or CRT-D device and an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted) shall be exited from the study (refer to Section 15.8.2.2). Subjects exposed to an Attain Stability Quad MRI SureScan LV Lead (Model 4798) through a lead attempt must be followed through at least one month or until all implant related AEs (system-, and/or procedure-related) have resolved or are unresolved with no further actions planned. Subjects who have either an Attain Stability Quad MRI SureScan LV Lead (Model 4798) (active or not active) or a Medtronic CRT-P or CRT-D device implanted will continued to be followed for safety until study completion.

Attain Stability Quad MRI SureScan LV Lead (Model 4798) Not Implanted

Subjects that are not anticipated to have an implant attempt (e.g. do not meet inclusion/exclusion criteria) must be exited from the study. Subjects that have a CRT system implant attempt, but who do not have an Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempted (See Section 15.8.2.2 for definition) will be exited from the study following their procedure unless an Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt is scheduled. If this attempt is more than 30 days from the baseline assessment, verification of the baseline data must be completed prior to a subsequent implant attempt.

Subjects with an unsuccessful Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt will be followed at pre hospital discharge and one month unless there are ongoing implant related AEs (system- and/or procedure related), in which case they will be followed beyond one month until the implant related (i.e., system-, and/or procedure related) AEs have been resolved or are considered unresolved with no further actions planned. The subjects may be followed via a clinic visit or by phone contact. In geographies where the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is market-released, subjects will be exited from the study after the assessment of implant procedure or CRT system related AEs if the initial attempt of one Attain Stability Quad MRI SureScan LV Lead (Model 4798) model was unsuccessful. The subject may undergo implant attempts with any market released LV lead that provides the best benefit to the patient, but data collection on these subsequent attempts will not be required as these subjects will be considered exited from the study.

15.17. Assessment of Efficacy

The primary efficacy objective is based on the pacing capture threshold data collected as discussed in Section 19.1.

15.18. Assessment of Safety

The primary safety objective is based on the Adverse Event data collected. Further information on the collection of Adverse Events is discussed in Section 17.1.1.

15.19. Recording Data

The study will collect data using Oracle Clinical, an electronic data management system for clinical studies. Sites will enter data onto CRFs within the Oracle Clinical database.

Data reported on the CRFs shall be derived from source documents, which may include worksheets, patient medical records, programmer printouts and device interrogation/save-to-media files. These source documents must be created and maintained by the investigational site team. Further detail on data management is provided in Section 21.2.

15.20. Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan or the Clinical Trial Agreement.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. In all geographies, prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported to Medtronic regardless of whether they are medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The deviation must be recorded in Oracle Clinical with an explanation for the deviations. In the occurrence of a corrupted device interrogation/save-to-media file, Medtronic will request a deviation to document that a readable device interrogation/save-to-media file is unavailable.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB/EC as well as Medtronic as soon as possible but no later than five (5) working days, or according to local requirements. Reporting of all other study deviations should comply with IRB/EC policies and/or local laws and deviations must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, and terminate the study). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic may provide site-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

16. Risks and Benefits

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of the product, from the research and development phase through the study phase and market release. The risk analysis process for the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is being performed in accordance with ISO 14971, and will ensure that the level of risk has been reduced as low as possible and is acceptable prior to starting the Attain Stability Quad Clinical Study.

Potential Risks

Standard risks associated with the medical device used in this study, an analysis of Adverse Device Effects and a history of modification or recall of device under investigation or equivalent devices are listed in the Instruction for Use Manual or Clinical Manual.

The potential adverse events (listed in alphabetical order) related to the use of transvenous leads inlcude, but are not limited to, the following conditions:

- Air embolism
- Avulsion or other damage to the endocardium, valve, or vein (particularly in fragile hearts)
- Cardiac dissection or perforation
- Cardiac tamponade
- Coronary sinus dissection
- Death
- Endocarditis or pericarditis
- Erosion through the skin
- Extracardiac muscle or nerve stimulation
- Fibrillation or other arrhythmias
- Heart Block
- Heart wall or vein wall rupture
- Hematoma/seroma
- Infection
- Lead conductor fracture or insulation failure
- Lead dislodgement
- Myocardial irritability
- Myopotential sensing
- Pericardial effusion or rub
- Pneumothorax
- Rejection phenomena (local tissue reaction, fibrotic tissue formation)
- Threshold elevation or exit block
- Thrombosis
- Thrombotic embolism

Additional potential adverse events related to the lead and the programmed paramenters include, but are not limited to, the following:

Table 10: Additional adverse events related to the lead and programmed parameters

Potential adverse event	Indicator of potential adverse event	Corrective actions to consider
Lead dislodgement[i]	Intermittent or continuous loss of capture or LV EGM signal integrity (including sensing)[i]	Reprogram the LV pacing polarity. Reposition the lead.
Lead dislodgement[i]	Intermittent or continuous oversensing	Reprogram the LV pacing polarity. Reposition the lead.
Lead conductor fracture	Intermittent or continuous loss of capture or LV EGM signal integrity (including sensing)[i]	Replace the lead. Reprogram the LV pacing polarity.
Lead conductor insulation failure	Intermittent or continuous loss of capture or LV EGM signal integrity (including sensing)[i]	Replace the lead. Reprogram the LV pacing polarity.
Threshold elevation or exit block	Loss of capture[i]	Adjust the implantable device output. Reprogram the LV pacing polarity. Replace or reposition the lead.

[I] Transient loss of capture or LV EGM signal integrity (including sensing) may occur following surgery until lead stabilization takes place. If stabilization does not occur, lead dislodgement may be suspected.

Implant techniques that may damage the lead include, but are not limited to, the following techniques:

Table 11: Implant Techniques that may damage the lead

Implant techniques that may damage the lead	Possible effects on the lead	Corrective action to consider
Forcing the lead through the introducer/delivery system	Electrode, conductor coil, or insulation damage	Replace the lead.
Use of too medial of an approach with venous introducer resulting in clavicle and first rib binding	Conductor coil fracture, insulation damage	Replace the lead.
Using too stiff a stylet	Conductor coil/insulation perforation	Replace the lead.
Puncturing the periosteum or tendon when using subclavian introducer approach resulting in binding	Conductor coil fracture, insulation damage	Replace the lead.
Advancing the lead through the non-coronary central access veins without the stylet or guide wire fully inserted	Tip distortion or insulation perforation	Replace the lead.
Inserting the proximal end of the guide wire through the lead tip seal without using the guide wire insertion tool	Lead tip seal damage or conductor coil/insulation damage	Replace the lead.

Subjects who are pregnant may be at increased risk (e.g., radiation exposure, and other unforeseen risk to the fetus), and are excluded from participation in the study. If a subject becomes pregnant during the study, she must notify the physician immediately. The subject will remain in the study for intention to treat analysis, but the investigator will avoid any procedures that may be determined harmful.

There may be other discomforts and risks related to the CRT-P or CRT-D device, the Attain Stability Quad MRI SureScan LV Lead (Model 4798), and/or this study that are not foreseen at this time. Interactions with concomitant medical treatment are not expected.

The adverse event collection requirements in this study will ensure that risks associated with the study device and the Attain Stability Quad MRI SureScan LV Lead (Model 4798) are adequately monitored.

16.2. Risk Minimization

Medtronic has minimized the risks to the subject by the following:

- Performing required laboratory and pre-clinical testing prior to the Attain Stability Quad Clinical Study; this information is available under separate cover in the RPI with the FDA IDE submission and the CER with the CE-Mark
- Implementing quality control measures into development and production processes
- Providing guidelines for subject selection and evaluation, and subject inclusion and exclusion criteria
- Providing adequate instructions via the Attain Stability Quad MRI SureScan LV Lead (Model 4798) User Manual, training, and labeling

- Selecting implanters that have demonstrated previous experience with implanting CRT-P or CRT-D devices and specifically LV leads
- Selecting investigators that have demonstrated previous experience with the programming, interrogating, and monitoring of CRT-P or CRT-D devices
- After enrollment in the Attain Stability Quad Clinical Study, at each protocol required follow-up, the investigator must interrogate the study device to verify appropriate study device function and to evaluate the subject's health and assess for any AEs

16.3. Potential Benefits

The potential benefits of having the Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted are similar to other LV leads currently available to the public. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is expected to increase lead stability and reduce the need for patients to undergo an additional procedure to replace a dislodged/displaced lead. Due to the active fixation helix, it may be possible to place the lead in veins of various sizes. There is a possibility that the Attain Stability Quad MRI SureScan LV Lead (Model 4798) may offer no additional benefit over similar LV leads. The information gained from this study could result in the improved management of other CRT patients.

16.4. Risk-Benefit Rationale

The risk-benefit analysis has shown that there are no major additional risks associated with the Attain Stability Quad MRI SureScan LV Lead (Model 4798), other than those associated with the implant, while benefits to the patient are possible. Any residual risk associated with this study is considered low and acceptable.

17. Adverse Event Assessments

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Medtronic has established procedures in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information. This study is conducted in accordance with these procedures and regulations.

Data collected in this study may be used in support of global regulatory approvals. Since the safety reporting requirements and classification systems vary for each regulatory agency, requirements from all geographies are taken into account for the collection and reporting of safety information. Adverse Events and Device Deficiencies will be reported in all geographies.

17.1. Adverse Event and Device Deficiency Assessment

17.1.1. Adverse Events

Adverse Event definitions are provided in Table 12. The following AEs will be collected throughout the study duration, starting at the time the informed consent form is signed:

- All procedure related AEs
- All system related AEs
- All accessory related AEs
- All cardiovascular related AEs
- All Serious Adverse Events (SAEs), regardless of relatedness

Reporting of these events to Medtronic will occur on an AE Form, including date of AE, treatment, resolution, assessment of both the seriousness of the AE and the relatedness to the investigational device or procedure. Each AE must be recorded on a separate AE eCRF. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. In addition, AEs impacting users or other persons, Non-subject Adverse Events, (reportable per ISO 14155) will be collected.

In all geographies, Unavoidable AEs, listed in Table 12, need not be reported unless the AE worsens or is present outside the stated timeframe post-implant.

For AEs that require immediate reporting (see Table 14), initial reporting may be done by contacting the study sponsor per the sponsor contact information. The original completed AE CRF must be submitted to Medtronic as soon as possible.

Any medication, whether cardiovascular or not, associated with the treatment of an AE must be reported. Medication changes that are not related to adverse events will not be collected.

Subject deaths are also required to be reported. Refer to Section 17.4 for Subject Death collection and reporting requirements.

17.1.2. Device Deficiencies

Device deficiency (DD) information will be collected throughout the study and reported to Medtronic. Note that DDs that result in an Adverse Device Effect (ADE) to the subject should be captured as an AE only. Device Deficiencies that did not lead to an AE but could have led to a Serious Adverse Device Effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting (see Table 14). For DDs that require immediate reporting, initial reporting may be done by contacting the study sponsor per the sponsor contact information.

17.1.3. Event Updates and Resolution

For any changes in status of a previously reported AE (i.e. change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE form. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject dies or exits the study, or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to their 6 month visit, all efforts should be made to continue following the subject until all unresolved system or procedure related adverse events, as classified by the investigator, are resolved or unresolved with no further actions planned.

At the time of study exit, all collected AEs with an outcome of ”Unresolved” must be reviewed and an update to the original AE must be reported. At a minimum, if there are no changes to the description, relatedness, test and procedures or actions taken, the outcome must be updated to reflect “Unresolved at time of study exit”.

17.2. Definitions/Classifications

Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system, and includes but is not restricted to: the CRT-P or CRT-D device, the RA, RV or LV leads, the programmer, and implant tools.

Table 12: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. (ISO 14155:2011, 3.2)
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. (ISO 14155:2011, 3.1)
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors and inadequate labeling (ISO 14155:2011, 3.15)
Relatedness	
Procedure Related	An Adverse Event that is directly related to the implantation or surgical modification of the system. NOTE: In general, this excludes events that are inherent to any surgical procedure (e.g. anesthesia complications) as well as indirect subsequent consequences of the procedure (e.g. reaction to pain medication).

System Related (includes all implantable components and features, associated introduction tools, operational and installed software and programmers as defined in the Clinical Investigation Plan)	An adverse event that results from the presence or performance of any component of the system. Device-related: An adverse event that results from the presence or performance (intended or otherwise) of the device. RA lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the RA lead. RV lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the RV lead. LV lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the LV lead. a) LV Lead Fixation-related: An adverse event that results from the presence or performance of the side-helix.
Accessory Related	Programmer Related: An adverse event that results from the presence or performance (intended or otherwise) of the programmer Implant tool-related: An adverse event that results from the presence or performance (intended or otherwise) of the implant tool.
Cardiovascular Related	An Adverse Event relating to the heart and the blood vessels or the circulation (e.g. Atrial Fibrillation, Myocardial Infarction, stroke, perivascular disease)
Heart Failure Related	An adverse event related to worsening heart failure signs and symptoms such as hypervolemic and hypovolemic status requiring the administration, alteration, adjustment or augmentation of HF therapy (diuretics, inotropes and/or vasodilators etc.) or the utilization of ultrafiltration devices.
MRI Related	An adverse event which is caused by the interaction between the pacing system and the MRI system that occurs during the MRI procedure and up through the one-month post-MRI/waiting period follow-up visit.

Not Related	Relationship to the device or procedures can be excluded when: ▪ The event is not a known side effect of the product category the device belongs to or of similar devices and procedures; ▪ The event has no temporal relationship with the use of the device or the procedures; ▪ The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; ▪ The discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure) do not impact the serious event; ▪ The event involves a body-site or an organ not expected to be affected by the device or procedure; ▪ The serious event can be attributed to another cause (e.g., an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors); ▪ The event does not depend on a false result given by the device used for diagnosis (when applicable); ▪ Harms to the subject are not clearly due to use error; ▪ In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The event is associated with the device or study procedures beyond reasonable doubt when: ▪ The event is a known side effect of the product category the device belongs to or of similar devices and procedures; ▪ The event has a temporal relationship with device use/application or procedures; ▪ The event involves a body-site or organ that the device or procedures are applied to or the device or procedures have an effect on; ▪ The serious event follows a known response pattern to the medical device (if the response pattern is previously known); ▪ The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure) impact on the serious event (when clinically feasible); ▪ Other possible causes (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug, or treatment) have been adequately ruled out; ▪ Harm to the subject is due to error in use; ▪ The event depends on a false result given by the device used for diagnosis (when applicable); ▪ In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Seriousness	
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. (ISO 14155:2011, 3.37)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011, 3.36)
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. (ISO 14155:2011, 3.42)

Complication	An adverse event that includes the following is considered a complication: • Results in death, • Involves any termination of significant device function, or • Requires an invasive intervention Non-invasive (21 CFR 812.3 (k)): when applied to a diagnostic device or procedure, means one that does not by design or intention: Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os *Note* (FDA): Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive. *** Only system or procedure related AEs will be classified as complication or observation
Observation	Any Adverse Event that is not a complication. *** Only system or procedure related AEs will be classified as complication or observation

<table>
<tr><th colspan="2">Other</th></tr>
<tr><td>Unavoidable Adverse Event</td><td>An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator's opinion, including, but not limited to:
<table>
<tr><th>Event Description</th><th>Timeframe (hours) from the Surgical Procedure</th></tr>
<tr><td>Anesthesia related nausea / vomiting</td><td>24</td></tr>
<tr><td>Low-grade fever (<100°F or 37.8°C)</td><td>48</td></tr>
<tr><td>Pocket site / Incisional pain</td><td>72</td></tr>
<tr><td>Mild to moderate bruising / ecchymosis</td><td>168</td></tr>
<tr><td>Sleep problems (insomnia)</td><td>72</td></tr>
<tr><td>Back pain related to laying on table</td><td>72</td></tr>
<tr><td>Shoulder pain/discomfort/stiffness related to shoulder immobilization during procedure</td><td>72</td></tr>
</table></td></tr>
</table>

17.3. Reporting of Adverse Events

17.3.1. Adverse Events and Device Deficiency Classification

All reported AEs and DDs will be reviewed by a Medtronic representative. Adverse Events will be classified according to the definitions provided.

Upon receipt of AEs at Medtronic, a Medtronic representative will review the AE/DD for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize the Medical Dictionary for Regulatory Activities (MedDRA), to assign a MedDRA term for each AE based on the information provided by the investigator.

Regulatory reporting of AEs and DDs that could have led to an SADE will be completed according to local regulatory requirements. Refer to Table 14 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the investigator to abide by any additional AE reporting requirements stipulated by the IRB/EC responsible for oversight of the study.

APPENDIX 1 contains the Foreseeable Adverse Event List (FAL), which is a list of adverse events related to the system or procedure that have been observed in previous studies and may be experienced by subjects. This list may help to assess if an AE is unanticipated in nature.

For emergency contact regarding a UADE, SAE and/or SADE, contact a Attain Stability Quad Clinical Study representative immediately (refer to the study contact list provided in the site's study documents binder/investigator site file or refer to the Sponsor Contact Information section provided in the CIP).

Adverse Events and Deaths will be classified according to the standard definitions as outlined below:

Table 13: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Device, RA Lead, RV Lead, LV Lead, Implant Tool(s), Programmer, Procedure, Cardiovascular, Heart Failure, MRI
	Sponsor	Device, RA Lead, RV Lead, LV Lead, Implant Tool(s), Programmer, Procedure
Seriousness	Investigator	SAE
	Sponsor	SAE, UADE/USADE, Device Deficiency with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

An independent Clinical Events Committee (CEC) will review and adjudicate, at a minimum, all events classified by the investigator or Medtronic as procedure or system related to determine relatedness and complication or observation classifications. In addition, the CEC will also review and adjudicate all Adverse Events resulting in death.

17.3.2. Adverse Events and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and device deficiencies will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator to abide by the adverse event reporting requirements stipulated by local law and the site's IRB/EC.

Table 14: Reporting Requirements

Serious Adverse Events (SAEs)	
Investigator submit to:	
Medtronic	**Canada:** Investigators are required to report SAEs to the sponsor immediately except for those SAEs that the protocol or other document (e.g. Investigator's Brochure (IB)) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. Medical Devices Regulations, sections 59-61. *A guidance for "immediately" is within 72 hours of the investigator becoming aware of the event; Report to sponsor, without unjustified delay ISO 14155:2011, sec 9.8.b).* **EMEA:** Immediately after the investigator first learns of the event or new information in relation with an already reported event. **All geographies:** Report to the sponsor, without unjustified delay, all serious adverse events.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.

Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Adverse Device Effects (ADEs),	
Investigator submit to:	
Medtronic	**EMEA:** Immediately after the investigator first learns of the event or new information in relation with an already reported event. **All geographies:** Submit in a timely manner after the investigator first learns of the effect.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Serious Adverse Device Effects (SADEs), Unanticipated Adverse Device Effects (UADEs), Unanticipated Serious Adverse Device Effects (USADEs),	
Investigator submit to:	
Medtronic	**US:** Submit as soon as possible, but no later than within 10 working days after the investigator first learns of the event. (21 CFR 812.150(a)(1)) **Canada:** SADEs on the patient, the user or any other person must be reported to the Sponsor within 72 hours after it comes to the attention of the qualified investigator. It is recommended for the investigator to report safety events as soon as possible but no longer than 15 calendar days." **All geographies:** Immediately after the investigator learns of the event or of new information in relation to an already reported event.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement
Ethics Committee	**All geographies:** Submit to Ethics Committees per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Investigators	**All geographies:** Submit per local reporting requirement.

All other reportable Adverse Events	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the event.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Device Deficiencies with SADE potential	
Investigator submit to:	
Medtronic	**Canada:** DDs that have resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person or could do so were it to reoccur must be reported to the Sponsor within 72 hours after it comes to the attention of the qualified investigator **EMEA:** Immediately after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency. **All other geographies:** Submit or report as required per local reporting requirements.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the deficiency.
Regulatory authorities	**Canada:** any DD that: a. has resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person; These must be reported by Medtronic to the Regulator within 10 days from the date Medtronic becomes aware. or b. could do so were it to reoccur. These must be reported by Medtronic to the Regulator within 30 days from the date Medtronic becomes aware. **All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.

17.4. Subject Death

17.4.1. Death Data Collection

All subject deaths must be reported by the investigator to Medtronic on an AE form (AE with outcome of death) as soon as possible after the investigator first learns of the death. In case of death, there should be one SAE with the outcome of death reported.

In the event of a subject's death, it is recommended that the implanted system be explanted and returned to Medtronic for analysis whenever possible per local process. Local laws and procedures must be followed where applicable.

System Interrogation Data Recommendations:

- After the subject has died but prior to explant, it is strongly recommended that the system be interrogated and a full summary interrogation (Interrogate All) performed when possible, and saved in a digital format (Save-to-Media). Store one copy of the save-to-media at the site and send a copy to Medtronic.
- Make the device interrogation/save-to-media file before any programming to prevent overwriting information in the device's memory and/or distinguishing between events detected during versus before the explant procedure.
- Recommend obtaining the exact date and time of death as lower temperatures after death can cause ERI and other "event flags" to be stored in the device memory.

If the system is not interrogated, an explanation must be entered on the AE form. For ICD systems, the ventricular tachycardia (VT) and ventricular fibrillation (VF) detection capabilities must be disabled to avoid inadvertent shocks. If any system component is returned to Medtronic, internal return product reporting systems may be used to gather additional information about the returned device/component.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic Attain Stability Quad Clinical Study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records should be sent to the Medtronic Attain Stability Quad Clinical Study team, if available. If an autopsy is conducted, the autopsy report should also be sent to the Medtronic Attain Stability Quad Clinical Study team if available and allowed by state/local law. When the death occurs at a remote site, it is the investigative site's responsibility to attempt retrieval of information about the death. Additionally, device disposition information should be updated. In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to system and/or procedure
- Device interrogation and Save-to-Media (if available)
- Device disposition information
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and allowed by state/local law)

17.4.2. Death Classification and Reporting

Sufficient information will be required in order to properly classify the subject's death. The Investigator shall classify each subject death per the following definitions:

Cardiac Death: A death directly related to the electrical or mechanical dysfunction of the heart.

Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be determined, SCD will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.

Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.

Non-cardiac Death: A death not classified as a cardiac death.

Unknown Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

Table 15: Subject Death Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-cardiac, Unknown

The Clinical Events Committee will review all deaths and provide a final adjudication of the death classification.

Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements.

17.5. Product Complaint Reporting

Product complaint reporting and vigilance reporting are applicable and AEs related to any market-released device during the study must be reported. The reporting of product complaints is not part of the Attain Stability Quad Clinical Study and should be done in addition to the AE reporting requirements. Refer to local regulations for reporting requirements.

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

- Abuse: Abnormal use (definition acc. #4.1 of Meddev 2.12-1 rev8)
- Misuse: Use error (definition acc. #4.20 of Meddev 2.12-1 rev8)

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the regulatory authorities (e.g. Competent Authority) as applicable for the following incidents immediately upon learning of them:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
    - Life-threatening illness or injury
    - Permanent impairment of a body function or permanent damage to a body structure
    - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

18. Data Review Committees

18.1. Clinical Events Committee

The study will utilize a Clinical Events Committee (CEC). At regular intervals, an independent CEC will review events and adjudicate at a minimum all system, and procedure-related events. Additionally, the CEC will provide an adjudication of the death classification for all reported deaths.

The CEC will consist of a minimum of three (3) non-Medtronic-employed physicians that are not participating investigators for the study, including a CEC chairperson.

Medtronic personnel may facilitate and participate in CEC meetings but will be non-voting members.

For AEs and deaths reviewed by the CEC, Medtronic will provide the CEC with the Investigator's description and classification and supportive documentation (when available). The CEC is responsible for reviewing the Investigator's assessment and supportive documentation (when available), reviewing applicable definitions, and determining final classifications for all adjudication parameters. For AEs, classification includes system/procedure relatedness and complication or observation. Additionally, the CEC will provide an adjudication for all reported deaths, including system/procedure relatedness and cardiac relatedness.

If the CEC disagrees with the investigator's classification of the event, the difference will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the CRF documenting the AE will be updated accordingly.

If the investigator does not agree with the CEC's adjudication classification, both determinations will be provided within the final report; however the CEC's adjudication will be used for data analysis. The disagreement will also be included in reporting to ethics committees and regulatory authorities, if required.

18.2. Data Monitoring Committee

A Data Monitoring Committee (DMC) will not be utilized for this study considering:

- An independent CEC will be formed to adjudicate at minimum all system and procedure related events and all deaths.
- This study does not meet FDA's recommended criteria (Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees) for when a study should use a DMC, primarily because the study is not evaluating the effectiveness of a treatment intended to prolong life or reduce the risk of a major adverse health outcome.
- As a result of risk analysis and mitigation efforts as outlined in Section 16, any residual risk associated with this study is considered low and acceptable.
- The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is a modification of the currently market approved Attain Performa lead Models 4298, 4398, and 4598 is a modification of the currently market approved Model 4396 LV lead. The Attain Stability Quad lead Model 4798 has a similar electrode spacing as the Attain Performa lead Models 4298, 4398, and 4598.
- Study will be conducted under FDA oversight via an investigational device exemption (IDE).

19. Statistical Design and Methods

This section presents statistical considerations for the study design and provides a high-level description of planned analysis and reporting. More details will be given in a separate Statistical Analysis Plan (SAP) that will be completed before data freeze for the primary objective analysis. Any deviation to the pre-specified statistical analyses will be noted in the study report. The analysis of the study objectives will be completed when the sample size requirements (see Table 18) for all the study primary and secondary objectives are met. An interim analysis will be conducted when 360 subjects are enrolled in the study. This interim analysis is specifically designed for one of the secondary objectives (details in Section 19.2.2).

19.1. Primary Objectives

19.1.1. Primary Safety Objective

Objective

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered safe if the probability of subjects free of Model 4798 lead-related complications at 6 months post-implant is greater than 87% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 87%).

Hypothesis:
H_0: $S_{(6\text{-month})} \leq 87\%$
H_1: $S_{(6\text{-month})} > 87\%$

where $S_{6\text{-month}}$ is the probability that a subject remains free from Model 4798 lead related complications through 6 months since implant.

Endpoint Justification

The study primary safety endpoint is Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complications. All reported system and procedure-related AEs will be reviewed by an event review committee for LV lead relatedness and severity (see Section 18.1).

Utilizing lead related complication free survival probability to evaluate lead safety performance is widely accepted across cardiac device manufacturers and in the medical literature. Current already market-released Quadripolar LV lead 6-month safety performance is summarized in Table 16. The population performance of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is expected to be similar to the Medtronic Attain Performa Model 4298 lead.

Table 16: Safety Performance of Market Released Quadripolar Lead

	Medtronic Attain Performa	St. Jude Medical Quartet[22]	Boston Scientific ACUITY X4[23]
6-month LV Lead Complication Free Survival Probability Estimate	Model 4298 (Canted): 96.0% Model 4398 (Straight): 98.8% Model 4598 (S-shape): 96.2%	96% at 3 months	Straight: 96.5% Spiral: 98.5%

Statistical Analysis Methods

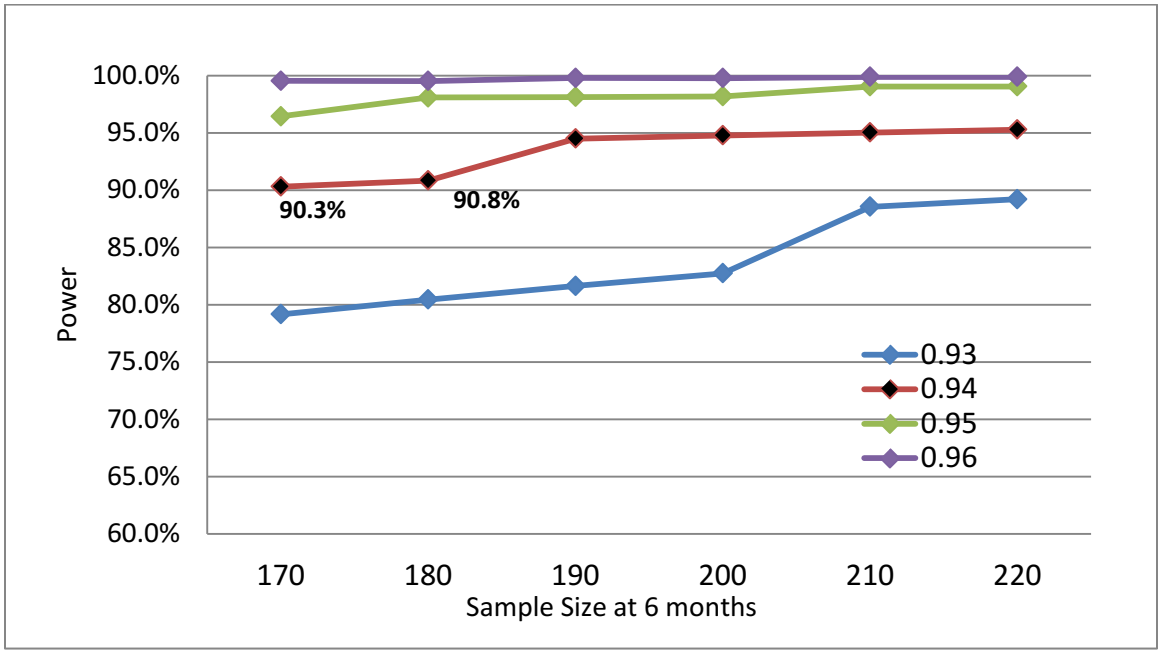
The primary objective will be analyzed using the time-to-first event Kaplan-Meier survival analysis method. Time 0 will be the day a subject undergoes the implant procedure of a Attain Stability Quad MRI SureScan LV Lead (Model 4798), which will be independent of success status of this implant procedure. Event date is the onset date of a subject's first complication that is related to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) according to CEC adjudication. Subjects who undergo an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt and do not experience any LV lead related complications will be censored at the time of their last known exposure to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) for the survival analysis. For any lost-to-follow up subject, the last contact date will be used as the censor date. The 1-sided 97.5% confidence limit lower bound for the survival probability at 6 months (183 days) will be calculated using the log-log survival function approach (Kalbfleisch and Prentice 2002).

Sample Size Consideration

The primary safety objective performance criterion is set to be identical to Medtronic's Attain Performa Clinical Study (IDE Number: G120213). Therefore, the sample size calculation assumptions are derived based on the Model 4298 lead study results. The Attain Performa Model 4298 lead reported a 6-month complication free survival probably of 96.0%, with 97.5% Confidence Lower Limit of 94.3% (PMA-s clinical report).

The binomial calculation (Z-test) is used for initial sample size estimation. In order to preserve the overall study power, a type II error less than 10% was used for the sample size calculation. A sample size of 170 subjects completing their 6-month visit achieves greater than 90% power to detect a difference of 7% using the one-sided binomial test. The target significance level is 0.025. These results assume that the population proportion under the null hypothesis is 87% with an expected value of 94% (Figure 5). To account for 15% attrition, the enrollment size for this objective is 200.

Figure 5: Primary Safety Objective Sample Size Consideration by Difference Performance Assumption



Determination of Patients / Data for Analysis

All consented subjects who undergo an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt will be included in the analysis cohort. If a patient experiences multiple Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant procedures during the study, the analysis cohort will only consider the first procedure. In the event multiple complications occur, the survival analysis endpoint is reached when the first Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complication occurs.

19.1.2. Primary Efficacy Objective #1

Objective

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet the first primary efficacy objective if the proportion of subjects with at least one Attain Stability Quad MRI SureScan LV Lead (Model 4798) pacing vector having a pacing capture threshold (PCT) less than or equal to 2.5 V at 0.5ms pulse width at 6 months post-implant is greater than 80% (i.e., the lower bound of the one-sided 97.5% confidence interval must be greater than 80%).

Hypothesis
H_0: $P1_{6\text{-month}} \leq 80\%$
H_A: $P1_{6\text{-month}} > 80\%$,

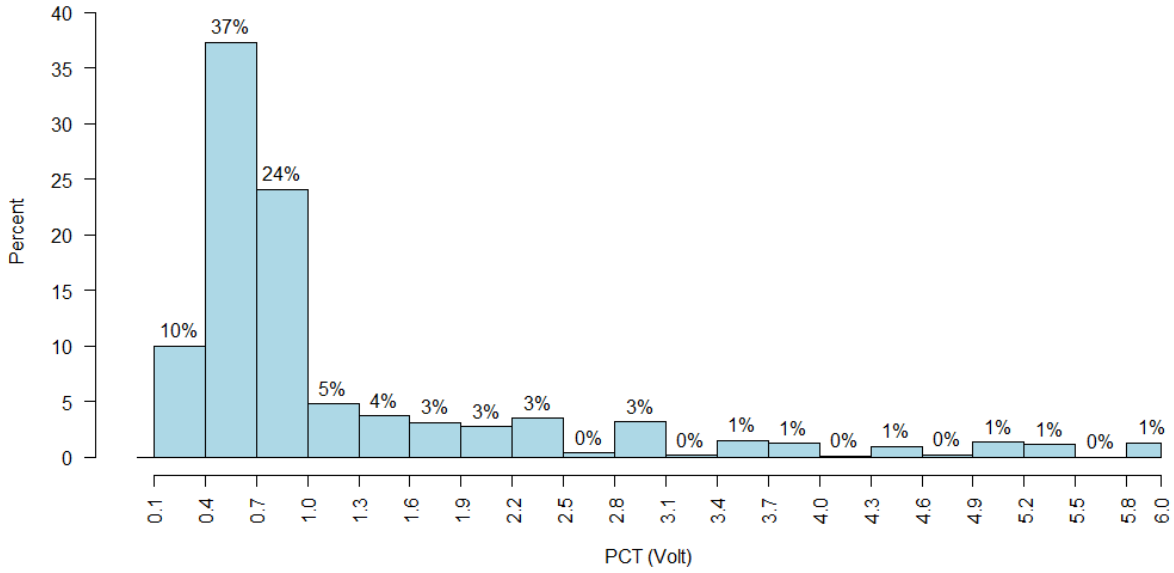
where $P1_{6\text{-month}}$ is the proportion of subjects with pacing voltage thresholds ≤ 2.5V at 0.5ms at 6 months follow-up visit post-implant for at least one LV lead pacing vector.

Endpoint Justification

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is equipped with the identical four electrodes to the Attain Performa LV leads. At the same time, the unique fixation mechanism may cause the distal end of the lead (tip) to be implanted away from the apical region of the heart, and therefore

the PCT may be slightly higher than the values observed in other Quadripolar LV leads. Therefore, we simulated the lead pacing threshold values based on the Attain Performa IDE study data, but excluding the PCT values collected at the most distal electrode. The simulation estimated that 89% of the subjects will achieve this endpoint (Figure 6).

Figure 6: Simulated PCT Distribution



Statistical Analysis Methods

All subjects with valid pacing thresholds measured at the 6 month follow-up visit will be included in this analysis. The proportion of subjects having at least one LV lead pacing vector with voltage thresholds less than or equal to 2.5V will be calculated. The lower bound of the 1-sided 97.5% Confidence Interval will be calculated using the Exact binomial method. Any subject in which no valid pacing threshold value is measured or who has an unable-to-capture result via all LV lead pacing vectors will be reviewed and adjudicated for a possible lead related AE but will not be included for this evaluation if the occurrence is deemed to be a system related event (e.g. lead dislodgement). However, this event may be counted against the safety primary endpoint based on the CEC's final classification.

Sample Size

The primary efficacy endpoint will be analyzed using the Exact binomial method. In order to preserve the overall study power, a type II error less than 10% was used for the sample size calculation. A sample size of 145 subjects achieves 91% power to detect a difference of 0.1 using a one-sided binomial test at a target significance level of 0.025. These results assume that the population proportion under the null hypothesis is 80%, with an expected proportion of 90%.

Determination of Patients / Data for Analysis

All subjects enrolled into this study satisfying the following conditions will be included in this analysis:

- Successfully implanted with a Medtronic Quad CRT-P or CRT-D device and Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- Completed 6-month follow-up visit
- Initially implanted Attain Stability Quad MRI SureScan LV Lead (Model 4798) is active at the 6–month follow-up visit
- At least one available and valid pacing threshold at the 6-month follow-up visit

19.1.3. Primary Efficacy Objective # 2

Objective

The Attain Stability Quad lead will meet the second primary efficacy objective if the proportion of subjects with at least one additional (or second) LV lead pacing vector having a pacing capture threshold less than or equal to 4.0 V at 0.5ms pulse width at 6 months post-implant is greater than 80% (i.e., the one-sided 97.5% lower confidence bound must be greater than 80%).

Hypothesis
H_0: $P2_{6\text{-month}} \leq 80\%$
H_A: $P2_{6\text{-month}} > 80\%$,

where $P2_{6\text{-month}}$ is the proportion of subjects with at least one additional LV lead pacing vector with pacing voltage thresholds ≤ 4.0V at 0.5ms at 6 months post-implant follow-up visit.

Endpoint Justification

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) has 16 LV programmable pacing vectors . Subjects may have the pacing configuration programmed or reprogrammed at each clinic visit. A pacing threshold of 4.0 V will allow an adequate safety margin for programming LV pacing output. The maximum pacing amplitude of the CRT-P or CRT-D devices capable of programming pacing output to any LV lead pacing vector is 8.0V. In actual clinical practice, a less than 3V safety margin is used for the programmed LV lead pacing output in 99% of the patients.

Statistical Analysis Methods

The efficacy endpoint #2 will be analyzed using the Exact binomial method. The proportion of subjects with at least 2 LV lead pacing vectors having voltage thresholds less than or equal to 4.0V at 0.5ms will be calculated. The lower bound of the 1-sided 97.5% Confidence Interval will be calculated using the Exact binomial method. Any subject in which no valid pacing threshold values are measured or with an Unable-to-capture result via all LV lead pacing vectors will be reviewed and adjudicated for possible lead related complications, and therefore may be counted against the study safety endpoint. However, it will be counted as a failure if there is not any additional LV lead pacing vectors (excluding the vector that is already include for the efficacy endpoint #1) are unable to capture with no lead related events reported.

Sample Size

The Attain Performa Model 4298 LV lead observed 97.7% subjects who were able to obtain a non-programmed pacing vector with PCT less than or equal to 4 volts. A sample size of 50 subjects completing the 6 month visit achieves 98% power to detect a difference of 0.18 using a one-sided binomial test at a target significance level of 0.025. These results assume that the population proportion under the null hypothesis is 80%, with the expected proportion of 97%.

Determination of Patients / Data for Analysis

All subjects enrolled into this study satisfying the following conditions will be included in this analysis:

- Successfully implanted with a Medtronic Quad CRT-P or CRT-D device and Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- Completed 6-month follow-up visit
- Initially implanted Attain Stability Quad MRI SureScan LV Lead (Model 4798) lead is active at the 6–month follow-up visit
- At least one available and valid pacing threshold at the 6-month follow-up visit. In the event a subject failed to provide more than one valid pacing threshold value, that subject will be considered as not having at least one additional LV lead pacing with PCT ≤ 4.0V at 0.5ms at 6 months post-implant follow-up visit

19.2. Secondary Objectives

19.2.1. Secondary Objective # 1

Objective - Implant procedure related information: success rate, implant related times

The Attain Stability Quad LV lead implant success rate will be estimated as the number of subjects with Attain Stability Quad MRI SureScan LV Lead (Model 4798) successfully implanted divided by the total number of subjects who had a Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt. A 2-sided 95% Confidence Interval will be calculated using the Exact Binomial method.

The distribution of implant related times will be summarized through statistical summaries such as mean, standard deviation, minimum, median and maximum. Only subjects with the Attain Stability Quad MRI SureScan LV Lead (Model 4798) successfully implanted will be included in this calculation. The total implant time is defined as time from initial incision to final skin closure. Fluoroscopy time is defined as the total time the fluoroscope is imaging. Cannulation time is defined as the time from insertion of the first CS cannulation catheter to the first successful CS cannulation. Successful lead placement time is defined as the time from lead insertion of the successfully placed lead to the time when the lead is placed in its first acceptable pacing location.

19.2.2. Secondary Objective # 2

Objective - 6-month reliability: post implant lead failure modes

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is a composite of two existing market released Medtronic products. The helix fixation is identical to the Attain Stability LV Lead Model 20066/4796 (market released outside of the US). The remainder of the lead is similar to the Attain Performa LV Lead Model 4298, released worldwide.

Historical datasets will be used as informative priors for lead related complications. More specifically, analysis of all complications related to fixation (helix performance) will use data from the Attain Stability (Model 20066/4796) research study, conducted outside of the US. Analysis of all other lead related complications will use data from the Attain Performa clinical study, conducted globally. Credible intervals will be constructed for each individual failure mode within the two groups.

Historical Data (for secondary endpoints only)

- Fixation-related LV lead complications - Data from the 37 patients who completed 6-month follow up with a successfully implanted 20066 lead in the Attain Stability study will be used as an informative prior.
- All other LV lead-related complications - Data from the 401 patients who completed 6-month follow up in the Attain Performa 4298 study will be used as an informative prior.

These historical datasets will be downweighted such that their effective sample size will not exceed the 9% of the total sample size (i.e at most 37 subjects at 6 months).

Statistical Analysis Methods

The weighted historical data will be incorporated using the power prior method[24]. The weight of the historical data will be adjusted using a loss function[25], which scales from 0 to 1 according to the similarity of the historical and observed data. This loss function adjusts the amount of weight the prior receives. The comparison between historical and observed data will be performed twice, once for each group of complications (fixation-related and all other). The objective of using a loss function with the power prior method is to reduce the influence of an informative prior in the parameter estimation, when the historical data does not agree with the current study data.

If analysis of failure rate shows a high level of agreement between historical and current study data or there is better performance for Attain Stability Quad MRI SureScan LV Lead (Model 4798) compared to historical data, the historical data will be weighted at or near a maximum level (9% of total effective sample size). If the Attain Stability Quad MRI SureScan LV Lead (Model 4798) performs worse than historical data, the historical data will receive very little or zero weight. Note that there will be two loss function weights, one for fixation-related complications and one for all other complications. Credible interval calculations will be done separately for individual failure modes within the two groups of complications (fixation and all other).

Denote by θ_c and θ_h the probabilities of lead complication for the current and historical studies respectively. The posterior distributions of θ_c and θ_h respectively, both with minimally informative priors are:

$$\theta_c = beta(y_c + 1, n_c - y_c + 1)$$
$$\theta_h = beta(y_h + 1, n_h - y_h + 1)$$

These posterior distributions are then stochastically compared using a posterior Bayesian p-value[26] as:

$$p = P(\theta_c \leq \theta_h)$$

The desired characteristics for the loss function are:

1. For $p \geq \sim 0.5$, there is a high level of agreement between current and historical data, therefore the loss function should allow a_0 to be close to 1, allowing for full weight of historical data.

2. Conversely, for $p < \sim 0.5$, there begins to be evidence of disagreement between current and historical data, and a_0 should start to down-weight the prior, i.e. a_0 approaches zero as p approaches zero.

The Weibull cumulative distribution function (CDF) meets these criteria:

$$a_0 = 1 - e^{-(p*5)^2}$$

Note that for the case where the number of samples in the prior is different than the effective number, a scaling factor will be applied, where n_h is the desired effective number of prior samples and N_h is the actual number of prior samples:

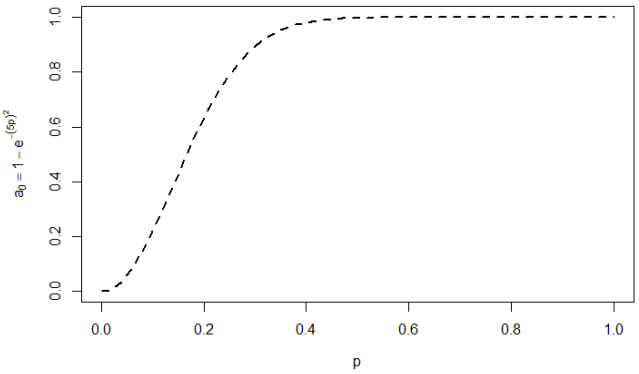
$$a_0 = \frac{n_h}{N_h}\left[1 - e^{-(p*5)^2}\right]$$

Sample values are listed in Table 17 below and illustrated in Figure 7. The comparison between current and historical data will be performed for all LV lead fixation related complications using Attain Stability (Model 20066) historical data and for all other LV lead related complications using Attain Performa historical data.

Table 17: Prior weight from Attain Stability (Model 20066) and prior weight from Attain Performa as a function of the posterior Bayesian p-value (p)

	Prior weight from Attain Stability (Model 20066)	Prior weight from Attain Performa
$\boldsymbol{p}$	$a_0 = 1 - e^{-(p*5)^2}$	$a_0 = \frac{37}{401}\left[1 - e^{-(p*5)^2}\right]$
0.01	0.002	0.000
0.05	0.061	0.006
0.1	0.221	0.020
0.2	0.632	0.058
0.5	0.998	0.092

Figure 7: Loss Function $a_0 = 1 - e^{-(p*5)^2}$

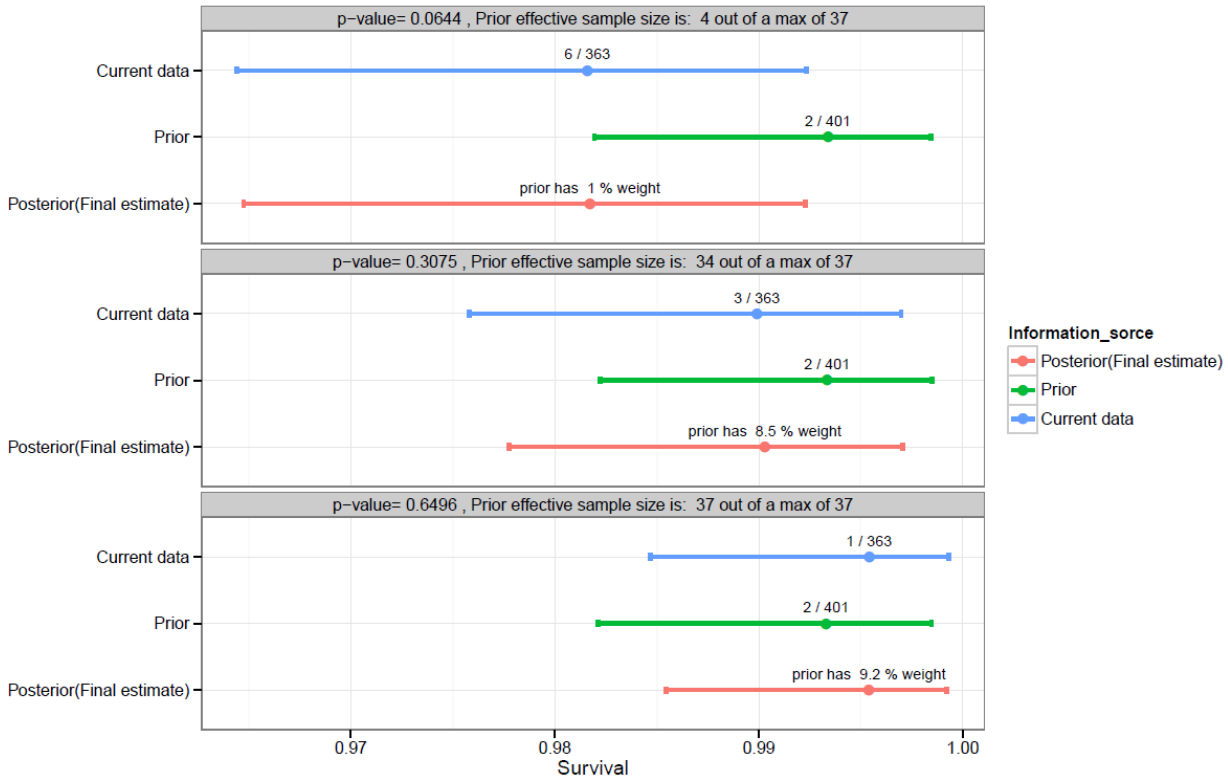


Note that the loss function proposed here does not reduce the strength of the prior when the current study outperforms the historical data. This implementation of the loss function is only concerned with negative impacts to patients, i.e. it penalizes an optimistic prior while not penalizing a pessimistic prior.

Also, note that this function is selected for the shape of the CDF rather than due to conventional statistical properties of the Weibull distribution.

Figure 8 illustrates the effect of the power prior coupled with the loss function. The figure shows credible intervals in scenarios where the prior is optimistic (better performance than current study), in agreement (similar performance to the current study), and pessimistic (worse performance than the clinical study). Note that the prior data source in Figure 8 is the Attain Performa study, with 401 patients. As will be discussed later, these data are scaled to represent a maximum of 37 patients (i.e. 9% weight).

Figure 8: Credible Intervals for Scenarios of Agreement Between Historical and Current Data



The prior data set in Figure 8 has 401 samples. However, the maximum effective historical data sample size is $n_h = 37$, for a maximum weight of 9%. Therefore, the prior will be scaled by a factor of (37/401). As an example, illustrated in the middle panel above, if the effective sample size is 34 out of 37, the prior has received 89% of the maximum weight, or 8.5%.

The panels in Figure 8 can be interpreted as follows:

- Top panel: The current data shows lower performance than the prior. The loss function produces a substantial penalty resulting in almost no weight to the prior (1%). The posterior (final estimate) is essentially the same as the current study.
- Middle panel: The current data is very similar to the prior. The loss function penalty is small, resulting in a prior weight of 8.5% (recall that the maximum weight is 9.2%). Because the agreement is good, the posterior(final estimate) is similar to both the prior and current study.
- Bottom panel: The current data is very similar, with slightly better performance than the prior. The loss function produces a weight very close to the maximum of 9.2%. The posterior (final estimate) is a balance between the prior and current study.

Sample Size

A Bayesian adaptive design is set up to enroll patients until a sufficient sample size is achieved to have high probability of meeting the required effective sample size of $n_e = 400$. The number of enrolled patients in the study may vary from 363 to 400 subjects due to the adaptations to the trial. This study follows methods from Berry, et.al.[27]

The interim analysis will take place after 360 subjects have been enrolled into the study.

The Adaptive Bayesian sample size algorithm will stop or continue enrollment accordingly to the following:

1.) If the predictive probability of $n_e \geq 400$ is larger than 80% then enrollment will stop.
2.) If the predictive probability of $n_e \geq 400$ is less than 80%, enroll sufficient additional patients to make the probability of $n_e \geq 400$ at least 80%.

At the time of the interim analysis, some patients will not have completed the full evaluation period. A longitudinal model will be employed to enable final observations to be imputed for those subjects with incomplete information.

There are 3 types of subjects at a given interim analysis:

1.) Subjects that have complete data
2.) Subjects that have partial data (censored value at a particular time)
3.) Subjects that have no information (subjects that have not been enrolled)

Predictive probabilities for types 2 and 3 will have to be computed. The predictive probability model that will be used is a piecewise exponential. This will allow the final outcomes for the subjects who have not had an event and have not completed 6 month follow up to be simulated.

Note this Bayesian approach to borrow information from historical datasets will only be used for the secondary objective #2.

19.2.3. Secondary Objective # 3

Objective – Electrical measurements (PCT and Impedance) at follow-ups

Pacing Capture Threshold (PCT) and impedance data will be collected using VectorExpress™. Pacing vector changes will be monitored for all implanted patients at follow-up visits.

Summary statistics for PCT and impedance at each time point (i.e. Implant, 6 months, etc.). The distribution of the electrical measurements at the final programmed pacing vector will be presented as n, mean, standard deviation, minimum, median and maximum. In the event of a replacement of a Medtronic Quad CRT-P or CRT-D device and/or the implanted LV lead, only measurements from the

Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted at the initial implant procedure will be included in the analysis cohort for this objective.

19.3. Additional Analysis

19.3.1. Poolability Analysis

Additional analysis will be conducted to summarize study primary objectives by patient characteristics, such as gender, age group, race and study site geography. The purpose of the poolability analysis is to identify if there is any clinical meaningful difference in a subgroup of patients. These analyses will not be statistically powered, and there is no pre-specified statistical significance level for these analyses.

19.3.2. Sensitivity Analysis

All subjects enrolled into this study and successfully implanted with a Medtronic Quad CRT-P or CRT-D device and Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be included in the primary efficacy analysis datasets (efficacy objectives #1 and #2). Sensitivity analysis such as the Tipping Point method or similar will be conducted to investigate the influence of subjects who were successfully implanted with the required system however missed a 6 month post implant follow-up test(s) (due to reasons such as missing in-office visit, subject exit, death and/or the initial implanted lead was deactivated). For this purpose, all subjects with successful implant who do not meet analysis cohort requirements, will be considered as the worst case scenario (i.e. failure to meet the efficacy endpoints).The results will be submitted as part of the clinical reports.

19.3.3. Additional Data Collection

Heart failure clinical outcomes will be assessed. The measurements, including NYHA classification, death, heart failure related hospitalization, heart failure related study exits and subject self-reported global assessment for each subject will be obtained at 6 months post-implant. Summary statistics will be provided.

19.3.3. Overall Study Sample Size Requirements

The sample size requirement at 6-months for each of the study objectives is displayed in Table 18. The first row does not account for attrition, while the second row is inflated by 15% attrition. The sample size for Secondary Objective #2 assumes the conservative case that the interim look results in, no borrowing of historical data. Therefore, the overall sample size for the study is 471.

Table 18: Required Sample Size by Study Objective

	Primary Safety Objective	Primary Efficacy Objective #1	Primary Efficacy Objective #2	Secondary Objective #1	Secondary Objective #2 (post-implant failure modes)	Secondary Objective #3	Overall
Number needed at 6-months	170	145	50	NA	400	NA	400
Number of enrollments	200	171	59	NA	471	NA	471

20. Ethics

20.1. Statement(s) of Compliance

This study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). Good Clinical Practice includes review and approval by an independent IRB/EC before initiating a study, continuing review of an ongoing study by an IRB/EC, and obtaining and documenting the freely given IC of a subject before initiating the study.

The clinical investigation shall not begin until all required approvals and documents from the IRB/EC and a regulatory authority, if needed, have been received. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

The Attain Stability Quad Clinical Study was designed to reflect the GCP principles outlined in ISO 14155:2011 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In accordance with ISO 14155:2011, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation. Adverse Event and Device Deficiency handling in the Attain Stability Quad Clinical Study is ISO 14155:2011 compliant for all participating geographies with the exception that only those AEs which are related to the subject's system, procedure, accessory, or are cardiovascular-related, and all Serious AEs, will be collected. This ensures any AEs which could potentially be relevant will be collected. The scope and duration of the Attain Stability Quad Clinical Study would make collection of all AEs to be a significant burden for investigators and investigative sites. Therefore, only a subset of AEs will be collected in this study, including any that could be potentially relevant.

The principles of the Declaration of Helsinki have been implemented through the IC process, IRB/EC approval, study training, clinical trial registration, pre-clinical testing, risk-benefit assessment and publication policy.

Ultimately, all sites in all geographies will follow and comply with:

- Principles of Declaration of Helsinki
- 21 CFR Part 11 (Electronic Records, Electronic Signatures) (per local law)
- 21 CFR Part 54 (Financial Disclosure by Clinical Investigators)
- The Clinical Trial Agreement
- The procedures described within this CIP
- Local Ethics Board Requirements

In addition to the regulatory requirements outlined above, the study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. These include but are not limited to:

- In the United States, the study will be conducted under an FDA IDE in compliance with 21 CFR Parts:
  - 50: Protection of Human Subjects
  - 56: Institutional Review Boards
  - 812: Investigational Device Exemptions
- In Canada, SOR/98-282, Section 59-88 will be followed and Mandatory Problem Reporting 59(1), 59(2), 60 (1)).
- In EMEA the study will be conducted in compliance with the Active Implantable Medical Device Directive (AIMDD) and Declaration of Helsinki version 2013.
- In Hong Kong and Malaysia, the study will be conducted in compliance with the Declaration of Helsinki version 2013.
- In EMEA, an IB is not required for this study as it is a post market study

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act FDAAA and Declaration of Helsinki on http://clinicaltrials.gov (PL 110-85, section 810(a)). In addition, the study may be registered in local regulatory databases where required by local law.

Approval of the CIP and CIP amendments is required from the following groups prior to any study procedures at a study site:

- Medtronic
- Principal Investigators (where required by local law/regulations)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent medical ethics committee or institutional review board.

Similarly, approval of subsequent revisions to the CIP is required at each study site from the above mentioned groups prior to implementation of the revised CIP at the site.

21. Study Administration

21.1. Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this Attain Stability Quad Clinical Study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the CTA, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the Subject IC, Data Protection Authorization (where applicable) and CTA. The principal investigator should also be available during monitoring visits.

Monitoring for the study, including site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

Monitoring visits may be conducted periodically to assess site study progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to IRB/EC approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs. Monitors review site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to site personnel. Monitors may work with study personnel to determine appropriate corrective action

recommendations and to identify trends within the study or at a particular site. Regulatory documents may be reviewed at each study site.

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of adverse events, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation.

21.2. Data Management

Data will be collected using Oracle Clinical, an electronic data management system for clinical studies. CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

Only authorized persons can complete CRFs. CRFs shall be signed by the Principle Investigator. The Principle Investigator can delegate the CRF sign off task to Sub-Investigators only. Delegation of authority will be specified on the appropriate documentation.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to make it anonymous, for instance, where the subject's name cannot be removed from the data carrier.

Procedures in the CIP require source documentation. Source documentation will be maintained at the site. Source documents, which may include worksheets, patient medical records, programmer printouts and device interrogation files, must be created and maintained by the investigational site team. For source documentation, the investigational site study team must sign and date any copies or printouts of original source documents with a statement that this is a complete and true reproduction of the original source document.

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. The CRF may be considered source for the following data collection elements recorded directly on the CRFs:

- Enrollment Notification
    - Site assigned patient reference
- Baseline
    - Administrative information
- Adverse Event eCRF
    - Date study site became aware of event
    - Relatedness of adverse event
- Device Deficiency eCRF
    - Date study site became aware of event
- Subject Death
    - Date study site became aware of death
    - Relatedness of death
- System Modification
    - Justification for explanted product not being returned to Medtronic
- Deviations

    - Reason for deviation
- Investigational product Disposition Log
    - Date the Investigational Attain Stability Quad lead was implanted/explanted

Even when the CRF may be considered as source, an alternate method of source documentation is always strongly encouraged.

Save-to-media data collected at office visits will be sent to Medtronic. Upon receipt, device data will be maintained within a Medtronic device database and retrieved for analysis and reporting.

21.3. Direct Access to Source Data/Documents

The sponsor or a regulatory authority may audit or inspect the study site to evaluate the conduct of the study. The clinical investigator(s)/institution(s) shall allow study related monitoring, audits, IRB/EC review and regulatory inspection.

21.4. Confidentiality

All records and other information about subjects participating in this study will be treated as confidential.

21.5. CIP Amendments

Approval of subsequent revisions to the CIP is required at each study site from the following groups prior to implementation of the revised CIP at the site:

- Medtronic
- Principal Investigators (where required by local law)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent medical ethics committee or institutional review board.

If a CIP amendment occurs, site personnel will need to be re-trained as necessary, and will need to submit any changes to their IRB/EC as required by the committee. Protocol amendments will also be reported to and approved by the FDA, or regulatory authority.

21.6. Warranty/Insurance Information

21.6.1. Warranty

Warranty information is provided in the product packaging for the commercially released CRT-P or CRT-D devices and leads, and additional copies are available upon request.

21.6.2. Insurance (EMEA)

Medtronic Bakken Research Center B.V. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the EC and/or Competent Authority (CA).

21.6.3. Insurance (Canada)

Medtronic of Canada is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate general liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a General Liability insurance statement/certificate will be provided to the Ethics Committee.

21.6.4. Insurance (Malaysia)

Medtronic International Ltd. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

21.6.5. Insurance (Hong Kong)

Medtronic Hong Kong Medical Ltd. Ltd. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

21.7. Record Retention

21.7.1. Investigator Records

The investigator is responsible for the preparation and retention of the records including, but not limited to, those cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (e.g., the study binder provided to the investigator) or Subject Study Binder. Case Report Forms must be maintained and signed electronically by an investigator within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law/regulation or hospital administration requires) after product approval. Measures shall be taken to avoid loss or premature destruction.

- All correspondence between the IRB/EC, sponsor, monitor, regulatory authority and/or the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
    - Signed and dated informed consent form, in accordance with local requirements
    - Observations of adverse events/adverse device effects/device deficiencies
    - Medical history
    - Baseline, Implant and follow-up data (if applicable)
    - Documentation of the dates and rationale for any deviation from the protocol
- Electronically signed and dated eCRFs and a blank set of CRFs where required by local law
- All approved versions of the CIP, IC
- Fully executed Clinical Trial Agreement
- Ethics Committee approval documentation. Written information that the investigator or other study staff, when member of the Ethics Committee, did not participate in the approval process.

Approval documentation must include the Ethics Board composition, where required per local law.
- Regulatory authority notification, correspondence and approval, where required per local law.
- List of investigation sites: This list is not yet final at the time of CIP development. The list will be provided under separate cover and will be maintained by the sponsor.
- Financial disclosure (investigators)
- Enrollment Log (for sites following ISO 14155)
- For sites where the Attain Stability Quad lead is considered investigational, device disposition logs containing Model and serial numbers of devices implanted, subject IDs of the subjects implanted, implant/used dates, explant dates, returned-to-sponsor dates and reasons and method of disposal/destruction
- Current curriculum vitae (signed and dated in EMEA only) of principal investigators and key members of investigation site team (as required by local law)
- Documentation of delegated tasks
- Study training records for investigation site team
- Assurance certificates (EMEA, Hong Kong, and Malaysia)
- Any other records that FDA and local regulatory agencies require to be maintained (e.g. Ethics Committee Roster, study equipment calibration information)
- Final Study Report including the statistical analysis

21.7.2. Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all CRFs, AEs and ADEs (reported per the country-specific collection requirements), DDs, deaths, crossovers and any deviations from the CIP. If any action is taken by an IRB/EC with respect to this Attain Stability Quad Clinical Study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Investigator reporting requirements for safety data are listed in Section 17.3).

Table 19: Investigator Reports Applicable for All Geographies per Medtronic Requirements

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing Ethics Committee of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and Ethics Committee	Any deviation from the clinical investigation plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Failure to obtain informed consent	Sponsor and Ethics Committee	Informed consent shall be obtained in writing and documented before a subject is enrolled into the Attain Stability Quad Clinical Study
Final Report	Ethics Committee and Relevant Authorities	This report must be submitted within 3 months of study completion or termination.

21.7.3. Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records that includes, but is not limited to:

- All correspondence which pertains to the Attain Stability Quad Clinical Study
- Executed Clinical Trial Agreement
- Financial disclosures (investigators)
- Current curriculum vitae (signed and dated in EMEA only) of principal investigators and key members of investigation site team (as required by local law)
- Device Disposition Logs containing Model and serial numbers of devices implanted, subject IDs of the subjects implanted, implant/used dates, explant dates, returned-to-sponsor dates and reasons and method of disposal/destruction
- Electronically signed and dated eCRFs
- All approved informed consent templates, and other information provided to the subjects and advertisements, including translations
- Copies of all Ethics Committee approval letters and relevant Ethics Committee correspondence and Ethics Committee voting list/roster/letter of assurance
- List of names, addresses, and professional position of the clinical investigators and coordinating clinical, if appointed.
- Names and addresses of the institutions in which the Attain Stability Quad Clinical Study will be conducted: This list is not yet final at the time of CIP development. The list will be provided under separate cover and will be maintained by the sponsor.
- Regulatory authorities correspondence, notification and approval as required by national legislation
- Insurance certificates (EMEA, Hong Kong, and Malaysia)
- Names/contact addresses of monitors
- Monitoring reports (interim monitoring visit reports, follow-up letters and close-out visit reports)
- Site qualification visit reports
- Statistical analyses and underlying supporting data
- Final report of the Attain Stability Quad Clinical Study
- The approved Clinical Investigation Plan and study related reports, and revisions
- Documentation of delegated tasks
- Study training records for site personnel and Medtronic personnel involved in the study
- Sample of CRFs
- Any other records that local regulatory agencies require to be maintained

21.7.4. Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of reviewing Ethics Committee, regulatory agency or FDA, provide accurate, complete and current information about any aspect of the Attain Stability Quad Clinical Study. Safety data Medtronic reporting requirements are listed in Section 17.3).

Table 20: Sponsor Reports for Canada

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, Ethics Committee, Relevant authorities, and Head of the Institution	Provide prompt notification of termination or suspension and reason(s).
Recall and device disposition	Investigators, Ethics Committee	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices.
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically.

Table 21: Sponsor Reports for EMEA, Malaysia, Hong Kong

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, Ethics Committee, Relevant authorities and Head of the Institution	Provide prompt notification of termination or suspension and reason(s) per local law. *(ISO 14155:2011)*
Withdrawal of Ethics Committee approval	Investigators, Ethics Committee and relevant authorities	Investigators and other Ethics Committees will be notified only if required by local laws or by the Ethics Committee.
Withdrawal of CA approval	Investigators, Ethics Committee, and relevant authorities	Investigators, Ethics Committees and relevant authorities will be notified only if required by local laws or by the Ethics Committee.
Progress Reports	Ethics Committee and regulatory authorities	This will be submitted to the Ethics Committee and regulatory authorities only if required by local law.
Final report	Investigators, Ethics Committee, and Regulatory authorities upon request	• The investigator shall have the opportunity to review and comment on the final report. • If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). • The signature of the principal Investigator in each site should be obtained.
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. *(ISO 14155:2011)* Site specific study deviations will be submitted to investigators periodically.

Table 22: Sponsor Reports for the United States

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Investigators, Ethics Committee, FDA, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(2))*
Withdrawal of FDA approval	Investigators, Ethics Committee, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(3))*
Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. *(21 CFR 812.150(b)(4))*
Progress Reports	Ethics Committee and FDA	Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(5), 812.36(f)*
Recall and device disposition	Investigators, Head of Institution, Ethics Committee, relevant authorities, and FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6))*
Failure to obtain informed consent	FDA	Investigator's report will be submitted to FDA within five working days of notification. *(21 CFR 812.150(b)(8))*
Final report	Investigators, Ethics Committee, Regulatory authorities upon request, and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and IRBs/MECs within six months after completion or termination of this study. *(21 CFR 812.150(b)(7))*
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically.
Other	IRB, FDA	Accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(b)(10))*

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in secured file cabinets at Medtronic during the course of this study. After closure of the study Medtronic will archive records and reports as required by applicable regulations.

21.8. Publication and Use of Information

Publications from the Attain Stability Quad Clinical Study will be handled according to Medtronic Policies and Standard Operating Procedures and as indicated in the CTA.

21.8.1. Publication Committee

The Attain Stability Quad Clinical Study will utilize a Publication Committee which will include the Steering Committee members as well as Medtronic personnel. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to:

- Manage elements addressed in the publication plan as outlined in this section
- Develop the final Publication Plan under separate cover
- Execute the Publication Plan
- Oversee the publication of primary, secondary and ancillary study results
- Review and prioritize publication proposals
- Provide input on publication content, and
- Determine authorship

In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan. Membership in the Publication Committee does not guarantee authorship. The committee will meet as needed.

21.8.2. Management of Primary, Secondary, and Ancillary Publications

The Publication Committee reviews, prioritizes and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary/ancillary objectives, respectively, as specified in the Clinical Investigation Plan. An ancillary publication is any publication that does not address the study objectives identified in the Clinical Investigation Plan. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this Attain Stability Quad Clinical Study and clinicians not participating in this Attain Stability Quad Clinical Study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual site data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

21.8.3. Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE), Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Medtronic personnel, must at a minimum meet all of the conditions below:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published

Decisions regarding authorship and contributor-ship will be made by the publication committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the

authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All investigators not listed as co-authors will be acknowledged as the "Medtronic Attain Stability Quad Clinical Study Investigators" and will be individually listed according to the guidelines of the applicable scientific journal when possible. Any other contributors will be acknowledged by name with their specific contribution indicated.

21.8.4. Transparency

Transparency of study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to all investigators, IRB/ECs and Competent Authorities of participating countries when required by local law
- Registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- Submitting for publication the primary study results after the study ends
- Disclosing conflicts of interest (e.g. financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- Making an individual sites study data accessible to the corresponding investigator after the completion of the study, if requested

21.9. Suspension or Early Termination

21.9.1. Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or regulatory authority, whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing IRB/EC oversight is required until the overall study closure process is complete. Upon study closure, subjects should be managed and followed per physician discretion.

21.9.2. Early Termination or Suspension

Early Termination of the Study is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single site. Study Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single site. In the event the whole study or a single site is terminated, subjects will be exited.

Study-Wide Termination or Suspension

Possible reasons for considering study suspension or termination of the study include but are not limited to:

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)

- Technical issues during the manufacturing process

Investigator/Site Termination or Suspension

Possible reasons for clinical investigator or site termination or suspension include but are not limited to:

- Failure to obtain initial IRB/EC approval or annual renewal of the study
- Persistent non-compliance to the clinical investigation (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment
- Noncompliance to regulations and the terms of the CTA (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.)
- Institutional Review Board/Ethics Committee suspension of the site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

21.9.3. Procedures for Termination or Suspension

Medtronic-Initiated and Regulatory Authority-Initiated

- Medtronic will promptly inform the clinical investigators of the (early) termination or suspension and the reasons and inform the regulatory authority(s) where required
- In the case of study termination or suspension for reasons other than a temporary IRB/EC approval lapse, the investigator will promptly inform the IRB/EC
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

Investigator-Initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the IRB/EC
- The investigator will promptly inform the regulatory authorities (for regions following ISO only)
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

Institutional Review Board Ethics Committee-Initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with IRB/EC policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)

- The investigator will promptly inform the subjects, and/or the personal physician of the subjects, with the rationale for the study termination or suspension
- The investigator will promptly inform the regulatory authorities (for regions following ISO 14155 only)

22. Appendices

APPENDIX 1: Foreseeable Adverse Event List

The information provided in this section pertains to foreseeable AEs that may be observed in study subjects and may collectively assist in identifying those events that are unexpected in nature. The foreseeable adverse events information consists of three parts: (1) listing of potential adverse events associated with implantation of CRT system and transvenous leads, (2) rates of AEs reported from previous Medtronic studies evaluating CRT systems and transvenous leads, and (3) AEs rates reported in published literature for procedures similar to the CRT system implant procedure. This information will be used in combination with device labeling, current event reporting information, and other published data to assess for an unexpected occurrence.

The implantation of the study device, CRT-P or CRT-D, involves surgery, therefore, standard AEs associated with a surgical procedure may be experienced (e.g. anesthesia complications, injury, infections, bleeding, exacerbation of pre-existing conditions, healing complications, etc.). The focus of this section is to specifically address in more detail, those events that are foreseeable due to the use, performance, and/or presence of the system under investigation.

Additional potential risks associated with the implantation of the CRT system and the Attain Stability Quad MRI SureScan LV Lead (Model 4798), as well as risk minimization are discussed within Section 16.

Treatment required for procedure and/or system related adverse events that are experienced may include medication, device reprogramming, device modification (e.g. repositioning, surgical abandonment, surgical removal), or other surgical and medical remedies. The AEs associated with the use of transvenous leads, pacing and defibrillation systems include, but are not limited to, the following:

Table 23: Listing of Potential Adverse Events Associated with System Implant

- acceleration of tachyarrhythmias (caused by device)
- air embolism
- bleeding
- body rejection phenomena, including local tissue reaction
- cardiac dissection
- cardiac perforation
- cardiac tamponade
- chronic nerve damage
- constrictive pericarditis
- death
- device migration
- endocarditis
- erosion
- excessive fibrotic tissue growth
- extrusion
- fibrillation or other arrhythmias
- fluid accumulation
- formation of hematomas/seromas or cysts
- heart block
- heart wall or vein wall rupture
- hemothorax
- infection
- keloid formation
- lead abrasion and discontinuity
- lead migration/dislodgment
- complications and mortality due to inability to deliver appropriate and intended therapy
- muscle and/or nerve stimulation
- myocardial damage
- myocardial irritability
- myopotential sensing
- pericardial effusion
- pericardial rub
- pneumothorax
- poor connection of the lead to the device, which may lead to oversensing, undersensing, or a loss of therapy
- stroke
- threshold elevation
- thrombotic embolism
- thrombosis
- tissue necrosis
- valve damage (particularly in fragile hearts)
- venous occlusion
- venous perforation

An additional potential AE associated with the use of transvenous left ventricular pacing leads is coronary sinus dissection.

Additional potential AEs associated with the use of ICD systems include, but are not limited to, the following events:

- inappropriate shocks
- potential mortality due to inability to defibrillate
- shunting current or insulating myocardium during defibrillation

Patients susceptible to frequent shocks despite medical management could develop psychological intolerance to an ICD system that might include the following conditions:

- dependency
- depression
- fear of premature battery depletion
- fear of shocking while conscious
- fear that shocking capability may be lost
- imagined shocking (phantom shock)

Adverse Events Reported in Previous Medtronic Studies

The listing below provides an example of reported system and procedure related AEs in recent Medtronic studies. This table includes a summary of combined system or procedure related AEs as reported in the Concerto-AT, Insync III US, 4194, 4195, 4196, 4396, Adaptive CRT, and Attain Performa studies along with their incidence. The observed rate is based on the study populations that included a total of 3,246 subjects. In total, there were 1749 system or procedure related events. This includes both serious and non-serious events. The rate is calculated as number of subjects that experience the event, not accounting for duration of follow-up.

Table 24: System or procedure-related adverse events from previous clinical studies

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Abdominal pain	1	1	0.03%	(0.00%, 0.17%)
Acidosis	1	1	0.03%	(0.00%, 0.17%)
Acute respiratory failure	4	4	0.12%	(0.03%, 0.32%)
Adverse drug reaction	1	1	0.03%	(0.00%, 0.17%)
Air embolism	1	1	0.03%	(0.00%, 0.17%)
Alcohol withdrawal syndrome	1	1	0.03%	(0.00%, 0.17%)
Alpha haemolytic streptococcal infection	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Anaemia	7	7	0.22%	(0.09%, 0.44%)
Anaemia postoperative	1	1	0.03%	(0.00%, 0.17%)
Anaphylactic shock	1	1	0.03%	(0.00%, 0.17%)
Anticoagulation drug level below therapeutic	1	1	0.03%	(0.00%, 0.17%)
Anxiety	3	3	0.09%	(0.02%, 0.27%)
Application site rash	2	2	0.06%	(0.01%, 0.22%)
Arterial haemorrhage	1	1	0.03%	(0.00%, 0.17%)
Arteriovenous fistula	1	1	0.03%	(0.00%, 0.17%)
Arteriovenous fistula operation	1	1	0.03%	(0.00%, 0.17%)
Arthralgia	1	1	0.03%	(0.00%, 0.17%)
Arthritis bacterial	1	1	0.03%	(0.00%, 0.17%)
Ascites	1	1	0.03%	(0.00%, 0.17%)
Atelectasis	2	2	0.06%	(0.01%, 0.22%)
Atrial fibrillation	19	19	0.59%	(0.35%, 0.91%)
Atrial flutter	4	4	0.12%	(0.03%, 0.32%)
Atrial tachycardia	5	4	0.12%	(0.03%, 0.32%)
Atrioventricular block	16	16	0.49%	(0.28%, 0.80%)
Back pain	3	3	0.09%	(0.02%, 0.27%)
Bacteraemia	1	1	0.03%	(0.00%, 0.17%)
Cardiac arrest	8	8	0.25%	(0.11%, 0.49%)
Cardiac failure	46	43	1.32%	(0.96%, 1.78%)
Cardiac failure chronic	5	5	0.15%	(0.05%, 0.36%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Cardiac pacemaker battery replacement	1	1	0.03%	(0.00%, 0.17%)
Cardiac perforation	8	8	0.25%	(0.11%, 0.49%)
Cardiac sarcoidosis	1	1	0.03%	(0.00%, 0.17%)
Cardiac tamponade	3	3	0.09%	(0.02%, 0.27%)
Cardiac vein dissection	38	37	1.14%	(0.80%, 1.57%)
Cardiac vein perforation	5	5	0.15%	(0.05%, 0.36%)
Cardiogenic shock	3	3	0.09%	(0.02%, 0.27%)
Cardiomyopathy	1	1	0.03%	(0.00%, 0.17%)
Cardiovascular disorder	1	1	0.03%	(0.00%, 0.17%)
Cellulitis	2	2	0.06%	(0.01%, 0.22%)
Cerebral infarction	1	1	0.03%	(0.00%, 0.17%)
Cerebrovascular accident	3	3	0.09%	(0.02%, 0.27%)
Chest discomfort	4	4	0.12%	(0.03%, 0.32%)
Chest pain	8	8	0.25%	(0.11%, 0.49%)
Chronic obstructive pulmonary disease	3	3	0.09%	(0.02%, 0.27%)
Circulatory collapse	1	1	0.03%	(0.00%, 0.17%)
Colitis	1	1	0.03%	(0.00%, 0.17%)
Complication of device insertion	1	1	0.03%	(0.00%, 0.17%)
Complication of device removal	4	4	0.12%	(0.03%, 0.32%)
Constipation	1	1	0.03%	(0.00%, 0.17%)
Contusion	2	2	0.06%	(0.01%, 0.22%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Cough	1	1	0.03%	(0.00%, 0.17%)
Cystitis	1	1	0.03%	(0.00%, 0.17%)
Decubitus ulcer	1	1	0.03%	(0.00%, 0.17%)
Deep vein thrombosis	14	14	0.43%	(0.24%, 0.72%)
Dehydration	1	1	0.03%	(0.00%, 0.17%)
Delirium	1	1	0.03%	(0.00%, 0.17%)
Device alarm issue	1	1	0.03%	(0.00%, 0.17%)
Device battery issue	1	1	0.03%	(0.00%, 0.17%)
Device capturing issue	30	29	0.89%	(0.60%, 1.28%)
Device computer issue	19	19	0.59%	(0.35%, 0.91%)
Device connection issue	19	19	0.59%	(0.35%, 0.91%)
Device damage	1	1	0.03%	(0.00%, 0.17%)
Device dislocation	125	107	3.30%	(2.71%, 3.97%)
Device electrical impedance issue	12	12	0.37%	(0.19%, 0.64%)
Device extrusion	2	1	0.03%	(0.00%, 0.17%)
Device failure	1	1	0.03%	(0.00%, 0.17%)
Device lead damage	13	13	0.40%	(0.21%, 0.68%)
Device lead issue	1	1	0.03%	(0.00%, 0.17%)
Device misuse	9	9	0.28%	(0.13%, 0.53%)
Device pacing issue	69	67	2.06%	(1.60%, 2.61%)
Device psychogenic complication	7	7	0.22%	(0.09%, 0.44%)
Device related infection	3	3	0.09%	(0.02%, 0.27%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Device signal detection issue	2	2	0.06%	(0.01%, 0.22%)
Device stimulation issue	443	349	10.75%	(9.71%, 11.87%)
Diabetes	1	1	0.03%	(0.00%, 0.17%)
Diarrhea	1	1	0.03%	(0.00%, 0.17%)
Dizziness	1	1	0.03%	(0.00%, 0.17%)
Dressler's syndrome	1	1	0.03%	(0.00%, 0.17%)
Drug hypersensitivity	3	3	0.09%	(0.02%, 0.27%)
Dysarthria	1	1	0.03%	(0.00%, 0.17%)
Dyspnoea	2	2	0.06%	(0.01%, 0.22%)
Dyspnoea exertional	1	1	0.03%	(0.00%, 0.17%)
Dyspnoea paroxysmal nocturnal	1	1	0.03%	(0.00%, 0.17%)
Ecchymosis	2	2	0.06%	(0.01%, 0.22%)
Electromagnetic interference	1	1	0.03%	(0.00%, 0.17%)
Endocarditis	1	1	0.03%	(0.00%, 0.17%)
Endocarditis staphylococcal	1	1	0.03%	(0.00%, 0.17%)
Erythema multiforme	1	1	0.03%	(0.00%, 0.17%)
Fatigue	5	5	0.15%	(0.05%, 0.36%)
Fluid overload	1	1	0.03%	(0.00%, 0.17%)
Gastroenteritis	1	1	0.03%	(0.00%, 0.17%)
Gastrointestinal haemorrhage	1	1	0.03%	(0.00%, 0.17%)
Haematoma	2	2	0.06%	(0.01%, 0.22%)
Haematuria	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Haemoptysis	2	2	0.06%	(0.01%, 0.22%)
Haemothorax	4	4	0.12%	(0.03%, 0.32%)
Hot flush	1	1	0.03%	(0.00%, 0.17%)
Hydrothorax	1	1	0.03%	(0.00%, 0.17%)
Hyperglycaemia	1	1	0.03%	(0.00%, 0.17%)
Hyperkalaemia	4	4	0.12%	(0.03%, 0.32%)
Hypersensitivity	1	1	0.03%	(0.00%, 0.17%)
Hypertension	1	1	0.03%	(0.00%, 0.17%)
Hyponatraemia	2	2	0.06%	(0.01%, 0.22%)
Hypotension	20	20	0.62%	(0.38%, 0.95%)
Hypovolaemia	1	1	0.03%	(0.00%, 0.17%)
Ileus	1	1	0.03%	(0.00%, 0.17%)
Impaired healing	2	2	0.06%	(0.01%, 0.22%)
Implant site bruising	2	2	0.06%	(0.01%, 0.22%)
Implant site cellulitis	1	1	0.03%	(0.00%, 0.17%)
Implant site effusion	1	1	0.03%	(0.00%, 0.17%)
Implant site erosion	1	1	0.03%	(0.00%, 0.17%)
Implant site erythema	6	6	0.18%	(0.07%, 0.40%)
Implant site haematoma	98	96	2.96%	(2.40%, 3.60%)
Implant site haemorrhage	6	6	0.18%	(0.07%, 0.40%)
Implant site hypoaesthesia	1	1	0.03%	(0.00%, 0.17%)
Implant site infection	44	44	1.36%	(0.99%, 1.82%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Implant site inflammation	3	3	0.09%	(0.02%, 0.27%)
Implant site irritation	5	5	0.15%	(0.05%, 0.36%)
Implant site oedema	3	3	0.09%	(0.02%, 0.27%)
Implant site pain	72	64	1.97%	(1.52%, 2.51%)
Implant site rash	3	3	0.09%	(0.02%, 0.27%)
Implant site swelling	4	4	0.12%	(0.03%, 0.32%)
Implant site warmth	1	1	0.03%	(0.00%, 0.17%)
Incision site complication	1	1	0.03%	(0.00%, 0.17%)
Incision site haemorrhage	5	5	0.15%	(0.05%, 0.36%)
Incision site pain	4	4	0.12%	(0.03%, 0.32%)
Incisional drainage	1	1	0.03%	(0.00%, 0.17%)
Infection	2	2	0.06%	(0.01%, 0.22%)
Infusion site extravasation	1	1	0.03%	(0.00%, 0.17%)
Intracardiac thrombus	6	6	0.18%	(0.07%, 0.40%)
Lead dislodgement	33	30	0.92%	(0.62%, 1.32%)
Leukocytosis	2	2	0.06%	(0.01%, 0.22%)
Localized oedema	1	1	0.03%	(0.00%, 0.17%)
Mediastinal effusion	1	1	0.03%	(0.00%, 0.17%)
Medical device discomfort	3	3	0.09%	(0.02%, 0.27%)
Medical device site reaction	1	1	0.03%	(0.00%, 0.17%)
Monoparesis	1	1	0.03%	(0.00%, 0.17%)
Muscle spasms	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Muscle twitching	1	1	0.03%	(0.00%, 0.17%)
Musculoskeletal chest pain	2	2	0.06%	(0.01%, 0.22%)
Musculoskeletal pain	42	40	1.23%	(0.88%, 1.67%)
Musculoskeletal stiffness	1	1	0.03%	(0.00%, 0.17%)
Myocardial infarction	1	1	0.03%	(0.00%, 0.17%)
Nausea	1	1	0.03%	(0.00%, 0.17%)
Neck pain	1	1	0.03%	(0.00%, 0.17%)
Nephrosclerosis	1	1	0.03%	(0.00%, 0.17%)
Neuropathy peripheral	1	1	0.03%	(0.00%, 0.17%)
Nodal rhythm	2	2	0.06%	(0.01%, 0.22%)
Non-cardiac chest pain	1	1	0.03%	(0.00%, 0.17%)
Oedema peripheral	12	12	0.37%	(0.19%, 0.64%)
Oliguria	1	1	0.03%	(0.00%, 0.17%)
Operative haemorrhage	1	1	0.03%	(0.00%, 0.17%)
Orthostatic hypotension	2	2	0.06%	(0.01%, 0.22%)
Oversensing	34	33	1.02%	(0.70%, 1.42%)
Oxygen saturation decreased	1	1	0.03%	(0.00%, 0.17%)
Pacemaker generated arrhythmia	6	6	0.18%	(0.07%, 0.40%)
Pain	1	1	0.03%	(0.00%, 0.17%)
Pain in extremity	1	1	0.03%	(0.00%, 0.17%)
Palpitations	9	9	0.28%	(0.13%, 0.53%)
Paraesthesia	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Pericardial effusion	16	15	0.46%	(0.26%, 0.76%)
Pericarditis	4	4	0.12%	(0.03%, 0.32%)
Phantom shocks	4	3	0.09%	(0.02%, 0.27%)
Phlebitis	2	2	0.06%	(0.01%, 0.22%)
Pleural effusion	21	21	0.65%	(0.40%, 0.99%)
Pneumonia	9	9	0.28%	(0.13%, 0.53%)
Pneumothorax	43	43	1.32%	(0.96%, 1.78%)
Pocket erosion	4	4	0.12%	(0.03%, 0.32%)
Post procedural haemorrhage	2	2	0.06%	(0.01%, 0.22%)
Presyncope	3	3	0.09%	(0.02%, 0.27%)
Procedural haemorrhage	1	1	0.03%	(0.00%, 0.17%)
Procedural headache	2	2	0.06%	(0.01%, 0.22%)
Procedural pain	1	1	0.03%	(0.00%, 0.17%)
Pruritus	1	1	0.03%	(0.00%, 0.17%)
Pruritus generalized	1	1	0.03%	(0.00%, 0.17%)
Pulmonary embolism	1	1	0.03%	(0.00%, 0.17%)
Pulmonary oedema	3	3	0.09%	(0.02%, 0.27%)
Pulmonary sepsis	1	1	0.03%	(0.00%, 0.17%)
Pulseless electrical activity	2	2	0.06%	(0.01%, 0.22%)
Pyrexia	5	5	0.15%	(0.05%, 0.36%)
Rash	8	8	0.25%	(0.11%, 0.49%)
Rash generalized	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Renal failure	8	8	0.25%	(0.11%, 0.49%)
Renal failure acute	2	2	0.06%	(0.01%, 0.22%)
Renal impairment	1	1	0.03%	(0.00%, 0.17%)
Respiratory acidosis	1	1	0.03%	(0.00%, 0.17%)
Respiratory distress	1	1	0.03%	(0.00%, 0.17%)
Respiratory failure	1	1	0.03%	(0.00%, 0.17%)
Sepsis	3	3	0.09%	(0.02%, 0.27%)
Sepsis syndrome	1	1	0.03%	(0.00%, 0.17%)
Septic shock	4	4	0.12%	(0.03%, 0.32%)
Sinus arrest	1	1	0.03%	(0.00%, 0.17%)
Sinus bradycardia	1	1	0.03%	(0.00%, 0.17%)
Sinus tachycardia	2	2	0.06%	(0.01%, 0.22%)
Staphylococcal infection	2	2	0.06%	(0.01%, 0.22%)
Stitch abscess	1	1	0.03%	(0.00%, 0.17%)
Subclavian vein thrombosis	2	2	0.06%	(0.01%, 0.22%)
Subcutaneous emphysema	1	1	0.03%	(0.00%, 0.17%)
Subcutaneous haematoma	1	1	0.03%	(0.00%, 0.17%)
Sudden cardiac death	10	10	0.31%	(0.15%, 0.57%)
Superior vena cava stenosis	1	1	0.03%	(0.00%, 0.17%)
Supraventricular extrasystoles	1	1	0.03%	(0.00%, 0.17%)
Supraventricular tachycardia	2	2	0.06%	(0.01%, 0.22%)
Syncope	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Tachycardia	1	1	0.03%	(0.00%, 0.17%)
Thrombophlebitis	2	2	0.06%	(0.01%, 0.22%)
Thrombosis	8	8	0.25%	(0.11%, 0.49%)
Thrombotic stroke	1	1	0.03%	(0.00%, 0.17%)
Toxicity to various agents	1	1	0.03%	(0.00%, 0.17%)
Twiddler's syndrome	5	5	0.15%	(0.05%, 0.36%)
Undersensing	7	7	0.22%	(0.09%, 0.44%)
Urinary retention	2	2	0.06%	(0.01%, 0.22%)
Vena cava thrombosis	1	1	0.03%	(0.00%, 0.17%)
Venous occlusion	1	1	0.03%	(0.00%, 0.17%)
Ventricular dyssynchrony	1	1	0.03%	(0.00%, 0.17%)
Ventricular extrasystoles	2	2	0.06%	(0.01%, 0.22%)
Ventricular fibrillation	1	1	0.03%	(0.00%, 0.17%)
Ventricular tachycardia	11	11	0.34%	(0.17%, 0.61%)
Vomiting	3	3	0.09%	(0.02%, 0.27%)
Weaning failure	1	1	0.03%	(0.00%, 0.17%)
Weight decreased	1	1	0.03%	(0.00%, 0.17%)
Wound dehiscence	1	1	0.03%	(0.00%, 0.17%)

Adverse Events in Literature

The potential AEs associated with the implantation of CRT-P or CRT-D systems have been documented in various articles in medical scientific literature. A summary of those events and their published incidence are included below.

1. Ahsan SY, Saberwal B, Lambiase PD, Chaubey S, Segal OR, Gopalamurugan AB, McCready J, Rogers DP, Lowe MD, and Chow AWC. An 8-year single-centre experience of cardiac

resynchronization therapy: procedural success, early and late complications, and left ventricular lead performance. Europace 2013;15:711-717.

Retrospective data were analyzed for all acute and chronic complications occurring over 490 consecutive CRT device procedures in 402 patients, from 2000 through 2008. Associated complications were reported by timeframe.

Table 25: Complications reported in Ahsan et al.

Table 3 Early and late complications by complication type[a]

Complication type	Early (<90 days) (*n*)	Late (>90 days) (*n*)	Mean time to late complication (months)
Death	1	0	–
Pneumothorax	2	0	–
Phrenic nerve stimulation requiring revision	3	4	11.4 (±8)
Infection	7	7	14.9 (±11)
Noise on RV/RA lead	1	3	17.0 (±22)
Box migration	2	1	15.0
RV/RA/LV lead fracture	1	4	33.1
Lead erosion	3	0	–
RV/RA lead displacement	6	6	4.9 (±2)
Inability to implant LV lead	13	–	–
LV lead displacement	5	5	6.8 (±4)
Total	44 (9.4%)	30 (6.1%)	

[a]This table shows all early and late complications and the mean time to their occurrence.

2. Dickstein K, Bogale N, Priori S, Auricchio A, Cleland JG, Gitt A, Limbourg T, Linde C, van Veldhuisen DJ, Brugada J; Scientific Committee; National Coordinators. The European Cardiac Resynchronization Therapy Survey. European Heart Journal 2009; 30:2450–2460.

The primary aim of this survey was to describe current European practice associated with CRT implantations. A total of 140 centers from 13 European countries contributed data from consecutive patients successfully implanted with a CRT device with or without an ICD between November 2008 and June 2009. The total number of patients enrolled was 2438.

Table 26: Complications reported in Dickstein et al.

Event	Incidence (%)
Peri-procedural complications	10
Bleeding	1
Pocket haematoma	3
Pneumothorax	1
Pericardial tamponade	0.3
Coronary sinus dissection	1
Phrenic nerve pacing	2
Lead dislocation	3

Post–implantation device related complications	4
Lead displacement	2
Lead malfunction	0
Phrenic nerve stimulation	2

3. Kirkfeldt R.E., Johansen J.B., Nohr E.A., Jorgensen O.D., Nielsen J.C. Complications after cardiac implantable electronic device implantations: An analysis of a complete, nationwide cohort in Denmark. European Heart Journal 2014 35:18 1186-1194.

This was a population-based cohort study in all Danish patients who underwent a Cardiac Implantable Electronic Device (CIED) procedure from May 2010 to April 2011. The study population consisted of 5918 consecutive patients. Total of 562 patients (9.5%) experienced at least one complication.

Table 27: Complications reported by Kirkfeldt et al. shows cumulative incidence of complications at 6 months[a].

Table 27: Complications reported by Kirkfeldt et al.

Complication type	**All (n=5918)**	**New Implant (n=4335)**	**Generator replacement (n=1136)**	**Upgrade/Lead revision (n=427)**
Any complication	562 (9.5; 8.7–10.2)	432 (9.9; 9.0–10.8)	67 (5.9; 4.5–7.3)	63 (14.8; 11.4–18.1)
Any major complication[b]	329 (5.6; 5.0–6.1)	253 (5.8; 5.1–6.5)	40 (3.5; 2.4–4.6)	36 (8.4; 5.8–11.1)
Any minor complication[c]	250 (4.2; 3.7–4.7)	189 (4.3; 3.7–4.9)	30 (2.6; 1.7–3.6)	31 (7.3; 4.8–9.7)
Major complications				
Lead related re-intervention	143 (2.4; 2.0–2.8)	120 (2.8; 2.3–3.2)	10 (0.9; 0.3–1.4)	13 (3.0; 1.4–4.7)
Infection	49 (0.8; 0.6–1.1)	24 (0.6; 0.3–0.8)	17 (1.5; 0.8–2.2)	8 (1.9; 0.6–3.2)
Local infection	22 (0.4; 0.2–0.5)	10 (0.2; 0.1–0.4)	8 (0.7; 0.2–1.1)	4 (1.0; 0.0–1.9)
Systemic infection/endocarditis	27 (0.5; 0.3–0.6)	14 (0.3; 0.2–0.5)	9 (0.8; 0.3–1.3)	4 (0.9; 0.0–1.9)
Pneumothorax requiring drainage	51 (0.9; 0.6–1.1)	45 (1.0; 0.7–1.3)	0	6 (1.4; 0.3–2.5)
Cardiac perforation	38 (0.6; 0.4–0.8)	35 (0.8; 0.5–1.1)	0	3 (0.7; 0.0–1.5)

Cardiac perforation (No intervention)	21 (0.4; 0.2–0.5)	18 (0.4; 0.2–0.6)	0	3 (0.7; 0.0–1.5)
Cardiac perforation (Intervention)	17 (0.3; 0.2–0.4)	17 (0.4; 0.2–0.6)	0	0
Pocket revision because of pain	25 (0.4; 0.3–0.6)	10 (0.2; 0.1–0.4)	9 (0.8; 0.3–1.3)	6 (1.4; 0.3–2.5)
Generator-lead interface problem with re-intervention	7 (0.1; 0.0–0.2)	3 (0.1; 0.0–0.1)	4 (0.4; 0.0–0.7)	0
Haematoma requiring re-intervention	10 (0.2; 0.1–0.3)	9 (0.2; 0.1–0.3)	1 (0.1; 0.0–0.3)	0
Other[d]	16 (0.3; 0.1–0.4)	16 (0.4; 0.2–0.5)	0	0
Minor complications				
Haematoma[e]	138 (2.3; 1.9–2.7)	104 (2.4; 1.9–2.8)	20 (1.8; 1.0–2.5)	14 (3.3; 1.6–5.0)
Wound infection treated with antibiotics	69 (1.2; 0.9–1.4)	47 (1.1; 0.8–1.4)	12 (1.0; 0.5–1.7)	10 (2.3; 0.9–3.8)
Pneumothorax conservatively treated	39 (0.7; 0.5–0.9)	32 (0.7; 0.5–1.0)	0	7 (1.6; 0.4–2.8)
Lead dislodgement without re-intervention	10 (0.2; 0.1–0.3)	9 (0.2; 0.1–0.3)	0	1 (0.2; 0.0–0.7)

[a]Reported as absolute frequencies and percentages with 95% CIs in parenthesis.

[b]All re-interventions were categorized as major complications due to their inherently higher risk of infections e.g. local CIED infections requiring re-intervention, systemic infections, pocket revisions etc.

[c]Minor complications included haematomas resulting in a prolonged hospital stay, hospital re-admissions, or additional out-patient visits, wound infections treated with antibiotics, pneumothorax conservatively treated, and lead dislodgements without re-intervention.

[d]Deep venous thrombosis (n=8), Twiddler's syndrome (n=3), wound revision (n=3), stroke (n=1), myocardial infarction (n=1)

[e]Resulting in prolonged hospital stay, hospital re-admission, or additional out-patient visit.

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Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	Attain Stability™ Quad Clinical Study
Study Product Name	Attain Stability™ Quad MRI SureScan Left Ventricular Lead (Model 4798)
Sponsor/Local Sponsor	**Sponsor:** Medtronic, Inc. Cardiac Rhythm and Heart Failure Clinical Research 8200 Coral Sea Street NE Mounds View, MN 55112 U.S.A. 1-800-328-2518 **Local Sponsors:** Canada Medtronic of Canada 99 Hereford Street Brampton, ON, L6Y 0R3 Canada +1-905-460-3800 Europe, Middle East, Africa (EMEA) Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands +31-43-35-66-566 Hong Kong Medtronic Hong Kong Medical Ltd. 1104-11, 11/F, Tower 1, The Gateway, Harbour City, Kowloon, Hong Kong SAR, China +852-2919-1300 Malaysia Medtronic International Ltd (Malaysia) B-23-1 Level 23, The Ascent, Paradigm No 1 Jalan SS7/26A Kelena Jaya 46301 Petaling Jaya Selangor Malaysia +603 7883 8000
Document Version	Version 3.0; 20/MAR/2017

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1. Sponsor Contact

Medtronic, Inc. is sponsoring the Attain Stability Quad Clinical Study. Regional contact information is provided below. This information may be subject to change during the course of the Attain Stability Quad Clinical Study. Periodic updates to study contact information will be sent to sites as needed.

Table 1: Study Sponsor Contact Information

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2. CROs/Core Laboratories

This information may be subject to change during the course of the Attain Stability Quad Clinical Study. Periodic updates to study contact information will be sent to sites as needed.

Table 2: CRO and Core Laboratory Information

Contact Information	Role
Cognizant Technology Solutions 500 Frank W. Burr Blvd. Teaneck, NJ 07666 United States Direct Phone: (201) 801-0233 Direct Fax: (201) 801-0243	Review of electronic case report forms and management of discrepancies

3. Version History

Version	Summary of Changes	Author(s)/Title
1.0	○ Initial Release	Melissa Thalin, Principal Clinical Research Specialist Rinie Peters, Associate Clinical Research Specialist Ann Vacca, Principal Customer Specialist Shelby Li, Senior Principal Statistician Joao Monteiro, Senior Statistician
2.0	○ Added slitting information for Implant analyzer PCT at synopsis and table 8 ○ Remote visits: ▪ Changed wording to clarify required actions ▪ Removed manual PCT test ▪ Deleted rationale for final vector programmed ○ Recurring 6 mth FU: ▪ Removed PNS test ▪ Removed Patient Global Assessment ○ System Modification ▪ Reduced electrical testing requirements ○ Patient Global Assessment ▪ Added to Glossary ▪ Removed from Baseline and 3 month visits ○ Vectors ▪ Added additional 4 CRT-P vectors (LV to Can) throughout ○ Investigator Lead Handling Assessment ▪ Added to Implant visit ○ Adjusted # of participating centers ○ Updated exclusion criteria #2 ○ Updates to grammar, version ,and footers	Melissa Thalin, Principal Clinical Research Specialist Rinie Peters, Associate Clinical Research Specialist

3.0	○ Modified Primary Efficacy objectives/endpoints to include PNS testing ○ Added reference to inclusion criteria that US patients should meet CRT device indications per the HRS/ACC/AHA guidelines ○ Added reference to exclusion criteria that subjects with significant allergy to contrast dye will be excluded ○ Added statement that EU will be full ISO 14155 compliant ○ Broadened the 3rd secondary endpoint definition to include summary statistics on all PCTs and lead impedances collected	Melissa Thalin, Principal Clinical Research Specialist

4. Investigator Statement

Investigators will be provided with a separate investigator agreement to document their obligation and commitment with respect to study conduct.

5. Index

6. List of Tables

7. List of Figures

8. Glossary

Table 3: Glossary of Terms

Term	Definition
2090	Medtronic CareLink Programmer with the application software installed.
2290	Medtronic Analyzer
Medtronic Attain Stability Quad MRI SureScan (Model 4798) LV Lead	The quadripolar LV lead being studied (investigational in the United States/Canada, commercially available in EMEA, Hong Kong, and Malaysia).
Active Fixation Helix	A non-electrically active side helix, positioned between the LV 3 and LV 4 electrodes that will allow fixation of the Attain Stability Quad MRI SureScan (Model 4798) LV Lead in the cardiac vein.
ADE	Adverse Device Effect
AE	Adverse Event
Ag	Silver
CABG	Coronary Artery Bypass Graft

Term	Definition
CAD	Coronary Artery Disease
CDF	Cumulative Distribution Function
CEC	Clinical Events Committee
CIP	Clinical Investigation Protocol
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy: Established pacing therapy for patients with heart failure
CRT-D	Cardiac Resynchronization Therapy - Defibrillator
CRT-P	Cardiac Resynchronization Therapy - Pacemaker
CS	Coronary Sinus
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency
DEKRA	Deutscher Kraftfahrzeug-Überwachungs-Verein (German Motor Vehicle Inspections Association)
DMC	Data Monitoring Committee
EC	Ethics Committee
EMEA	Europe, the Middle East, and Africa
eCRF	Electronic Case Report Form
MEC/IRB/HREB/Ethics Board	Ethics Committee
FAL	Foreseeable Adverse Event List
FDA	Food and Drug Administration
Fr	French
GCP	Good Clinical Practice

Term	Definition
HF	Heart Failure
HTN	Hypertension
IC	Informed Consent
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IDE	Investigation Device Exemption
Ir	Iridium
IRB	Institutional Review Board
LAR	Legally Authorized Representative
LBBB	Left Bundle Branch Block
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MCRD	Monolithic Controlled Release Device which is located on the Attain Stability Quad MRI SureScan LV Lead (Model 4798) electrodes which elutes steroid to reduce inflammatory response within the cardiac vein.
Mechanical Stop	A component on the Attain Stability Quad MRI SureScan (Model 4798) LV Lead located at the base of the helix to prevent wedging of endothelial tissue in the helix and to prevent tissue ingrowth.
MedDRA	Medical Dictionary for Regulatory Activities
OC	Oracle Clinical (database management system)
OTW	Over-the-wire
PCT	Pacing Capture Threshold
Patient Global Assessment	Self-reported assessment to provide information on patient condition compared to previous heart failure status

Term	Definition
PHD	Pre-Hospital Discharge means the point at which a subject has been released from the hospital post implant procedure.
PMA	Premarket Approval
PNS	Phrenic Nerve Stimulation
POR	Power On Reset
Pt	Platinum
PTCA	Percutaneous Transluminal Coronary Angioplasty
QOL	Quality of Life
RA	Right Atrial
RRT	Recommended Replacement Time
RV	Right Ventricular
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SDN	Software Distribution Network
TÜV	Technischer Überwachungsverein (German safety validation organization)
UADE	Unanticipated Adverse Device Effect
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

9. Synopsis

Title	Attain Stability™ Quad Clinical Study
Product Name	Attain Stability™ Quad MRI SureScan Left Ventricular Lead (Model 4798)
Sponsor	Medtronic, Inc. Cardiac Rhythm and Heart Failure Clinical Research 8200 Coral Sea Street NE Mounds View, MN 55112 U.S.A. 1-800-328-2518
Local Sponsor	Canada Medtronic of Canada 99 Hereford Street Brampton, ON, L6Y 0R3 Canada +1-905-460-3800 EMEA Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands +31-43-35-66-566 Hong Kong Medtronic Hong Kong Medical Ltd. 1104-11, 11/F, Tower 1, The Gateway, Harbour City, Kowloon, Hong Kong SAR, China +852-2919-1300 Malaysia Medtronic International Ltd (Malaysia) B-23-1 Level 23, The Ascent, Paradigm, No 1 Jalan SS7/26A Kelena Jaya 46301 Petaling Jaya Selangor Malaysia +603 7883 8000
Indication under investigation	All subjects included in the study will be implanted with a Medtronic market released de novo CRT-P or CRT-D device, compatible market released Medtronic RA and Medtronic RV leads and an Attain Stability Quad SureScan LV lead (Model 4798). For subjects enrolled who are receiving an upgrade to a CRT system, existing non-Medtronic RV and/or existing non-Medtronic RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used.

	Given the vast similarities between the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the Attain Performa family of leads, the proposed indications for use are the same. The indications are as follows: The Attain Stability Quad MRI SureScan 4798 steroid-eluting, quadripolar electrode, IS4 transvenous lead is indicated for chronic pacing in the left ventricle via the cardiac vein, when used with a compatible Medtronic Cardiac Resynchronization Therapy (CRT) system. Extended bipolar pacing is available using this lead in combination with a compatible market approved CRT-D system and RV defibrillation lead.
Investigation Purpose	The Attain Stability Quad Clinical Study is a prospective, non-randomized, multi-site, global, Investigational Device Exemption (IDE) interventional clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV lead (Model 4798). This study will not be considered investigational in geographies with CE Mark of the Attain Stability Quadripolar LV lead (4798). However, data collected from all study subjects will be represented in the final report and the PMA Supplement (PMA-S) to the Model 4196 Original PMA.
Product Status	The Attain Stability Quad Clinical Study will be conducted using a research system composed of an approved Medtronic CRT-D or CRT-P System and an Attain Stability Quad MRI SureScan LV Lead (Model 4798). The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is an active fixation quadripolar LV lead based on the Attain Performa lead family models (4298, 4398, and 4598). The lead incorporates an active fixation helix similar to the Attain Stability bipolar LV lead (Model 20066/4796) which is designed to allow an implanter more options in lead location. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered investigational in geographies where the product is not available commercially and will be labeled for clinical use only. These geographies include but are not limited to the US and Canada. Investigational Attain Stability Quad MRI SureScan LV Leads (Model 4798) will be distributed to a site only when Medtronic has received all required documentation (including but not limited to Ethic Committee approval, a signed Clinical Trial Agreement and documentation of training) and has

	notified the site of site readiness. Distribution of the investigational product to study sites will be managed by Medtronic and can only be ordered by Medtronic personnel. Sites with these clinically labeled Attain Stability Quad MRI SureScan LV Leads (Model 4798) will track disposition upon receipt or return of the lead but also upon implant or explant of the lead. Disposition logs will be available within the electronic data management system and shall be maintained at each site in all geographies to track investigational product information. For geographies where the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is not considered investigational, commercially approved devices will be used. Sites that use commercially available Attain Stability Quad MRI SureScan LV Leads (Model 4798) will track device disposition upon implant or explant on the lead CRFs. The Medtronic approved CRT-P or CRT-D devices will be programmed and interrogated using a Medtronic CareLink (2090) programmer. Medtronic may incorporate additional programmers as they receive regulatory approval. The CareLink Monitor Model 2490C is an external monitor that is indicated for use in the transfer of patient and device data from implanted Medtronic devices. The CareLink Monitor Model 2490C interrogates implanted devices and temporarily stores these data, collaborates with the appropriate Medtronic server to confirm the establishment of an Internet connection with server, performs any required file translation functions necessary for data transfer, executes data file transfer, and collaborates with the appropriate Medtronic server to confirm data file transfer through the Internet connection with the server. The CareLink Monitor 2490C is not a programmer and cannot be used to program implanted device parameters. CareLink monitors are not a substitute for appropriate medical attention in the event of an emergency and should only be used as directed by a physician. Approved Medtronic CRT-P and CRT-D devices used in this study qualify for use with the Medtronic CareLink Monitor and Medtronic CareLink Network. Medtronic may incorporate additional home monitors as they receive regulatory approval.

	Medtronic's commercially available Model 2290 Analyzer must be available at each center during the implant procedure to determine acceptable electrical parameters. Medtronic may incorporate additional analyzers as they receive regulatory approval.
Primary Objective(s)	**<u>Primary Safety Objective: Lead complication-free rate at 6 months</u>** The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered safe if the probability of subjects free of Model 4798 lead-related complications at 6 months post-implant is greater than 87% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 87%). The study primary safety endpoint is Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complications through 6 months post implant. All reported system and procedure-related AEs will be reviewed by an event review committee for LV lead relatedness and severity (complication vs observation, refer to 17.1.2 for definitions). **<u>Primary Efficacy Objectives: Lead pacing capture thresholds at 6 months</u>** To demonstrate the effectiveness of the Attain Stability Quad MRI SureScan LV lead (Model 4798) the study will evaluate the likelihood that there are at least two programmable vectors for each patient post implant. The effectiveness of this lead will be evaluated based on two primary efficacy objectives. More specifically, both primary efficacy objectives must be met simultaneously. **<u>Primary Efficacy Objective #1</u>** The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet the objective if the proportion of subjects with at least one LV lead pacing vector having a pacing capture threshold less than or equal to 2.5 V at 0.5ms pulse width (with absence of Phrenic Nerve Stimulation (PNS) at 5.0 V) at 6 months post-implant is greater than 80% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 80%). The endpoint for the primary efficacy objective is whether or not there is at least one Model 4798 LV lead pacing vector with pacing capture voltage thresholds less than or equal to 2.5V (with

	absence of PNS at 5.0 V). This endpoint will be measured at the 6-month post implant follow-up visit. **<u>Primary Efficacy Objective #2</u>** The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet the objective if the proportion of subjects with at least one additional LV lead pacing vector having a pacing capture threshold less than or equal to 4.0 V at 0.5ms pulse width (with absence of PNS at 5.0 V) at 6 months post-implant is greater than 80% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 80%). The co-primary efficacy endpoint is whether or not a second Model 4798 lead configuration has a pacing capture threshold less than or equal to 4V (with absence of PNS at 5.0 V), excluding the pacing vector that is already counted to the primary efficacy endpoint #1. This endpoint will be measured at 6-month post implant follow-up visit.

Secondary

Objective(s)	The secondary objectives are descriptive in nature and are intended to provide additional information about the Attain Stability Quad Model 4798 LV lead. There will be no established performance requirements for these secondary objectives. o Implant procedure related information: success rate, implant related times o Endpoints will include implant success rate and procedure durations. o 6-month reliability: post implant lead failure modes (i.e. complication rate) o Endpoint is Model 4798 lead related complications. o Electrical measurements (PCT and Impedance) at follow-ups o Endpoints are the electrical measurements (pacing capture thresholds and impedance values) for the four extended bipolar (CRT-D) or unipolar (CRT-P) vectors, i.e.

	LV1 to RVCoil/Can, LV2 to RV Coil/Can, LV3 to RV Coil/Can and LV4 to RV Coil/Can (refer to 15.8.2.3 for the testing procedure requirements)
Study Design	The Attain Stability Quad Clinical Study is a prospective, non-randomized, multi-site, global, Investigational Device Exemption (IDE) interventional clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV lead (Model 4798) in patients indicated for a de novo LV lead implant. This will be assessed through primary safety and primary efficacy endpoints. All subjects included in the study will be implanted with a Medtronic market released de novo CRT-P or CRT-D device and an Attain Stability Quad MRI SureScan LV Lead (Model 4798). Compatible market released Medtronic RA and Medtronic RV leads will be required. For subjects enrolled who are receiving an upgrade to a CRT system, existing non-Medtronic RV and/or existing non-Medtronic RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used. Up to 471 subjects will be enrolled into the study and up to 471 Attain Stability Quad MRI SureScan LV Leads (Model 4798) implanted, to ensure a minimum effective sample size of 400 Model 4798 leads implanted with 6 months post implant follow up visits (assuming 15% attrition). For the secondary endpoint of individual lead failure modes, Bayesian methods utilizing data from up to 37 historical patients will be used. All other objectives will be analyzed using only patients enrolled in this study. After a successful implant, threshold testing will occur per protocol requirement. Subjects will then be followed at implant, three months, six months and every six months thereafter until FDA approval is obtained or until study closure, whichever comes first. The study duration is expected to be approximately 19 months. This represents an estimated 13 months for subject enrollment and 6 months for subject follow-up for the last subject enrolled. Subjects are anticipated to be in the study for on average 12 months. The first enrollment is projected to occur in May 2017.
Sample Size	Up to 471 subjects will be enrolled into the study, to ensure a minimum effective sample size of 400 Model

	4798 leads implanted with 6 months post implant follow up visits (assuming 15% attrition) at up to 56 sites worldwide.
Inclusion/Exclusion Criteria	**Inclusion Criteria:** • Patient meets CRT implant criteria as determined by local regulatory and/or hospital policy (i.e. US subjects should meet CRT device indications per the HRS/ACC/AHA guidelines) • Patient (or legally authorized representative) has signed and dated the study-specific Consent Form • Patient is 18 years of age or older, or is of legal age to give informed consent per local and national law • Patient is expected to remain available for follow-up visits **Exclusion Criteria:** • Patient has had a previous unsuccessful LV lead implant attempt • Patient has a previous CRT system or LV lead implanted (for example, transvenous or epicardial) • Patient is currently implanted with a recalled (i.e. market-withdrawn, recalled or safety alert) RA and/or RV lead • Patient has known coronary venous vasculature that is inadequate for lead placement • Patient has unstable angina pectoris or has had an acute myocardial infarction (MI) within the past 30 days • Patient has had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the past 90 days • Patient has contraindications for standard transvenous cardiac pacing (e.g., mechanical right heart valve) • Patient has had a heart transplant (patients waiting for heart transplants are allowed in the study) • Patient has known renal insufficiency and/or significant allergy to contrast dye that would prevent them from receiving an occlusive venogram during the implant procedure • Patient is contraindicated for <1mg dexamethasone acetate • Patient is enrolled in any concurrent drug and/or device study that may confound the results of this study

	• Patient has a terminal illness and is not expected to survive more than six months • Patient meets exclusion criteria required by local law (e.g. age, pregnancy, breast feeding, etc.) • Patient is unable to tolerate an urgent thoracotomy
Study Procedures and Assessments	Clinical data will be collected at the study milestones: at enrollment, baseline, implant/PHD, 3M, 6M, thereafter every occurring 6M and study exit visits: **Enrollment/Baseline:** o Subject Informed Consent o Inclusion/Exclusion criteria verified o Subject demographics o Cardiovascular medications o Cardiovascular medical history o NYHA classification o Kansas City Cardiomyopathy Questionnaire (KCCQ) **Implant:** o Occlusive venogram with pre-determined target vessel location identified o Analyzer PCT data collection post lead fixation and prior to connecting the leads to the CRT-P/D device: 1. Pre-slitting the cannulation catheter and following guide wire/stylet has been pulled back proximal to the helix and electrodes 2. Post slitting the cannulation catheter o Investigator Lead Handling Assessment o System and procedure information PHD CRT System Testing and Programming using the implanted CRT-P or CRT-D device and the device programmer: <u>Lead Impedance</u> o Collect LV Lead Impedances using Vector Express on all vectors o Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector

	○ Retain printouts at the site Pacing Capture Thresholds (PCT) ○ Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors ○ NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) ○ Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site Phrenic Nerve Stimulation (PNS) ○ Test for presence of PNS at 8.0V at 0.5ms on final programmed vector ○ NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms ○ NOTE: PNS observed during this testing will not be considered an AE Other Data Collection ○ Rationale for selecting specific LV lead pacing vector for final programming ○ Final device interrogation/save-to-media ○ AE Assessment ○ Study deviations ○ Device deficiencies **3 Month (remote or in office visit):** Lead Impedance ○ Obtain LV Lead Impedance Test for the final programmed vector ○ Retain printouts at the site Pacing Capture Thresholds (PCT) ○ Obtain PCTs at 0.5ms pulse width on the final programmed vector ○ NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) ○ Retain printouts at the site Phrenic Nerve Stimulation (PNS) (in office visit only) ○ Test for presence of PNS at 8.0V at 0.5ms on final programmed vector ○ NOTE: If PNS is present at 8.0V at 0.5ms,

	measure the PNS threshold at 0.5ms ○ NOTE: PNS observed during this testing will not be considered an AE <u>Other Data Collection</u> ○ NYHA classification ○ Final device interrogation/save-to-media (or CareLink transmission) ○ AE Assessment ○ Study deviations ○ Device deficiencies **6 Month:** <u>Lead Impedance</u> ○ Collect LV Lead Impedances using Vector Express on all vectors ○ Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site <u>Pacing Capture Thresholds (PCT)</u> ○ Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors ○ NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) ○ Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site <u>Phrenic Nerve Stimulation (PNS)</u> ○ Test for presence of PNS at 8.0V at 0.5ms on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can ○ Test for presence of PNS at 8.0V at 0.5ms on final programmed vector ▪ NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms ○ Test for presence of PNS at 5.0V at 0.5ms

	on the two efficacy endpoints (one vector with PCT ≤ 2.5 V and an additional vector with PCT ≤ 4.0 V) ○ NOTE: PNS observed during any PNS testing will not be considered an AE <u>Other Data Collection</u> ○ NYHA classification ○ Patient Global Assessment ○ Kansas City Cardiomyopathy Questionnaire (KCCQ) ○ Rationale for selecting specific LV lead pacing vector for final programming ○ Final device interrogation/save-to-media ○ AE Assessment ○ Study deviations ○ Device deficiencies **12 Month:** <u>Lead Impedance</u> ○ Collect LV Lead Impedances using Vector Express on all vectors ○ Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site <u>Pacing Capture Thresholds (PCT)</u> ○ Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors ○ NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) ○ Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site <u>Phrenic Nerve Stimulation (PNS)</u> ○ Test for presence of PNS at 8.0V at 0.5ms on final programmed vector ○ NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms

	○ NOTE: PNS observed during this testing will not be considered an AE Other Data Collection ○ NYHA classification ○ Patient Global Assessment ○ Kansas City Cardiomyopathy Questionnaire (KCCQ) ○ Rationale for selecting specific LV lead pacing vector for final programming ○ Final device interrogation/save-to-media ○ AE Assessment ○ Study deviations ○ Device deficiencies **Recurring 6 Month follow-ups (remote or in office visit):** Lead Impedance ○ Obtain LV Lead Impedance Test for the final programmed vector ○ Retain printouts at the site Pacing Capture Thresholds (PCT) ○ Obtain PCTs at 0.5ms pulse width on the final programmed vector ○ NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) ○ Retain printouts at the site Other Data Collection ○ NYHA classification ○ Final device interrogation/save-to-media (or CareLink transmission) ○ AE Assessment ○ Study deviations ○ Device deficiencies **Study Exit:** ○ Report the reason for exit ○ Final Interrogation file (or CareLink transmissions) for exits occurring prior to the 6 month visit) ○ Study Deviations ○ AEs ○ Device Deficiencies
Safety Assessments	Adverse Event and Device Deficiency handling in the Attain Stability Quad Clinical Study is ISO 14155:2011 compliant for all participating geographies with the

	exception that only those AEs which are related to the subject's system, procedure, accessory, or are cardiovascular-related, heart failure-related, MRI-related, and all Serious AEs, will be collected (refer to Section 17 for AE assessment). This ensures any AEs which could potentially be relevant will be collected. Reporting of these events to Medtronic will occur on an Adverse Event (AE) Form, including date of AE, treatment, resolution, assessment of both the seriousness of the AE and the relatedness to the investigational device or procedure. Each AE must be recorded on a separate AE eCRF. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened.
Statistics	The primary objective will be analyzed using the time-to-first event Kaplan-Meier survival analysis method. A minimum number of subjects who have completed their 6 months post-implant visits will be required. Time 0 will be the day a subject undergoes the implant procedure of an Attain Stability Quad MRI SureScan LV Lead (Model 4798), which will be independent of success status of this implant procedure. Event date is the onset date of a subject's first complication that is related to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) according to CEC adjudication. Subjects who undergo an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt and do not experience any LV lead related complications, will be censored at the time of their last known exposure to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) for the survival analysis. For any lost-to-follow up subject, the last contact date will be used as the censor date. The 1-sided 97.5% confidence limit lower bound for the survival probability at 6 months (183 days) will be calculated using the log-log survival function approach (Kalbfleisch and Prentice 2002).

10. Introduction

10.1. Background

Several clinical trials (including MIRCLE[1], MIRACLE-ICD[2], CONTAK-CD[3], MUSTIC[4], PATH-CHF[5], COMPANION[6], MADIT CRT[7], and CARE-HF[8]) have demonstrated the benefit of cardiac resynchronization therapy (CRT) among patients with moderate to severe heart failure (HF) with a prolonged QRS duration and depressed Left Ventricular (LV) function.

Approximately 5.7 million people in the United States (US) are living with HF[9]. Heart Failure may be a chronic condition which causes the heart to not pump oxygenated blood efficiently through the body due to stiffening of the heart muscle. Heart Failure may affect one or both sides of the heart. It is most often caused by coronary artery disease (CAD) or uncontrolled hypertension (HTN). Patients who suffer from HF experience a variety of different symptoms including most often fatigue, cough, shortness of breath, swollen feet (edema) and weight gain.

Heart Failure is treated with medications and sometimes cardiac devices (i.e. pacemaker or defibrillator with CRT). Medications work to relieve symptoms and reverse the effects of HF. Cardiac Resynchronization Therapy devices treat HF by synchronizing the left and right ventricles of the heart which improves the heart's ability to pump oxygenated blood to the body.[10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21]

Cardiac Resynchronization Therapy devices are primarily made up of 4 main components; the can or battery, a Right Atrial (RA) lead, a Right Ventricular (RV) lead, and a Left Ventricular (LV) lead.

The LV lead specifically is important at maintaining ventricular synchrony. In 2014, Medtronic released the Attain® Performa™ family of LV leads (models 4298, 4398 and 4598). The three different shapes of these leads (double canted, straight, and S-shaped) were designed to enable the lead to be passively fixed within different anatomies of coronary vessels. In addition, the 4 strategically placed electrodes on the lead were designed to offer 16 different electrical vector programming configurations.

Medtronic also released the Attain Stability bipolar LV lead (Model 20066/4796) (CE Mark approved in September 30, 2013) in Europe. This lead has a side helix which enables it to be actively fixated to the vessel wall. The active fixation is an advantageous component in vessels that are wide or have short take-offs. The next generation of LV lead is known as the Attain Stability™ Quad MRI SureScan LV lead (Model 4798). This is a quadripolar lead similar to its Attain Performa predecessor leads and has a side helix for active fixation like the Attain Stability bipolar lead.

10.2. Purpose

The Attain Stability Quad Clinical Study is a prospective, non-randomized, multi-site, global, Investigational Device Exemption (IDE), interventional clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability™ Quad MRI SureScan LV Lead (Model 4798). This study will not be considered investigational in geographies with CE Mark of the Attain Stability™ Quad MRI SureScan LV lead (Model 4798). However, data collected from all study subjects will be represented in the final clinical report and the PMA Supplement (PMA-S) to the Attain Ability Model 4196 Original PMA (P080006, approved April 7, 2009). Subjects successfully implanted with the Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be followed at implant, three months, six months and every six months thereafter until FDA approval is obtained or until study closure, whichever comes first.

11. Objectives and Endpoints

11.1. Objectives

11.1.1. Primary Objective(s)

Primary Safety Objective: Lead complication-free rate at 6 months

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered safe if the probability of subjects free of Model 4798 lead-related complications at 6 months post-implant is greater than 87% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 87%).

Primary Efficacy Objectives: Lead pacing capture thresholds at 6 months

To demonstrate the effectiveness of the Attain Stability Quad MRI SureScan LV Lead (Model 4798), the study will evaluate the likelihood that there are at least two programmable vectors for each patient post implant. The effectiveness of this lead will be evaluated based on two primary efficacy objectives. More specifically, both primary efficacy objectives must be met simultaneously.

Primary Efficacy Objective #1

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet this objective if the proportion of subjects with at least one LV lead pacing vector having a pacing capture threshold less than or equal to 2.5 V at 0.5 ms pulse width (with absence of Phrenic Nerve Stimulation (PNS) at 5.0 V) at 6 months post-implant is greater than 80% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 80%).

Primary Efficacy Objective #2

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet this objective if the proportion of subjects with at least one additional (or second) LV lead pacing vector having a pacing capture threshold less than or equal to 4.0 V at 0.5 ms pulse width (with absence of PNS at 5.0 V) at 6 months post-implant is greater than 80% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 80%).

11.1.2. Secondary Objective(s)

The secondary objectives are descriptive in nature and are intended to provide additional information about the Attain Stability Quad MRI SureScan LV Lead (Model 4798). There will be no established performance requirements for these secondary objectives.

- To summarize implant procedure related information: success rate, implant related times
- To estimate 6-month reliability: post implant lead failure modes (i.e. complication rate)
- To estimate electrical measurement values (Pacing Capture Thresholds (PCTs) and Lead Impedance) at 6 months post-implant

11.2. Endpoints

11.2.1 Primary Endpoints

Primary Safety Endpoint

The study primary safety endpoint is Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complications through 6 months post implant. All reported system and procedure-related AEs will be reviewed by an event review committee for LV lead relatedness and severity (complication vs observation, refer to 17.1.2 for definitions).

Primary Efficacy Endpoint #1

The Model 4798 LV lead has sixteen (16) programmable pacing vectors. The endpoint for the primary efficacy objective is whether or not there is at least one Model 4798 LV lead pacing vector with pacing

capture voltage thresholds less than or equal to 2.5V (with absence of PNS at 5.0 V). This endpoint will be measured at the 6-month post implant follow-up visit.

Primary Efficacy Endpoint #2

The co-primary efficacy endpoint is whether or not a second Model 4798 lead configuration has a pacing capture threshold less than or equal to 4V (with absence of PNS at 5.0 V), excluding the pacing vector that is already counted to the primary efficacy endpoint #1. This endpoint will be measured at 6-month post implant follow-up visit.

11.2.2 Secondary Endpoints

To summarize implant procedure related information

Implant procedure related endpoints will include implant success rate and procedure durations.

To estimate 6-month reliability

The Model 4798 LV lead 6-month reliability endpoint is Model 4798 lead related complications.

To estimate electrical measurement values (Pacing Capture Thresholds (PCTs) and Lead Impedance) at 6 months post-implant

The electrical measurements endpoints are pacing capture thresholds and impedance values collected at each time point (i.e. Implant, 6 months, etc.) (refer to 15.8.2.3 for the testing procedure requirements).

12. Study Design

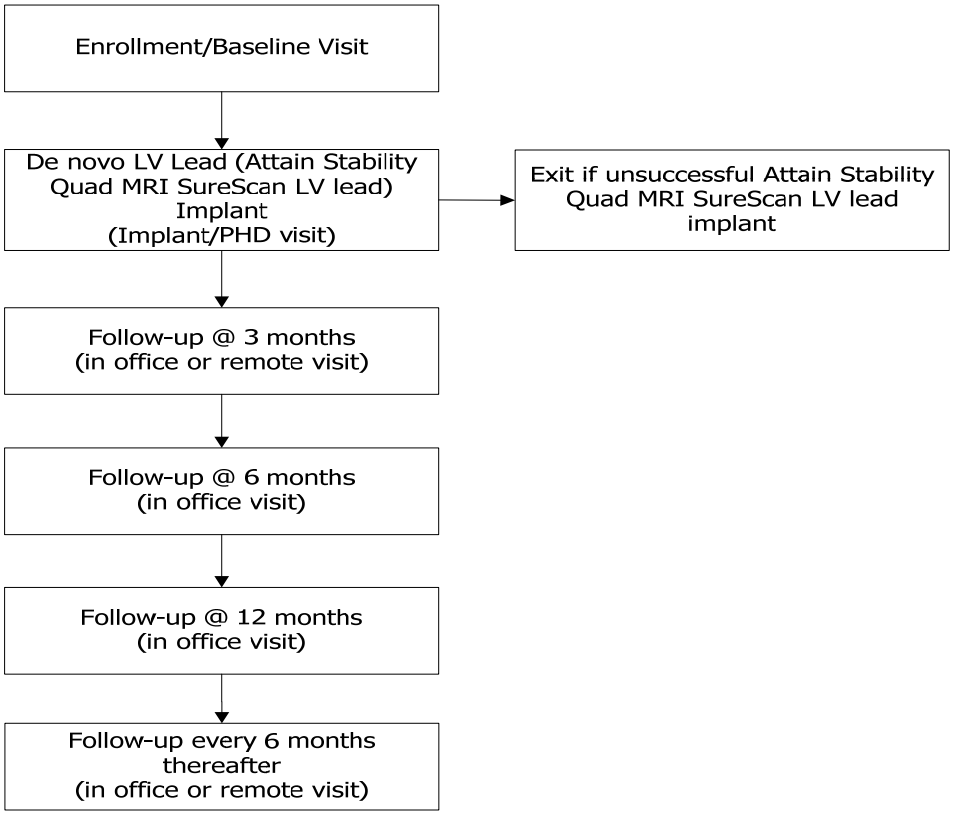
The Attain Stability Quad Clinical Study is a prospective, non-randomized, multi-site, global, Investigational Device Exemption (IDE), interventional clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) in patients indicated for a de novo LV lead implant. This will be assessed through a primary safety and primary efficacy endpoints.

All subjects included in the study will be implanted with a Medtronic market released de novo CRT-P or CRT-D device and an Attain Stability Quad MRI SureScan LV Lead (Model 4798). Compatible market released Medtronic RA and Medtronic RV leads will be required. For subjects enrolled who are receiving an upgrade to a CRT system, existing non-Medtronic RV and/or existing non-Medtronic RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used.

Up to 471 subjects will be enrolled into the study and up to 471 Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted, to ensure a minimum effective sample size of 400 Model 4798 leads implanted with 6 months post implant follow up visits (assuming 15% attrition). For the secondary endpoint of individual lead failure modes, Bayesian methods utilizing data from up to 37 historical patients will be used. All other objectives will be analyzed using only patients enrolled in this study. After a successful implant, threshold testing should occur to show at least one LV vector with pacing capture threshold (PCT) ≤ 2.5 V @ 0.5ms and with sufficient safety margin was programmed. Subjects will then be followed at implant, three months, six months and every six months thereafter until FDA approval is obtained or until study closure, whichever comes first.

See Figure 1 and Section 15 for further detail on study procedures and data collection as well as time-points for data collection.

Figure 1: Study Visits



The study is expected to be conducted at up to 56 sites worldwide. Participating geographies are expected to include, but are not limited to: the United States, Canada, EMEA, Malaysia, and Hong Kong. To ensure a widespread distribution of data and to minimize site bias in the study results, the maximum number of subjects allowed at a single site is 50 subjects.

12.1. Duration

The study duration is expected to be approximately 19 months. This represents an estimated 13 months for subject enrollment and 6 months for subject follow-up for the last subject enrolled. Subjects are anticipated to be in the study for on average 12 months. The first enrollment is projected to occur in May 2017. Subjects will complete visits at enrollment/baseline, implant, 3 months, 6 months, and then every 6 months thereafter. Subjects will not be replaced with newly enrolled subjects upon early exit. As described in Section 19, the sample size accounts for attrition.

12.2. Rationale

Upon market release, this Attain Stability Quad MRI SureScan LV Lead (Model 4798) will provide physicians an alternative option to actively fixate the lead utilizing a side helix feature to achieve stability. The Attain Stability Quad Clinical Study is designed to demonstrate that the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is safe and effective. See Section 19 for further background information and evaluation of clinical data. See Section 10 for further background on the study design.

12.3. Study Oversight

The study will utilize a Steering Committee (SC). The SC is responsible for the scientific content of the study and for providing input for the execution of the study. Members of the SC may be study site investigators. The purpose of the SC is to provide unbiased opinions and expertise to the Attain Stability Quad Clinical Study design and process. The SC will support the execution of the Attain Stability Quad Clinical Study and provide guidance, feedback and direction to the clinical study. The SC is comprised of the members as indicated in Table 4 below.

Table 4: Steering Committee Members

Committee Member	Contact information
George H. Crossley III, MD Steering Committee Co-Chair	Electrophysiology Fellowship Program Director Vanderbilt University Medical Center 1211 Medical Center Drive Nashville, TN 37232 United States (615) 322-5000 george.crossley@vanderbilt.edu
Kevin P. Jackson, MD Steering Committee Co-Chair	Electrophysiologist Duke Cardiology of Raleigh Medical Office Building 6 3320 Wake Forest Road 2nd Floor, Suite 200 Raleigh, NC 27609 United States (919) 862-5100 k.j@duke.edu
Dr. Maria Grazia Bongiorni	Electrophysiologist University Hospital of Pisa Lungarno Antonio Pacinotti 43, 56126 Pisa PI Italia +39 050 221 2111 m.g.bongiorni@med.unipi.it
Prof. Svein Faerestrand	Electrophysiologist University of Bergen Jonas Liesvei 65 Bergen, Norway 5021 +47 55 97 67 04 svein.faerestrand@helse-bergen.no
Dr. Axel Kloppe	Electrophysiologist Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil GmbH, Bürkle-de-la-Camp-Platz 1, 44789 Bochum, Germany +49 234 3026050 axel.kloppe@bergmannsheil.de

Melissa Kong, MD	Electrophysiologist Silicon Valley Cardiology 1300 Stockbridge Ave Redwood City, CA 94061 United States (650) 363-5262 mhkong1@gmail.com
Raymond Yee, MD	Electrophysiologist London Health Sciences Centre 339 Windemere Road London, ON N6A 5A5 Canada (519) 663-3671 ryee@uwo.ca
Francois Philippon, MD	Electrophysiologist Institut Universitaire de Cardiologie et de Pneumologie de Quebec 2725 Chemin Ste-Foy Quebec G1V 4G5 Canada (418) 656-8711 francois.philippon@fmed.ulaval.ca

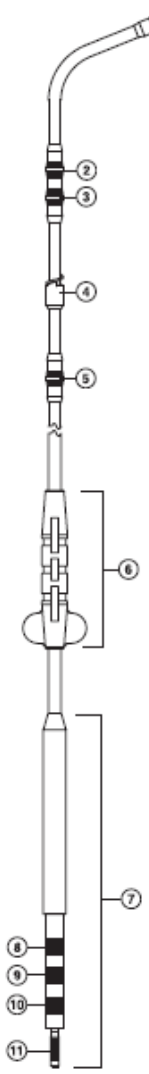
The study will also utilize a Clinical Events Committee (CEC) who will be responsible for adjudicating adverse events and deaths, including procedure and/or system-related complications. Further details for the CEC are provided in Section 18.1.

13. Product Description

13.1. General

The Medtronic Attain Stability Quad MRI SureScan (Model 4798) is a steroid-eluting, quadripolar electrode, transvenous, over-the-wire (OTW), IS4-LLLL compatible, active fixation, cardiac vein pacing LV lead. This lead is similar to the Attain Performa family of quadripolar leads (Models 4298, 4398, and 4598) but also has a side helix for active fixation which is similar to the Attain Stability bipolar lead (Model 20066/4796) (available outside of the United States). Figure 2 is a drawing of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) illustrating the specifications and location of the four electrodes in comparison to the side helix.

Figure 2: Attain Stability Quad MRI SureScan LV Lead (Model 4798) Specifications Drawing



[1] Electrode LV1 (the distal electrode): nominally 5.8 mm^2 geometric pacing surface area

[2] Electrode LV2: nominally 5.8 mm^2 geometric pacing surface area

[3] Electrode LV3: nominally 5.8 mm^2 geometric pacing surface area

[4] Helix assembly

[5] Electrode LV4 (the proximal electrode): nominally 5.8 mm^2 geometric pacing surface area

[6] Anchoring sleeve

[7] IS4 connector

[8] Contact LV4

[9] Contact LV3

[10] Contact LV2

[11] Contact LV1

Table 5 provides compares of the Attain Performa family of leads design features to the Attain Stability Quad MRI SureScan LV Lead (Model 4798).

Table 5: Comparison of Medtronic Quadripolar LV Leads

	Attain Performa			Attain Stability Quad
Design Feature	Model 4298	Model 4398	Model 4598	Model 4798
Shape	Double Canted	Straight	S-Shaped	Single Canted
Implant Method	Guide wire, stylet, or hybrid guide wire via Medtronic Delivery System	Same as 4298	Same as 4298	Guide wire, stylet, or hybrid guide wire via Medtronic Delivery System and active fixation
Delivery System Inner Diameter	≥ 5.7 Fr ID	Same as 4298	Same as 4298	Same as 4298
Lead Body Diameter	5.3 Fr proximal/3.9 Fr distal	Same as 4298	Same as 4298	4.4 Fr proximal/3.9 Fr distal
Lead Body Conductor	Single Quadfilar Coil (Multiconductor)	Same as 4298	Same as 4298	Same as 4298
Conductor Material	Ag core-low Titanium MP35Ncoil	Same as 4298	Same as 4298	Same as 4298
Insulation (Outer/Inner)	Polyurethane 55D SI-PI	Same as 4298	Same as 4298	Same as 4298
Polarity	Selectable Quad-electrode	Same as 4298	Same as 4298	Same as 4298
Electrode Material	PT/Ir* alloy with TiN coating	Same as 4298	Same as 4298	Same as 4298
Fixation Helix Material	N/A	N/A	N/A	Pt/Ir** alloy
Electrode Spacing	21mm/ 1.3mm/ 21mm	Same as 4298	Same as 4298	Same as 4298
Surface Area per	5.8	Same as 4298	Same as 4298	Same as 4298

Electrode (mm^2)				
Steroid and Dose / MCRD	Dexamethasone acetate Each (4) Ring 72µg	Same as 4298	Same as 4298	Same as 4298
Total Target Dose	288 µg/lead	Same as 4298	Same as 4298	Same as 4298

*90/10 Platinum Iridium
**80/20 Platinum Iridium

Similar to the Attain Performa family of leads, the Attain Stability Quad MRI SureScan LV Lead (Model 4798) contains 4 electrodes with surface area of 5.8 mm^2 per electrode and is designed to function as cathodes or anodes, depending on how the device LV pacing vector is programmed:

- electrode LV1, the distal electrode, positioned near the distal tip of the lead
- electrode LV2, positioned 21 mm proximal to electrode LV1
- electrode LV3, positioned 1.3 mm proximal to electrode LV2
- electrode LV4, the proximal electrode, positioned 21 mm proximal to electrode LV3

The electrode spacing on the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is identical to the approved Attain Performa family of leads. This includes a non-uniform electrode spacing consisting of a reduced electrode spacing configuration (LV2-LV3) that alters the size of the electric field that is generated when stimulating the heart tissue. This close electrode spacing is designed to reduce the likelihood of stimulating the phrenic nerve while still allowing for optimal lead placement and acceptable pacing capture thresholds.

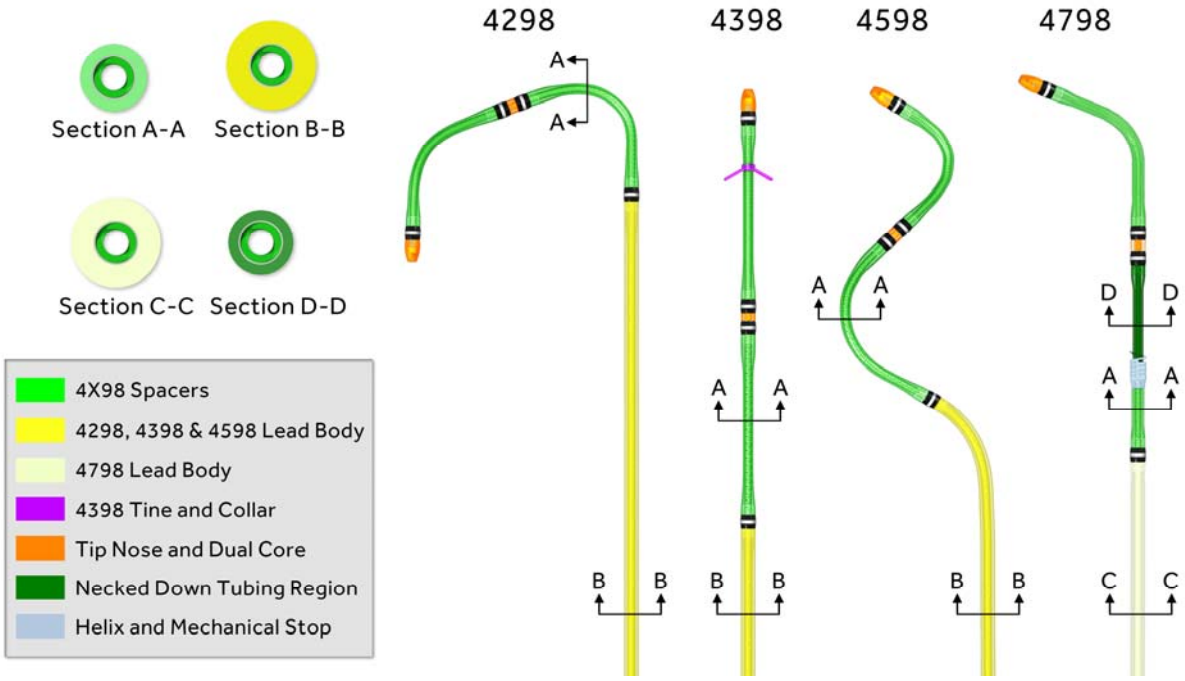
Similar to Attain Performa, each electrode contains a Monolithic Controlled Release Device (MCRD) for elution of steroid to reduce inflammatory response within the cardiac vein. The MCRDs contain a combined-total target dosage of 288 µg of dexamethasone acetate steroid. The target dose of the steroid is 72 µg at each MCRD. Upon exposure to body fluids, the steroid elutes from the MCRDs. The steroid suppresses the inflammatory response that is believed to cause threshold rise typically associated with implanted pacing electrodes.

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) has the same lead body conductor (Single Quadfilar Coil (Multiconductor), conductor material (Ag core-low Titanium MP35N coil), insulation (outer/inner) (Polyurethane 55D SI-PI), and requires a similar delivery system inner diameter as the Attain Performa family of leads (≥ 5.7 Fr ID).

Unlike the Attain Performa family of leads, the Attain Stability Quad MRI SureScan LV Lead (Model 4798) has a slightly smaller lead body diameter. The lead body diameter of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is 4.4 Fr proximal (compared to 5.3 Fr on the Attain Performa family of leads) and 3.9 French distal (same as Attain Performa family of leads). This slightly smaller lead body tubing diameter is designed to enhance torquability and steerability to facilitate adherence of the side helix in the target location.

Figure 3 is a visual comparison between the Attain Perform leads and the Attain Stability Quad MRI SureScan LV Lead (Model 4798) illustrating the similar electrode location but different lead body diameter.

Figure 3: Comparison of Attain Performa Leads and the Attain Stability Lead Model 4798



A detailed comparison of the Attain Stability bipolar lead (Model 4796) and Attain Stability Quad lead (Model 4798) is presented in Table 6.

Table 6: Comparison of Medtronic Attain Stability Bipolar and Quadripolar LV Leads

	Attain Stability	Attain Stability Quad
Design Feature	Model 4796/20066	Model 4798
Shape	Single Canted	Same as 4796/20066
Implant Method	Guide wire, Stylet, or hybrid guide wire via Medtronic Delivery System and active fixation	Same as 4796/20066
Delivery System Inner Diameter	≥ 5.7 Fr ID	Same as 4796/20066
Lead body diameter	3.9 Fr proximal / 3.4 Fr distal	4.4 Fr proximal /3.9 Fr distal
Lead Body Conductor	Single 2 Filar Coil (Multiconductor)	Single Quadfilar Coil (Multiconductor)
Conductor Material	Ag core-low Titanium MP35N coil	Same as 4796/20066

	Attain Stability	Attain Stability Quad
Design Feature	Model 4796/20066	Model 4798
Shape	Single Canted	Same as 4796/20066
Insulation (Outer/Inner)	Polyurethane 55D SI-PI	Same as 4796/20066
Polarity	bipolar	Selectable Quad-electrode
Electrode Material	Pt/Ir* alloy with TiN coating	Same as 4796/20066
Fixation Helix Material	Pt/Ir** alloy	Same as 4796/20066
Electrode Spacing	21 mm	21mm / 1.3mm / 21mm
Surface Area per electrode (mm^2)	5.8	Same as 4796/20066
Steroid and Dose / MCRD	Dexamethasone acetate Tip 160µg , Ring 72µg	Dexamethasone acetate Each (4) Ring 72µg
Total Target Dose	232µg/lead	288 µg/lead
Molded Tip Seal	Silicone (with steroid), pierced hole	Silicone (without steroid), cross-cut hole
Fixation Method	Helix	Same as 4796/20066
Connector	IS-1 B1	IS4-LLLL
Length (cm)	88 cm only	78 and 88 cm

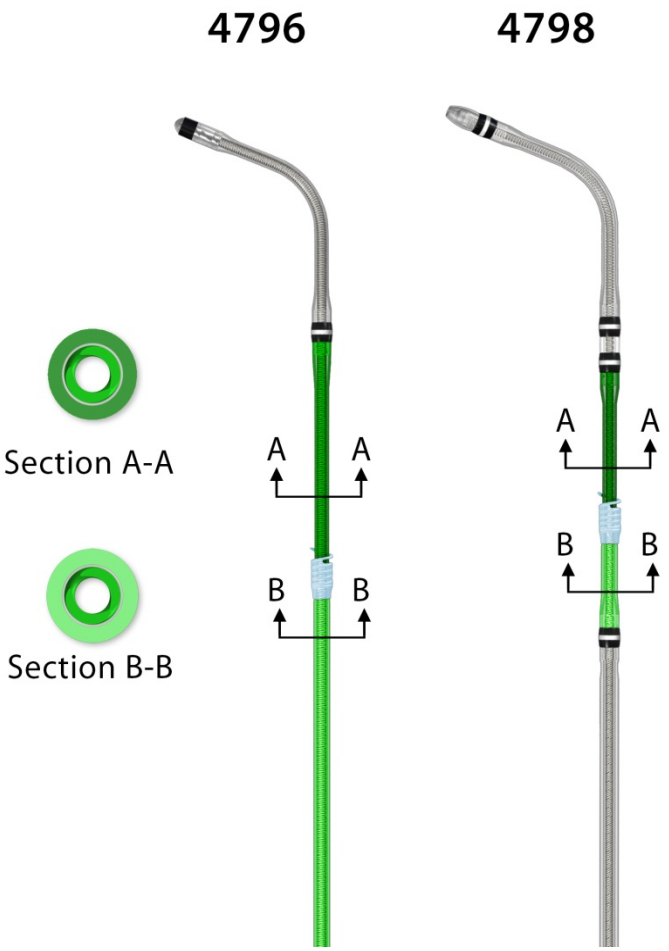
*90/10 Platinum Iridium
**80/20 Platinum Iridium

The non-electrically active side fixation helix component is similar to the Attain Stability Bipolar LV lead (Model 20066/4796) and is designed to enable active fixation in the cardiac vein. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) side helix is positioned between the LV3 and LV4 electrode; specifically 10 mm proximal from the LV3 electrode (see Figure 2).

A mechanical stop component is located at the base of the helix to prevent wedging of the endothelial tissue in the helix and to prevent tissue ingrowth. The helix component is platinum (Pt) iridium (Ir) alloy (Pt/Ir 80/20). This same Pt/Ir material is also used in the market released right ventricular active fixation lead Models 5076, 3830, and 4076. Both the helix and mechanical stop components are identical to those used on the CE Mark approved Medtronic Attain Stability model 20066/4796 active fixation lead and are shown in Figure 4.

The Model 4798 lead has one distal curve/cant. This distal curve geometry (angle) is identical to the Attain Performa model 4298, as well as Attain Ability models 4196 and 4296 most distal cant. The single distal cant is also identical to the CE Mark approved model 20066/4796 active fixation lead (Figure 4). The purpose of the distal cant is to provide physicians the ability to "steer" the distal tip of the lead when navigating difficult vein anatomy or acute vasculature angulation by rotating the lead (counterclockwise) and aligning the distal tip towards the desired direction. The distal cant for the Model 4798 lead is not intended, or necessary, to provide any fixation of the implanted lead as any retention force from the cant would be negligible compared to the stability provided by the properly implanted and verified fixated helix.

Figure 4: Attain Stability Bipolar (Model 20066/4796) & Attain Stability Quad MRI SureScan (Model 4798) Active Fixation Leads



The Attain Stability Quad Clinical Study will be conducted to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) in combination with CRT system components mentioned in

Table 7.

Table 7: Study Component Information

Component	US/Canada	EMEA/Hong Kong/Malaysia
Attain Stability Quad MRI SureScan LV Lead (Model 4798)	Investigational	Market-released
Medtronic CRT-P or Medtronic CRT-D (with Vector Express capabilities)	Market-released	Market-released
Medtronic RV lead (non-Medtronic and non-recalled/non-market withdrawn/non-safety alerted lead acceptable for upgrades)	Market-released	Market-released
Medtronic RA lead (optional) (non-Medtronic and non-recalled/non-market withdrawn/non-safety alerted lead acceptable for upgraded systems)	Market-released	Market-released

Given the similarities between the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the Attain Performa family of leads, the proposed indications for use are the same. The indications are as follows:

Proposed Indication Statement for Use for the Attain Stability Quad Lead:

The Attain Stability Quad MRI SureScan 4798 steroid-eluting, quadripolar electrode, IS4 transvenous lead is indicated for chronic pacing in the left ventricle via the cardiac vein, when used with a compatible Medtronic Cardiac Resynchronization Therapy (CRT) System. Extended bipolar pacing is available using this lead in combination with a compatible market approved CRT-D system and RV lead.

Market-Released Right Atrial Lead

Commercially available Medtronic RA lead models with an IS-1 connector are required when an RA lead is implanted with de novo CRT systems. An RA lead is not required to be implanted in circumstances determined appropriate per physician's medical assessment. Medtronic commercially available RA leads with an IS-1 connector are recommended but compatible non-Medtronic leads are permissible in enrolled patients receiving a CRT system upgrades.

Medtronic Market-Released Right Ventricular Lead

Commercially available Medtronic RV defibrillation leads with a DF4 connector are required for de novo CRT systems. Medtronic RV defibrillation leads with DF1 connectors may be incorporated in the study as DF1-compatible CRT-P and CRT-D devices are made available for the study. A non-Medtronic RV lead is permissible in enrolled patients receiving a CRT system upgrades.

13.2. Manufacturer

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is manufactured by Medtronic, Inc.

13.3. Packaging

Packaging and labeling for all market approved system components can be found with each package insert. Manuals can be found on http://manuals.medtronic.com. For CE Marked devices the labeling is in the appropriate local language.

For investigational products (e.g. in the US and Canada), the language of labeling and clinical manuals will be in English and/or local language where it is required. Investigational products will be clearly labeled e.g. "exclusively for clinical investigation."

In Canada, each investigational device will be labelled with the statements "Investigational Device"; "To be Used by Qualified Investigators Only"; "Instrument de recherche" and "Réservé uniquement à l'usage de chercheurs compétents".

13.4. Intended Population

In the Attain Stability Quad Clinical Study, the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is to be used in subjects where a de novo LV lead is indicated. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is intended to be used in conjunction with a market released Medtronic CRT-P or Medtronic CRT-D device, a Medtronic (for de novo CRT implants) RV lead, and a Medtronic (for de novo CRT implants) RA lead (optional).

A complete SureScan system is required for use in the MRI environment. Before performing an MRI scan, refer to the SureScan MRI technical manual for MRI-specific warnings and precautions.

13.5. Equipment

All commercially available equipment will be used according to their approved intended use.

Medtronic CareLink (2090) Programmer

The Medtronic approved CRT-P or CRT-D devices will be programmed and interrogated using a Medtronic CareLink (2090) programmer. Medtronic may incorporate additional programmers as they receive regulatory approval.

Medtronic CareLink Home Monitor 2490C and Network

The CareLink Monitor Model 2490C is an external monitor that is indicated for use in the transfer of patient and device data from implanted Medtronic devices. The CareLink Monitor Model 2490C interrogates implanted devices and temporarily stores these data, collaborates with the appropriate Medtronic server to confirm the establishment of an Internet connection with server, performs any required file translation functions necessary for data transfer, executes data file transfer, and collaborates with the appropriate Medtronic server to confirm data file transfer through the Internet connection with the server. The CareLink Monitor 2490C is not a programmer and cannot be used to program implanted device parameters. CareLink monitors are not a substitute for appropriate medical attention in the event of an emergency and should only be used as directed by a physician. Approved Medtronic CRT-P and CRT-D devices used in this study qualify for use with the Medtronic CareLink Monitor and Medtronic

CareLink Network. Medtronic may incorporate additional home monitors as they receive regulatory approval.

Pacing System Analyzer

Medtronic's commercially available Model 2290 Analyzer must be available at each center during the implant procedure to determine acceptable electrical parameters. Medtronic may incorporate additional analyzers as they receive regulatory approval.

13.6. Product Use

See Section 13 Product Description.

13.7. Product Receipt, Tracking, and Accountability

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered investigational in geographies where the product is not available commercially and will be labeled for clinical use only. These geographies include but are not limited to the US and Canada. Investigational Attain Stability Quad Leads will be distributed to a site only when Medtronic has received all required documentation (including but not limited to Ethic Committee approval, a signed Clinical Trial Agreement and documentation of training) and has notified the site of site readiness.

Distribution of the investigational product to study sites will be managed by Medtronic and investigational products can only be ordered by Medtronic personnel. Sites with these clinically labeled Attain Stability Quad MRI SureScan LV Leads (Model 4798) will track disposition upon receipt or return of the lead but also upon implant or explant of the lead. Disposition logs will be available within the electronic data management system and shall be maintained at each site in all geographies to track investigational product information. The logs should be updated when an investigational product is received, opened, implanted explanted, disposed of or returned to Medtronic. The logs will track the following investigational lead data (but are not limited to) model and serial numbers of devices delivered to the site, subject IDs of the subjects, implanted, received dates of devices, implant/used dates, explant dates, returned-to-sponsor dates and reasons, initials of all persons who received, used or disposed each device, and method of disposal. Medtronic will perform periodic reconciliation of investigational product to ensure traceability.

For geographies where the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is not considered investigational, commercially approved devices will be used. Sites that use commercially available Attain Stability Quad MRI SureScan LV Lead (Model 4798) will track device disposition upon implant or explant of the lead on the CRFs.

13.8. Product Storage

All investigational products must be stored in a secure location at the site. It is the responsibility of the investigator to correctly handle, store and track the investigational products. Further details may be found in the Clinical Manual or User Manual (dependent on each geography's commercial release of the product).

13.9. Product Return

All explanted, open but unused, and defective products (devices or leads, etc.) should be returned to Medtronic for analysis whenever possible and when permissible by local laws and regulations. If the products are explanted but not returned, a justification is required to be reported on the appropriate case report form(s) or disposition log(s) (note that this is not considered a study deviation). In geographies where the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is considered investigational, the Disposition Log must be updated in the event of an explant. To receive a Returned Product Mailer Kit, please contact your local Medtronic field personnel or representative. All unused investigational products must be returned to Medtronic upon study closure at the site.

14. Selection of Subjects

14.1. Study Population

Patients of both genders that are 18 years of age and older (or of legal age to give informed consent per local and national law) that are indicated for a de novo LV lead implantation and who meet all inclusion and no exclusion criteria are eligible for an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt. There will be no control group for this study.

14.2. Subject Enrollment

Patients who meet all of the inclusion and none of the exclusion criteria (see sections 14.3 and 14.4) are eligible to be enrolled in this study. Upon signing and dating the Informed Consent Form (ICF), the patient is considered a subject enrolled in the study.

14.3. Inclusion Criteria

- Patient meets CRT implant criteria as determined by local regulatory and/or hospital policy (i.e. US subjects should meet CRT device indications per the HRS/ACC/AHA guidelines)
- Patient (or legally authorized representative) has signed and dated the study-specific Informed Consent Form
- Patient is 18 years of age or older, or is of legal age to give informed consent per local and national law
- Patient is expected to remain available for follow-up visits

14.4. Exclusion Criteria

- Patient has had a previous unsuccessful LV lead implant attempt
- Patient has a previous CRT system or LV lead implanted (for example, transvenous or epicardial)
- Patient is currently implanted with a recalled (i.e. market-withdrawn, recalled or safety alert) RA and/or RV lead
- Patient has known coronary venous vasculature that is inadequate for lead placement
- Patient has unstable angina pectoris or has had an acute myocardial infarction (MI) within the past 30 days
- Patient has had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the past 90 days
- Patient has contraindications for standard transvenous cardiac pacing (e.g., mechanical right heart valve)
- Patient has had a heart transplant (patients waiting for heart transplants are allowed in the study)
- Patient has known renal insufficiency and/or significant allergy to contrast dye that would prevent them from receiving an occlusive venogram during the implant procedure
- Patient is contraindicated for <1mg dexamethasone acetate
- Patient is enrolled in any concurrent drug and/or device study that may confound the results of this study
- Patient has a terminal illness and is not expected to survive more than six months
- Patient meets exclusion criteria required by local law (e.g. age, pregnancy, breast feeding, etc.)
- Patient is unable to tolerate an urgent thoracotomy

14.5. Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Subjects will be evaluated at baseline to confirm eligibility for enrollment with defined inclusion/exclusion criteria
- Subject demographics and medical history will be collected at baseline and differences that may affect primary endpoints will be identified
- To ensure widespread distribution of data between sites, the maximum number of subjects allowed per site is 50
- All implanters in the study will be experienced in the implant of CRT-P and/or CRT-D systems
- Data collection requirements and study procedures will be standardized across all sites and geographies

- All study site personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials, and required to follow the CIP
- Per the specifications in the Monitoring Plan, monitoring visits will be conducted for adherence to the CIP and to verify the CRF data against source data
- Pre-defined statistical methods specified in the CIP and the Statistical Analysis Plan (SAP) will be followed
- The SC members will not have influence on the treatment decisions by study site investigators during the trial
- An independent and blinded CEC will regularly review and adjudicate reported adverse events and deaths (per Section 18.1)
- Registration of the trial on ClinicalTrials.gov and the publication plan will ensure that study results will be reported
- All study investigators are required to meet 21 CFR Part 54, Financial Disclosure by Clinical Investigators, to identify potential bias due to financial interest in the outcome of the study

In summary, potential sources of bias that may be encountered in this Attain Stability Quad Clinical Study have been considered and minimized by careful study design.

15. Study Procedures

Prior to performing study related procedures, all sites must have Ethics Committee (EC) and associated regulatory authority approval if applicable (e.g., Competent Authority approval) as well as documentation from Medtronic of site readiness.

Medtronic representatives may perform the following activities at the study sites during the study, if appropriately trained and under supervision of the Principal Investigator:

- Study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support at all visits (e.g. programming of the CRT-P or CRT-D device according to study requirements, performing device interrogations/save-to-media, etc.), but no CRF data entry shall be performed by Medtronic personnel
- Monitoring activities

15.1. Study Personnel Requirements

Site personnel training and delegation will be completed prior to participation in the Attain Stability Quad Clinical Study. The site personnel training consists of required training topics (CIP, Informed Consent Form, CRFs, regulations). Members of the study site team will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study.

All Principal Investigators shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Be qualified practitioners and experienced in the diagnosis, management, and treatment of HF subjects with CRT devices
- Be experienced in the field of application and trained in the use of the Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- Disclose potential conflicts of interest, including financial that interfere with the conduct of the clinical investigation or interpretation of results
- Be knowledgeable with the method of obtaining an informed consent

In addition, the Principal Investigator shall be able to demonstrate that the proposed investigational site:

- Has an experienced CRT implanter who is experienced and trained in the handling/implanting of CRT-P and/or CRT-D devices
- Has the required number of eligible subjects needed within the agreed recruitment period
- Has one or more qualified investigators, a qualified investigation site team and adequate facilities for the foreseen duration of the clinical investigation

15.2. Site Activation

During the activation process (prior to subject enrollment), Medtronic will train site personnel on the CIP, the implant procedure, relevant standards and regulations, informed consent process, and on data collection and reporting tools. If new members join the study site team, they will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study. For new members, local Ethics Committee notification requirements must be met, as well as Medtronic requirements noted on the training and delegation form.

A Clinical Trial Agreement (CTA) shall be entered into effect by Medtronic, the participating investigation site and/or the principal clinical investigator at each investigational site as per local legal requirements, and returned, fully executed, to Medtronic prior to the commencement of any study activities. Financial aspects of conducting and reporting a study will be specified in the agreement. By signing and dating the agreement the investigator indicates approval of the CIP.

Prior to performing study related activities, all sites must have Ethics Committee approval, as applicable for that geography.

All local and regional regulatory requirements will be fulfilled prior to site activation and enrollment of subjects into the study. Each study site must have written documentation from Medtronic of site and investigator readiness before beginning any study-related activities. Requirements for activation vary by geography, and may include, but are not limited to the following:

- Written documentation of Ethics Committee approval of the current version of the CIP and ICF, subject materials (e.g. Global Assessment and KCCQ), and voting list (as required by local law)
- Regulatory authority approval or notification (as required per local law)
- Fully executed CTA on file with the sponsor
- Financial Disclosure (for Principal Investigators and Co-Investigators)
- Current Curriculum Vitae (CV) (signed and dated as required by local law) of investigators and key members (as required by local law) of the investigation site team on file with the sponsor
- Documentation of delegated tasks

- Documentation of study site personnel training

Additional requirements imposed by the Ethics Committee and regulatory authority shall be followed, if applicable.

Medtronic will provide each study site with documentation of study site readiness; this letter must be sent prior to subject enrollment.

15.3. Equipment Requirements

The following equipment must be available at each site to support study activities:

- Medtronic 2290 Analyzer (or latest market released Medtronic analyzer)
- Medtronic 2090 programmer (or latest market released Medtronic programmer)
- Attain Stability Quad MRI SureScan LV Lead (Model 4798) (either clinically labeled product or commercial released product located at the site or carried to the implant by the Medtronic representative)
- Computer with high speed internet access using a web browser compatible with the electronic data management system for electronic database entry

The equipment necessary for the assessment for the study includes the Medtronic 2290 Analyzer and Medtronic 2090 programmer. The maintenance and calibration of the equipment used for this study will be assessed outside of this clinical study. Sites are responsible for maintaining and calibrating non-analyzer/programmer equipment used in the course of this study in accordance with established site practice or local regulation. Records should be kept and able to be provided upon request by the Sponsor or regulatory agency.

15.4. Schedule of Events

Clinical data will be collected at the study milestones detailed in Table 8. Data will be collected via electronic case report forms (eCRFs), still cine images, analyzer/programmer print-outs, and interrogation files. Post-implant follow-ups apply only to those subjects in whom an Attain Stability Quad MRI SureScan LV Lead (Model 4798) was successfully implanted or an implant was attempted. Subject visits will occur at enrollment, baseline, implant/pre-hospital discharge (PHD), 3 months post-implant, 6 months post-implant, and every 6 months thereafter until PMA approval of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted or study termination, whichever comes first. Medtronic personnel may assist study personnel during implant and study visits.

Table 8: Data Collection and Study Procedure Requirements at Subject Visits

STUDY PROCEDURE	Enrollment/ Baseline	Implant/ PHD	3 months post-implant (remote or in office visit)	6 months post-implant (in office visit)	12 months post-implant (in office visit)	Recurring 6 month follow-ups (remote or in office visit)	Exit
Subject Informed Consent	✓						
Inclusion / Exclusion criteria verified	✓						
Subject demographics	✓						
Cardiovascular medications	✓						
Cardiovascular medical history	✓						
NYHA classification	✓		✓	✓	✓	✓	
Patient Global Assessment				✓	✓		
Kansas City Cardiomyopathy Questionnaire (KCCQ)	✓			✓	✓		
Occlusive venogram with pre-determined pacing location identified		✓					
Analyzer PCT data collection (pre and post slitting the cannulation catheter)		✓ (Implant)					
Investigator Lead Handling Assessment		✓ (Implant)					
System and procedure information		✓					
Lead Impedance (all 16 vectors)		✓	✓ (final programmed vector only)	✓	✓	✓ (final programmed vector only)	
Pacing Capture Thresholds (all 16 vectors)		✓	✓ (final programmed vector only)	✓	✓	✓ (final programmed vector only)	
Phrenic Nerve Stimulation (final programmed vector)		✓	✓ (in office visit only)	✓	✓		
Phrenic Nerve Stimulation (vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can)				✓			
Phrenic Nerve Stimulation (Primary Endpoint vectors)				✓			
Rationale for selecting specific LV lead pacing vector for final programming		✓		✓	✓		
Final device interrogation/save-to-media		✓	✓ (CareLink transmission is acceptable for remote visits)	✓	✓	✓ (CareLink transmission is acceptable for remote visits)	✓ (required only if subject exits prior to 6 months post-implant visit; CareLink transmission is acceptable)
AE Assessment		✓	✓	✓	✓	✓	✓
Exit Subject							✓
Adverse Events (incl. AE with outcome of death)	As they occur						
Device Deficiencies							
System Modifications							
Study Deviations							

Table 9 below specifies permitted time windows for the required subject visits. Subject visit target dates and windows for each follow-up will be made available to the study site. Should a subject miss a visit or the visit falls outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits. Data analyses will include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation.

Table 9: Visit Windows

Visit	Window
Implant	0-30 days since Baseline Assessment
	(days since implant)
Pre-hospital discharge	0-7
3-month	76 - 106
6-month	183 - 213
12-month	350 - 380
18-month	518 - 578
24-month	701 - 761

15.5. Subject Consent

Informed consent (IC) is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate (ISO 14155:2011). This process includes obtaining IC and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (data protection authorization; i.e. HIPAA in the US) as required by law. Informed Consent Forms are required to be approved by the study site's Institutional Review Board (IRB) or Ethics Committee (EC) and Medtronic, and signed and dated by the subject and the Principal Investigator. A subject may only consent after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate.

Prior to enrolling subjects, each site must have documented IRB/EC approval of the IC Form (ICF) and the data protection authorization as required by law. Any changes to a previously approved ICF throughout the course of the study must be reviewed and approved by Medtronic and the IRB/EC reviewing the application before being used to consent or re-consent a study subject. The document(s) must be controlled (i.e. versioned and dated) to ensure it is clear which version(s) was approved by Medtronic and the IRB/EC. All important new information should be provided in written form to new and existing subjects throughout the study. If relevant, all affected subjects must be asked to confirm their continuing IC in writing.

Prior to initiation of any study-specific procedures, IC must be obtained from the subject (or legally authorized representative). Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize sites to submit subject information to the study sponsor. The IC process must be conducted by the principal investigator or an authorized designee, and the ICF and data protection authorization, as required by law, must be given to the subject in a language he/she is able to read and understand.

The process of obtaining informed consent shall:

- Ensure that the principal investigator or an authorized designee conducts the IC process.
- Include all aspects of the Attain Stability Quad Clinical Study that are relevant to the subject's decision to participate throughout the clinical study.
- Avoid any coercion or undue improper influence on, or inducement of the subject to participate.
- Not waive or appear to waive the subject's legal rights.
- Ensure the ICF and data protection authorization, as required by law, are given to the subject in a non-technical language the subject is able to read and understand.
- Provide ample time and opportunity for the subject to read and understand the ICF to inquire about details of the study, and to consider participation. All questions about the study should be answered to the satisfaction of the subject.
- Include a personally dated signature of the subject acknowledging that their participation in the study is voluntary.
- Include a personally dated signature by the principal investigator or authorized designee responsible for conducting the IC process, as required by local law.
- Include any other locally required signatories, such as witnesses, as indicated by country-specific legislations.
- Provide the subject with a copy of the ICF, the data protection authorization, as required by law, and any other written information, signed and dated if required by local law.
- Ensure subjects are notified of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study.

If IC is obtained the same day the subject begins participating in study-related procedures, it must be documented that consent was obtained prior to participation in any study-related procedures. It is best practice for the IC process to be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write, witnessed (impartial third party) IC will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the ICF. Informed consent shall be obtained through a supervised oral process. An independent witness must be present throughout the process. The ICF and any other information must be read aloud and explained to the prospective subject, if allowed by local law. The witness signs and personally dates the ICF, attesting that the information was accurately explained and that informed consent was freely given. The subject should "make his mark" (sign or otherwise physically mark the document so as to indicate consent) on the ICF as well. The ICF should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

The original of the signed ICF must be filed in the hospital/clinical chart and/or with the subject's study documents. A second signed original or a copy should be given to the subject for their records (if applicable).

The ICF and data protection authorization, as required by law, must be available for monitoring, auditing and regulatory inspections.

Geography specific ICF Templates will be provided under separate cover.

15.6. Enrollment

The point of enrollment is defined as the time at which a patient has signed and dated the ICF. The date the subject signed (or legally authorized representative) the ICF and data protection authorization, as required by law, must be documented in the subject's medical records. At that point, the patient is considered a subject in the study, a study subject ID number will be assigned, and the subject must be followed for the duration of the study unless the subject exits the study prior to study closure. Each investigational center will be responsible for maintaining subject identification records (e.g. subject identification log) according to ISO 14155.

Enrollment will occur on the same day as the baseline visit. Once IC is obtained, report AEs/deaths, study deviations and subject exits as they occur. To accurately track subject enrollment, Medtronic should be notified of the enrollment as soon as possible after a patient has signed the ICF.

15.7. Baseline

The baseline visit can be a stand-alone visit or can occur on the same day as, but not later than, the implant visit. The following procedures will be completed/data will be collected at the baseline visit:

- Subject Informed Consent
- Inclusion/Exclusion criteria verified
- Subject demographics
- Cardiovascular medications
- Cardiovascular medical history
- NYHA classification
- Kansas City Cardiomyopathy Questionnaire (KCCQ)

Cardiovascular medications include ACE inhibitors, ARBs, antiarrhythmic, anti-coagulants, antithrombotics, and antiplatelet, antihypertensive, antilipidemics (statins), beta blockers, calcium channel blockers, diuretics, digitalis, inotropes, nitrates, digoxin, and vasodilators.

If implant does not occur within 30 days of enrollment, verification of all inclusion and all exclusion criteria must be repeated before an implant attempt.

15.8. Implant/PHD

Information collected at Implant/PHD will include data from the day of the implant procedure until released from the hospital. The implant CRF will be used to collect data at implant. Implantation of the CRT device and right heart leads should be performed according to the Instruction for Use (IFU) in geographies where the devices are commercially available.

Any Medtronic commercially released right atrial (RA) and any Medtronic commercially released right ventricular (RV) lead may be implanted. Existing non-Medtronic RV and/or RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used in enrolled who are receiving an upgrade to

a CRT system. The right-heart leads should be implanted according to the labeling provided with the applicable lead.

The implanted system device must include a Medtronic commercially released CRT device which can be programmed to utilize all electrodes, allowing upgrades from implantable pulse generators (IPGs) and implantable cardioverter defibrillators (ICDs). Device and lead requirements are as follows:

- Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- For de novo CRT implants, any Medtronic commercially released transvenous (active or passive fixation) RA pacing lead (unless medical justification to exclude this lead) and any Medtronic commercially released transvenous (active or passive fixation) RV lead
- For upgrades to a CRT system, existing non-Medtronic RV and/or non-Medtronic RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used in enrolled who are receiving an upgrade to a CRT system
- Medtronic commercially released CRT devices that measure discrete LV electrical values from all four electrodes (i.e. Vector Express)

15.8.1. Final System Configuration

For information on the requirements for the implanted system refer to Section 13. The system is successfully implanted when the Medtronic CRT device is successfully connected to the RA, RV and the LV lead (except if a medical condition such as chronic atrial fibrillation excludes the need for an RA lead). The configuration of the successfully implanted system components will be collected. This will include the serial number of each implanted component (CRT-D or CRT-P device, and leads), and the location of lead placement.

15.8.2. Implant Procedure

Implantation of the CRT device and cardiac leads must be performed by a trained clinical study investigator and according to the manufacturer's instructions for use. It is recommended to use Medtronic catheters that are compatible with the Attain Stability Quad MRI SureScan LV Lead (Model 4798) (e.g., > 7 Fr) during the implant for gaining access to the coronary sinus (CS).

For complete information regarding the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the implant procedure, reference the Clinical Manual in the US and Canada or the Instructions for Intended Use (Technical Manual in EMEA, Hong Kong, and Malaysia). These documents are located under a separate cover.

15.8.2.1. Venogram

An occlusive venogram is required for venous visualization of the subject's coronary vasculature and will be used to pre-determine a desired target pacing location prior to placing the Attain Stability Quad MRI SureScan LV Lead (Model 4798). Once the pre-determined target pacing location is determined, a venous image will be collected. A copy of the venous image will be submitted to Medtronic and kept on file at the center.

15.8.2.2. Implanting the LV lead

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be implanted according to the implant instructions found within the lead packaging. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) can be positioned with the aid of a guide wire (0.36 mm to 0.46 mm or 0.014 inches to 0.018

inches in diameter), stylet, an inner catheter, or an inner catheter plus hybrid guide wire. If a stylet is used for lead positioning, only use the stylets packaged with the lead or in a stylet kit (downsized knob). Always use a stylet that is 3 cm shorter than the lead length listed on the IS4 connector label. Other stylets may extend beyond the lead tip causing injury or perforation of the cardiac vein or heart. If using a Medtronic integrated valve system (e.g. SureValve), rotate the helix counterclockwise to allow safe passage of the helix when inserting the lead into the delivery system to prevent the side helix from inadvertently attaching to the valve. Rust stylets are not recommended with this lead due to the risk of conductor coil/insulation perforation.

Follow the Attain Stability Quad MRI SureScan LV Lead (Model 4798) package insert carefully for fixating the side helix to the vein. Consider using a J-shaped stylet if fixation is unsuccessful. An overview of the key implanting tips includes:

- Rotate the lead counterclockwise when inserting the lead through the SureValve to prevent the helix from attaching to the valve
- Refrain from wedging the lead into the vessel so that the lead can easily rotate during fixation allowing torque to transfer from the proximal end to the distal end of the lead
- To fixate the side helix in the desired location, rotate the lead clockwise with the guidewire inserted in the lead which will provide extra stiffness to the lead
- Ensure the guidewire is removed to allow for lead pliability to visualize and confirm lead fixation during the Push Test and the Pull Test
- To reposition the lead, insert the guidewire and rotate the lead counterclockwise without applying tension to the lead to unfixate

Information on surgical data, such as tool use, and implant times, etc. will be collected during the implant procedure.

In an event that one Attain Stability Quad MRI SureScan LV Lead (Model 4798) is determined to be not suitable for a patient after the initial lead insertion; the implanting physician must assess the onset of any potential AEs. A second Attain Stability Quad MRI SureScan LV Lead (Model 4798) may only be introduced upon confirmation that no system-related AEs resulted from the first Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt. Any LV lead related AE observed during the initial LV lead attempt prohibits an attempt of a second Attain Stability Quad MRI SureScan LV Lead (Model 4798).

If the subject does not have a successful Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant at the conclusion of the initial implant procedure, the subject should be followed until procedure or system related AEs are resolved or are unresolved with no further actions planned, whichever occurs later.

If an attempt to implant the Attain Stability Quad MRI SureScan LV Lead (Model 4798) does not occur, or if the Model 4798 LV lead cannot be implanted, the reasons why the lead was not attempted or attempted but not implanted must be documented on the Implant and Study Exit CRF. See additional definitions below.

No Attain Stability Quad MRI SureScan LV Lead (Model 4798) Attempted (lead not inserted into the body)

An Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt is defined as any time a Model 4798 lead is introduced into the body. Subjects that do not have an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempted will be exited from the study following their implant procedure

unless another Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt is scheduled. Adverse events, device deficiencies and deviations must be documented before the subject is exited.

Attain Stability Quad MRI SureScan LV Lead (Model 4798) Attempted but Not Implanted

An Attain Stability Quad MRI SureScan LV Lead (Model 4798) that is inserted into the body that is not successfully placed will be considered an unsuccessful Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt. Note: An unsuccessful implant itself is not considered an AE. Adverse Events occurring during an unsuccessful implant (e.g. dissection, perforation) will be recorded and classified. Subjects with an unsuccessful Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt will be followed until procedure or system related AEs have been resolved or are deemed unresolvable with no further action planned.

15.8.2.3. CRT System Testing and Programming During Implant

Prior to connecting the leads to the CRT can, initial electrical measurements will be taken using the Analyzer (Model 2290 or market released equivalent) to confirm adequate pacing thresholds (PCTs) prior to closing the pocket per the site's standard testing method. These PCTs will be collected on the same vector, at two time points once the lead is fixated and prior to connecting the leads to the can using the Analyzer. The time points are as follows;

1.) Prior to slitting the cannulation catheter – Collect the first PCT using the Analyzer after the lead is fixated and the guidewire/stylet has been pulled back proximal to the helix and electrodes.

2.) Post slitting the cannulation catheter – Collect the second PCT using the Analyzer after the lead is fixated and following slitting of the cannulation catheter.

These PCT measurements will be collected on the CRF. This data will only be collected if an Attain Stability Quad MRI SureScan LV Lead (Model 4798) is successfully placed.

Pacing voltage thresholds are measured to determine whether the underlying myocardium will respond effectively to pacing and to evaluate lead stability in the cardiac vein. It is required to perform LV pacing threshold measurements during implant using the pacing threshold test at a 0.5ms pulse width. It is recommended to begin at 2.5 Volts and decrease amplitude after at least 3 pulses until capture is lost. If there is no capture at 2.5 V; stop the test and repeat at a higher voltage using the 0.5ms pulse width. The lowest amplitude where capture consistently occurs is the pacing threshold value. Collect data using the Analyzer (Model 2290 or market released equivalent).

It is recommended that physicians locate a final LV pacing site that can be captured using less than or equal to 2.5 V at 0.5ms, R-wave sensing of at least 4.0 mV, and does not cause diaphragmatic stimulation at 10V at 0.5ms. For additional details regarding the left ventricular leads and implant tools, refer to the respective technical manuals provided with each product.

Individual patient venous anatomies as well as pathologies present in the left ventricular myocardium are factors that will influence LV lead placement. Therefore, the best cardiac vein lead electrode location to stimulate the LV may vary for each patient.

15.8.2.4. Final Lead Placement Data Collection

Following fixation and once the final position of the lead is determined, collect a venous image of the final placement of the lead. A copy of the venous image will be submitted to Medtronic and kept on file at the center.

15.8.2.5. Pre-Hospital Discharge CRT System Testing and Programming

The following electrical testing will be performed using the implanted CRT-P or CRT-D device and the device programmer once the leads are connected to the CRT-P or CRT-D and pre-hospital discharge:

Lead Impedance

- Collect LV Lead Impedances using Vector Express on all vectors
- Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors
- NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Phrenic Nerve Stimulation (PNS)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

Other data collected prior to hospital discharge following the implant includes;

- Rationale for selecting specific LV lead pacing vector for final programming
- Final device interrogation/save-to-media
- AE Assessment
- Study deviations
- Device deficiencies

15.9. 3 Months Post-Implant (remote or in office visit)

The 3 month scheduled follow-ups may be done remotely or in office. For remote visits, CareLink transmissions may substitute device interrogations. The following procedures will be completed and data will be collected at the 3 month Follow-up visit;

Lead Impedance

- Obtain LV Lead Impedance Test for the final programmed vector
- Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Obtain PCTs at 0.5ms pulse width on the final programmed vector
- NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Retain printouts at the site

Phrenic Nerve Stimulation (PNS) (in office visit only)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

- NYHA classification
- Final device interrogation/save-to-media (or CareLink transmission)
- AE Assessment
- Study deviations
- Device deficiencies

15.10. 6 Months Post-Implant (in office visit)

The following procedures will be completed and data will be collected during the 6 months in office Follow-up visit.

Lead Impedance

- Collect LV Lead Impedances using Vector Express on all vectors
- Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors
- NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Phrenic Nerve Stimulation (PNS)

- Test for presence of PNS at 8.0V at 0.5ms on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can
- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
  - NOTE: If at any tested vector PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- Test for presence of PNS at 5.0V at 0.5ms on the two efficacy endpoints (one vector with PCT ≤ 2.5 V and an additional vector with PCT ≤ 4.0 V)
- NOTE: PNS observed during any PNS testing will not be considered an AE

Other Data Collection

- NYHA classification
- Patient Global Assessment
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Rationale for selecting specific LV lead pacing vector for final programming
- Final device interrogation/save-to-media
- AE Assessment
- Study deviations
- Device deficiencies

15.11. 12 Months Post-Implant (in office visit)

The following procedures will be completed and data will be collected during the 12 month in office Follow-up visit.

Lead Impedance

- Collect LV Lead Impedances using Vector Express on all vectors
- Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors
- NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Phrenic Nerve Stimulation (PNS)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

- NYHA classification
- Patient Global Assessment
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Rationale for selecting specific LV lead pacing vector for final programming
- Final device interrogation/save-to-media
- AE Assessment
- Study deviations
- Device deficiencies

15.12. Recurring 6 Month Follow-ups (remote or in office visit)

After the 12 Month Follow-Up visit, subjects will be seen every 6 months. These scheduled follow-ups are considered "Recurring 6 month follow-up visits". These scheduled follow-ups may be done remotely or in office. For remote visits, CareLink transmissions may substitute device interrogations. The following procedures will be completed during these visits:

Lead Impedance

- Obtain LV Lead Impedance Test for the final programmed vector
- Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Obtain PCTs at 0.5ms pulse width on the final programmed vector
- NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Retain printouts at the site

Other Data Collection

- NYHA classification
- Final device interrogation/save-to-media (or CareLink transmission)
- AE Assessment
- Study deviations
- Device deficiencies

15.13. Device Interrogation/Save-to-Media

For the implant and follow-up visits, a final "Interrogate All" device interrogation file (.pdd) must be obtained and saved in a digital format (Save-to-Media). Store one copy of the save-to-media at the site and send a copy to Medtronic. Do not clear device data.

A device interrogation (final "Interrogate All") and Save-to-Media should also be completed at the time of study exit (prior to 6 month visit), a system modification (initial and final "Interrogate All"), and in the case of a death (where possible).

15.14. System Modifications

A system modification will be reported in the event the device and/or leads require invasive modification (e.g. generator or lead explant, generator or lead replacement, lead repositioning, etc.). In the event of a system modification, regardless of outcome of the modification, subjects should remain in the study

when possible and the follow-up visit schedule for the subject will remain unchanged. For a system modification the following information/activities are required to be collected:

- Modification or replace/explant date
- Reason for modification
- Information on device or lead modified
- Information on any replacement device(s)
- Final device interrogation/save-to-media
- Study deviations
- AEs and device deficiencies (as applicable)

It is recommended that all explanted Medtronic products (device, leads, etc.) are returned to Medtronic for analysis per local process and when permissible by local laws and regulations.

In the event that subject has a re-attempt after a previous unsuccessful system modification, the subsequent attempt(s) must be reported via CRF as separate system modifications.

Attain Stability Quad MRI SureScan LV Lead (Model 4798) repositioned or replaced with another Attain Stability Quad MRI SureScan LV Lead (Model 4798)

If the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is repositioned or replaced, the following LV lead electrical tests and data collection must be completed:

Lead Impedance

- Obtain LV Lead Impedance Test for the final programmed vector
- Perform a manual test for a missing value
- NOTE: Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Obtain a PCT at 0.5ms pulse width using Vector Express on the final programmed vector
- Perform a manual test for a missing value
- NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- NOTE: Retain printouts at the site

Phrenic Nerve Stimulation (PNS)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

- Record the reason why the final configuration was selected for final programming
- Record any programming changes to the LV lead apart from the LV lead pacing vector since the last visit and provide rationale for the change(s)

Attain Stability Quad MRI SureScan LV Lead (Model 4798) capped or explanted without replacement with another Attain Stability Quad MRI SureScan LV Lead (Model 4798)

If the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is capped or explanted without replacement while the subject is in the study, subjects will continue to be followed per their original follow-up schedule for safety monitoring until study closure. LV lead electrical testing and interrogation files will not be required at follow-ups for subjects without the full protocol required system implanted.

Explant of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the Medtronic CRT-P or CRT-D device without replacement with another Attain Stability Quad MRI SureScan LV Lead (Model 4798) and Medtronic CRT-P or CRT-D device

Subjects who have their Attain Stability Quad MRI SureScan LV Lead (Model 4798) and Medtronic CRT-P or CRT-D device explanted without replacement during a system modification procedure should be exited from the study as soon as all system related and/or system modification procedure related AEs are resolved. If no system or procedure related AEs are present at the conclusion of such a system modification procedure, the subject should be exited immediately.

Medtronic CRT-P or CRT-D device explanted without replacement, Attain Stability Quad MRI SureScan LV Lead (Model 4798) remains implanted

If the Medtronic CRT-P or CRT-D device is explanted and a replacement device will be implanted, all attempts should be made to replace with another Medtronic CRT-P or CRT-D device. In the event that an explanted Medtronic CRT-P or CRT-D device cannot be replaced with a new Medtronic CRT-P or CRT-D device, subjects who still have an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted will continued to be followed for safety monitoring in person per their original follow-up schedule until study closure. Events related to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) should be reported. Left ventricular lead electrical testing will not be required at follow-ups for subjects without the full protocol required system implanted. In an event that a second Attain Stability Quad MRI SureScan LV Lead (Model 4798) was implanted as a result of an Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complication, the subject will be followed for safety, however the second implanted Attain Stability Quad MRI SureScan LV Lead (Model 4798) will not be included for the analyses of study objectives except reportable system related adverse events.

15.15. Study Exit

Study Exit is defined as the moment when a subject officially stops participating in the study. Date and reason for subject exit must be reported to Medtronic at the earliest opportunity.

Subjects will be exited from the study for any of the following situations:

- Study completed
- Subject lost to follow-up
- Subject did not meet eligibility criteria and was not yet implanted with an Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- Subject did not have a successful implant and no attempt at re-implant is made
- Subject did not provide consent or data protection authorization, as required by law
- Subject chooses to exit (i.e. revokes consent)
- Investigator withdraws subject

Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing system- and procedure-related AEs are resolved, unresolved with no further actions planned, or 30 days post the 6 month visit, whichever occurs first. Following exit, subjects will continue to receive standard medical care. There will be no further required study-related follow-up visits for these subjects. All data through the time of the subject's exit will be available for data analyses.

If possible, the following procedures should be performed / data collected at the exit visit:

- Report the reason for exit
- Final interrogation file (or CareLink transmission) for exits occurring prior to the 6 month visit
- Study deviations
- AEs and device deficiencies (as applicable)

After subjects are exited from the study they should receive standard medical care and should be managed and followed per physician discretion.

15.15.1. Study Completed

All subjects will be followed until FDA Pre-Market Approval (PMA) of the Attain Stability Quad MRI SureScan LV Lead (Model 4798). Medtronic will notify sites when the study is complete. Upon exiting subjects, if the current follow-up visit and exit visit are combined, then both the follow-up CRF and a Study Exit CRF need to be completed but only one device interrogation/save-to-media needs to be completed and collected. If AEs are unresolved at time of exit, it should be noted on the AE CRF that the AE is unresolved at time of study exit.

15.15.2. Lost to Follow-up

In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be recorded. In addition, follow the regulations set forth by the governing IRB or EC.

15.15.3. Study Exit Upon Sponsor Request

A subject must be exited from the study if the sponsor suspends study enrollment and a subject has signed the ICF but no implant attempt of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) has occurred (see Section 15.8.2.2).

15.16. Subject Withdrawal or Discontinuation

15.16.1. Subject Chooses to Exit (i.e. revokes consent)

A subject can withdraw from the study at any time. If the subject wishes to exit from the study (i.e. the subject revokes consent), the site is required to document the reason for exit on the Exit CRF. In addition, study sites shall follow the regulations set forth by the governing Ethics Committee. For countries following ISO 14155, permission may be requested to follow up with the patient outside of the study due to withdrawal based on problems related to the investigational feature safety or performance. If possible, the following data should be collected prior to subject withdrawal:

- Report the reason for subject withdrawal
- Final device interrogation/save-to-media
- Study deviations
- AEs and device deficiencies (as applicable)

15.16.2. Investigator Withdraws Subject

No subjects should be withdrawn by investigators unless compelling medical justification is present. It is recommended investigators discuss any withdrawals with the study sponsor prior to exiting subjects. If

an Investigator withdrawal is necessary, the following data should be collected prior to subject withdrawal if possible:

- Report the reason for subject withdrawal
- Final device interrogation/save-to-media
- Study deviations
- AEs and device deficiencies (as applicable)

The following are reasons for investigator-initiated subject withdrawal;

Medical Necessity

A subject may be exited from the study if an investigator feels it is necessary to withdraw the subject from the study due to a medical condition or other reason. In such cases, the subject will be notified and provided an explanation regarding the reasons for the study exit.

Explant of Medtronic CRT-P or CRT-D Device and Attain Stability Quad MRI SureScan LV Lead (Model 4798)

Subjects in which the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the Medtronic CRT-P or CRT-D device are explanted without replacement (i.e., subject no longer has a Medtronic CRT-P or CRT-D device and an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted) shall be exited from the study (refer to Section 15.8.2.2). Subjects exposed to an Attain Stability Quad MRI SureScan LV Lead (Model 4798) through a lead attempt must be followed through at least one month or until all implant related AEs (system-, and/or procedure-related) have resolved or are unresolved with no further actions planned. Subjects who have either an Attain Stability Quad MRI SureScan LV Lead (Model 4798) (active or not active) or a Medtronic CRT-P or CRT-D device implanted will continued to be followed for safety until study completion.

Attain Stability Quad MRI SureScan LV Lead (Model 4798) Not Implanted

Subjects that are not anticipated to have an implant attempt (e.g. do not meet inclusion/exclusion criteria) must be exited from the study. Subjects that have a CRT system implant attempt, but who do not have an Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempted (See Section 15.8.2.2 for definition) will be exited from the study following their procedure unless an Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt is scheduled. If this attempt is more than 30 days from the baseline assessment, verification of the baseline data must be completed prior to a subsequent implant attempt.

Subjects with an unsuccessful Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt will be followed at pre hospital discharge and one month unless there are ongoing implant related AEs (system- and/or procedure related), in which case they will be followed beyond one month until the implant related (i.e., system, and/or procedure related) AEs have been resolved or are considered unresolved with no further actions planned. The subjects may be followed via a clinic visit or by phone contact. In geographies where the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is market-released, subjects will be exited from the study after the assessment of implant procedure or CRT system related AEs if the initial attempt of one Attain Stability Quad MRI SureScan LV Lead (Model 4798) model was unsuccessful. The subject may undergo implant attempts with any market released LV lead that provides the best benefit to the patient, but data collection on these subsequent attempts will not be required as these subjects will be considered exited from the study.

15.17. Assessment of Efficacy

The primary efficacy objective is based on the pacing capture threshold data collected as discussed in Section 19.1.

15.18. Assessment of Safety

The primary safety objective is based on the Adverse Event data collected. Further information on the collection of Adverse Events is discussed in Section 17.1.1.

15.19. Recording Data

The study will collect data using Oracle Clinical, an electronic data management system for clinical studies. Sites will enter data onto CRFs within the Oracle Clinical database.

Data reported on the CRFs shall be derived from source documents, which may include worksheets, patient medical records, programmer printouts and device interrogation/save-to-media files. These source documents must be created and maintained by the investigational site team. Further detail on data management is provided in Section 21.2.

15.20. Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan or the Clinical Trial Agreement.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. In all geographies, prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported to Medtronic regardless of whether they are medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The deviation must be recorded in Oracle Clinical with an explanation for the deviations. In the occurrence of a corrupted device interrogation/save-to-media file, Medtronic will request a deviation to document that a readable device interrogation/save-to-media file is unavailable.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB/EC as well as Medtronic as soon as possible but no later than five (5) working days, or according to local requirements. Reporting of all other study deviations should comply with IRB/EC policies and/or local laws and deviations must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, and terminate the study). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic may provide site-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

16. Risks and Benefits

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of the product, from the research and development phase through the study phase and market release. The risk analysis process for the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is being performed in accordance with ISO 14971, and will ensure that the level of risk has been reduced as low as possible and is acceptable prior to starting the Attain Stability Quad Clinical Study.

Potential Risks

Standard risks associated with the medical device used in this study, an analysis of Adverse Device Effects and a history of modification or recall of device under investigation or equivalent devices are listed in the Instruction for Use Manual or Clinical Manual.

The potential adverse events (listed in alphabetical order) related to the use of transvenous leads include, but are not limited to, the following conditions:

- Air embolism
- Avulsion or other damage to the endocardium, valve, or vein (particularly in fragile hearts)
- Cardiac dissection or perforation
- Cardiac tamponade
- Coronary sinus dissection
- Death
- Endocarditis or pericarditis
- Erosion through the skin
- Extracardiac muscle or nerve stimulation
- Fibrillation or other arrhythmias
- Heart Block
- Heart wall or vein wall rupture
- Hematoma/seroma
- Infection
- Lead conductor fracture or insulation failure
- Lead dislodgement
- Myocardial irritability
- Myopotential sensing
- Pericardial effusion or rub
- Pneumothorax
- Rejection phenomena (local tissue reaction, fibrotic tissue formation)
- Threshold elevation or exit block
- Thrombosis
- Thrombotic embolism

Additional potential adverse events related to the lead and the programmed parameters include, but are not limited to, the following:

Table 10: Additional adverse events related to the lead and programmed parameters

Potential adverse event	Indicator of potential adverse event	Corrective actions to consider
Lead dislodgement[i]	Intermittent or continuous loss of capture or LV EGM signal integrity (including sensing)[i]	Reprogram the LV pacing polarity. Reposition the lead.
Lead dislodgement[i]	Intermittent or continuous oversensing	Reprogram the LV pacing polarity. Reposition the lead.
Lead conductor fracture	Intermittent or continuous loss of capture or LV EGM signal integrity (including sensing)[i]	Replace the lead. Reprogram the LV pacing polarity.
Lead conductor insulation failure	Intermittent or continuous loss of capture or LV EGM signal integrity (including sensing)[i]	Replace the lead. Reprogram the LV pacing polarity.
Threshold elevation or exit block	Loss of capture[i]	Adjust the implantable device output. Reprogram the LV pacing polarity. Replace or reposition the lead.

[I] Transient loss of capture or LV EGM signal integrity (including sensing) may occur following surgery until lead stabilization takes place. If stabilization does not occur, lead dislodgement may be suspected.

Implant techniques that may damage the lead include, but are not limited to, the following techniques:

Table 11: Implant Techniques that may damage the lead

Implant techniques that may damage the lead	Possible effects on the lead	Corrective action to consider
Forcing the lead through the introducer/delivery system	Electrode, conductor coil, or insulation damage	Replace the lead.
Use of too medial of an approach with venous introducer resulting in clavicle and first rib binding	Conductor coil fracture, insulation damage	Replace the lead.
Using too stiff a stylet	Conductor coil/insulation perforation	Replace the lead.
Puncturing the periosteum or tendon when using subclavian introducer approach resulting in binding	Conductor coil fracture, insulation damage	Replace the lead.
Advancing the lead through the non-coronary central access veins without the stylet or guide wire fully inserted	Tip distortion or insulation perforation	Replace the lead.
Inserting the proximal end of the guide wire through the lead tip seal without using the guide wire insertion tool	Lead tip seal damage or conductor coil/insulation damage	Replace the lead.

Subjects who are pregnant may be at increased risk (e.g., radiation exposure, and other unforeseen risk to the fetus), and are excluded from participation in the study. If a subject becomes pregnant during the study, she must notify the physician immediately. The subject will remain in the study for intention to treat analysis, but the investigator will avoid any procedures that may be determined harmful.

There may be other discomforts and risks related to the CRT-P or CRT-D device, the Attain Stability Quad MRI SureScan LV Lead (Model 4798), and/or this study that are not foreseen at this time. Interactions with concomitant medical treatment are not expected.

The adverse event collection requirements in this study will ensure that risks associated with the study device and the Attain Stability Quad MRI SureScan LV Lead (Model 4798) are adequately monitored.

16.2. Risk Minimization

Medtronic has minimized the risks to the subject by the following:

- Performing required laboratory and pre-clinical testing prior to the Attain Stability Quad Clinical Study; this information is available under separate cover in the RPI with the FDA IDE submission and the CER with the CE-Mark
- Implementing quality control measures into development and production processes
- Providing guidelines for subject selection and evaluation, and subject inclusion and exclusion criteria
- Providing adequate instructions via the Attain Stability Quad MRI SureScan LV Lead (Model 4798) User Manual, training, and labeling

- Selecting implanters that have demonstrated previous experience with implanting CRT-P or CRT-D devices and specifically LV leads
- Selecting investigators that have demonstrated previous experience with the programming, interrogating, and monitoring of CRT-P or CRT-D devices
- After enrollment in the Attain Stability Quad Clinical Study, at each protocol required follow-up, the investigator must interrogate the study device to verify appropriate study device function and to evaluate the subject's health and assess for any AEs

16.3. Potential Benefits

The potential benefits of having the Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted are similar to other LV leads currently available to the public. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is expected to increase lead stability and reduce the need for patients to undergo an additional procedure to replace a dislodged/displaced lead. Due to the active fixation helix, it may be possible to place the lead in veins of various sizes. There is a possibility that the Attain Stability Quad MRI SureScan LV Lead (Model 4798) may offer no additional benefit over similar LV leads. The information gained from this study could result in the improved management of other CRT patients.

16.4. Risk-Benefit Rationale

The risk-benefit analysis has shown that there are no major additional risks associated with the Attain Stability Quad MRI SureScan LV Lead (Model 4798), other than those associated with the implant, while benefits to the patient are possible. Any residual risk associated with this study is considered low and acceptable.

17. Adverse Event Assessments

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Medtronic has established procedures in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information. This study is conducted in accordance with these procedures and regulations.

Data collected in this study may be used in support of global regulatory approvals. Since the safety reporting requirements and classification systems vary for each regulatory agency, requirements from all geographies are taken into account for the collection and reporting of safety information. Adverse Events and Device Deficiencies will be reported in all geographies.

17.1. Adverse Event and Device Deficiency Assessment

17.1.1. Adverse Events

Adverse Event definitions are provided in Table 12. The following AEs will be collected throughout the study duration, starting at the time the informed consent form is signed:

- All procedure related AEs
- All system related AEs
- All accessory related AEs
- All cardiovascular related AEs
- All Serious Adverse Events (SAEs), regardless of relatedness

Reporting of these events to Medtronic will occur on an AE Form, including date of AE, treatment, resolution, assessment of both the seriousness of the AE and the relatedness to the investigational device or procedure. Each AE must be recorded on a separate AE eCRF. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. In addition, AEs impacting users or other persons, Non-subject Adverse Events, (reportable per ISO 14155) will be collected.

In all geographies, Unavoidable AEs, listed in Table 12, need not be reported unless the AE worsens or is present outside the stated timeframe post-implant.

For AEs that require immediate reporting (see Table 14), initial reporting may be done by contacting the study sponsor per the sponsor contact information. The original completed AE CRF must be submitted to Medtronic as soon as possible.

Any medication, whether cardiovascular or not, associated with the treatment of an AE must be reported. Medication changes that are not related to adverse events will not be collected.

Subject deaths are also required to be reported. Refer to Section 17.4 for Subject Death collection and reporting requirements.

17.1.2. Device Deficiencies

Device deficiency (DD) information will be collected throughout the study and reported to Medtronic. Note that DDs that result in an Adverse Device Effect (ADE) to the subject should be captured as an AE only. Device Deficiencies that did not lead to an AE but could have led to a Serious Adverse Device Effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting (see Table 14). For DDs that require immediate reporting, initial reporting may be done by contacting the study sponsor per the sponsor contact information.

17.1.3. Event Updates and Resolution

For any changes in status of a previously reported AE (i.e. change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE form. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject dies or exits the study, or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to their 6 month visit, all efforts should be made to continue following the subject until all unresolved system or procedure related adverse events, as classified by the investigator, are resolved or unresolved with no further actions planned.

At the time of study exit, all collected AEs with an outcome of ”Unresolved” must be reviewed and an update to the original AE must be reported. At a minimum, if there are no changes to the description, relatedness, test and procedures or actions taken, the outcome must be updated to reflect “Unresolved at time of study exit”.

17.2. Definitions/Classifications

Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system, and includes but is not restricted to: the CRT-P or CRT-D device, the RA, RV or LV leads, the programmer, and implant tools.

Table 12: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. (ISO 14155:2011, 3.2)
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. (ISO 14155:2011, 3.1)
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors and inadequate labeling (ISO 14155:2011, 3.15)
Relatedness	
Procedure Related	An Adverse Event that is directly related to the implantation or surgical modification of the system. NOTE: In general, this excludes events that are inherent to any surgical procedure (e.g. anesthesia complications) as well as indirect subsequent consequences of the procedure (e.g. reaction to pain medication).

System Related (includes all implantable components and features, associated introduction tools, operational and installed software and programmers as defined in the Clinical Investigation Plan)	An adverse event that results from the presence or performance of any component of the system. Device-related: An adverse event that results from the presence or performance (intended or otherwise) of the device. RA lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the RA lead. RV lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the RV lead. LV lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the LV lead. a) LV Lead Fixation-related: An adverse event that results from the presence or performance of the side-helix.
Accessory Related	Programmer Related: An adverse event that results from the presence or performance (intended or otherwise) of the programmer Implant tool-related: An adverse event that results from the presence or performance (intended or otherwise) of the implant tool.
Cardiovascular Related	An Adverse Event relating to the heart and the blood vessels or the circulation (e.g. Atrial Fibrillation, Myocardial Infarction, stroke, perivascular disease)
Heart Failure Related	An adverse event related to worsening heart failure signs and symptoms such as hypervolemic and hypovolemic status requiring the administration, alteration, adjustment or augmentation of HF therapy (diuretics, inotropes and/or vasodilators etc.) or the utilization of ultrafiltration devices.
MRI Related	An adverse event which is caused by the interaction between the pacing system and the MRI system that occurs during the MRI procedure and up through the one-month post-MRI/waiting period follow-up visit.

Not Related	Relationship to the device or procedures can be excluded when: ▪ The event is not a known side effect of the product category the device belongs to or of similar devices and procedures; ▪ The event has no temporal relationship with the use of the device or the procedures; ▪ The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; ▪ The discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure) do not impact the serious event; ▪ The event involves a body-site or an organ not expected to be affected by the device or procedure; ▪ The serious event can be attributed to another cause (e.g., an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors); ▪ The event does not depend on a false result given by the device used for diagnosis (when applicable); ▪ Harm to the subject are not clearly due to use error; ▪ In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The event is associated with the device or study procedures beyond reasonable doubt when: ▪ The event is a known side effect of the product category the device belongs to or of similar devices and procedures; ▪ The event has a temporal relationship with device use/application or procedures; ▪ The event involves a body-site or organ that the device or procedures are applied to or the device or procedures have an effect on; ▪ The serious event follows a known response pattern to the medical device (if the response pattern is previously known); ▪ The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure) impact on the serious event (when clinically feasible); ▪ Other possible causes (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug, or treatment) have been adequately ruled out; ▪ Harm to the subject is due to error in use; ▪ The event depends on a false result given by the device used for diagnosis (when applicable); ▪ In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Seriousness	
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. (ISO 14155:2011, 3.37)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011, 3.36)
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. (ISO 14155:2011, 3.42)

Complication	An adverse event that includes the following is considered a complication: • Results in death, • Involves any termination of significant device function, or • Requires an invasive intervention Non-invasive (21 CFR 812.3 (k)): when applied to a diagnostic device or procedure, means one that does not by design or intention: Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os *Note* (FDA): Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive. *** Only system or procedure related AEs will be classified as complication or observation
Observation	Any Adverse Event that is not a complication. *** Only system or procedure related AEs will be classified as complication or observation

<table>
<tr><th colspan="2">Other</th></tr>
<tr><td>Unavoidable Adverse Event</td><td>An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator's opinion, including, but not limited to:
<table>
<tr><th>Event Description</th><th>Timeframe (hours) from the Surgical Procedure</th></tr>
<tr><td>Anesthesia related nausea / vomiting</td><td>24</td></tr>
<tr><td>Low-grade fever (<100°F or 37.8°C)</td><td>48</td></tr>
<tr><td>Pocket site / Incisional pain</td><td>72</td></tr>
<tr><td>Mild to moderate bruising / ecchymosis</td><td>168</td></tr>
<tr><td>Sleep problems (insomnia)</td><td>72</td></tr>
<tr><td>Back pain related to laying on table</td><td>72</td></tr>
<tr><td>Shoulder pain/discomfort/stiffness related to shoulder immobilization during procedure</td><td>72</td></tr>
</table></td></tr>
</table>

17.3. Reporting of Adverse Events

17.3.1. Adverse Events and Device Deficiency Classification

All reported AEs and DDs will be reviewed by a Medtronic representative. Adverse Events will be classified according to the definitions provided.

Upon receipt of AEs at Medtronic, a Medtronic representative will review the AE/DD for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize the Medical Dictionary for Regulatory Activities (MedDRA), to assign a MedDRA term for each AE based on the information provided by the investigator.

Regulatory reporting of AEs and DDs that could have led to an SADE will be completed according to local regulatory requirements. Refer to Table 14 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the investigator to abide by any additional AE reporting requirements stipulated by the IRB/EC responsible for oversight of the study.

APPENDIX 1 contains the Foreseeable Adverse Event List (FAL), which is a list of adverse events related to the system or procedure that have been observed in previous studies and may be experienced by subjects. This list may help to assess if an AE is unanticipated in nature.

For emergency contact regarding a UADE, SAE and/or SADE, contact a Attain Stability Quad Clinical Study representative immediately (refer to the study contact list provided in the site's study documents binder/investigator site file or refer to the Sponsor Contact Information section provided in the CIP).

Adverse Events and Deaths will be classified according to the standard definitions as outlined below:

Table 13: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Device, RA Lead, RV Lead, LV Lead, Implant Tool(s), Programmer, Procedure, Cardiovascular, Heart Failure, MRI
	Sponsor	Device, RA Lead, RV Lead, LV Lead, Implant Tool(s), Programmer, Procedure
Seriousness	Investigator	SAE
	Sponsor	SAE, UADE/USADE, Device Deficiency with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

An independent Clinical Events Committee (CEC) will review and adjudicate, at a minimum, all events classified by the investigator or Medtronic as procedure or system related to determine relatedness and complication or observation classifications. In addition, the CEC will also review and adjudicate all Adverse Events resulting in death.

17.3.2. Adverse Events and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and device deficiencies will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator to abide by the adverse event reporting requirements stipulated by local law and the site's IRB/EC.

Table 14: Reporting Requirements

Serious Adverse Events (SAEs)	
Investigator submit to:	
Medtronic	**Canada:** Investigators are required to report SAEs to the sponsor immediately except for those SAEs that the protocol or other document (e.g. Investigator's Brochure (IB)) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. Medical Devices Regulations, sections 59-61. *A guidance for "immediately" is within 72 hours of the investigator becoming aware of the event; Report to sponsor, without unjustified delay ISO 14155:2011, sec 9.8.b).* **EMEA:** Immediately after the investigator first learns of the event or new information in relation with an already reported event. **All geographies:** Report to the sponsor, without unjustified delay, all serious adverse events.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.

Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Adverse Device Effects (ADEs),	
Investigator submit to:	
Medtronic	**EMEA:** Immediately after the investigator first learns of the event or new information in relation with an already reported event. **All geographies:** Submit in a timely manner after the investigator first learns of the effect.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Serious Adverse Device Effects (SADEs), Unanticipated Adverse Device Effects (UADEs), Unanticipated Serious Adverse Device Effects (USADEs),	
Investigator submit to:	
Medtronic	**US:** Submit as soon as possible, but no later than within 10 working days after the investigator first learns of the event. (21 CFR 812.150(a)(1)) **Canada:** SADEs on the patient, the user or any other person must be reported to the Sponsor within 72 hours after it comes to the attention of the qualified investigator. It is recommended for the investigator to report safety events as soon as possible but no longer than 15 calendar days." **All geographies:** Immediately after the investigator learns of the event or of new information in relation to an already reported event.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement
Ethics Committee	**All geographies:** Submit to Ethics Committees per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Investigators	**All geographies:** Submit per local reporting requirement.

All other reportable Adverse Events	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the event.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Device Deficiencies with SADE potential	
Investigator submit to:	
Medtronic	**Canada:** DDs that have resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person or could do so were it to reoccur must be reported to the Sponsor within 72 hours after it comes to the attention of the qualified investigator **EMEA:** Immediately after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency. **All other geographies:** Submit or report as required per local reporting requirements.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the deficiency.
Regulatory authorities	**Canada:** any DD that: a. has resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person; These must be reported by Medtronic to the Regulator within 10 days from the date Medtronic becomes aware. or b. could do so were it to reoccur. These must be reported by Medtronic to the Regulator within 30 days from the date Medtronic becomes aware. **All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.

17.4. Subject Death

17.4.1. Death Data Collection

All subject deaths must be reported by the investigator to Medtronic on an AE form (AE with outcome of death) as soon as possible after the investigator first learns of the death. In case of death, there should be one SAE with the outcome of death reported.

In the event of a subject's death, it is recommended that the implanted system be explanted and returned to Medtronic for analysis whenever possible per local process. Local laws and procedures must be followed where applicable.

System Interrogation Data Recommendations:

- After the subject has died but prior to explant, it is strongly recommended that the system be interrogated and a full summary interrogation (Interrogate All) performed when possible, and saved in a digital format (Save-to-Media). Store one copy of the save-to-media at the site and send a copy to Medtronic.
- Make the device interrogation/save-to-media file before any programming to prevent overwriting information in the device's memory and/or distinguishing between events detected during versus before the explant procedure.
- Recommend obtaining the exact date and time of death as lower temperatures after death can cause ERI and other "event flags" to be stored in the device memory.

If the system is not interrogated, an explanation must be entered on the AE form. For ICD systems, the ventricular tachycardia (VT) and ventricular fibrillation (VF) detection capabilities must be disabled to avoid inadvertent shocks. If any system component is returned to Medtronic, internal return product reporting systems may be used to gather additional information about the returned device/component.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic Attain Stability Quad Clinical Study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records should be sent to the Medtronic Attain Stability Quad Clinical Study team, if available. If an autopsy is conducted, the autopsy report should also be sent to the Medtronic Attain Stability Quad Clinical Study team if available and allowed by state/local law. When the death occurs at a remote site, it is the investigative site's responsibility to attempt retrieval of information about the death. Additionally, device disposition information should be updated. In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to system and/or procedure
- Device interrogation and Save-to-Media (if available)
- Device disposition information
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and allowed by state/local law)

17.4.2. Death Classification and Reporting

Sufficient information will be required in order to properly classify the subject's death. The Investigator shall classify each subject death per the following definitions:

Cardiac Death: A death directly related to the electrical or mechanical dysfunction of the heart.

Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be determined, SCD will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.

Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.

Non-cardiac Death: A death not classified as a cardiac death.

Unknown Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

Table 15: Subject Death Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-cardiac, Unknown

The Clinical Events Committee will review all deaths and provide a final adjudication of the death classification.

Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements.

17.5. Product Complaint Reporting

Product complaint reporting and vigilance reporting are applicable and AEs related to any market-released device during the study must be reported. The reporting of product complaints is not part of the Attain Stability Quad Clinical Study and should be done in addition to the AE reporting requirements. Refer to local regulations for reporting requirements.

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

- Abuse: Abnormal use (definition acc. #4.1 of Meddev 2.12-1 rev8)
- Misuse: Use error (definition acc. #4.20 of Meddev 2.12-1 rev8)

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the regulatory authorities (e.g. Competent Authority) as applicable for the following incidents immediately upon learning of them:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
    - Life-threatening illness or injury
    - Permanent impairment of a body function or permanent damage to a body structure
    - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

18. Data Review Committees

18.1. Clinical Events Committee

The study will utilize a Clinical Events Committee (CEC). At regular intervals, an independent CEC will review events and adjudicate at a minimum all system, and procedure-related events. Additionally, the CEC will provide an adjudication of the death classification for all reported deaths.

The CEC will consist of a minimum of three (3) non-Medtronic-employed physicians that are not participating investigators for the study, including a CEC chairperson.

Medtronic personnel may facilitate and participate in CEC meetings but will be non-voting members.

For AEs and deaths reviewed by the CEC, Medtronic will provide the CEC with the Investigator's description and classification and supportive documentation (when available). The CEC is responsible for reviewing the Investigator's assessment and supportive documentation (when available), reviewing applicable definitions, and determining final classifications for all adjudication parameters. For AEs, classification includes system/procedure relatedness and complication or observation. Additionally, the CEC will provide an adjudication for all reported deaths, including system/procedure relatedness and cardiac relatedness.

If the CEC disagrees with the investigator's classification of the event, the difference will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the CRF documenting the AE will be updated accordingly.

If the investigator does not agree with the CEC's adjudication classification, both determinations will be provided within the final report; however the CEC's adjudication will be used for data analysis. The disagreement will also be included in reporting to ethics committees and regulatory authorities, if required.

18.2. Data Monitoring Committee

A Data Monitoring Committee (DMC) will not be utilized for this study considering:

- An independent CEC will be formed to adjudicate at minimum all system and procedure related events and all deaths.
- This study does not meet FDA's recommended criteria (Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees) for when a study should use a DMC, primarily because the study is not evaluating the effectiveness of a treatment intended to prolong life or reduce the risk of a major adverse health outcome.
- As a result of risk analysis and mitigation efforts as outlined in Section 16, any residual risk associated with this study is considered low and acceptable.
- The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is a modification of the currently market approved Attain Performa lead Models 4298, 4398, and 4598 is a modification of the currently market approved Model 4396 LV lead. The Attain Stability Quad lead Model 4798 has a similar electrode spacing as the Attain Performa lead Models 4298, 4398, and 4598.
- Study will be conducted under FDA oversight via an investigational device exemption (IDE).

19. Statistical Design and Methods

This section presents statistical considerations for the study design and provides a high-level description of planned analysis and reporting. More details will be given in a separate Statistical Analysis Plan (SAP) that will be completed before data freeze for the primary objective analysis. Any deviation to the pre-specified statistical analyses will be noted in the study report. The analysis of the study objectives will be completed when the sample size requirements (see Table 18) for all the study primary and secondary objectives are met. An interim analysis will be conducted when 360 subjects are enrolled in the study. This interim analysis is specifically designed for one of the secondary objectives (details in Section 19.2.2).

19.1. Primary Objectives

19.1.1. Primary Safety Objective

Objective

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered safe if the probability of subjects free of Model 4798 lead-related complications at 6 months post-implant is greater than 87% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 87%).

Hypothesis:
H_0: $S_{(6\text{-month})} \leq 87\%$
H_1: $S_{(6\text{-month})} > 87\%$

where $S_{6\text{-month}}$ is the probability that a subject remains free from Model 4798 lead related complications through 6 months since implant.

Endpoint Justification

The study primary safety endpoint is Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complications. All reported system and procedure-related AEs will be reviewed by an event review committee for LV lead relatedness and severity (see Section 18.1).

Utilizing lead related complication free survival probability to evaluate lead safety performance is widely accepted across cardiac device manufacturers and in the medical literature. Current already market-released Quadripolar LV lead 6-month safety performance is summarized in Table 16. The population performance of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is expected to be similar to the Medtronic Attain Performa Model 4298 lead.

Table 16: Safety Performance of Market Released Quadripolar Lead

	Medtronic Attain Performa[20]	**St. Jude Medical Quartet[22]**	**Boston Scientific ACUITY X4[23]**
6-month LV Lead Complication Free Survival Probability Estimate	Model 4298 (Canted): 96.0% Model 4398 (Straight): 98.8% Model 4598 (S-shape): 96.2%	96% at 3 months	Straight: 96.5% Spiral: 98.5%

Statistical Analysis Methods

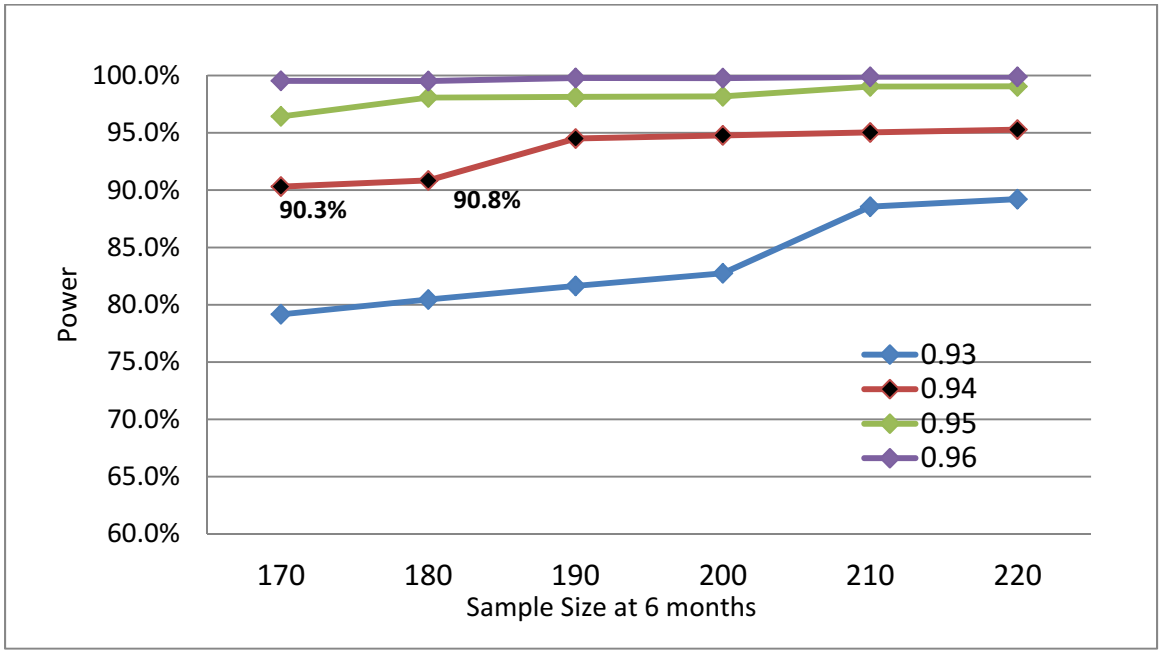
The primary objective will be analyzed using the time-to-first event Kaplan-Meier survival analysis method. Time 0 will be the day a subject undergoes the implant procedure of a Attain Stability Quad MRI SureScan LV Lead (Model 4798), which will be independent of success status of this implant procedure. Event date is the onset date of a subject's first complication that is related to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) according to CEC adjudication. Subjects who undergo an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt and do not experience any LV lead related complications will be censored at the time of their last known exposure to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) for the survival analysis. For any lost-to-follow up subject, the last contact date will be used as the censor date. The 1-sided 97.5% confidence limit lower bound for the survival probability at 6 months (183 days) will be calculated using the log-log survival function approach (Kalbfleisch and Prentice 2002).

Sample Size Consideration

The primary safety objective performance criterion is set to be identical to Medtronic's Attain Performa Clinical Study (IDE Number: G120213). Therefore, the sample size calculation assumptions are derived based on the Model 4298 lead study results. The Attain Performa Model 4298 lead reported a 6-month complication free survival probably of 96.0%, with 97.5% Confidence Lower Limit of 94.3% (PMA-s clinical report).

The binomial calculation (Z-test) is used for initial sample size estimation. In order to preserve the overall study power, a type II error less than 10% was used for the sample size calculation. A sample size of 170 subjects completing their 6-month visit achieves greater than 90% power to detect a difference of 7% using the one-sided binomial test. The target significance level is 0.025. These results assume that the population proportion under the null hypothesis is 87% with an expected value of 94% (Figure 5). To account for 15% attrition, the enrollment size for this objective is 200.

Figure 5: Primary Safety Objective Sample Size Consideration by Difference Performance Assumption



Determination of Patients / Data for Analysis

All consented subjects who undergo an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt will be included in the analysis cohort. If a patient experiences multiple Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant procedures during the study, the analysis cohort will only consider the first procedure. In the event multiple complications occur, the survival analysis endpoint is reached when the first Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complication occurs.

19.1.2. Primary Efficacy Objective #1

Objective

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet the first primary efficacy objective if the proportion of subjects with at least one Attain Stability Quad MRI SureScan LV Lead (Model 4798) pacing vector having a pacing capture threshold (PCT) less than or equal to 2.5 V at 0.5ms pulse width (with absence of PNS at 5.0 V) at 6 months post-implant is greater than 80% (i.e., the lower bound of the one-sided 97.5% confidence interval must be greater than 80%).

Hypothesis
H_0: $P1_{6\text{-month}} \leq 80\%$
H_A: $P1_{6\text{-month}} > 80\%$,

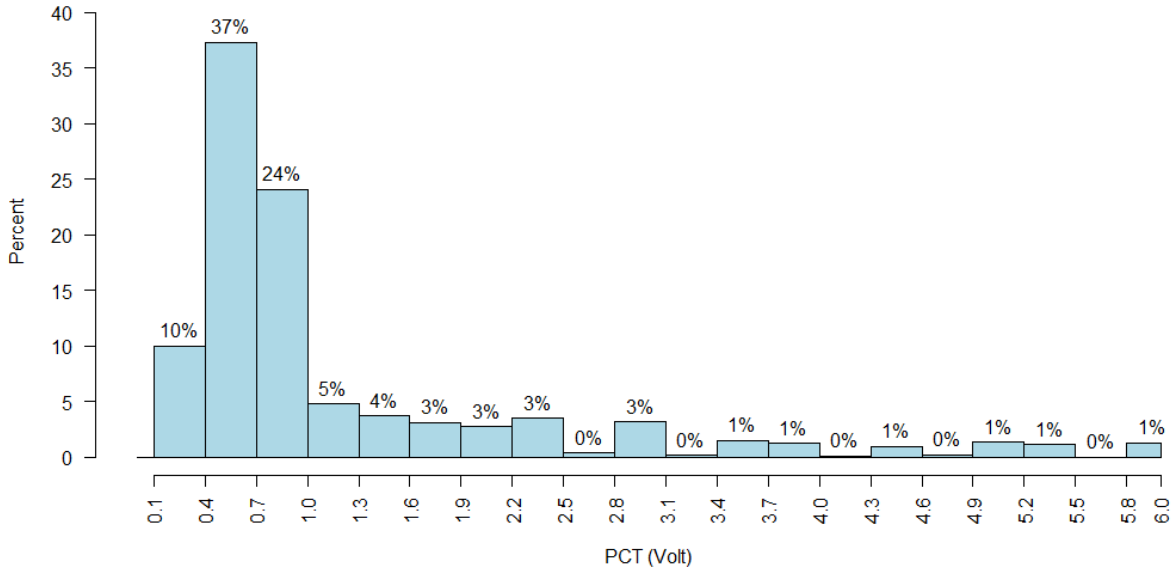
where $P1_{6\text{-month}}$ is the proportion of subjects with pacing voltage thresholds ≤ 2.5V at 0.5ms (with absence of PNS at 5.0 V) at 6 months follow-up visit post-implant for at least one LV lead pacing vector.

Endpoint Justification

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is equipped with the identical four electrodes to the Attain Performa LV leads. At the same time, the unique fixation mechanism may cause the distal end of the lead (tip) to be implanted away from the apical region of the heart, and therefore

the PCT may be slightly higher than the values observed in other Quadripolar LV leads. Therefore, we simulated the lead pacing threshold values based on the Attain Performa IDE study data, but excluding the PCT values collected at the most distal electrode. The simulation estimated that 89% of the subjects will achieve this endpoint (Figure 6).

Figure 6: Simulated PCT Distribution



Statistical Analysis Methods

All subjects with valid pacing thresholds measured at the 6 month follow-up visit will be included in this analysis. The proportion of subjects having at least one LV lead pacing vector with voltage thresholds less than or equal to 2.5V (with absence of PNS at 5.0 V) will be calculated. The lower bound of the 1-sided 97.5% Confidence Interval will be calculated using the Exact binomial method. Any subject in which no valid pacing threshold value is measured or who has an unable-to-capture result via all LV lead pacing vectors will be reviewed and adjudicated for a possible lead related AE but will not be included for this evaluation if the occurrence is deemed to be a system related event (e.g. lead dislodgement). However, this event may be counted against the safety primary endpoint based on the CEC's final classification.

Sample Size

The primary efficacy endpoint will be analyzed using the Exact binomial method. In order to preserve the overall study power, a type II error less than 10% was used for the sample size calculation. A sample size of 145 subjects achieves 91% power to detect a difference of 0.1 using a one-sided binomial test at a target significance level of 0.025. These results assume that the population proportion under the null hypothesis is 80%, with an expected proportion of 90%.

Determination of Patients / Data for Analysis

All subjects enrolled into this study satisfying the following conditions will be included in this analysis:

- Successfully implanted with a Medtronic Quad CRT-P or CRT-D device and Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- Completed 6-month follow-up visit
- Initially implanted Attain Stability Quad MRI SureScan LV Lead (Model 4798) is active at the 6–month follow-up visit
- At least one available and valid pacing threshold at the 6-month follow-up visit

19.1.3. Primary Efficacy Objective # 2

Objective

The Attain Stability Quad lead will meet the second primary efficacy objective if the proportion of subjects with at least one additional (or second) LV lead pacing vector having a pacing capture threshold less than or equal to 4.0 V at 0.5ms pulse width (with absence of PNS at 5.0 V) at 6 months post-implant is greater than 80% (i.e., the one-sided 97.5% lower confidence bound must be greater than 80%).

Hypothesis
H_0: $P2_{6\text{-month}} \leq 80\%$
H_A: $P2_{6\text{-month}} > 80\%$,

where $P2_{6\text{-month}}$ is the proportion of subjects with at least one additional LV lead pacing vector with pacing voltage thresholds ≤ 4.0V at 0.5ms (with absence of PNS at 5.0 V) at 6 months post-implant follow-up visit.

Endpoint Justification

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) has 16 LV programmable pacing vectors . Subjects may have the pacing configuration programmed or reprogrammed at each clinic visit. A pacing threshold of 4.0 V (with absence of PNS at 5.0 V) will allow an adequate safety margin for programming LV pacing output. The maximum pacing amplitude of the CRT-P or CRT-D devices capable of programming pacing output to any LV lead pacing vector is 8.0V. In actual clinical practice, a less than 3V safety margin is used for the programmed LV lead pacing output in 99% of the patients.

Statistical Analysis Methods

The efficacy endpoint #2 will be analyzed using the Exact binomial method. The proportion of subjects with at least 2 LV lead pacing vectors having voltage thresholds less than or equal to 4.0V at 0.5ms (with absence of PNS at 5.0 V) will be calculated. The lower bound of the 1-sided 97.5% Confidence Interval will be calculated using the Exact binomial method. Any subject in which no valid pacing threshold values are measured or with an Unable-to-capture result via all LV lead pacing vectors will be reviewed and adjudicated for possible lead related complications, and therefore may be counted against the study safety endpoint. However, it will be counted as a failure if there is not any additional LV lead pacing vectors (excluding the vector that is already include for the efficacy endpoint #1) are unable to capture with no lead related events reported.

Sample Size

The Attain Performa Model 4298 LV lead observed 97.7% subjects who were able to obtain a non-programmed pacing vector with PCT less than or equal to 4 volts (with absence of PNS at 5.0 V). A sample size of 50 subjects completing the 6 month visit achieves 98% power to detect a difference of

0.18 using a one-sided binomial test at a target significance level of 0.025. These results assume that the population proportion under the null hypothesis is 80%, with the expected proportion of 97%.

Determination of Patients / Data for Analysis

All subjects enrolled into this study satisfying the following conditions will be included in this analysis:

- Successfully implanted with a Medtronic Quad CRT-P or CRT-D device and Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- Completed 6-month follow-up visit
- Initially implanted Attain Stability Quad MRI SureScan LV Lead (Model 4798) lead is active at the 6–month follow-up visit
- At least one available and valid pacing threshold at the 6-month follow-up visit. In the event a subject failed to provide more than one valid pacing threshold value, that subject will be considered as not having at least one additional LV lead pacing with PCT ≤ 4.0V at 0.5ms at 6 months post-implant follow-up visit

19.2. Secondary Objectives

19.2.1. Secondary Objective # 1

Objective - Implant procedure related information: success rate, implant related times

The Attain Stability Quad LV lead implant success rate will be estimated as the number of subjects with Attain Stability Quad MRI SureScan LV Lead (Model 4798) successfully implanted divided by the total number of subjects who had a Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt. A 2-sided 95% Confidence Interval will be calculated using the Exact Binomial method.

The distribution of implant related times will be summarized through statistical summaries such as mean, standard deviation, minimum, median and maximum. Only subjects with the Attain Stability Quad MRI SureScan LV Lead (Model 4798) successfully implanted will be included in this calculation. The total implant time is defined as time from initial incision to final skin closure. Fluoroscopy time is defined as the total time the fluoroscope is imaging. Cannulation time is defined as the time from insertion of the first CS cannulation catheter to the first successful CS cannulation. Successful lead placement time is defined as the time from lead insertion of the successfully placed lead to the time when the lead is placed in its first acceptable pacing location.

19.2.2. Secondary Objective # 2

Objective - 6-month reliability: post implant lead failure modes

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is a composite of two existing market released Medtronic products. The helix fixation is identical to the Attain Stability LV Lead Model 20066/4796 (market released outside of the US). The remainder of the lead is similar to the Attain Performa LV Lead Model 4298, released worldwide.

Historical datasets will be used as informative priors for lead related complications. More specifically, analysis of all complications related to fixation (helix performance) will use data from the Attain Stability (Model 20066/4796) research study, conducted outside of the US[21]. Analysis of all other lead related complications will use data from the Attain Performa clinical study, conducted globally. Credible intervals will be constructed for each individual failure mode within the two groups.

Historical Data (for secondary endpoints only)

- Fixation-related LV lead complications - Data from the 37 patients who completed 6-month follow up with a successfully implanted 20066 lead in the Attain Stability study will be used as an informative prior.
- All other LV lead-related complications - Data from the 401 patients who completed 6-month follow up in the Attain Performa 4298 study will be used as an informative prior.

These historical datasets will be down weighted such that their effective sample size will not exceed the 9% of the total sample size (i.e. at most 37 subjects at 6 months).

Statistical Analysis Methods

The weighted historical data will be incorporated using the power prior method[24]. The weight of the historical data will be adjusted using a loss function[25], which scales from 0 to 1 according to the similarity of the historical and observed data. This loss function adjusts the amount of weight the prior receives. The comparison between historical and observed data will be performed twice, once for each group of complications (fixation-related and all other). The objective of using a loss function with the power prior method is to reduce the influence of an informative prior in the parameter estimation, when the historical data does not agree with the current study data.

If analysis of failure rate shows a high level of agreement between historical and current study data or there is better performance for Attain Stability Quad MRI SureScan LV Lead (Model 4798) compared to historical data, the historical data will be weighted at or near a maximum level (9% of total effective sample size). If the Attain Stability Quad MRI SureScan LV Lead (Model 4798) performs worse than historical data, the historical data will receive very little or zero weight. Note that there will be two loss function weights, one for fixation-related complications and one for all other complications. Credible interval calculations will be done separately for individual failure modes within the two groups of complications (fixation and all other).

Denote by θ_c and θ_h the probabilities of lead complication for the current and historical studies respectively. The posterior distributions of θ_c and θ_h respectively, both with minimally informative priors are:

$$\theta_c = beta(y_c + 1, n_c - y_c + 1)$$
$$\theta_h = beta(y_h + 1, n_h - y_h + 1)$$

These posterior distributions are then stochastically compared using a posterior Bayesian p-value[26] as:

$$p = P(\theta_c \leq \theta_h)$$

The desired characteristics for the loss function are:

1. For $p \geq \sim 0.5$, there is a high level of agreement between current and historical data, therefore the loss function should allow a_0 to be close to 1, allowing for full weight of historical data.

2. Conversely, for $p < \sim 0.5$, there begins to be evidence of disagreement between current and historical data, and a_0 should start to down-weight the prior, i.e. a_0 approaches zero as p approaches zero.

The Weibull cumulative distribution function (CDF) meets these criteria:

$$a_0 = 1 - e^{-(p*5)^2}$$

Note that for the case where the number of samples in the prior is different than the effective number, a scaling factor will be applied, where n_h is the desired effective number of prior samples and N_h is the actual number of prior samples:

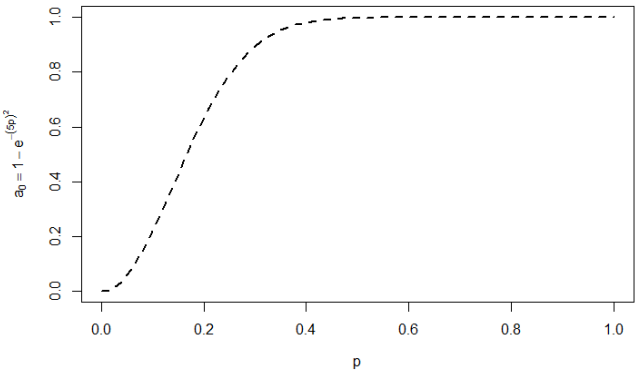
$$a_0 = \frac{n_h}{N_h}\left[1 - e^{-(p*5)^2}\right]$$

Sample values are listed in Table 17 below and illustrated in Figure 7. The comparison between current and historical data will be performed for all LV lead fixation related complications using Attain Stability (Model 20066) historical data and for all other LV lead related complications using Attain Performa historical data.

Table 17: Prior weight from Attain Stability (Model 20066) and prior weight from Attain Performa as a function of the posterior Bayesian p-value (p)

	Prior weight from Attain Stability (Model 20066)	Prior weight from Attain Performa
$\boldsymbol{p}$	$a_0 = 1 - e^{-(p*5)^2}$	$a_0 = \frac{37}{401}\left[1 - e^{-(p*5)^2}\right]$
0.01	0.002	0.000
0.05	0.061	0.006
0.1	0.221	0.020
0.2	0.632	0.058
0.5	0.998	0.092

Figure 7: Loss Function $a_0 = 1 - e^{-(p*5)^2}$

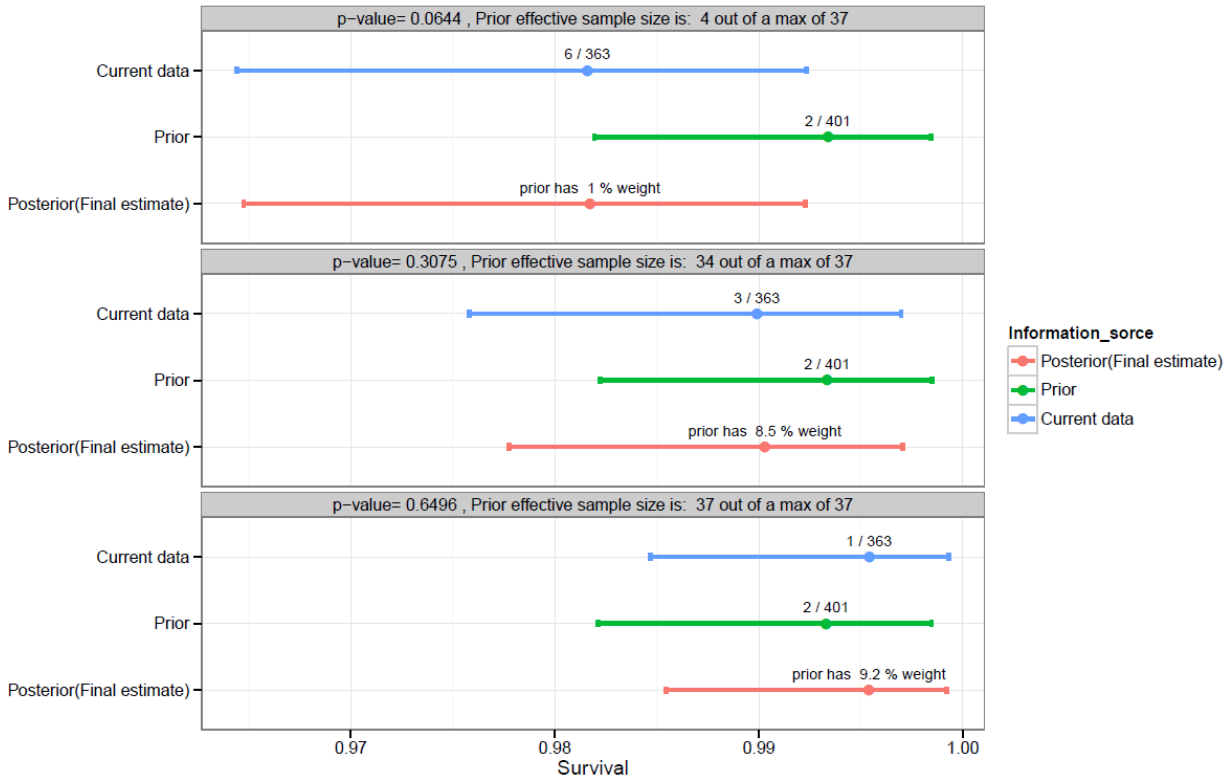


Note that the loss function proposed here does not reduce the strength of the prior when the current study outperforms the historical data. This implementation of the loss function is only concerned with negative impacts to patients, i.e. it penalizes an optimistic prior while not penalizing a pessimistic prior.

Also, note that this function is selected for the shape of the CDF rather than due to conventional statistical properties of the Weibull distribution.

Figure 8 illustrates the effect of the power prior coupled with the loss function. The figure shows credible intervals in scenarios where the prior is optimistic (better performance than current study), in agreement (similar performance to the current study), and pessimistic (worse performance than the clinical study). Note that the prior data source in Figure 8 is the Attain Performa study, with 401 patients. As will be discussed later, these data are scaled to represent a maximum of 37 patients (i.e. 9% weight).

Figure 8: Credible Intervals for Scenarios of Agreement Between Historical and Current Data



The prior data set in Figure 8 has 401 samples. However, the maximum effective historical data sample size is $n_h = 37$, for a maximum weight of 9%. Therefore, the prior will be scaled by a factor of (37/401). As an example, illustrated in the middle panel above, if the effective sample size is 34 out of 37, the prior has received 89% of the maximum weight, or 8.5%.

The panels in Figure 8 can be interpreted as follows:

- Top panel: The current data shows lower performance than the prior. The loss function produces a substantial penalty resulting in almost no weight to the prior (1%). The posterior (final estimate) is essentially the same as the current study.
- Middle panel: The current data is very similar to the prior. The loss function penalty is small, resulting in a prior weight of 8.5% (recall that the maximum weight is 9.2%). Because the agreement is good, the posterior(final estimate) is similar to both the prior and current study.
- Bottom panel: The current data is very similar, with slightly better performance than the prior. The loss function produces a weight very close to the maximum of 9.2%. The posterior (final estimate) is a balance between the prior and current study.

Sample Size

A Bayesian adaptive design is set up to enroll patients until a sufficient sample size is achieved to have high probability of meeting the required effective sample size of $n_e = 400$. The number of enrolled patients in the study may vary from 363 to 400 subjects due to the adaptations to the trial. This study follows methods from Berry, et.al.[27]

The interim analysis will take place after 360 subjects have been enrolled into the study.

The Adaptive Bayesian sample size algorithm will stop or continue enrollment accordingly to the following:

1.) If the predictive probability of $n_e \geq 400$ is larger than 80% then enrollment will stop.
2.) If the predictive probability of $n_e \geq 400$ is less than 80%, enroll sufficient additional patients to make the probability of $n_e \geq 400$ at least 80%.

At the time of the interim analysis, some patients will not have completed the full evaluation period. A longitudinal model will be employed to enable final observations to be imputed for those subjects with incomplete information.

There are 3 types of subjects at a given interim analysis:

1.) Subjects that have complete data
2.) Subjects that have partial data (censored value at a particular time)
3.) Subjects that have no information (subjects that have not been enrolled)

Predictive probabilities for types 2 and 3 will have to be computed. The predictive probability model that will be used is a piecewise exponential. This will allow the final outcomes for the subjects who have not had an event and have not completed 6 month follow up to be simulated.

Note this Bayesian approach to borrow information from historical datasets will only be used for the secondary objective #2.

19.2.3. Secondary Objective # 3

Objective – Electrical measurements (PCT and Impedance) at follow-ups

Pacing Capture Threshold (PCT) and impedance data will be collected using VectorExpress™. Pacing vector changes will be monitored for all implanted patients at follow-up visits.

Summary statistics for PCT and impedance at each time point (i.e. Implant, 6 months, etc.). The distribution of the electrical measurements at the final programmed pacing vector will be presented as n, mean, standard deviation, minimum, median and maximum. In the event of a replacement of a Medtronic Quad CRT-P or CRT-D device and/or the implanted LV lead, only measurements from the

Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted at the initial implant procedure will be included in the analysis cohort for this objective.

19.3. Additional Analysis

19.3.1. Poolability Analysis

Additional analysis will be conducted to summarize study primary objectives by patient characteristics, such as gender, age group, race and study site geography. The purpose of the poolability analysis is to identify if there is any clinical meaningful difference in a subgroup of patients. These analyses will not be statistically powered, and there is no pre-specified statistical significance level for these analyses.

19.3.2. Sensitivity Analysis

All subjects enrolled into this study and successfully implanted with a Medtronic Quad CRT-P or CRT-D device and Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be included in the primary efficacy analysis datasets (efficacy objectives #1 and #2). Sensitivity analysis such as the Tipping Point method or similar will be conducted to investigate the influence of subjects who were successfully implanted with the required system however missed a 6 month post implant follow-up test(s) (due to reasons such as missing in-office visit, subject exit, death and/or the initial implanted lead was deactivated). For this purpose, all subjects with successful implant who do not meet analysis cohort requirements, will be considered as the worst case scenario (i.e. failure to meet the efficacy endpoints).The results will be submitted as part of the clinical reports.

19.3.3. Additional Data Collection

Heart failure clinical outcomes will be assessed. The measurements, including NYHA classification, death, heart failure related hospitalization, heart failure related study exits and subject self-reported global assessment for each subject will be obtained at 6 months post-implant. Summary statistics will be provided.

19.3.3. Overall Study Sample Size Requirements

The sample size requirement at 6-months for each of the study objectives is displayed in Table 18. The first row does not account for attrition, while the second row is inflated by 15% attrition. The sample size for Secondary Objective #2 assumes the conservative case that the interim look results in, no borrowing of historical data. Therefore, the overall sample size for the study is 471.

Table 18: Required Sample Size by Study Objective

	Primary Safety Objective	Primary Efficacy Objective #1	Primary Efficacy Objective #2	Secondary Objective #1	Secondary Objective #2 (post-implant failure modes)	Secondary Objective #3	Overall
Number needed at 6-months	170	145	50	NA	400	NA	400
Number of enrollments	200	171	59	NA	471	NA	471

20. Ethics

20.1. Statement(s) of Compliance

This study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). Good Clinical Practice includes review and approval by an independent IRB/EC before initiating a study, continuing review of an ongoing study by an IRB/EC, and obtaining and documenting the freely given IC of a subject before initiating the study.

The clinical investigation shall not begin until all required approvals and documents from the IRB/EC and a regulatory authority, if needed, have been received. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

The Attain Stability Quad Clinical Study was designed to reflect the GCP principles outlined in ISO 14155:2011 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In accordance with ISO 14155:2011, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation. Adverse Event and Device Deficiency handling in the Attain Stability Quad Clinical Study is ISO 14155:2011 compliant for all participating geographies with the exception that only those AEs which are related to the subject's system, procedure, accessory, or are cardiovascular-related, and all Serious AEs, will be collected. This ensures any AEs which could potentially be relevant will be collected. The scope and duration of the Attain Stability Quad Clinical Study would make collection of all AEs to be a significant burden for investigators and investigative sites. Therefore, only a subset of AEs will be collected in this study, including any that could be potentially relevant.

The principles of the Declaration of Helsinki have been implemented through the IC process, IRB/EC approval, study training, clinical trial registration, pre-clinical testing, risk-benefit assessment and publication policy.

Ultimately, all sites in all geographies will follow and comply with:

- Principles of Declaration of Helsinki
- 21 CFR Part 11 (Electronic Records, Electronic Signatures) (per local law)
- 21 CFR Part 54 (Financial Disclosure by Clinical Investigators)
- The Clinical Trial Agreement
- The procedures described within this CIP
- Local Ethics Board Requirements

In addition to the regulatory requirements outlined above, the study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. These include but are not limited to:

- In the United States, the study will be conducted under an FDA IDE in compliance with 21 CFR Parts:
  - 50: Protection of Human Subjects
  - 56: Institutional Review Boards
  - 812: Investigational Device Exemptions
- In Canada, SOR/98-282, Section 59-88 will be followed and Mandatory Problem Reporting 59(1), 59(2), 60 (1)).
- In EMEA the study will be conducted in compliance with the Active Implantable Medical Device Directive (AIMDD), Declaration of Helsinki version 2013, and full compliance with ISO 14155.
- In Hong Kong and Malaysia, the study will be conducted in compliance with the Declaration of Helsinki version 2013.
- In EMEA, an IB is not required for this study as it is a post market study

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act FDAAA and Declaration of Helsinki on http://clinicaltrials.gov (PL 110-85, section 810(a)). In addition, the study may be registered in local regulatory databases where required by local law.

Approval of the CIP and CIP amendments is required from the following groups prior to any study procedures at a study site:

- Medtronic
- Principal Investigators (where required by local law/regulations)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent medical ethics committee or institutional review board.

Similarly, approval of subsequent revisions to the CIP is required at each study site from the above mentioned groups prior to implementation of the revised CIP at the site.

21. Study Administration

21.1. Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this Attain Stability Quad Clinical Study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the CTA, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the Subject IC, Data Protection Authorization (where applicable) and CTA. The principal investigator should also be available during monitoring visits.

Monitoring for the study, including site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

Monitoring visits may be conducted periodically to assess site study progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to IRB/EC approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs. Monitors review site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to site personnel. Monitors may work with study personnel to determine appropriate corrective action

recommendations and to identify trends within the study or at a particular site. Regulatory documents may be reviewed at each study site.

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of adverse events, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation.

21.2. Data Management

Data will be collected using Oracle Clinical, an electronic data management system for clinical studies. CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

Only authorized persons can complete CRFs. CRFs shall be signed by the Principle Investigator. The Principle Investigator can delegate the CRF sign off task to Sub-Investigators only. Delegation of authority will be specified on the appropriate documentation.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to make it anonymous, for instance, where the subject's name cannot be removed from the data carrier.

Procedures in the CIP require source documentation. Source documentation will be maintained at the site. Source documents, which may include worksheets, patient medical records, programmer printouts and device interrogation files, must be created and maintained by the investigational site team. For source documentation, the investigational site study team must sign and date any copies or printouts of original source documents with a statement that this is a complete and true reproduction of the original source document.

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. The CRF may be considered source for the following data collection elements recorded directly on the CRFs:

- Enrollment Notification
    - Site assigned patient reference
- Baseline
    - Administrative information
- Adverse Event eCRF
    - Date study site became aware of event
    - Relatedness of adverse event
- Device Deficiency eCRF
    - Date study site became aware of event
- Subject Death
    - Date study site became aware of death
    - Relatedness of death
- System Modification
    - Justification for explanted product not being returned to Medtronic
- Deviations

    - Reason for deviation
- Investigational product Disposition Log
    - Date the Investigational Attain Stability Quad lead was implanted/explanted

Even when the CRF may be considered as source, an alternate method of source documentation is always strongly encouraged.

Save-to-media data collected at office visits will be sent to Medtronic. Upon receipt, device data will be maintained within a Medtronic device database and retrieved for analysis and reporting.

21.3. Direct Access to Source Data/Documents

The sponsor or a regulatory authority may audit or inspect the study site to evaluate the conduct of the study. The clinical investigator(s)/institution(s) shall allow study related monitoring, audits, IRB/EC review and regulatory inspection.

21.4. Confidentiality

All records and other information about subjects participating in this study will be treated as confidential.

21.5. CIP Amendments

Approval of subsequent revisions to the CIP is required at each study site from the following groups prior to implementation of the revised CIP at the site:

- Medtronic
- Principal Investigators (where required by local law)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent medical ethics committee or institutional review board.

If a CIP amendment occurs, site personnel will need to be re-trained as necessary, and will need to submit any changes to their IRB/EC as required by the committee. Protocol amendments will also be reported to and approved by the FDA, or regulatory authority.

21.6. Warranty/Insurance Information

21.6.1. Warranty

Warranty information is provided in the product packaging for the commercially released CRT-P or CRT-D devices and leads, and additional copies are available upon request.

21.6.2. Insurance (EMEA)

Medtronic Bakken Research Center B.V. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the EC and/or Competent Authority (CA).

21.6.3. Insurance (Canada)

Medtronic of Canada is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate general liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a General Liability insurance statement/certificate will be provided to the Ethics Committee.

21.6.4. Insurance (Malaysia)

Medtronic International Ltd. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

21.6.5. Insurance (Hong Kong)

Medtronic Hong Kong Medical Ltd. Ltd. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

21.7. Record Retention

21.7.1. Investigator Records

The investigator is responsible for the preparation and retention of the records including, but not limited to, those cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (e.g., the study binder provided to the investigator) or Subject Study Binder. Case Report Forms must be maintained and signed electronically by an investigator within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law/regulation or hospital administration requires) after product approval. Measures shall be taken to avoid loss or premature destruction.

- All correspondence between the IRB/EC, sponsor, monitor, regulatory authority and/or the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
    - Signed and dated informed consent form, in accordance with local requirements
    - Observations of adverse events/adverse device effects/device deficiencies
    - Medical history
    - Baseline, Implant and follow-up data (if applicable)
    - Documentation of the dates and rationale for any deviation from the protocol
- Electronically signed and dated eCRFs and a blank set of CRFs where required by local law
- All approved versions of the CIP, IC
- Fully executed Clinical Trial Agreement
- Ethics Committee approval documentation. Written information that the investigator or other study staff, when member of the Ethics Committee, did not participate in the approval process.

Approval documentation must include the Ethics Board composition, where required per local law.
- Regulatory authority notification, correspondence and approval, where required per local law.
- List of investigation sites: This list is not yet final at the time of CIP development. The list will be provided under separate cover and will be maintained by the sponsor.
- Financial disclosure (investigators)
- Enrollment Log (for sites following ISO 14155)
- For sites where the Attain Stability Quad lead is considered investigational, device disposition logs containing Model and serial numbers of devices implanted, subject IDs of the subjects implanted, implant/used dates, explant dates, returned-to-sponsor dates and reasons and method of disposal/destruction
- Current curriculum vitae (signed and dated in EMEA only) of principal investigators and key members of investigation site team (as required by local law)
- Documentation of delegated tasks
- Study training records for investigation site team
- Assurance certificates (EMEA, Hong Kong, and Malaysia)
- Any other records that FDA and local regulatory agencies require to be maintained (e.g. Ethics Committee Roster, study equipment calibration information)
- Final Study Report including the statistical analysis

21.7.2. Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all CRFs, AEs and ADEs (reported per the country-specific collection requirements), DDs, deaths, crossovers and any deviations from the CIP. If any action is taken by an IRB/EC with respect to this Attain Stability Quad Clinical Study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Investigator reporting requirements for safety data are listed in Section 17.3).

Table 19: Investigator Reports Applicable for All Geographies per Medtronic Requirements

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing Ethics Committee of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and Ethics Committee	Any deviation from the clinical investigation plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Failure to obtain informed consent	Sponsor and Ethics Committee	Informed consent shall be obtained in writing and documented before a subject is enrolled into the Attain Stability Quad Clinical Study
Final Report	Ethics Committee and Relevant Authorities	This report must be submitted within 3 months of study completion or termination.

21.7.3. Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records that includes, but is not limited to:

- All correspondence which pertains to the Attain Stability Quad Clinical Study
- Executed Clinical Trial Agreement
- Financial disclosures (investigators)
- Current curriculum vitae (signed and dated in EMEA only) of principal investigators and key members of investigation site team (as required by local law)
- Device Disposition Logs containing Model and serial numbers of devices implanted, subject IDs of the subjects implanted, implant/used dates, explant dates, returned-to-sponsor dates and reasons and method of disposal/destruction
- Electronically signed and dated eCRFs
- All approved informed consent templates, and other information provided to the subjects and advertisements, including translations
- Copies of all Ethics Committee approval letters and relevant Ethics Committee correspondence and Ethics Committee voting list/roster/letter of assurance
- List of names, addresses, and professional position of the clinical investigators and coordinating clinical, if appointed.
- Names and addresses of the institutions in which the Attain Stability Quad Clinical Study will be conducted: This list is not yet final at the time of CIP development. The list will be provided under separate cover and will be maintained by the sponsor.
- Regulatory authorities correspondence, notification and approval as required by national legislation
- Insurance certificates (EMEA, Hong Kong, and Malaysia)
- Names/contact addresses of monitors
- Monitoring reports (interim monitoring visit reports, follow-up letters and close-out visit reports)
- Site qualification visit reports
- Statistical analyses and underlying supporting data
- Final report of the Attain Stability Quad Clinical Study
- The approved Clinical Investigation Plan and study related reports, and revisions
- Documentation of delegated tasks
- Study training records for site personnel and Medtronic personnel involved in the study
- Sample of CRFs
- Any other records that local regulatory agencies require to be maintained

21.7.4. Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of reviewing Ethics Committee, regulatory agency or FDA, provide accurate, complete and current information about any aspect of the Attain Stability Quad Clinical Study. Safety data Medtronic reporting requirements are listed in Section 17.3).

Table 20: Sponsor Reports for Canada

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, Ethics Committee, Relevant authorities, and Head of the Institution	Provide prompt notification of termination or suspension and reason(s).
Recall and device disposition	Investigators, Ethics Committee	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices.
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically.

Table 21: Sponsor Reports for EMEA, Malaysia, Hong Kong

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, Ethics Committee, Relevant authorities and Head of the Institution	Provide prompt notification of termination or suspension and reason(s) per local law. *(ISO 14155:2011)*
Withdrawal of Ethics Committee approval	Investigators, Ethics Committee and relevant authorities	Investigators and other Ethics Committees will be notified only if required by local laws or by the Ethics Committee.
Withdrawal of CA approval	Investigators, Ethics Committee, and relevant authorities	Investigators, Ethics Committees and relevant authorities will be notified only if required by local laws or by the Ethics Committee.
Progress Reports	Ethics Committee and regulatory authorities	This will be submitted to the Ethics Committee and regulatory authorities only if required by local law.
Final report	Investigators, Ethics Committee, and Regulatory authorities upon request	• The investigator shall have the opportunity to review and comment on the final report. • If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). • The signature of the principal Investigator in each site should be obtained.
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. *(ISO 14155:2011)* Site specific study deviations will be submitted to investigators periodically.

Table 22: Sponsor Reports for the United States

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Investigators, Ethics Committee, FDA, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(2))*
Withdrawal of FDA approval	Investigators, Ethics Committee, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(3))*
Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. *(21 CFR 812.150(b)(4))*
Progress Reports	Ethics Committee and FDA	Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(5), 812.36(f)*
Recall and device disposition	Investigators, Head of Institution, Ethics Committee, relevant authorities, and FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6))*
Failure to obtain informed consent	FDA	Investigator's report will be submitted to FDA within five working days of notification. *(21 CFR 812.150(b)(8))*
Final report	Investigators, Ethics Committee, Regulatory authorities upon request, and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and IRBs/MECs within six months after completion or termination of this study. *(21 CFR 812.150(b)(7))*
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically.
Other	IRB, FDA	Accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(b)(10))*

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in secured file cabinets at Medtronic during the course of this study. After closure of the study Medtronic will archive records and reports as required by applicable regulations.

21.8. Publication and Use of Information

Publications from the Attain Stability Quad Clinical Study will be handled according to Medtronic Policies and Standard Operating Procedures and as indicated in the CTA.

21.8.1. Publication Committee

The Attain Stability Quad Clinical Study will utilize a Publication Committee which will include the Steering Committee members as well as Medtronic personnel. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to:

- Manage elements addressed in the publication plan as outlined in this section
- Develop the final Publication Plan under separate cover
- Execute the Publication Plan
- Oversee the publication of primary, secondary and ancillary study results
- Review and prioritize publication proposals
- Provide input on publication content, and
- Determine authorship

In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan. Membership in the Publication Committee does not guarantee authorship. The committee will meet as needed.

21.8.2. Management of Primary, Secondary, and Ancillary Publications

The Publication Committee reviews, prioritizes and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary/ancillary objectives, respectively, as specified in the Clinical Investigation Plan. An ancillary publication is any publication that does not address the study objectives identified in the Clinical Investigation Plan. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this Attain Stability Quad Clinical Study and clinicians not participating in this Attain Stability Quad Clinical Study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual site data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

21.8.3. Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE), Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Medtronic personnel, must at a minimum meet all of the conditions below:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published

Decisions regarding authorship and contributor-ship will be made by the publication committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the

authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All investigators not listed as co-authors will be acknowledged as the "Medtronic Attain Stability Quad Clinical Study Investigators" and will be individually listed according to the guidelines of the applicable scientific journal when possible. Any other contributors will be acknowledged by name with their specific contribution indicated.

21.8.4. Transparency

Transparency of study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to all investigators, IRB/ECs and Competent Authorities of participating countries when required by local law
- Registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- Submitting for publication the primary study results after the study ends
- Disclosing conflicts of interest (e.g. financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- Making an individual sites study data accessible to the corresponding investigator after the completion of the study, if requested

21.9. Suspension or Early Termination

21.9.1. Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or regulatory authority, whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing IRB/EC oversight is required until the overall study closure process is complete. Upon study closure, subjects should be managed and followed per physician discretion.

21.9.2. Early Termination or Suspension

Early Termination of the Study is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single site. Study Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single site. In the event the whole study or a single site is terminated, subjects will be exited.

Study-Wide Termination or Suspension

Possible reasons for considering study suspension or termination of the study include but are not limited to:

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)

- Technical issues during the manufacturing process

Investigator/Site Termination or Suspension

Possible reasons for clinical investigator or site termination or suspension include but are not limited to:

- Failure to obtain initial IRB/EC approval or annual renewal of the study
- Persistent non-compliance to the clinical investigation (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment
- Noncompliance to regulations and the terms of the CTA (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.)
- Institutional Review Board/Ethics Committee suspension of the site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

21.9.3. Procedures for Termination or Suspension

Medtronic-Initiated and Regulatory Authority-Initiated

- Medtronic will promptly inform the clinical investigators of the (early) termination or suspension and the reasons and inform the regulatory authority(s) where required
- In the case of study termination or suspension for reasons other than a temporary IRB/EC approval lapse, the investigator will promptly inform the IRB/EC
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

Investigator-Initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the IRB/EC
- The investigator will promptly inform the regulatory authorities (for regions following ISO only)
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

Institutional Review Board Ethics Committee-Initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with IRB/EC policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)

- The investigator will promptly inform the subjects, and/or the personal physician of the subjects, with the rationale for the study termination or suspension
- The investigator will promptly inform the regulatory authorities (for regions following ISO 14155 only)

22. Appendices

APPENDIX 1: Foreseeable Adverse Event List

The information provided in this section pertains to foreseeable AEs that may be observed in study subjects and may collectively assist in identifying those events that are unexpected in nature. The foreseeable adverse events information consists of three parts: (1) listing of potential adverse events associated with implantation of CRT system and transvenous leads, (2) rates of AEs reported from previous Medtronic studies evaluating CRT systems and transvenous leads, and (3) AEs rates reported in published literature for procedures similar to the CRT system implant procedure. This information will be used in combination with device labeling, current event reporting information, and other published data to assess for an unexpected occurrence.

The implantation of the study device, CRT-P or CRT-D, involves surgery, therefore, standard AEs associated with a surgical procedure may be experienced (e.g. anesthesia complications, injury, infections, bleeding, exacerbation of pre-existing conditions, healing complications, etc.). The focus of this section is to specifically address in more detail, those events that are foreseeable due to the use, performance, and/or presence of the system under investigation.

Additional potential risks associated with the implantation of the CRT system and the Attain Stability Quad MRI SureScan LV Lead (Model 4798), as well as risk minimization are discussed within Section 16.

Treatment required for procedure and/or system related adverse events that are experienced may include medication, device reprogramming, device modification (e.g. repositioning, surgical abandonment, surgical removal), or other surgical and medical remedies. The AEs associated with the use of transvenous leads, pacing and defibrillation systems include, but are not limited to, the following:

Table 23: Listing of Potential Adverse Events Associated with System Implant

- acceleration of tachyarrhythmias (caused by device)
- air embolism
- bleeding
- body rejection phenomena, including local tissue reaction
- cardiac dissection
- cardiac perforation
- cardiac tamponade
- chronic nerve damage
- constrictive pericarditis
- death
- device migration
- endocarditis
- erosion
- excessive fibrotic tissue growth
- extrusion
- fibrillation or other arrhythmias
- fluid accumulation
- formation of hematomas/seromas or cysts
- heart block
- heart wall or vein wall rupture
- hemothorax
- infection
- keloid formation
- lead abrasion and discontinuity
- lead migration/dislodgment
- complications and mortality due to inability to deliver appropriate and intended therapy
- muscle and/or nerve stimulation
- myocardial damage
- myocardial irritability
- myopotential sensing
- pericardial effusion
- pericardial rub
- pneumothorax
- poor connection of the lead to the device, which may lead to oversensing, undersensing, or a loss of therapy
- stroke
- threshold elevation
- thrombotic embolism
- thrombosis
- tissue necrosis
- valve damage (particularly in fragile hearts)
- venous occlusion
- venous perforation

An additional potential AE associated with the use of transvenous left ventricular pacing leads is coronary sinus dissection.

Additional potential AEs associated with the use of ICD systems include, but are not limited to, the following events:

- inappropriate shocks
- potential mortality due to inability to defibrillate
- shunting current or insulating myocardium during defibrillation

Patients susceptible to frequent shocks despite medical management could develop psychological intolerance to an ICD system that might include the following conditions:

- dependency
- depression
- fear of premature battery depletion
- fear of shocking while conscious
- fear that shocking capability may be lost
- imagined shocking (phantom shock)

Adverse Events Reported in Previous Medtronic Studies

The listing below provides an example of reported system and procedure related AEs in recent Medtronic studies. This table includes a summary of combined system or procedure related AEs as reported in the Concerto-AT, Insync III US, 4194, 4195, 4196, 4396, Adaptive CRT, and Attain Performa studies along with their incidence. The observed rate is based on the study populations that included a total of 3,246 subjects. In total, there were 1749 system or procedure related events. This includes both serious and non-serious events. The rate is calculated as number of subjects that experience the event, not accounting for duration of follow-up.

Table 24: System or procedure-related adverse events from previous clinical studies

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Abdominal pain	1	1	0.03%	(0.00%, 0.17%)
Acidosis	1	1	0.03%	(0.00%, 0.17%)
Acute respiratory failure	4	4	0.12%	(0.03%, 0.32%)
Adverse drug reaction	1	1	0.03%	(0.00%, 0.17%)
Air embolism	1	1	0.03%	(0.00%, 0.17%)
Alcohol withdrawal syndrome	1	1	0.03%	(0.00%, 0.17%)
Alpha haemolytic streptococcal infection	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Anaemia	7	7	0.22%	(0.09%, 0.44%)
Anaemia postoperative	1	1	0.03%	(0.00%, 0.17%)
Anaphylactic shock	1	1	0.03%	(0.00%, 0.17%)
Anticoagulation drug level below therapeutic	1	1	0.03%	(0.00%, 0.17%)
Anxiety	3	3	0.09%	(0.02%, 0.27%)
Application site rash	2	2	0.06%	(0.01%, 0.22%)
Arterial haemorrhage	1	1	0.03%	(0.00%, 0.17%)
Arteriovenous fistula	1	1	0.03%	(0.00%, 0.17%)
Arteriovenous fistula operation	1	1	0.03%	(0.00%, 0.17%)
Arthralgia	1	1	0.03%	(0.00%, 0.17%)
Arthritis bacterial	1	1	0.03%	(0.00%, 0.17%)
Ascites	1	1	0.03%	(0.00%, 0.17%)
Atelectasis	2	2	0.06%	(0.01%, 0.22%)
Atrial fibrillation	19	19	0.59%	(0.35%, 0.91%)
Atrial flutter	4	4	0.12%	(0.03%, 0.32%)
Atrial tachycardia	5	4	0.12%	(0.03%, 0.32%)
Atrioventricular block	16	16	0.49%	(0.28%, 0.80%)
Back pain	3	3	0.09%	(0.02%, 0.27%)
Bacteraemia	1	1	0.03%	(0.00%, 0.17%)
Cardiac arrest	8	8	0.25%	(0.11%, 0.49%)
Cardiac failure	46	43	1.32%	(0.96%, 1.78%)
Cardiac failure chronic	5	5	0.15%	(0.05%, 0.36%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Cardiac pacemaker battery replacement	1	1	0.03%	(0.00%, 0.17%)
Cardiac perforation	8	8	0.25%	(0.11%, 0.49%)
Cardiac sarcoidosis	1	1	0.03%	(0.00%, 0.17%)
Cardiac tamponade	3	3	0.09%	(0.02%, 0.27%)
Cardiac vein dissection	38	37	1.14%	(0.80%, 1.57%)
Cardiac vein perforation	5	5	0.15%	(0.05%, 0.36%)
Cardiogenic shock	3	3	0.09%	(0.02%, 0.27%)
Cardiomyopathy	1	1	0.03%	(0.00%, 0.17%)
Cardiovascular disorder	1	1	0.03%	(0.00%, 0.17%)
Cellulitis	2	2	0.06%	(0.01%, 0.22%)
Cerebral infarction	1	1	0.03%	(0.00%, 0.17%)
Cerebrovascular accident	3	3	0.09%	(0.02%, 0.27%)
Chest discomfort	4	4	0.12%	(0.03%, 0.32%)
Chest pain	8	8	0.25%	(0.11%, 0.49%)
Chronic obstructive pulmonary disease	3	3	0.09%	(0.02%, 0.27%)
Circulatory collapse	1	1	0.03%	(0.00%, 0.17%)
Colitis	1	1	0.03%	(0.00%, 0.17%)
Complication of device insertion	1	1	0.03%	(0.00%, 0.17%)
Complication of device removal	4	4	0.12%	(0.03%, 0.32%)
Constipation	1	1	0.03%	(0.00%, 0.17%)
Contusion	2	2	0.06%	(0.01%, 0.22%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Cough	1	1	0.03%	(0.00%, 0.17%)
Cystitis	1	1	0.03%	(0.00%, 0.17%)
Decubitus ulcer	1	1	0.03%	(0.00%, 0.17%)
Deep vein thrombosis	14	14	0.43%	(0.24%, 0.72%)
Dehydration	1	1	0.03%	(0.00%, 0.17%)
Delirium	1	1	0.03%	(0.00%, 0.17%)
Device alarm issue	1	1	0.03%	(0.00%, 0.17%)
Device battery issue	1	1	0.03%	(0.00%, 0.17%)
Device capturing issue	30	29	0.89%	(0.60%, 1.28%)
Device computer issue	19	19	0.59%	(0.35%, 0.91%)
Device connection issue	19	19	0.59%	(0.35%, 0.91%)
Device damage	1	1	0.03%	(0.00%, 0.17%)
Device dislocation	125	107	3.30%	(2.71%, 3.97%)
Device electrical impedance issue	12	12	0.37%	(0.19%, 0.64%)
Device extrusion	2	1	0.03%	(0.00%, 0.17%)
Device failure	1	1	0.03%	(0.00%, 0.17%)
Device lead damage	13	13	0.40%	(0.21%, 0.68%)
Device lead issue	1	1	0.03%	(0.00%, 0.17%)
Device misuse	9	9	0.28%	(0.13%, 0.53%)
Device pacing issue	69	67	2.06%	(1.60%, 2.61%)
Device psychogenic complication	7	7	0.22%	(0.09%, 0.44%)
Device related infection	3	3	0.09%	(0.02%, 0.27%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Device signal detection issue	2	2	0.06%	(0.01%, 0.22%)
Device stimulation issue	443	349	10.75%	(9.71%, 11.87%)
Diabetes	1	1	0.03%	(0.00%, 0.17%)
Diarrhea	1	1	0.03%	(0.00%, 0.17%)
Dizziness	1	1	0.03%	(0.00%, 0.17%)
Dressler's syndrome	1	1	0.03%	(0.00%, 0.17%)
Drug hypersensitivity	3	3	0.09%	(0.02%, 0.27%)
Dysarthria	1	1	0.03%	(0.00%, 0.17%)
Dyspnoea	2	2	0.06%	(0.01%, 0.22%)
Dyspnoea exertional	1	1	0.03%	(0.00%, 0.17%)
Dyspnoea paroxysmal nocturnal	1	1	0.03%	(0.00%, 0.17%)
Ecchymosis	2	2	0.06%	(0.01%, 0.22%)
Electromagnetic interference	1	1	0.03%	(0.00%, 0.17%)
Endocarditis	1	1	0.03%	(0.00%, 0.17%)
Endocarditis staphylococcal	1	1	0.03%	(0.00%, 0.17%)
Erythema multiforme	1	1	0.03%	(0.00%, 0.17%)
Fatigue	5	5	0.15%	(0.05%, 0.36%)
Fluid overload	1	1	0.03%	(0.00%, 0.17%)
Gastroenteritis	1	1	0.03%	(0.00%, 0.17%)
Gastrointestinal haemorrhage	1	1	0.03%	(0.00%, 0.17%)
Haematoma	2	2	0.06%	(0.01%, 0.22%)
Haematuria	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Haemoptysis	2	2	0.06%	(0.01%, 0.22%)
Haemothorax	4	4	0.12%	(0.03%, 0.32%)
Hot flush	1	1	0.03%	(0.00%, 0.17%)
Hydrothorax	1	1	0.03%	(0.00%, 0.17%)
Hyperglycaemia	1	1	0.03%	(0.00%, 0.17%)
Hyperkalaemia	4	4	0.12%	(0.03%, 0.32%)
Hypersensitivity	1	1	0.03%	(0.00%, 0.17%)
Hypertension	1	1	0.03%	(0.00%, 0.17%)
Hyponatraemia	2	2	0.06%	(0.01%, 0.22%)
Hypotension	20	20	0.62%	(0.38%, 0.95%)
Hypovolaemia	1	1	0.03%	(0.00%, 0.17%)
Ileus	1	1	0.03%	(0.00%, 0.17%)
Impaired healing	2	2	0.06%	(0.01%, 0.22%)
Implant site bruising	2	2	0.06%	(0.01%, 0.22%)
Implant site cellulitis	1	1	0.03%	(0.00%, 0.17%)
Implant site effusion	1	1	0.03%	(0.00%, 0.17%)
Implant site erosion	1	1	0.03%	(0.00%, 0.17%)
Implant site erythema	6	6	0.18%	(0.07%, 0.40%)
Implant site haematoma	98	96	2.96%	(2.40%, 3.60%)
Implant site haemorrhage	6	6	0.18%	(0.07%, 0.40%)
Implant site hypoaesthesia	1	1	0.03%	(0.00%, 0.17%)
Implant site infection	44	44	1.36%	(0.99%, 1.82%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Implant site inflammation	3	3	0.09%	(0.02%, 0.27%)
Implant site irritation	5	5	0.15%	(0.05%, 0.36%)
Implant site oedema	3	3	0.09%	(0.02%, 0.27%)
Implant site pain	72	64	1.97%	(1.52%, 2.51%)
Implant site rash	3	3	0.09%	(0.02%, 0.27%)
Implant site swelling	4	4	0.12%	(0.03%, 0.32%)
Implant site warmth	1	1	0.03%	(0.00%, 0.17%)
Incision site complication	1	1	0.03%	(0.00%, 0.17%)
Incision site haemorrhage	5	5	0.15%	(0.05%, 0.36%)
Incision site pain	4	4	0.12%	(0.03%, 0.32%)
Incisional drainage	1	1	0.03%	(0.00%, 0.17%)
Infection	2	2	0.06%	(0.01%, 0.22%)
Infusion site extravasation	1	1	0.03%	(0.00%, 0.17%)
Intracardiac thrombus	6	6	0.18%	(0.07%, 0.40%)
Lead dislodgement	33	30	0.92%	(0.62%, 1.32%)
Leukocytosis	2	2	0.06%	(0.01%, 0.22%)
Localized oedema	1	1	0.03%	(0.00%, 0.17%)
Mediastinal effusion	1	1	0.03%	(0.00%, 0.17%)
Medical device discomfort	3	3	0.09%	(0.02%, 0.27%)
Medical device site reaction	1	1	0.03%	(0.00%, 0.17%)
Monoparesis	1	1	0.03%	(0.00%, 0.17%)
Muscle spasms	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Muscle twitching	1	1	0.03%	(0.00%, 0.17%)
Musculoskeletal chest pain	2	2	0.06%	(0.01%, 0.22%)
Musculoskeletal pain	42	40	1.23%	(0.88%, 1.67%)
Musculoskeletal stiffness	1	1	0.03%	(0.00%, 0.17%)
Myocardial infarction	1	1	0.03%	(0.00%, 0.17%)
Nausea	1	1	0.03%	(0.00%, 0.17%)
Neck pain	1	1	0.03%	(0.00%, 0.17%)
Nephrosclerosis	1	1	0.03%	(0.00%, 0.17%)
Neuropathy peripheral	1	1	0.03%	(0.00%, 0.17%)
Nodal rhythm	2	2	0.06%	(0.01%, 0.22%)
Non-cardiac chest pain	1	1	0.03%	(0.00%, 0.17%)
Oedema peripheral	12	12	0.37%	(0.19%, 0.64%)
Oliguria	1	1	0.03%	(0.00%, 0.17%)
Operative haemorrhage	1	1	0.03%	(0.00%, 0.17%)
Orthostatic hypotension	2	2	0.06%	(0.01%, 0.22%)
Oversensing	34	33	1.02%	(0.70%, 1.42%)
Oxygen saturation decreased	1	1	0.03%	(0.00%, 0.17%)
Pacemaker generated arrhythmia	6	6	0.18%	(0.07%, 0.40%)
Pain	1	1	0.03%	(0.00%, 0.17%)
Pain in extremity	1	1	0.03%	(0.00%, 0.17%)
Palpitations	9	9	0.28%	(0.13%, 0.53%)
Paraesthesia	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Pericardial effusion	16	15	0.46%	(0.26%, 0.76%)
Pericarditis	4	4	0.12%	(0.03%, 0.32%)
Phantom shocks	4	3	0.09%	(0.02%, 0.27%)
Phlebitis	2	2	0.06%	(0.01%, 0.22%)
Pleural effusion	21	21	0.65%	(0.40%, 0.99%)
Pneumonia	9	9	0.28%	(0.13%, 0.53%)
Pneumothorax	43	43	1.32%	(0.96%, 1.78%)
Pocket erosion	4	4	0.12%	(0.03%, 0.32%)
Post procedural haemorrhage	2	2	0.06%	(0.01%, 0.22%)
Presyncope	3	3	0.09%	(0.02%, 0.27%)
Procedural haemorrhage	1	1	0.03%	(0.00%, 0.17%)
Procedural headache	2	2	0.06%	(0.01%, 0.22%)
Procedural pain	1	1	0.03%	(0.00%, 0.17%)
Pruritus	1	1	0.03%	(0.00%, 0.17%)
Pruritus generalized	1	1	0.03%	(0.00%, 0.17%)
Pulmonary embolism	1	1	0.03%	(0.00%, 0.17%)
Pulmonary oedema	3	3	0.09%	(0.02%, 0.27%)
Pulmonary sepsis	1	1	0.03%	(0.00%, 0.17%)
Pulseless electrical activity	2	2	0.06%	(0.01%, 0.22%)
Pyrexia	5	5	0.15%	(0.05%, 0.36%)
Rash	8	8	0.25%	(0.11%, 0.49%)
Rash generalized	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Renal failure	8	8	0.25%	(0.11%, 0.49%)
Renal failure acute	2	2	0.06%	(0.01%, 0.22%)
Renal impairment	1	1	0.03%	(0.00%, 0.17%)
Respiratory acidosis	1	1	0.03%	(0.00%, 0.17%)
Respiratory distress	1	1	0.03%	(0.00%, 0.17%)
Respiratory failure	1	1	0.03%	(0.00%, 0.17%)
Sepsis	3	3	0.09%	(0.02%, 0.27%)
Sepsis syndrome	1	1	0.03%	(0.00%, 0.17%)
Septic shock	4	4	0.12%	(0.03%, 0.32%)
Sinus arrest	1	1	0.03%	(0.00%, 0.17%)
Sinus bradycardia	1	1	0.03%	(0.00%, 0.17%)
Sinus tachycardia	2	2	0.06%	(0.01%, 0.22%)
Staphylococcal infection	2	2	0.06%	(0.01%, 0.22%)
Stitch abscess	1	1	0.03%	(0.00%, 0.17%)
Subclavian vein thrombosis	2	2	0.06%	(0.01%, 0.22%)
Subcutaneous emphysema	1	1	0.03%	(0.00%, 0.17%)
Subcutaneous haematoma	1	1	0.03%	(0.00%, 0.17%)
Sudden cardiac death	10	10	0.31%	(0.15%, 0.57%)
Superior vena cava stenosis	1	1	0.03%	(0.00%, 0.17%)
Supraventricular extrasystoles	1	1	0.03%	(0.00%, 0.17%)
Supraventricular tachycardia	2	2	0.06%	(0.01%, 0.22%)
Syncope	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Tachycardia	1	1	0.03%	(0.00%, 0.17%)
Thrombophlebitis	2	2	0.06%	(0.01%, 0.22%)
Thrombosis	8	8	0.25%	(0.11%, 0.49%)
Thrombotic stroke	1	1	0.03%	(0.00%, 0.17%)
Toxicity to various agents	1	1	0.03%	(0.00%, 0.17%)
Twiddler's syndrome	5	5	0.15%	(0.05%, 0.36%)
Undersensing	7	7	0.22%	(0.09%, 0.44%)
Urinary retention	2	2	0.06%	(0.01%, 0.22%)
Vena cava thrombosis	1	1	0.03%	(0.00%, 0.17%)
Venous occlusion	1	1	0.03%	(0.00%, 0.17%)
Ventricular dyssynchrony	1	1	0.03%	(0.00%, 0.17%)
Ventricular extrasystoles	2	2	0.06%	(0.01%, 0.22%)
Ventricular fibrillation	1	1	0.03%	(0.00%, 0.17%)
Ventricular tachycardia	11	11	0.34%	(0.17%, 0.61%)
Vomiting	3	3	0.09%	(0.02%, 0.27%)
Weaning failure	1	1	0.03%	(0.00%, 0.17%)
Weight decreased	1	1	0.03%	(0.00%, 0.17%)
Wound dehiscence	1	1	0.03%	(0.00%, 0.17%)

Adverse Events in Literature

The potential AEs associated with the implantation of CRT-P or CRT-D systems have been documented in various articles in medical scientific literature. A summary of those events and their published incidence are included below.

1. Ahsan SY, Saberwal B, Lambiase PD, Chaubey S, Segal OR, Gopalamurugan AB, McCready J, Rogers DP, Lowe MD, and Chow AWC. An 8-year single-centre experience of cardiac

resynchronization therapy: procedural success, early and late complications, and left ventricular lead performance. Europace 2013;15:711-717.

Retrospective data were analyzed for all acute and chronic complications occurring over 490 consecutive CRT device procedures in 402 patients, from 2000 through 2008. Associated complications were reported by timeframe.

Table 25: Complications reported in Ahsan et al.

Table 3 Early and late complications by complication type[a]

Complication type	Early (<90 days) (*n*)	Late (>90 days) (*n*)	Mean time to late complication (months)
Death	1	0	–
Pneumothorax	2	0	–
Phrenic nerve stimulation requiring revision	3	4	11.4 (±8)
Infection	7	7	14.9 (±11)
Noise on RV/RA lead	1	3	17.0 (±22)
Box migration	2	1	15.0
RV/RA/LV lead fracture	1	4	33.1
Lead erosion	3	0	–
RV/RA lead displacement	6	6	4.9 (±2)
Inability to implant LV lead	13	–	–
LV lead displacement	5	5	6.8 (±4)
Total	44 (9.4%)	30 (6.1%)	

[a]This table shows all early and late complications and the mean time to their occurrence.

2. Dickstein K, Bogale N, Priori S, Auricchio A, Cleland JG, Gitt A, Limbourg T, Linde C, van Veldhuisen DJ, Brugada J; Scientific Committee; National Coordinators. The European Cardiac Resynchronization Therapy Survey. European Heart Journal 2009; 30:2450–2460.

The primary aim of this survey was to describe current European practice associated with CRT implantations. A total of 140 centers from 13 European countries contributed data from consecutive patients successfully implanted with a CRT device with or without an ICD between November 2008 and June 2009. The total number of patients enrolled was 2438.

Table 26: Complications reported in Dickstein et al.

Event	**Incidence (%)**
Peri-procedural complications	10
Bleeding	1
Pocket haematoma	3
Pneumothorax	1
Pericardial tamponade	0.3
Coronary sinus dissection	1
Phrenic nerve pacing	2
Lead dislocation	3

Post–implantation device related complications	4
Lead displacement	2
Lead malfunction	0
Phrenic nerve stimulation	2

3. Kirkfeldt R.E., Johansen J.B., Nohr E.A., Jorgensen O.D., Nielsen J.C. Complications after cardiac implantable electronic device implantations: An analysis of a complete, nationwide cohort in Denmark. European Heart Journal 2014 35:18 1186-1194.

This was a population-based cohort study in all Danish patients who underwent a Cardiac Implantable Electronic Device (CIED) procedure from May 2010 to April 2011. The study population consisted of 5918 consecutive patients. Total of 562 patients (9.5%) experienced at least one complication.

Table 27: Complications reported by Kirkfeldt et al. shows cumulative incidence of complications at 6 months[a].

Table 27: Complications reported by Kirkfeldt et al.

Complication type	**All (n=5918)**	**New Implant (n=4335)**	**Generator replacement (n=1136)**	**Upgrade/Lead revision (n=427)**
Any complication	562 (9.5; 8.7–10.2)	432 (9.9; 9.0–10.8)	67 (5.9; 4.5–7.3)	63 (14.8; 11.4–18.1)
Any major complication[b]	329 (5.6; 5.0–6.1)	253 (5.8; 5.1–6.5)	40 (3.5; 2.4–4.6)	36 (8.4; 5.8–11.1)
Any minor complication[c]	250 (4.2; 3.7–4.7)	189 (4.3; 3.7–4.9)	30 (2.6; 1.7–3.6)	31 (7.3; 4.8–9.7)
Major complications				
Lead related re-intervention	143 (2.4; 2.0–2.8)	120 (2.8; 2.3–3.2)	10 (0.9; 0.3–1.4)	13 (3.0; 1.4–4.7)
Infection	49 (0.8; 0.6–1.1)	24 (0.6; 0.3–0.8)	17 (1.5; 0.8–2.2)	8 (1.9; 0.6–3.2)
Local infection	22 (0.4; 0.2–0.5)	10 (0.2; 0.1–0.4)	8 (0.7; 0.2–1.1)	4 (1.0; 0.0–1.9)
Systemic infection/endocarditis	27 (0.5; 0.3–0.6)	14 (0.3; 0.2–0.5)	9 (0.8; 0.3–1.3)	4 (0.9; 0.0–1.9)
Pneumothorax requiring drainage	51 (0.9; 0.6–1.1)	45 (1.0; 0.7–1.3)	0	6 (1.4; 0.3–2.5)
Cardiac perforation	38 (0.6; 0.4–0.8)	35 (0.8; 0.5–1.1)	0	3 (0.7; 0.0–1.5)

Cardiac perforation (No intervention)	21 (0.4; 0.2–0.5)	18 (0.4; 0.2–0.6)	0	3 (0.7; 0.0–1.5)
Cardiac perforation (Intervention)	17 (0.3; 0.2–0.4)	17 (0.4; 0.2–0.6)	0	0
Pocket revision because of pain	25 (0.4; 0.3–0.6)	10 (0.2; 0.1–0.4)	9 (0.8; 0.3–1.3)	6 (1.4; 0.3–2.5)
Generator-lead interface problem with re-intervention	7 (0.1; 0.0–0.2)	3 (0.1; 0.0–0.1)	4 (0.4; 0.0–0.7)	0
Haematoma requiring re-intervention	10 (0.2; 0.1–0.3)	9 (0.2; 0.1–0.3)	1 (0.1; 0.0–0.3)	0
Other[d]	16 (0.3; 0.1–0.4)	16 (0.4; 0.2–0.5)	0	0
Minor complications				
Haematoma[e]	138 (2.3; 1.9–2.7)	104 (2.4; 1.9–2.8)	20 (1.8; 1.0–2.5)	14 (3.3; 1.6–5.0)
Wound infection treated with antibiotics	69 (1.2; 0.9–1.4)	47 (1.1; 0.8–1.4)	12 (1.0; 0.5–1.7)	10 (2.3; 0.9–3.8)
Pneumothorax conservatively treated	39 (0.7; 0.5–0.9)	32 (0.7; 0.5–1.0)	0	7 (1.6; 0.4–2.8)
Lead dislodgement without re-intervention	10 (0.2; 0.1–0.3)	9 (0.2; 0.1–0.3)	0	1 (0.2; 0.0–0.7)

[a]Reported as absolute frequencies and percentages with 95% CIs in parenthesis.

[b]All re-interventions were categorized as major complications due to their inherently higher risk of infections e.g. local CIED infections requiring re-intervention, systemic infections, pocket revisions etc.

[c]Minor complications included haematomas resulting in a prolonged hospital stay, hospital re-admissions, or additional out-patient visits, wound infections treated with antibiotics, pneumothorax conservatively treated, and lead dislodgements without re-intervention.

[d]Deep venous thrombosis (n=8), Twiddler's syndrome (n=3), wound revision (n=3), stroke (n=1), myocardial infarction (n=1)

[e]Resulting in prolonged hospital stay, hospital re-admission, or additional out-patient visit.

23. References

[1] Model 8040 InSync MIRACLE Study (IDE # G980219).

[2] Model 7272 InSync ICD Study (IDE # G990176).

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Medtronic	CONFIDENTIAL	DOCUMENT/RECORD

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Document Name	Version
Clinical Investigation Plan Attain Stability Quad	2.0

Title	Clinical Investigation Plan Attain Stability Quad

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Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	Attain Stability™ Quad Clinical Study
Study Product Name	Attain Stability™ Quad MRI SureScan Left Ventricular Lead (Model 4798)
Sponsor/Local Sponsor	**Sponsor:** Medtronic, Inc. Cardiac Rhythm and Heart Failure Clinical Research 8200 Coral Sea Street NE Mounds View, MN 55112 U.S.A. 1-800-328-2518 **Local Sponsors:** Canada Medtronic of Canada 99 Hereford Street Brampton, ON, L6Y 0R3 Canada +1-905-460-3800 Europe, Middle East, Africa (EMEA)Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands +31-43-35-66-566 Hong Kong Medtronic Hong Kong Medical Ltd. 1104-11, 11/F, Tower 1, The Gateway, Harbour City, Kowloon, Hong Kong SAR, China +852-2919-1300 Malaysia Medtronic International Ltd (Malaysia) B-23-1 Level 23, The Ascent, Paradigm No 1 Jalan SS7/26A Kelena Jaya 46301 PetalingJaya Selangor Malaysia +603 7883 8000
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Confidentiality Statement

1. Sponsor Contact

Medtronic, Inc. is sponsoring the Attain Stability Quad Clinical Study. Regional contact information is provided below. This information may be subject to change during the course of the Attain Stability Quad Clinical Study. Periodic updates to study contact information will be sent to sites as needed.

Table 1: Study Sponsor Contact Information

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2. CROs/Core Laboratories

This information may be subject to change during the course of the Attain Stability Quad Clinical Study. Periodic updates to study contact information will be sent to sites as needed.

Table 2: CRO and Core Laboratory Information

Contact Information	Role
Cognizant Technology Solutions 500 Frank W. Burr Blvd. Teaneck, NJ 07666 United States Direct Phone: (201) 801-0233 Direct Fax: (201) 801-0243	Review of electronic case report forms and management of discrepancies

3. Version History

Version	Summary of Changes	Author(s)/Title
1.0	○ Initial Release	Melissa Thalin, Principal Clinical Research Specialist Rinie Peters, Associate Clinical Research Specialist Ann Vacca, Principal Customer Specialist Shelby Li, Senior Principal Statistician Joao Monteiro, Senior Statistician
2.0	○ Added slitting information for Implant analyzer PCT at synopsis and table 8 ○ Remote visits: ▪ Changed wording to clarify required actions ▪ Removed manual PCT test ▪ Deleted rationale for final vector progammed ○ Recurring 6 mth FU: ▪ Removed PNS test ▪ Removed Patient Global Assessment ○ System Modification ▪ Reduced electrical testing requirements ○ Patient Global Assessment ▪ Added to Glossary ▪ Removed from Baseline and 3 month visits ○ Vectors ▪ Added additional 4 CRT-P vectors (LV to Can) throughout ○ Investigator Lead Handling Assessment ▪ Added to Implant visit ○ Adjusted # of participating centers ○ Updated exclusion criteria #2 ○ Updates to grammer, version ,and footers	Melissa Thalin, Principal Clinical Research Specialist Rinie Peters, Associate Clinical Research Specialist

4. Investigator Statement

Investigators will be provided with a separate investigator agreement to document their obligation and commitment with respect to study conduct.

5. Index

6. List of Tables

7. List of Figures

8. Glossary

Table 3: Glossary of Terms

Term	Definition
2090	Medtronic CareLink Programmer with the application software installed.
2290	Medtronic Analyzer
Medtronic Attain Stability Quad MRI SureScan (Model 4798) LV Lead	The quadripolar LV lead being studied (investigational in the United States/Canada, commercially available in EMEA, Hong Kong, and Malaysia).
Active Fixation Helix	A non-electrically active side helix, positioned between the LV 3 and LV 4 electrodes that will allow fixation of the Attain Stability Quad MRI SureScan (Model 4798) LV Lead in the cardiac vein.
ADE	Adverse Device Effect
AE	Adverse Event
Ag	Silver
CABG	Coronary Artery Bypass Graft

Term	Definition
CAD	Coronary Artery Disease
CDF	Cumulative Distribution Function
CEC	Clinical Events Committee
CIP	Clinical Investigation Protocol
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy: Established pacing therapy for patients with heart failure
CRT-D	Cardiac Resynchronization Therapy - Defibrillator
CRT-P	Cardiac Resynchronization Therapy - Pacemaker
CS	Coronary Sinus
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency
DEKRA	Deutscher Kraftfahrzeug-Überwachungs-Verein (German Motor Vehicle Inspections Association)
DMC	Data Monitoring Committee
EC	Ethics Committee
EMEA	Europe, the Middle East, and Africa
eCRF	Electronic Case Report Form
MEC/IRB/HREB/Ethics Board	Ethics Committee
FAL	Foreseeable Adverse Event List
FDA	Food and Drug Administration
Fr	French
GCP	Good Clinical Practice

Term	Definition
HF	Heart Failure
HTN	Hypertension
IC	Informed Consent
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IDE	Investigation Device Exemption
Ir	Iridium
IRB	Institutional Review Board
LAR	Legally Authorized Representative
LBBB	Left Bundle Branch Block
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MCRD	Monolithic Controlled Release Device which is located on the Attain Stability Quad MRI SureScan LV Lead (Model 4798) electrodes which elutes steroid to reduce inflammatory response within the cardiac vein.
Mechanical Stop	A component on the Attain Stability Quad MRI SureScan (Model 4798) LV Lead located at the base of the helix to prevent wedging of endothelial tissue in the helix and to prevent tissue ingrowth.
MedDRA	Medical Dictionary for Regulatory Activities
OC	Oracle Clinical (database management system)
OTW	Over-the-wire
PCT	Pacing Capture Threshold
Patient Global Assessment	Self-reported assessment to provide information on patient condition compared to previous heart failure status

Term	Definition
PHD	Pre-Hospital Discharge means the point at which a subject has been released from the hospital post implant procedure.
PMA	Premarket Approval
PNS	Phrenic Nerve Stimulation
POR	Power On Reset
Pt	Platinum
PTCA	Percutaneous Transluminal Coronary Angioplasty
QOL	Quality of Life
RA	Right Atrial
RRT	Recommended Replacement Time
RV	Right Ventricular
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SDN	Software Distribution Network
TÜV	Technischer Überwachungsverein (German safety validation organization)
UADE	Unanticipated Adverse Device Effect
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

9. Synopsis

Title	Attain Stability™ Quad Clinical Study
Product Name	Attain Stability™ Quad MRI SureScan Left Ventricular Lead (Model 4798)
Sponsor	Medtronic, Inc. Cardiac Rhythm and Heart Failure Clinical Research 8200 Coral Sea Street NE Mounds View, MN 55112 U.S.A. 1-800-328-2518
Local Sponsor	Canada Medtronic of Canada 99 Hereford Street Brampton, ON, L6Y 0R3 Canada +1-905-460-3800 EMEA Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht The Netherlands +31-43-35-66-566 Hong Kong Medtronic Hong Kong Medical Ltd. 1104-11, 11/F, Tower 1, The Gateway, Harbour City, Kowloon, Hong Kong SAR, China +852-2919-1300 Malaysia Medtronic International Ltd (Malaysia) B-23-1 Level 23, The Ascent, Paradigm, No 1 Jalan SS7/26A Kelena Jaya 46301 Petaling Jaya Selangor Malaysia +603 7883 8000
Indication under investigation	All subjects included in the study will be implanted with a Medtronic market released de novo CRT-P or CRT-D device, compatible market released Medtroinc RA and Medtronic RV leads and an Attain Stability QuadSureScan LV lead (Model 4798). For subjects enrolled who are receiving an upgrade to a CRT system, existing non-Medtronic RV and/or existing non-Medtronic RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used.

	Given the vast similarities between the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the Attain Performa family of leads, the proposed indications for use are the same. The indications are as follows: The Attain Stability Quad MRI SureScan 4798 steroid-eluting, quadripolar electrode, IS4 transvenous lead is indicated for chronic pacing in the left ventricle via the cardiac vein, when used with a compatible Medtronic Cardiac Resynchronization Therapy (CRT) system. Extended bipolar pacing is available using this lead in combination with a compatible market approved CRT-D system and RV defibrillation lead.
Investigation Purpose	The Attain Stability Quad Clinical Study is a prospective, non-randomized, multi-site, global, Investigational Device Exemption (IDE) interventional clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV lead (Model 4798). This study will not be considered investigational in geographies with CE Mark of the Attain Stability Quadripolar LV lead (4798). However, data collected from all study subjects will be represented in the final report and the PMA Supplement (PMA-S) to the Model 4196 Original PMA.
Product Status	The Attain Stability Quad Clinical Study will be conducted using a research system composed of an approved CRT-D or CRT-P System. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is an active fixation quadripolar LV lead based on the Attain Performa lead family models (4298, 4398, and 4598). The lead incorporates an active fixation helix similar to the Attain Stability bipolar LV lead (Model 20066/4796) which is designed to allow an implanter more options in lead location. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered investigational in geographies where the product is not available commercially and will be labeled for clinical use only. These geographies include but are not limited to the US and Canada. Investigational Attain Stability Quad Leads will be distributed to a site only when Medtronic has received all required documentation (including but not limited to Ethic Committee approval, a signed Clinical Trial Agreement and documentation of training) and has notified the site of site readiness. Distribution of the investigational product to study sites will be managed by Medtronic and can only be

	ordered by Medtronic personnel. Site with these clinically labeled Attain Stability Quad MRI SureScan LV Leads (Model 4798) will track disposition upon receipt or return of the lead but also upon implant or explant of the lead. Disposition logs will be available within the electronic data management system and shall be maintained at each site in all geographies to track investigational product information. For geographies where the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is not considered investigational, commercially approved devices will be used. Sites that use commercially available Attain Stability Quad MRI SureScan LV Leads (Model 4798) will track device disposition upon implant or explant on the lead CRFs. The Medtronic approved CRT-P or CRT-D devices will be programmed and interrogated using a Medtronic CareLink (2090) programmer. Medtronic may incorporate additional programmers as they receive regulatory approval. The CareLink Monitor Model 2490C is an external monitor that is indicated for use in the transfer of patient and device data from implanted Medtronic devices. The CareLink Monitor Model 2490C interrogates implanted devices and temporarily stores these data, collaborates with the appropriate Medtronic server to confirm the establishment of an Internet connection with server, performs any required file translation functions necessary for data transfer, executes data file transfer, and collaborates with the appropriate Medtronic server to confirm data file transfer through the Internet connection with the server. The CareLink Monitor 2490C is not a programmer and cannot be used to program implanted device parameters. CareLink monitors are not a substitute for appropriate medical attention in the event of an emergency and should only be used as directed by a physician. Approved Medtronic CRT-P and CRT-D devices used in this study qualify for use with the Medtronic CareLink Monitor and Medtronic CareLink Network. Medtronic may incorporate additional home monitors as they receive regulatory approval. Medtronic's commercially available Model 2290 Analyzer must be available at each center during the implant

	procedure to determine acceptable electrical parameters. Medtronic may incorporate additional analyzers as they receive regulatory approval.
Primary Objective(s)	**<u>Primary Safety Objective: Lead complication-free rate at 6 months</u>** The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered safe if the probability of subjects free of Model 4798 lead-related complications at 6 months post-implant is greater than 87% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 87%). The study primary safety endpoint is Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complications through 6 months post implant. All reported system and procedure-related AEs will be reviewed by an event review committee for LV lead relatedness and severity (complication vs observation, refer to 17.1.2 for defintions). **<u>Primary Efficacy Objectives: Lead pacing capture thresholds at 6 months</u>** To demonstrate the effectiveness of the Attain Stability Quad MRI SureScan LV lead (Model 4798) the study will evaluate the likelihood that there are at least two programmable vectors for each patient post implant. The effectiveness of this lead will be evaluated based on two primary efficacy objectives. More specifically, both primary efficacy objectives must be met simultaneously. **<u>Primary Efficacy Objective #1</u>** The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet the objective if the proportion of subjects with at least one LV lead pacing vector having a pacing capture threshold less than or equal to 2.5 V at 0.5ms pulse width at 6 months post-implant is greater than 80% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 80%). The endpoint for the primary efficacy objective is whether or not there is at least one Model 4798 LV lead pacing vector with pacing capture voltage thresholds less than or equal to 2.5V. This endpoint will be measured at the 6-month post implant follow-up visit.

	Primary Efficacy Objective #2 The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet the objective if the proportion of subjects with at least one additional LV lead pacing vector having a pacing capture threshold less than or equal to 4.0 V at 0.5ms pulse width at 6 months post-implant is greater than 80% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 80%). The co-primary efficacy endpoint is whether or not a second Model 4798 lead configuration has a pacing capture threshold less than or equal to 4V, excluding the pacing vector that is already counted to the primary efficacy endpoint #1. This endpoint will be measured at 6-month post implant follow-up visit.

Secondary

Objective(s)	The secondary objectives are descriptive in nature and are intended to provide additional information about the Attain Stability Quad Model 4798 LV lead. There will be no established performance requirements for these secondary objectives. o Implant procedure related information: success rate, implant related times o Endpoints will include implant success rate and procedure durations. o 6-month reliability: post implant lead failure modes (i.e. complication rate) o Endpoint is Model 4798 lead related complications. o Electrical measurements (PCT and Impedance) at follow-ups o Endpoints are the electrical measurements (pacing capture thresholds and impedance values) for the four extended bipolar (CRT-D) or unipolar (CRT-P) vectors, i.e. LV1 to RVCoil/Can, LV2 to RV Coil/Can, LV3 to RV Coil/Can and LV4 to RV Coil/Can (refer to 15.8.2.3 for the testing procedure requirements)

Study Design	The Attain Stability Quad Clinical Study is a prospective, non-randomized, multi-site, global, Investigational Device Exemption (IDE) interventional clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV lead (Model 4798) in patients indicated for a de novo LV lead implant. This will be assessed through primary safety and primary efficacy endpoints. All subjects included in the study will be implanted with a Medtronic market released de novo CRT-P or CRT-D device and an Attain Stability Quad MRI SureScan LV Lead (Model 4798). Compatible market released Medtronic RA and Medtronic RV leads will be required. For subjects enrolled who are receiving an upgrade to a CRT system, existing non-Medtronic RV and/or existing non-Medtronic RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used. Up to 471 subjects will be enrolled into the study and up to 471 Attain Stability Quad MRI SureScan LV Leads (Model 4798) implanted, to ensure a minimum effective sample size of 400 Model 4798 leads implanted with 6 months post implant follow up visits (assuming 15% attrition). For the secondary endpoint of individual lead failure modes, Bayesian methods utilizing data from up to 37 historical patients will be used. All other objectives will be analyzed using only patients enrolled in this study. After a successful implant, threshold testing will occur per protocol requirement. Subjects will then be followed at implant, three months, six months and every six months thereafter until FDA approval is obtained or until study closure, whichever comes first. The study duration is expected to be approximately 19 months. This represents 13 months for subject enrollment and 6 months for subject follow-up for the last subject enrolled. Subjects are anticipated to be in the study for on average 12 months. The first enrollment is projected to occur in May 2017.
Sample Size	Up to 471 subjects will be enrolled into the study, to ensure a minimum effective sample size of 400 Model 4798 leads implanted with 6 months post implant follow up visits (assuming 15% attrition) at up to 56 sites worldwide.
Inclusion/Exclusion Criteria	**Inclusion Criteria:** • Patient meets CRT implant criteria as determined

	by local regulatory and/or hospital policy • Patient (or legally authorized representative) has signed and dated the study-specific Consent Form • Patient is 18 years of age or older, or is of legal age to give informed consent per local and national law • Patient is expected to remain available for follow-up visits **Exclusion Criteria:** • Patient has had a previous unsuccessful LV lead implant attempt • Patient has a previous CRT system or LV lead implanted (for example, transvenous or epicardial) • Patient is currently implanted with a recalled (i.e. market-withdrawn, recalled or safety alert) RA and/or RV lead • Patient has known coronary venous vasculature that is inadequate for lead placement • Patient has unstable angina pectoris or has had an acute myocardial infarction (MI) within the past 30 days • Patient has had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the past 90 days • Patient has contraindications for standard transvenous cardiac pacing (e.g., mechanical right heart valve) • Patient has had a heart transplant (patients waiting for heart transplants are allowed in the study) • Patient has known renal insufficiency that would prevent them from receiving an occlusive venogram during the implant procedure • Patient is contraindicated for <1mg dexamethasone acetate • Patient is enrolled in any concurrent drug and/or device study that may confound the results of this study • Patient has a terminal illness and is not expected to survive more than six months • Patient meets exclusion criteria required by local law (e.g. age, pregnancy, breast feeding, etc.) • Patient is unable to tolerate an urgent thoracotomy
Study Procedures and Assessments	Clinical data will be collected at the study milestones: at enrollment, baseline, implant/PHD, 3M, 6M, thereafter

	every occurring 6M and study exit visits: **Enrollment/Baseline:** ○ Subject Informed Consent ○ Inclusion/Exclusion criteria verified ○ Subject demographics ○ Cardiovascular medications ○ Cardiovascular medical history ○ NYHA classification ○ Kansas City Cardiomyopathy Questionnaire (KCCQ) **Implant:** ○ Occlusive venogram with pre-determined target vessel location identified ○ Analyzer PCT data collection post lead fixation and prior to connecting the leads to the CRT-P/D device: 1. Pre-slitting the cannulation catheter and following guidewire/stylet has been pulled back proximal to the helix and electrodes 2. Post slitting the cannulation catheter ○ Investigator Lead Handling Assessment ○ System and procedure information PHD CRT System Testing and Programming using the implanted CRT-P or CRT-D device and the device programmer: <u>Lead Impedance</u> ○ Collect LV Lead Impedances using Vector Express on all vectors ○ Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site <u>Pacing Capture Thresholds (PCT)</u> ○ Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors ○ NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)

	○ Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site <u>Phrenic Nerve Stimulation (PNS)</u> ○ Test for presence of PNS at 8.0V at 0.5ms on final programmed vector ○ NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms ○ NOTE: PNS observed during this testing will not be considered an AE <u>Other Data Collection</u> ○ Rationale for selecting specific LV lead pacing vector for final programming ○ Final device interrogation/save-to-media ○ AE Assessment ○ Study deviations ○ Device deficiencies **3 Month (remote or in office visit):** <u>Lead Impedance</u> ○ Obtain LV Lead Impedance Test for the final programmed vector ○ Retain printouts at the site <u>Pacing Capture Thresholds (PCT)</u> ○ Obtain PCTs at 0.5ms pulse width on the final programmed vector ○ NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) ○ Retain printouts at the site <u>Phrenic Nerve Stimulation (PNS) (in office visit only)</u> ○ Test for presence of PNS at 8.0V at 0.5ms on final programmed vector ○ NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms ○ NOTE: PNS observed during this testing will not be considered an AE <u>Other Data Collection</u> ○ NYHA classification ○ Final device interrogation/save-to-media (or CareLink transmission) ○ AE Assessment

	○ Study deviations ○ Device deficiencies **6 Month:** <u>Lead Impedance</u> ○ Collect LV Lead Impedances using Vector Express on all vectors ○ Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site <u>Pacing Capture Thresholds (PCT)</u> ○ Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors ○ NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) ○ Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site <u>Phrenic Nerve Stimulation (PNS)</u> ○ Test for presence of PNS at 8.0V at 0.5ms on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can ○ Test for presence of PNS at 8.0V at 0.5ms on final programmed vector ○ NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms ○ NOTE: PNS observed during this testing will not be considered an AE <u>Other Data Collection</u> ○ NYHA classification ○ Patient Global Assessment ○ Kansas City Cardiomyopathy Questionnaire (KCCQ) ○ Rationale for selecting specific LV lead pacing vector for final programming ○ Final device interrogation/save-to-media

	○ AE Assessment ○ Study deviations ○ Device deficiencies **12 Month:** <u>Lead Impedance</u> ○ Collect LV Lead Impedances using Vector Express on all vectors ○ Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site <u>Pacing Capture Thresholds (PCT)</u> ○ Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors ○ NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) ○ Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector ○ Retain printouts at the site <u>Phrenic Nerve Stimulation (PNS)</u> ○ Test for presence of PNS at 8.0V at 0.5ms on final programmed vector ○ NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms ○ NOTE: PNS observed during this testing will not be considered an AE <u>Other Data Collection</u> ○ NYHA classification ○ Patient Global Assessment ○ Kansas City Cardiomyopathy Questionnaire (KCCQ) ○ Rationale for selecting specific LV lead pacing vector for final programming ○ Final device interrogation/save-to-media ○ AE Assessment ○ Study deviations ○ Device deficiencies

	Recurring 6 Month follow-ups (remote or inoffice visit): Lead Impedance o Obtain LV Lead Impedance Test for the final programmed vector o Retain printouts at the site Pacing Capture Thresholds (PCT) o Obtain PCTs at 0.5ms pulse width on the final programmed vector o NOTE: A onetime manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms) o Retain printouts at the site Other Data Collection o NYHA classification o Final device interrogation/save-to-media (or CareLink transmission) o AE Assessment o Study deviations o Device deficiencies **Study Exit:** o Report the reason for exit o Final Interrogation file (or Carelink transmissions) for exits occuring prior to the 6 month visit) o Study Deviations o AEs o Device Deficiencies
Safety Assessments	Adverse Event and Device Deficiency handling in the Attain Stability Quad Clinical Study is ISO 14155:2011 compliant for all participating geographies with the exception that only those AEs which are related to the subject's system, procedure, accessory, or are cardiovascular-related, heart failure-related, MRI-related, and all Serious AEs, will be collected (refer to Section 17 for AE assessment). This ensures any AEs which could potentially be relevant will be collected. Reporting of these events to Medtronic will occur on an Adverse Event (AE) Form, including date of AE, treatment, resolution, assessment of both the seriousness of the AE and the relatedness to the investigational device or procedure. Each AE must be recorded on a separate AE eCRF. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened.

Statistics	The primary objective will be analyzed using the time-to-first event Kaplan-Meier survival analysis method. A minimum number of subjects who have completed their 6 months post-implant visits will be required. Time 0 will be the day a subject undergoes the implant procedure of a Attain Stability Quad MRI SureScan LV Lead (Model 4798), which will be independent of success status of this implant procedure. Event date is the onset date of a subject's first complication that is related to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) according to CEC adjudication. Subjects who undergo an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt and do not experience any LV lead related complications, will be censored at the time of their last known exposure to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) for the survival analysis. For any lost-to-follow up subject, the last contact date will be used as the censor date. The 1-sided 97.5% confidence limit lower bound for the survival probability at 6 months (183 days) will be calculated using the log-log survival function approach (Kalbfleisch and Prentice 2002).

10. Introduction

10.1. Background

Several clinical trials (including MIRCLE[1], MIRACLE-ICD[2], CONTAK-CD[3], MUSTIC[4], PATH-CHF[5], COMPANION[6], MADIT CRT[7], and CARE-HF[8]) have demonstrated the benefit of cardiac resynchronization therapy (CRT) among patients with moderate to severe heart failure (HF) with a prolonged QRS duration and depressed Left Ventricular (LV) function.

Approximately 5.7 million people in the United States (US) are living with HF[9]. Heart Failure may be a chronic condition which causes the heart to not pump oxygenated blood efficiently through the body due to stiffening of the heart muscle. Heart Failure may affect one or both sides of the heart. It is most often caused by coronary artery disease (CAD) or uncontrolled hypertension (HTN). Patients who suffer from HF experience a variety of different symptoms including most often fatigue, cough, shortness of breath, swollen feet (edema) and weight gain.

Heart Failure is treated with medications and sometimes cardiac devices (i.e. pacemaker or defibrillator with CRT). Medications work to relieve symptoms and reverse the effects of HF. Cardiac Resynchronization Therapy devices treat HF by synchronizing the left and right ventricles of the heart which improves the heart's ability to pump oxygenated blood to the body.[10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21]

Cardiac Resynchronization Therapy devices are primarily made up of 4 main components; the can or battery, a Right Atrial (RA) lead, a Right Ventricular (RV) lead, and a Left Ventricular (LV) lead.

The LV lead specifically is important at maintaining ventricular synchrony. In 2014, Medtronic released the Attain® Performa™ family of LV leads (models 4298, 4398 and 4598). The three different shapes of these leads (double canted, straight, and S-shaped) were designed to enable the lead to be passively fixed within different anatomies of coronary vessels. In addition, the 4 strategically placed electrodes on the lead were designed to offer 16 different electrical vector programming configurations.

Medtronic also released the Attain Stability bipolar LV lead (Model 20066/4796) (CE Mark approved in September 30, 2013) in Europe. This lead has a side helix which enables it to be actively fixated to the vessel wall. The active fixation is an advantageous component in vessels that are wide or have short take-offs. The next generation of LV lead is known as the Attain Stability™ Quad MRI SureScan LV lead (Model 4798). This is a quadripolar lead similar to its Attain Performa predecessor leads and has a side helix for active fixation like the Attain Stability bipolar lead.

10.2. Purpose

The Attain Stability Quad Clinical Study is a prospective, non-randomized, multi-site, global, Investigational Device Exemption (IDE), interventional clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability™ Quad MRI SureScan LV Lead (Model 4798). This study will not be considered investigational in geographies with CE Mark of the Attain Stability™ Quad MRI SureScan LV lead (Model 4798). However, data collected from all study subjects will be represented in the final clinical report and the PMA Supplement (PMA-S) to the Attain Ability Model 4196 Original PMA (P080006, approved April 7, 2009). Subjects successfully implanted with the Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be followed at implant, three months, six months and every six months thereafter until FDA approval is obtained or until study closure, whichever comes first.

11. Objectives and Endpoints

11.1. Objectives

11.1.1. Primary Objective(s)

Primary Safety Objective: Lead complication-free rate at 6 months

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered safe if the probability of subjects free of Model 4798 lead-related complications at 6 months post-implant is greater than 87% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 87%).

Primary Efficacy Objectives: Lead pacing capture thresholds at 6 months

To demonstrate the effectiveness of the Attain Stability Quad MRI SureScan LV Lead (Model 4798), the study will evaluate the likelihood that there are at least two programmable vectors for each patient post implant. The effectiveness of this lead will be evaluated based on two primary efficacy objectives. More specifically, both primary efficacy objectives must be met simultaneously.

Primary Efficacy Objective #1

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet this objective if the proportion of subjects with at least one LV lead pacing vector having a pacing capture threshold less than or equal to 2.5 V at 0.5 ms pulse width at 6 months post-implant is greater than 80% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 80%).

Primary Efficacy Objective #2

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet this objective if the proportion of subjects with at least one additional (or second) LV lead pacing vector having a pacing capture threshold less than or equal to 4.0 V at 0.5 ms pulse width at 6 months post-implant is greater than 80% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 80%).

11.1.2. Secondary Objective(s)

The secondary objectives are descriptive in nature and are intended to provide additional information about the Attain Stability Quad MRI SureScan LV Lead (Model 4798). There will be no established performance requirements for these secondary objectives.

- To summarize implant procedure related information: success rate, implant related times
- To estimate 6-month reliability: post implant lead failure modes (i.e. complication rate)
- To estimate electrical measurement values (Pacing Capture Thresholds (PCTs) and Lead Impedance) at 6 months post-implant

11.2. Endpoints

11.2.1 Primary Endpoints

Primary Safety Endpoint

The study primary safety endpoint is Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complications through 6 months post implant. All reported system and procedure-related AEs will be reviewed by an event review committee for LV lead relatedness and severity (complication vs observation, refer to 17.1.2 for defintions).

Primary Efficacy Endpoint #1

The Model 4798 LV lead has sixteen (16) programmable pacing vectors. The endpoint for the primary efficacy objective is whether or not there is at least one Model 4798 LV lead pacing vector with pacing capture voltage thresholds less than or equal to 2.5V. This endpoint will be measured at the 6-month post implant follow-up visit.

Primary Efficacy Endpoint #2

The co-primary efficacy endpoint is whether or not a second Model 4798 lead configuration has a pacing capture threshold less than or equal to 4V, excluding the pacing vector that is already counted to the primary efficacy endpoint #1. This endpoint will be measured at 6-month post implant follow-up visit.

11.2.2 Secondary Endpoints

To summarize implant procedure related information

Implant procedure related endpoints will include implant success rate and procedure durations.

To estimate 6-month reliability

The Model 4798 LV lead 6-month reliability endpoint is Model 4798 lead related complications.

To estimate electrical measurement values (Pacing Capture Thresholds (PCTs) and Lead Impedance) at 6 months post-implant

The electrical measurements are pacing capture thresholds and impedance values for the four extended bipolar (CRT-D) vectors (i.e. LV1 to RVCoil, LV2 to RV Coil, LV3 to RV Coil, LV4 to RV Coil) or the unipolar (CRT-P) vectors (i.e. LV1 to Can, LV2 to Can, LV3 to Can, LV4 to Can) (refer to 15.8.2.3 for the testing procedure requirements).

12. Study Design

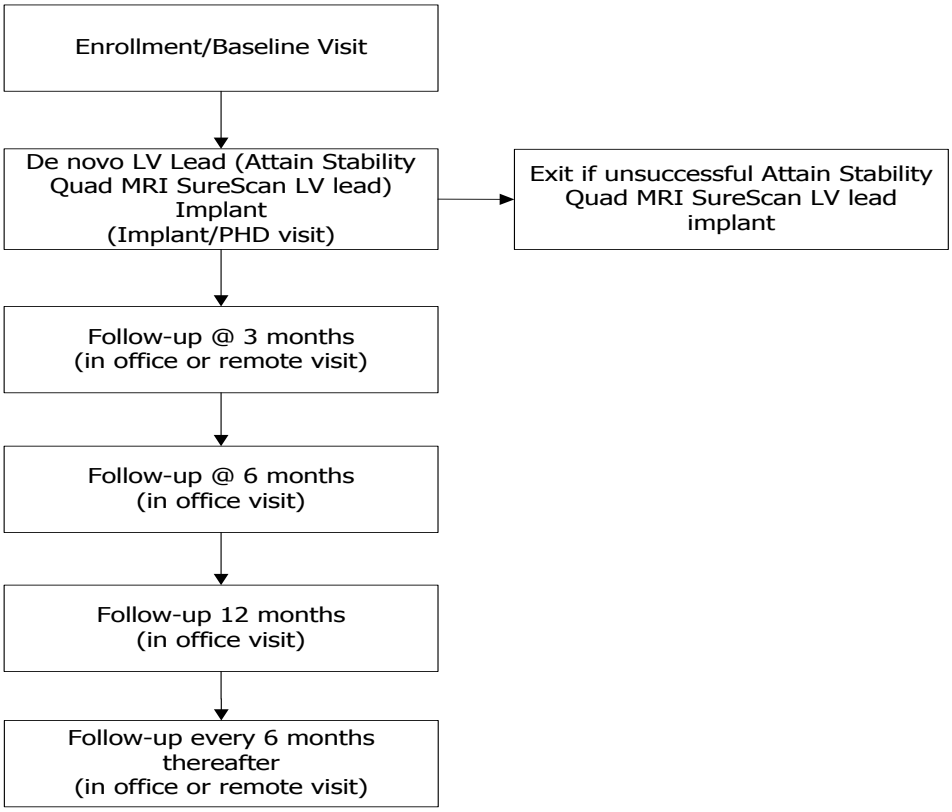
The Attain Stability Quad Clinical Study is a prospective, non-randomized, multi-site, global, Investigational Device Exemption (IDE), interventional clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) in patients indicated for a de novo LV lead implant. This will be assessed through a primary safety and primary efficacy endpoints.

All subjects included in the study will be implanted with a Medtronic market released de novo CRT-P or CRT-D device and an Attain Stability Quad MRI SureScan LV Lead (Model 4798). Compatible market released Medtronic RA and Medtronic RV leads will be required. For subjects enrolled who are receiving an upgrade to a CRT system, existing non-Medtronic RV and/or existing non-Medtronic RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used.

Up to 471 subjects will be enrolled into the study and up to 471 Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted, to ensure a minimum effective sample size of 400 Model 4798 leads implanted with 6 months post implant follow up visits (assuming 15% attrition). For the secondary endpoint of individual lead failure modes, Bayesian methods utilizing data from up to 37 historical patients will be used. All other objectives will be analyzed using only patients enrolled in this study. After a successful implant, threshold testing will occur to show one LV vector with pacing capture threshold (PCT) ≤ 2.5 V @ 0.5ms and with sufficient safety margin was programmed. Subjects will then be followed at implant, three months, six months and every six months thereafter until FDA approval is obtained or until study closure, whichever comes first.

See Figure 1 and Section 15 for further detail on study procedures and data collection as well as time-points for data collection.

Figure 1: Study Visits



The study is expected to be conducted at up to 56 sites worldwide. Participating geographies are expected to include, but are not limited to: the United States, Canada, EMEA, Malaysia, and Hong Kong. To ensure a widespread distribution of data and to minimize site bias in the study results, the maximum number of subjects allowed at a single site is 50 subjects.

12.1. Duration

The study duration is expected to be approximately 19 months. This represents 13 months for subject enrollment and 6 months for subject follow-up for the last subject enrolled. Subjects are anticipated to be in the study for on average 12 months. The first enrollment is projected to occur in May 2017. Subjects will complete visits at enrollment/baseline, implant, 3 months, 6 months, and then every 6 months thereafter. Subjects will not be replaced with newly enrolled subjects upon early exit. As described in Section 19, the sample size accounts for attrition.

12.2. Rationale

Upon market release, this Attain Stability Quad MRI SureScan LV Lead (Model 4798) will provide physicians an alternative option to actively fixate the lead utilizing a side helix feature to achieve stability. The Attain Stability Quad Clinical Study is designed to demonstrate that the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is safe and effective. See Section 19 for further background information and evaluation of clinical data. See Section 10 for further background on the study design.

12.3. Study Oversight

The study will utilize a Steering Committee (SC). The SC is responsible for the scientific content of the study and for providing input for the execution of the study. Members of the SC may be study site investigators. The purpose of the SC is to provide unbiased opinions and expertise to the Attain Stability Quad Clinical Study design and process. The SC will support the execution of the Attain Stability Quad Clinical Study and provide guidance, feedback and direction to the clinical study. The SC is comprised of the members as indicated in Table 4 below.

Table 4: Steering Committee Members

Committee Member	Contact information
George H. Crossley III, MD Steering Committee Co-Chair	Electrophysiology Fellowship Program Director Vanderbilt University Medical Center 1211 Medical Center Drive Nashville, TN 37232 United States (615) 322-5000 george.crossley@vanderbilt.edu
Kevin P. Jackson, MD Steering Committee Co-Chair	Electrophysiologist Duke Cardiology of Raleigh Medical Office Building 6 3320 Wake Forest Road 2nd Floor, Suite 200 Raleigh, NC 27609 United States (919) 862-5100 k.j@duke.edu
Dr. Maria Grazia Bongiorni	Electrophysiologist University Hospital of Pisa Lungarno Antonio Pacinotti 43, 56126 Pisa PI Italia +39 050 221 2111 m.g.bongiorni@med.unipi.it
Prof. Svein Faerestrand	Electrophysiologist University of Bergen Jonas Liesvei 65 Bergen, Norway 5021 +47 55 97 67 04 svein.faerestrand@helse-bergen.no
Dr. Axel Kloppe	Electrophysiologist Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil GmbH, Bürkle-de-la-Camp-Platz 1, 44789 Bochum, Germany +49 234 3026050 axel.kloppe@bergmannsheil.de

Melissa Kong, MD	Electrophysiologist Silicon Valley Cardiology 1300 Stockbridge Ave Redwood City, CA 94061 United States (650) 363-5262 mhkong1@gmail.com
Raymond Yee, MD	Electrophysiologist London Health Sciences Centre 339 Windemere Road London, ON N6A 5A5 Canada (519) 663-3671 ryee@uwo.ca
Francois Philippon, MD	Electrophysiologist Institut Universitaire de Cardiologie et de Pneumologie de Quebec 2725 Chemin Ste-Foy Quebec G1V 4G5 Canada (418) 656-8711 francois.philippon@fmed.ulaval.ca

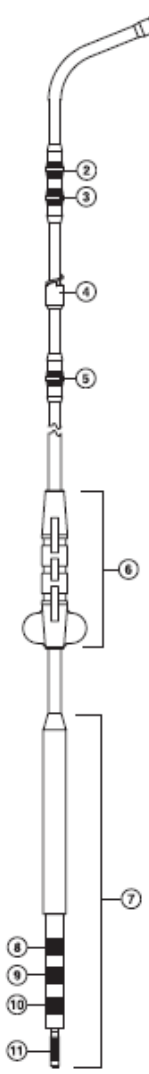
The study will also utilize a Clinical Events Committee (CEC) who will be responsible for adjudicating adverse events and deaths, including procedure and/or system-related complications. Further details for the CEC are provided in Section 18.1.

13. Product Description

13.1. General

The Medtronic Attain Stability Quad MRI SureScan (Model 4798) is a steroid-eluting, quadripolar electrode, transvenous, over-the-wire (OTW), IS4-LLLL compatible, active fixation, cardiac vein pacing LV lead. This lead is similar to the Attain Performa family of quadripolar leads (Models 4298, 4398, and 4598) but also has a side helix for active fixation which is similar to the Attain Stability bipolar lead (Model 20066/4796) (available outside of the United States). Figure 2 is a drawing of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) illustrating the specifications and location of the four electrodes in comparison to the side helix.

Figure 2: Attain Stability Quad MRI SureScan LV Lead (Model 4798) Specifications Drawing



[1] Electrode LV1 (the distal electrode): nominally 5.8 mm^2 geometric pacing surface area
[2] Electrode LV2: nominally 5.8 mm^2 geometric pacing surface area
[3] Electrode LV3: nominally 5.8 mm^2 geometric pacing surface area
[4] Helix assembly
[5] Electrode LV4 (the proximal electrode): nominally 5.8 mm^2 geometric pacing surface area
[6] Anchoring sleeve
[7] IS4 connector
[8] Contact LV4
[9] Contact LV3
[10] Contact LV2
[11] Contact LV1

Table 5 provides compares of the Attain Performa family of leads design features to the Attain Stability Quad MRI SureScan LV Lead (Model 4798).

Table 5: Comparison of Medtronic Quadripolar LV Leads

	Attain Performa			Attain Stability Quad
Design Feature	Model 4298	Model 4398	Model 4598	Model 4798
Shape	Double Canted	Straight	S-Shaped	Single Canted
Implant Method	Guide wire, stylet, or hybrid guide wire via Medtronic Delivery System	Same as 4298	Same as 4298	Guide wire, stylet, or hybrid guide wire via Medtronic Delivery System and active fixation
Delivery System Inner Diameter	≥ 5.7 Fr ID	Same as 4298	Same as 4298	Same as 4298
Lead Body Diameter	5.3 Fr proximal/3.9 Fr distal	Same as 4298	Same as 4298	4.4 Fr proximal/3.9 Fr distal
Lead Body Conductor	Single Quadfilar Coil (Multiconductor)	Same as 4298	Same as 4298	Same as 4298
Conductor Material	Ag core-low Titanium MP35Ncoil	Same as 4298	Same as 4298	Same as 4298
Insulation (Outer/Inner)	Polyurethane 55D SI-PI	Same as 4298	Same as 4298	Same as 4298
Polarity	Selectable Quad-electrode	Same as 4298	Same as 4298	Same as 4298
Electrode Material	PT/Ir* alloy with TiN coating	Same as 4298	Same as 4298	Same as 4298
Fixation Helix Material	N/A	N/A	N/A	Pt/Ir** alloy
Electrode Spacing	21mm/ 1.3mm/ 21mm	Same as 4298	Same as 4298	Same as 4298
Surface Area per	5.8	Same as 4298	Same as 4298	Same as 4298

Electrode (mm^2)				
Steroid and Dose / MCRD	Dexamethasone acetate Each (4) Ring 72µg	Same as 4298	Same as 4298	Same as 4298
Total Target Dose	288 µg/lead	Same as 4298	Same as 4298	Same as 4298

*90/10 Platinum Iridium
**80/20 Platinum Iridium

Similar to the Attain Performa family of leads, the Attain Stability Quad MRI SureScan LV Lead (Model 4798) contains 4 electrodes with surface area of 5.8 mm^2 per electrode and is designed to function as cathodes or anodes, depending on how the device LV pacing vector is programmed:

- electrode LV1, the distal electrode, positioned near the distal tip of the lead
- electrode LV2, positioned 21 mm proximal to electrode LV1
- electrode LV3, positioned 1.3 mm proximal to electrode LV2
- electrode LV4, the proximal electrode, positioned 21 mm proximal to electrode LV3

The electrode spacing on the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is identical to the approved Attain Performa family of leads. This includes a non-uniform electrode spacing consisting of a reduced electrode spacing configuration (LV2-LV3) that alters the size of the electric field that is generated when stimulating the heart tissue. This close electrode spacing is designed to reduce the likelihood of stimulating the phrenic nerve while still allowing for optimal lead placement and acceptable pacing capture thresholds.

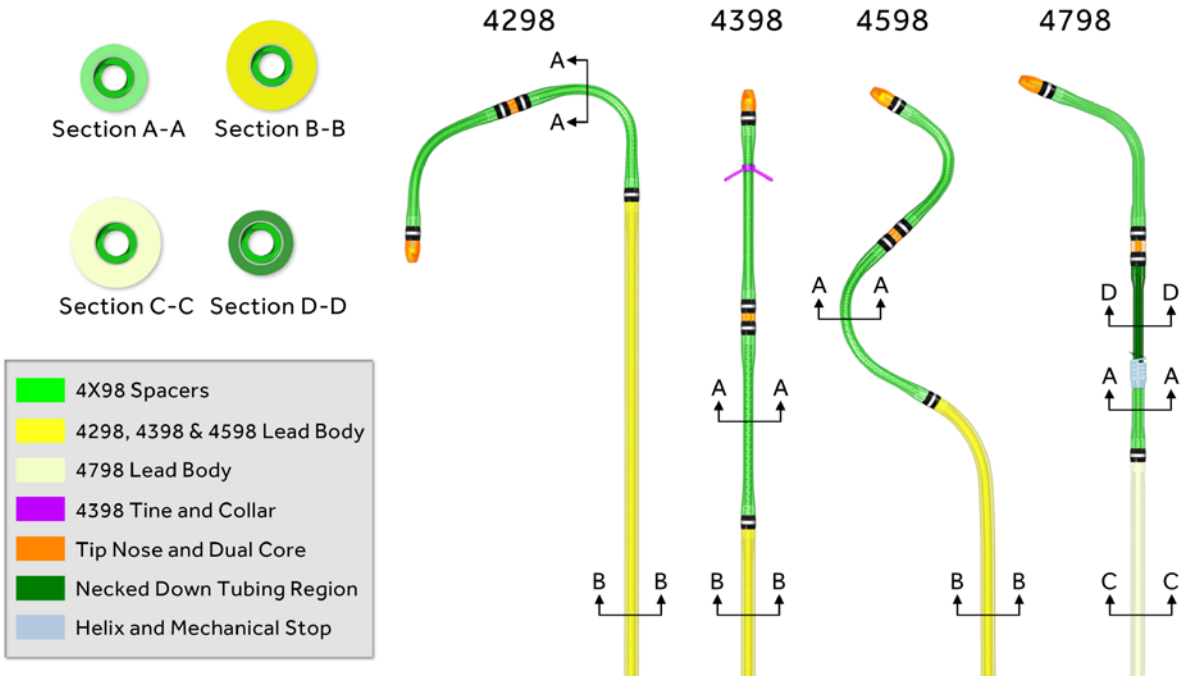
Similar to Attain Performa, each electrode contains a Monolithic Controlled Release Device (MCRD) for elution of steroid to reduce inflammatory response within the cardiac vein. The MCRDs contain a combined-total target dosage of 288 µg of dexamethasone acetate steroid. The target dose of the steroid is 72 µg at each MCRD. Upon exposure to body fluids, the steroid elutes from the MCRDs. The steroid suppresses the inflammatory response that is believed to cause threshold rise typically associated with implanted pacing electrodes.

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) has the same lead body conductor (Single Quadfilar Coil (Multiconductor), conductor material (Ag core-low Titanium MP35N coil), insulation (outer/inner) (Polyurethane 55D SI-PI), and requires a similar delivery system inner diameter as the Attain Performa family of leads (≥ 5.7 Fr ID).

Unlike the Attain Performa family of leads, the Attain Stability Quad MRI SureScan LV Lead (Model 4798) has a slightly smaller lead body diameter. The lead body diameter of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is 4.4 Fr proximal (compared to 5.3 Fr on the Attain Performa family of leads) and 3.9 French distal (same as Attain Performa family of leads). This slightly smaller lead body tubing diameter is designed to enhance torquability and steerability to facilitate adherence of the side helix in the target location.

Figure 3 is a visual comparison between the Attain Perform leads and the Attain Stability Quad MRI SureScan LV Lead (Model 4798) illustrating the similar electrode location but different lead body diameter.

Figure 3: Comparison of Attain Performa Leads and the Attain Stability Lead Model 4798



A detailed comparison of the Attain Stability bipolar lead (Model 4796) and Attain Stability Quad lead (Model 4798) is presented in Table 6.

Table 6: Comparison of Medtronic Attain Stability Bipolar and Quadripolar LV Leads

	Attain Stability	Attain Stability Quad
Design Feature	Model 4796/20066	Model 4798
Shape	Single Canted	Same as 4796/20066
Implant Method	Guide wire, Stylet, or hybrid guide wire via Medtronic Delivery System and active fixation	Same as 4796/20066
Delivery System Inner Diameter	≥ 5.7 Fr ID	Same as 4796/20066
Lead body diameter	3.9 Fr proximal / 3.4 Fr distal	4.4 Fr proximal /3.9 Fr distal
Lead Body Conductor	Single 2 Filar Coil (Multiconductor)	Single Quadfilar Coil (Multiconductor)
Conductor Material	Ag core-low Titanium MP35N coil	Same as 4796/20066

	Attain Stability	Attain Stability Quad
Design Feature	Model 4796/20066	Model 4798
Shape	Single Canted	Same as 4796/20066
Insulation (Outer/Inner)	Polyurethane 55D SI-PI	Same as 4796/20066
Polarity	bipolar	Selectable Quad-electrode
Electrode Material	Pt/Ir* alloy with TiN coating	Same as 4796/20066
Fixation Helix Material	Pt/Ir** alloy	Same as 4796/20066
Electrode Spacing	21 mm	21mm / 1.3mm / 21mm
Surface Area per electrode (mm^2)	5.8	Same as 4796/20066
Steroid and Dose / MCRD	Dexamethasone acetate Tip 160µg , Ring 72µg	Dexamethasone acetate Each (4) Ring 72µg
Total Target Dose	232µg/lead	288 µg/lead
Molded Tip Seal	Silicone (with steroid), pierced hole	Silicone (without steroid), cross-cut hole
Fixation Method	Helix	Same as 4796/20066
Connector	IS-1 B1	IS4-LLLL
Length (cm)	88 cm only	78 and 88 cm

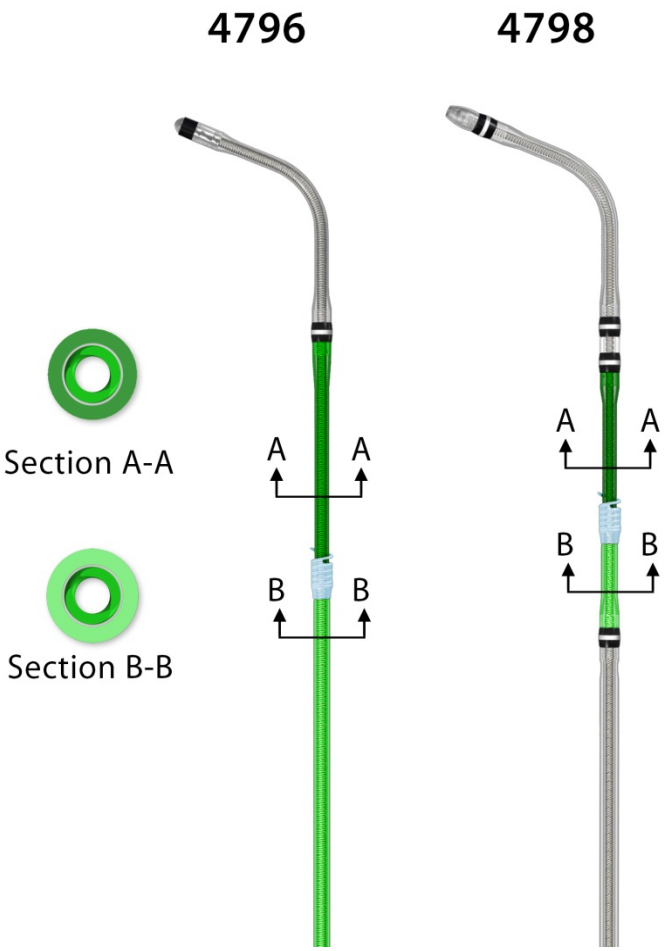
*90/10 Platinum Iridium
**80/20 Platinum Iridium

The non-electrically active side fixation helix component is similar to the Attain Stability Bipolar LV lead (Model 20066/4796) and is designed to enable active fixation in the cardiac vein. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) side helix is positioned between the LV3 and LV4 electrode; specifically 10 mm proximal from the LV3 electrode (see Figure 2).

A mechanical stop component is located at the base of the helix to prevent wedging of the endothelial tissue in the helix and to prevent tissue ingrowth. The helix component is platinum (Pt) iridium (Ir) alloy (Pt/Ir 80/20). This same Pt/Ir material is also used in the market released right ventricular active fixation lead Models 5076, 3830, and 4076. Both the helix and mechanical stop components are identical to those used on the CE Mark approved Medtronic Attain Stability model 20066/4796 active fixation lead and are shown in Figure 4.

The Model 4798 lead has one distal curve/cant. This distal curve geometry (angle) is identical to the Attain Performa model 4298, as well as Attain Ability models 4196 and 4296 most distal cant. The single distal cant is also identical to the CE Mark approved model 20066/4796 active fixation lead (Figure 4). The purpose of the distal cant is to provide physicians the ability to "steer" the distal tip of the lead when navigating difficult vein anatomy or acute vasculature angulation by rotating the lead (counterclockwise) and aligning the distal tip towards the desired direction. The distal cant for the Model 4798 lead is not intended, or necessary, to provide any fixation of the implanted lead as any retention force from the cant would be negligible compared to the stability provided by the properly implanted and verified fixated helix.

Figure 4: Attain Stability Bipolar (Model 20066/4796) & Attain Stability Quad MRI SureScan (Model 4798) Active Fixation Leads



The Attain Stability Quad Clinical Study will be conducted to evaluate the safety and efficacy of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) in combination with CRT system components mentioned in Table 7.

Table 7: Study Component Information

Component	US/Canada	EMEA/Hong Kong/Malaysia
Attain Stability Quad MRI SureScan LV Lead (Model 4798)	Investigational	Market-released
Medtronic CRT-P or Medtronic CRT-D (with VectorExpress capabilities)	Market-released	Market-released
Medtronic RV lead (non-Medtronic and non-recalled/non-market withdrawaled/non-safety alerted lead acceptable for upgrades)	Market-released	Market-released
Medtronic RA lead (optional) (non-Medtronic and non-recalled/non-market withdrawn/non-safety alerted lead acceptable for upgraded systems)	Market-released	Market-released

Given the similarities between the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the Attain Performa family of leads, the proposed indications for use are the same. The indications are as follows:

Proposed Indication Statement for Use for the Attain Stability Quad Lead:

The Attain Stability Quad MRI SureScan 4798 steroid-eluting, quadripolar electrode, IS4 transvenous lead is indicated for chronic pacing in the left ventricle via the cardiac vein, when used with a compatible Medtronic Cardiac Resynchronization Therapy (CRT) System. Extended bipolar pacing is available using this lead in combination with a compatible market approved CRT-D system and RV lead.

Market-Released Right Atrial Lead

Commercially available Medtronic RA lead models with an IS-1 connector are required when an RA lead is implanted with de novo CRT systems. An RA lead is not required to be implanted in circumstances determined appropriate per physician's medical assessment. Medtronic commercially available RA leads with an IS-1 connector are recommended but compatible non-Medtronic leads are permissible in enrolled patients receving a CRT system upgrades.

Medtronic Market-Released Right Ventricular Lead

Commercially available Medtronic RV defibrillation leads with a DF4 connector are required for de novo CRT systems. Medtronic RV defibrillation leads with DF1 connectors may be incorporated in the study as DF1-compatible CRT-P and CRT-D devices are made available for the study. A non-Medtronic RV lead is permissible in enrolled patients receving a CRT system upgrades.

13.2. Manufacturer

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is manufactured by Medtronic, Inc.

13.3. Packaging

Packaging and labeling for all market approved system components can be found with each package insert. Manuals can be found on http://manuals.medtronic.com. For CE Marked devices the labeling is in the appropriate local language.

For investigational products (e.g. in the US and Canada), the language of labeling and clinical manuals will be in English and/or local language where it is required. Investigational products will be clearly labeled e.g. "exclusively for clinical investigation."

In Canada, each investigational device will be labelled with the statements "Investigational Device"; "To be Used by Qualified Investigators Only"; "Instrument de recherche" and "Réservé uniquement à l'usage de chercheurs compétents".

13.4. Intended Population

In the Attain Stability Quad Clinical Study, the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is to be used in subjects where a de novo LV lead is indicated. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is intended to be used in conjunction with a market released Medtronic CRT-P or CRT-D device, a Medtronic (for de novo CRT implants) RV lead, and a Medtronic (for de novo CRT implants) RA lead (optional).

A complete SureScan system is required for use in the MRI environment. Before performing an MRI scan, refer to the SureScan MRI technical manual for MRI-specific warnings and precautions.

13.5. Equipment

All commercially available equipment will be used according to their approved intended use.

Medtronic CareLink (2090) Programmer

The Medtronic approved CRT-P or CRT-D devices will be programmed and interrogated using a Medtronic CareLink (2090) programmer. Medtronic may incorporate additional programmers as they receive regulatory approval.

Medtronic CareLink Home Monitor 2490C and Network

The CareLink Monitor Model 2490C is an external monitor that is indicated for use in the transfer of patient and device data from implanted Medtronic devices. The CareLink Monitor Model 2490C interrogates implanted devices and temporarily stores these data, collaborates with the appropriate Medtronic server to confirm the establishment of an Internet connection with server, performs any required file translation functions necessary for data transfer, executes data file transfer, and collaborates with the appropriate Medtronic server to confirm data file transfer through the Internet connection with the server. The CareLink Monitor 2490C is not a programmer and cannot be used to program implanted device parameters. CareLink monitors are not a substitute for appropriate medical attention in the event of an emergency and should only be used as directed by a physician. Approved Medtronic CRT-P and CRT-D devices used in this study qualify for use with the Medtronic CareLink Monitor and Medtronic

CareLink Network. Medtronic may incorporate additional home monitors as they receive regulatory approval.

Pacing System Analyzer

Medtronic's commercially available Model 2290 Analyzer must be available at each center during the implant procedure to determine acceptable electrical parameters. Medtronic may incorporate additional analyzers as they receive regulatory approval.

13.6. Product Use

See Section 13 Product Description.

13.7. Product Receipt, Tracking, and Accountability

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered investigational in geographies where the product is not available commercially and will be labeled for clinical use only. These geographies include but are not limited to the US and Canada. Investigational Attain Stability Quad Leads will be distributed to a site only when Medtronic has received all required documentation (including but not limited to Ethic Committee approval, a signed Clinical Trial Agreement and documentation of training) and has notified the site of site readiness.

Distribution of the investigational product to study sites will be managed by Medtronic and investigational products can only be ordered by Medtronic personnel. Sites with these clinically labeled Attain Stability Quad MRI SureScan LV Leads (Model 4798) will track disposition upon receipt or return of the lead but also upon implant or explant of the lead. Disposition logs will be available within the electronic data management system and shall be maintained at each site in all geographies to track investigational product information. The logs should be updated when an investigational product is received, opened, implanted explanted, disposed of or returned to Medtronic. The logs will track the following investigational lead data (but are not limited to) model and serial numbers of devices delivered to the site, subject IDs of the subjects, implanted, received dates of devices, implant/used dates, explant dates, returned-to-sponsor dates and reasons, initials of all persons who received, used or disposed each device, and method of disposal. Medtronic will perform periodic reconciliation of investigational product to ensure traceability.

For geographies where the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is not considered investigational, commercially approved devices will be used. Sites that use commercially available Attain Stability Quad MRI SureScan LV Lead (Model 4798) will track device disposition upon implant or explant of the lead on the CRFs.

13.8. Product Storage

All investigational products must be stored in a secure location at the site. It is the responsibility of the investigator to correctly handle, store and track the investigational products. Further details may be found in the Clinical Manual or User Manual (dependent on each geography's commercial release of the product).

13.9. Product Return

All explanted, open but unused, and defective products (devices or leads, etc.) should be returned to Medtronic for analysis whenever possible and when permissible by local laws and regulations. If the products are explanted but not returned, a justification is required to be reported on the appropriate case report form(s) or disposition log(s) (note that this is not considered a study deviation). In geographies where the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is considered investigational, the Disposition Log must be updated in the event of an explant. To receive a Returned Product Mailer Kit, please contact your local Medtronic field personnel or representative. All unused investigational products must be returned to Medtronic upon study closure at the site.

14. Selection of Subjects

14.1. Study Population

Patients of both genders that are 18 years of age and older (or of legal age to give informed consent per local and national law) that are indicated for a de novo LV lead implantation and who meet all inclusion and no exclusion criteria are eligible for an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt. There will be no control group for this study.

14.2. Subject Enrollment

Patients who meet all of the inclusion and none of the exclusion criteria (see sections 14.3 and 14.4) are eligible to be enrolled in this study. Upon signing and dating the Informed Consent Form (ICF), the patient is considered a subject enrolled in the study.

14.3. Inclusion Criteria

- Patient meets CRT implant criteria as determined by local regulatory and/or hospital policy
- Patient (or legally authorized representative) has signed and dated the study-specific Informed Consent Form
- Patient is 18 years of age or older, or is of legal age to give informed consent per local and national law
- Patient is expected to remain available for follow-up visits

14.4. Exclusion Criteria

- Patient has had a previous unsuccessful LV lead implant attempt
- Patient has a previous CRT system or LV lead implanted (for example, transvenous or epicardial)
- Patient is currently implanted with a recalled (i.e. market-withdrawn, recalled or safety alert) RA and/or RV lead
- Patient has known coronary venous vasculature that is inadequate for lead placement
- Patient has unstable angina pectoris or has had an acute myocardial infarction (MI) within the past 30 days
- Patient has had a coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) within the past 90 days
- Patient has contraindications for standard transvenous cardiac pacing (e.g., mechanical right heart valve)
- Patient has had a heart transplant (patients waiting for heart transplants are allowed in the study)
- Patient has known renal insufficiency that would prevent them from receiving an occlusive venogram during the implant procedure
- Patient is contraindicated for <1mg dexamethasone acetate
- Patient is enrolled in any concurrent drug and/or device study that may confound the results of this study
- Patient has a terminal illness and is not expected to survive more than six months
- Patient meets exclusion criteria required by local law (e.g. age, pregnancy, breast feeding, etc.)
- Patient is unable to tolerate an urgent thoracotomy

14.5. Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Subjects will be evaluated at baseline to confirm eligibility for enrollment with defined inclusion/exclusion criteria
- Subject demographics and medical history will be collected at baseline and differences that may affect primary endpoints will be identified
- To ensure widespread distribution of data between sites, the maximum number of subjects allowed per site is 50
- All implanters in the study will be experienced in the implant of CRT-P and/or CRT-D systems
- Data collection requirements and study procedures will be standardized across all sites and geographies

- All study site personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials, and required to follow the CIP
- Per the specifications in the Monitoring Plan, monitoring visits will be conducted for adherence to the CIP and to verify the CRF data against source data
- Pre-defined statistical methods specified in the CIP and the Statistical Analysis Plan (SAP) will be followed
- The SC members will not have influence on the treatment decisions by study site investigators during the trial
- An independent and blinded CEC will regularly review and adjudicate reported adverse events and deaths (per Section 18.1)
- Registration of the trial on ClinicalTrials.gov and the publication plan will ensure that study results will be reported
- All study investigators are required to meet 21 CFR Part 54, Financial Disclosure by Clinical Investigators, to identify potential bias due to financial interest in the outcome of the study

In summary, potential sources of bias that may be encountered in this Attain Stability Quad Clinical Study have been considered and minimized by careful study design.

15. Study Procedures

Prior to performing study related procedures, all sites must have Ethics Committee (EC) and associated regulatory authority approval if applicable (e.g., Competent Authority approval) as well as documentation from Medtronic of site readiness.

Medtronic representatives may perform the following activities at the study sites during the study, if appropriately trained and under supervision of the Principal Investigator:

- Study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support at all visits (e.g. programming of the CRT-P or CRT-D device according to study requirements, performing device interrogations/save-to-media, etc.), but no CRF data entry shall be performed by Medtronic personnel
- Monitoring activities

15.1. Study Personnel Requirements

Site personnel training and delegation will be completed prior to participation in the Attain Stability Quad Clinical Study. The site personnel training consists of required training topics (CIP, Informed Consent Form, CRFs, regulations). Members of the study site team will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study.

All Principal Investigators shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Be qualified practitioners and experienced in the diagnosis, management, and treatment of HF subjects with CRT devices
- Be experienced in the field of application and trained in the use of the Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- Disclose potential conflicts of interest, including financial that interfere with the conduct of the clinical investigation or interpretation of results
- Be knowledgeable with the method of obtaining an informed consent

In addition, the Principal Investigator shall be able to demonstrate that the proposed investigational site:

- Has an experienced CRT implanter who is experienced and trained in the handling/implanting of CRT-P and/or CRT-D devices
- Has the required number of eligible subjects needed within the agreed recruitment period
- Has one or more qualified investigators, a qualified investigation site team and adequate facilities for the foreseen duration of the clinical investigation

15.2. Site Activation

During the activation process (prior to subject enrollment), Medtronic will train site personnel on the CIP, the implant procedure, relevant standards and regulations, informed consent process, and on data collection and reporting tools. If new members join the study site team, they will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study. For new members, local Ethics Committee notification requirements must be met, as well as Medtronic requirements noted on the training and delegation form.

A Clinical Trial Agreement (CTA) shall be entered into effect by Medtronic, the participating investigation site and/or the principal clinical investigator at each investigational site as per local legal requirements, and returned, fully executed, to Medtronic prior to the commencement of any study activities. Financial aspects of conducting and reporting a study will be specified in the agreement. By signing and dating the agreement the investigator indicates approval of the CIP.

Prior to performing study related activities, all sites must have Ethics Committee approval, as applicable for that geography.

All local and regional regulatory requirements will be fulfilled prior to site activation and enrollment of subjects into the study. Each study site must have written documentation from Medtronic of site and investigator readiness before beginning any study-related activities. Requirements for activation vary by geography, and may include, but are not limited to the following:

- Written documentation of Ethics Committee approval of the current version of the CIP and ICF, subject materials (e.g. Global Assessment and KCCQ), and voting list (as required by local law)
- Regulatory authority approval or notification (as required per local law)
- Fully executed CTA on file with the sponsor
- Financial Disclosure (for Principal Investigators and Co-Investigators)
- Current Curriculum Vitae (CV) (signed and dated as required by local law) of investigators and key members (as required by local law) of the investigation site team on file with the sponsor
- Documentation of delegated tasks

- Documentation of study site personnel training

Additional requirements imposed by the Ethics Committee and regulatory authority shall be followed, if applicable.

Medtronic will provide each study site with documentation of study site readiness; this letter must be sent prior to subject enrollment.

15.3. Equipment Requirements

The following equipment must be available at each site to support study activities:

- Medtronic 2290 Analyzer (or latest market released Medtronic analyzer)
- Medtronic 2090 programmer (or latest market released Medtronic programmer)
- Attain Stability Quad MRI SureScan LV Lead (Model 4798) (either clinically labeled product or commercial released product located at the site or carried to the implant by the Medtronic representative)
- Computer with high speed internet access using a web browser compatible with the electronic data management system for electronic database entry

The equipment necessary for the assessment for the study includes the Medtronic 2290 Analyzer and Medtronic 2090 programmer. The maintenance and calibration of the equipment used for this study will be assessed outside of this clinical study. Sites are responsible for maintaining and calibrating non-analyzer/programmer equipment used in the course of this study in accordance with established site practice or local regulation. Records should be kept and able to be provided upon request by the Sponsor or regulatory agency.

15.4. Schedule of Events

Clinical data will be collected at the study milestones detailed in Table 8. Data will be collected via electronic case report forms (eCRFs), still cine images, analyzer/programmer print-outs, and interrogation files. Post-implant follow-ups apply only to those subjects in whom an Attain Stability Quad MRI SureScan LV Lead (Model 4798) was successfully implanted or an implant was attempted. Subject visits will occur at enrollment, baseline, implant/pre-hospital discharge (PHD), 3 months post-implant, 6 months post-implant, and every 6 months thereafter until PMA approval of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted or study termination, whichever comes first. Medtronic personnel may assist study personnel during implant and study visits.

Table 8: Data Collection and Study Procedure Requirements at Subject Visits

STUDY PROCEDURE	Enrollment /Baseline	Implant/ PHD	3 months post-implant (remote or inoffice visit)	6 months post-implant (inoffice visit)	12 months post-implant (inoffice visit)	Recurring 6 month follow-ups (remote or inoffice visit)	Exit
Subject Informed Consent	✓						
Inclusion / Exclusion criteria verified	✓						
Subject demographics	✓						
Cardiovascular medications	✓						
Cardiovascular medical history	✓						
NYHA classification	✓		✓	✓	✓	✓	
Patient Global Assessment				✓	✓		
Kansas City Cardiomyopathy Questionnaire (KCCQ)	✓			✓	✓		
Occlusive venogram with pre-determined pacing location identified		✓					
Analyzer PCT data collection (pre and post slitting the cannulation catheter)		✓ (Implant)					
Investigator Lead Handling Assessment		✓ (Implant)					
System and procedure information		✓					
Lead Impedance (all 16 vectors)		✓	✓ (final programmed vector only)	✓	✓	✓ (final programmed vector only)	
Pacing Capture Thresholds (all 16 vectors)		✓	✓ (final programmed vector only)	✓	✓	✓ (final programmed vector only)	
Phrenic Nerve Stimulation (final programmed vector)		✓	✓ (inoffice visit only)	✓	✓		
Phrenic Nerve Stimulation (vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can)				✓			
Rationale for selecting specific LV lead pacing vector for final programming		✓		✓	✓		
Final device interrogation/save-to-media		✓	✓ (CareLink transmission is acceptable for remote visits)	✓	✓	✓ (CareLink transmission is acceptable for remote visits)	✓ (required only if subject exits prior to 6 months post-implant visit; CareLink transmission is acceptable)
AE Assessment		✓	✓	✓	✓	✓	✓
Exit Subject							✓
Adverse Events (incl. AE with outcome of death)	As they occur						
Device Deficiencies							
System Modifications							
Study Deviations							

Table 9 below specifies permitted time windows for the required subject visits. Subject visit target dates and windows for each follow-up will be made available to the study site. Should a subject miss a visit or the visit falls outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits. Data analyses will include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation.

Table 9: Visit Windows

Visit	Window
Implant	0-30 days since Baseline Assessment
	(days since implant)
Pre-hospital discharge	0-7
3-month	76 - 106
6-month	183 - 213
12-month	350 - 380
18-month	518 - 578
24-month	701 - 761

15.5. Subject Consent

Informed consent (IC) is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate (ISO 14155:2011). This process includes obtaining IC and an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (data protection authorization; i.e. HIPAA in the US) as required by law. Informed Consent Forms are required to be approved by the study site's Institutional Review Board (IRB) or Ethics Committee (EC) and Medtronic, and signed and dated by the subject and the Principal Investigator. A subject may only consent after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate.

Prior to enrolling subjects, each site must have documented IRB/EC approval of the IC Form (ICF) and the data protection authorization as required by law. Any changes to a previously approved ICF throughout the course of the study must be reviewed and approved by Medtronic and the IRB/EC reviewing the application before being used to consent or re-consent a study subject. The document(s) must be controlled (i.e. versioned and dated) to ensure it is clear which version(s) was approved by Medtronic and the IRB/EC. All important new information should be provided in written form to new and existing subjects throughout the study. If relevant, all affected subjects must be asked to confirm their continuing IC in writing.

Prior to initiation of any study-specific procedures, IC must be obtained from the subject (or legally authorized representative). Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize sites to submit subject information to the study sponsor. The IC process must be conducted by the principal investigator or an authorized designee, and the ICF and data protection authorization, as required by law, must be given to the subject in a language he/she is able to read and understand.

The process of obtaining informed consent shall:

- Ensure that the principal investigator or an authorized designee conducts the IC process.
- Include all aspects of the Attain Stability Quad Clinical Study that are relevant to the subject's decision to participate throughout the clinical study.
- Avoid any coercion or undue improper influence on, or inducement of the subject to participate.
- Not waive or appear to waive the subject's legal rights.
- Ensure the ICF and data protection authorization, as required by law, are given to the subject in a non-technical language the subject is able to read and understand.
- Provide ample time and opportunity for the subject to read and understand the ICF to inquire about details of the study, and to consider participation. All questions about the study should be answered to the satisfaction of the subject.
- Include a personally dated signature of the subject acknowledging that their participation in the study is voluntary.
- Include a personally dated signature by the principal investigator or authorized designee responsible for conducting the IC process, as required by local law.
- Include any other locally required signatories, such as witnesses, as indicated by country-specific legislations.
- Provide the subject with a copy of the ICF, the data protection authorization, as required by law, and any other written information, signed and dated if required by local law.
- Ensure subjects are notified of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study.

If IC is obtained the same day the subject begins participating in study-related procedures, it must be documented that consent was obtained prior to participation in any study-related procedures. It is best practice for the IC process to be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write, witnessed (impartial third party) IC will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the ICF. Informed consent shall be obtained through a supervised oral process. An independent witness must be present throughout the process. The ICF and any other information must be read aloud and explained to the prospective subject, if allowed by local law. The witness signs and personally dates the ICF, attesting that the information was accurately explained and that informed consent was freely given. The subject should "make his mark" (sign or otherwise physically mark the document so as to indicate consent) on the ICF as well. The ICF should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study.

The original of the signed ICF must be filed in the hospital/clinical chart and/or with the subject's study documents. A second signed original or a copy should be given to the subject for their records (if applicable).

The ICF and data protection authorization, as required by law, must be available for monitoring, auditing and regulatory inspections.

Geography specific ICF Templates will be provided under separate cover.

15.6. Enrollment

The point of enrollment is defined as the time at which a patient has signed and dated the ICF. The date the subject signed (or legally authorized representative) the ICF and data protection authorization, as required by law, must be documented in the subject's medical records. At that point, the patient is considered a subject in the study, a study subject ID number will be assigned, and the subject must be followed for the duration of the study unless the subject exits the study prior to study closure. Each investigational center will be responsible for maintaining subject identification records (e.g. subject identification log) according to ISO 14155.

Enrollment will occur on the same day as the baseline visit. Once IC is obtained, report AEs/deaths, study deviations and subject exits as they occur. To accurately track subject enrollment, Medtronic should be notified of the enrollment as soon as possible after a patient has signed the ICF.

15.7. Baseline

The baseline visit can be a stand-alone visit or can occur on the same day as, but not later than, the implant visit. The following procedures will be completed/data will be collected at the baseline visit:

- Subject Informed Consent
- Inclusion/Exclusion criteria verified
- Subject demographics
- Cardiovascular medications
- Cardiovascular medical history
- NYHA classification
- Kansas City Cardiomyopathy Questionnaire (KCCQ)

Cardiovascular medications include ACE inhibitors, ARBs, antiarrhythmic, anti-coagulants, antithrombotics, and antiplatelet, antihypertensive, antilipidemics (statins), beta blockers, calcium channel blockers, diuretics, digitalis, inotropes, nitrates, digoxin, and vasodilators.

If implant does not occur within 30 days of enrollment, verification of all inclusion and all exclusion criteria must be repeated before an implant attempt.

15.8. Implant/PHD

Information collected at Implant/PHD will include data from the day of the implant procedure until released from the hospital. The implant CRF will be used to collect data at implant. Implantation of the CRT device and right heart leads should be performed according to the Instruction for Use (IFU) in geographies where the devices are commercially available.

Any Medtronic commercially released right atrial (RA) and any Medtronic commercially released right ventricular (RV) lead may be implanted. Existing non-Medtronic RV and/or RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used in enrolled who are receiving an upgrade to

a CRT system. The right-heart leads should be implanted according to the labeling provided with the applicable lead.

The implanted system device must include a Medtronic commercially released CRT device which can be programmed to utilize all electrodes, allowing upgrades from implantable pulse generators (IPGs) and implantable cardioverter defibrillators (ICDs). Device and lead requirements are as follows:

- Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- For de novo CRT implants, any Medtronic commercially released transvenous (active or passive fixation) RA pacing lead (unless medical justification to exclude this lead) and any Medtronic commercially released transvenous (active or passive fixation) RV lead
- For upgrades to a CRT system, existing non-Medtronic RV and/or non-Medtronic RA leads that are not recalled, market withdrawn, and/or have a medical alert may be used in enrolled who are receiving an upgrade to a CRT system
- Medtronic commercially released CRT devices that measure discrete LV electrical values from all four electrodes (i.e. Vector Express)

15.8.1. Final System Configuration

For information on the requirements for the implanted system refer to Section 13. The system is successfully implanted when the Medtronic CRT device is successfully connected to the RA, RV and the LV lead (except if a medical condition such as chronic atrial fibrillation excludes the need for an RA lead). The configuration of the successfully implanted system components will be collected. This will include the serial number of each implanted component (CRT-D or CRT-P device, and leads), and the location of lead placement.

15.8.2. Implant Procedure

Implantation of the CRT device and cardiac leads must be performed by a trained clinical study investigator and according to the manufacturer's instructions for use. It is recommended to use Medtronic catheters that are compatible with the Attain Stability Quad MRI SureScan LV Lead (Model 4798) (e.g., > 7 Fr) during the implant for gaining access to the coronary sinus (CS).

For complete information regarding the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the implant procedure, reference the Clinical Manual in the US and Canada or the Instructions for Intended Use (Technical Manual in EMEA, Hong Kong, and Malaysia). These documents are located under a separate cover.

15.8.2.1. Venogram

An occlusive venogram is required for venous visualization of the subject's coronary vasculature and will be used to pre-determine a desired target pacing location prior to placing the Attain Stability Quad MRI SureScan LV Lead (Model 4798). Once the pre-determined target pacing location is determined, a venous image will be collected. A copy of the venous image will be submitted to Medtronic and kept on file at the center.

15.8.2.2. Implanting the LV lead

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be implanted according to the implant instructions found within the lead packaging. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) can be positioned with the aid of a guide wire (0.36 mm to 0.46 mm or 0.014 inches to 0.018

inches in diameter), stylet, an inner catheter, or an inner catheter plus hybrid guide wire. If a stylet is used for lead positioning, only use the stylets packaged with the lead or in a stylet kit (downsized knob). Always use a stylet that is 3 cm shorter than the lead length listed on the IS4 connector label. Other stylets may extend beyond the lead tip causing injury or perforation of the cardiac vein or heart. If using a Medtronic integrated valve system (e.g. SureValve), rotate the helix counterclockwise to allow safe passage of the helix when inserting the lead into the delivery system to prevent the side helix from inadvertently attaching to the valve. Rust stylets are not recommended with this lead due to the risk of conductor coil/insulation perforation.

Follow the Attain Stability Quad MRI SureScan LV Lead (Model 4798) package insert carefully for fixating the side helix to the vein. Consider using a J-shaped stylet if fixation is unsuccessful. An overview of the key implanting tips includes:

- Rotate the lead counterclockwise when inserting the lead through the SureValve to prevent the helix from attaching to the valve
- Refrain from wedging the lead into the vessel so that the lead can easily rotate during fixation allowing torque to transfer from the proximal end to the distal end of the lead
- To fixate the side helix in the desired location, rotate the lead clockwise with the guidewire inserted in the lead which will provide extra stiffness to the lead
- Ensure the guidewire is removed to allow for lead pliability to visualize and confirm lead fixation during the Push Test and the Pull Test
- To reposition the lead, insert the guidewire and rotate the lead counterclockwise without applying tension to the lead to unfixate

Information on surgical data, such as tool use, and implant times, etc. will be collected during the implant procedure.

In an event that one Attain Stability Quad MRI SureScan LV Lead (Model 4798) is determined to be not suitable for a patient after the initial lead insertion; the implanting physician must assess the onset of any potential AEs. A second Attain Stability Quad MRI SureScan LV Lead (Model 4798) may only be introduced upon confirmation that no system-related AEs resulted from the first Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt. Any LV lead related AE observed during the initial LV lead attempt prohibits an attempt of a second Attain Stability Quad MRI SureScan LV Lead (Model 4798).

If the subject does not have a successful Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant at the conclusion of the initial implant procedure, the subject should be followed until procedure or system related AEs are resolved or are unresolved with no further actions planned, whichever occurs later.

If an attempt to implant the Attain Stability Quad MRI SureScan LV Lead (Model 4798) does not occur, or if the Model 4798 LV lead cannot be implanted, the reasons why the lead was not attempted or attempted but not implanted must be documented on the Implant and Study Exit CRF. See additional definitions below.

No Attain Stability Quad MRI SureScan LV Lead (Model 4798) Attempted (lead not inserted into the body)

An Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt is defined as any time a Model 4798 lead is introduced into the body. Subjects that do not have an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempted will be exited from the study following their implant procedure

unless another Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt is scheduled. Adverse events, device deficiencies and deviations must be documented before the subject is exited.

Attain Stability Quad MRI SureScan LV Lead (Model 4798) Attempted but Not Implanted

An Attain Stability Quad MRI SureScan LV Lead (Model 4798) that is inserted into the body that is not successfully placed will be considered an unsuccessful Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt. Note: An unsuccessful implant itself is not considered an AE. Adverse Events occurring during an unsuccessful implant (e.g. dissection, perforation) will be recorded and classified. Subjects with an unsuccessful Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt will be followed until procedure or system related AEs have been resolved or are deemed unresolvable with no further action planned.

15.8.2.3. CRT System Testing and Programming During Implant

Prior to connecting the leads to the CRT can, initial electrical measurements will be taken using the Analyzer (Model 2290 or market released equivalent) to confirm adequate pacing thresholds (PCTs) prior to closing the pocket per the site's standard testing method. These PCTs will be collected on the same vector, at two timepoints once the lead is fixated and prior to connecting the leads to the can using the Analyzer. The timepoints are as follows;

1.) Prior to slitting the cannulation catheter – Collect the first PCT using the Analyzer after the lead is fixated and the guidewire/stylet has been pulled back proximal to the helix and electrodes.

2.) Post slitting the cannulation catheter – Collect the second PCT using the Anlyzer after the lead is fixated and following slitting of the cannulation catheter.

These PCT measurements will be collected on the CRF. This data will only be collected if an Attain Stability Quad MRI SureScan LV Lead (Model 4798) is successfully placed.

Pacing voltage thresholds are measured to determine whether the underlying myocardium will respond effectively to pacing and to evaluate lead stability in the cardiac vein. It is required to perform LV pacing threshold measurements during implant using the pacing threshold test at a 0.5ms pulse width. It is recommended to begin at 2.5 Volts and decrease amplitude after at least 3 pulses until capture is lost. If there is no capture at 2.5 V; stop the test and repeat at a higher voltage using the 0.5ms pulse width. The lowest amplitude where capture consistently occurs is the pacing threshold value. Collect data using the Analyzer (Model 2290 or market released equivalent).

It is recommended that physicians locate a final LV pacing site that can be captured using less than or equal to 2.5 V at 0.5ms, R-wave sensing of at least 4.0 mV, and does not cause diaphragmatic stimulation at 10V at 0.5ms. For additional details regarding the left ventricular leads and implant tools, refer to the respective technical manuals provided with each product.

Individual patient venous anatomies as well as pathologies present in the left ventricular myocardium are factors that will influence LV lead placement. Therefore, the best cardiac vein lead electrode location to stimulate the LV may vary for each patient.

15.8.2.4. Final Lead Placement Data Collection

Following fixation and once the final position of the lead is determined, collect a venous image of the final placement of the lead. A copy of the venous image will be submitted to Medtronic and kept on file at the center.

15.8.2.5. Pre-Hospital Discharge CRT System Testing and Programming

The following electrical testing will be performed using the implanted CRT-P or CRT-D device and the device programmer once the leads are connected to the CRT-P or CRT-D and pre-hospital discharge:

Lead Impedance

- Collect LV Lead Impedances using Vector Express on all vectors
- Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Phrenic Nerve Stimulation (PNS)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

Other data collected prior to hospital discharge following the implant includes;

- Rationale for selecting specific LV lead pacing vector for final programming
- Final device interrogation/save-to-media
- AE Assessment
- Study deviations
- Device deficiencies

15.9. 3 Months Post-Implant (remote or in office visit)

The 3 month scheduled follow-ups may be done remotely or inoffice. For remote visits, CareLink transmissions may substitute device interrogations. The following procedures will be completed and data will be collected at the 3 month Follow-up visit;

Lead Impedance

- Obtain LV Lead Impedance Test for the final programmed vector
- Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Obtain PCTs at 0.5ms pulse width on the final programmed vector
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Retain printouts at the site

Phrenic Nerve Stimulation (PNS) (in office visit only)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

- NYHA classification
- Final device interrogation/save-to-media (or CareLink transmission)
- AE Assessment
- Study deviations
- Device deficiencies

15.10. 6 Months Post-Implant (in office visit)

The following procedures will be completed and data will be collected during the 6 months in office Follow-up visit.

Lead Impedance

- Collect LV Lead Impedances using Vector Express on all vectors
- Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Phrenic Nerve Stimulation (PNS)

- Test for presence of PNS at 8.0V at 0.5ms on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can
- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If at any tested vector PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

- NYHA classification
- Patient Global Assessment
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Rationale for selecting specific LV lead pacing vector for final programming
- Final device interrogation/save-to-media
- AE Assessment
- Study deviations
- Device deficiencies

15.11. 12 Months Post-Implant (in office visit)

The following procedures will be completed and data will be collected during the 12 month in office Follow-up visit.

Lead Impedance

- Collect LV Lead Impedances using Vector Express on all vectors
- Perform a manual LV Lead Impedance Test for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Perform PCTs at 0.5ms pulse width using Vector Express on all 16 vectors
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Perform a manual PCT test at 0.5ms pulse width for missing Vector Express values on vectors LV1 to RVcoil/Can, LV2 to RVcoil/Can, LV3 to RVcoil/Can, LV4 to RVcoil/Can and the final programmed vector
- Retain printouts at the site

Phrenic Nerve Stimulation (PNS)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

- NYHA classification
- Patient Global Assessment
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Rationale for selecting specific LV lead pacing vector for final programming
- Final device interrogation/save-to-media
- AE Assessment
- Study deviations
- Device deficiencies

15.12. Recurring 6 Month Follow-ups (remote or inoffice visit)

After the 12 Month Follow-Up visit, subjects will be seen every 6 months. These scheduled follow-ups are considered "Recurring 6 month follow-up visits". These scheduled follow-ups may be done remotely or inoffice. For remote visits, CareLink transmissions may substitute device interrogations. The following procedures will be completed during these visits:

Lead Impedance

- Obtain LV Lead Impedance Test for the final programmed vector
- Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Obtain PCTs at 0.5ms pulse width on the final programmed vector
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- Retain printouts at the site

Other Data Collection

- NYHA classification
- Final device interrogation/save-to-media (or CareLink transmission)
- AE Assessment
- Study deviations
- Device deficiencies

15.13. Device Interrogation/Save-to-Media

For the implant and follow-up visits, a final "Interrogate All" device interrogation file (.pdd) must be obtained and saved in a digital format (Save-to-Media). Store one copy of the save-to-media at the site and send a copy to Medtronic. Do not clear device data.

A device interrogation (final "Interrogate All") and Save-to-Media should also be completed at the time of study exit (prior to 6 month visit), a system modification (initial and final "Interrogate All"), and in the case of a death (where possible).

15.14. System Modifications

A system modification will be reported in the event the device and/or leads require invasive modification (e.g. generator or lead explant, generator or lead replacement, lead repositioning, etc.). In the event of a system modification, regardless of outcome of the modification, subjects should remain in the study

when possible and the follow-up visit schedule for the subject will remain unchanged. For a system modification the following information/activities are required to be collected:

- Modification or replace/explant date
- Reason for modification
- Information on device or lead modified
- Information on any replacement device(s)
- Final device interrogation/save-to-media
- Study deviations
- AEs and device deficiencies (as applicable)

It is recommended that all explanted Medtronic products (device, leads, etc.) are returned to Medtronic for analysis per local process and when permissible by local laws and regulations.

In the event that subject has a re-attempt after a previous unsuccessful system modification, the subsequent attempt(s) must be reported via CRF as separate system modifications.

Attain Stability Quad MRI SureScan LV Lead (Model 4798) repositioned or replaced with another Attain Stability Quad MRI SureScan LV Lead (Model 4798)

If the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is repositioned or replaced, the following LV lead electrical tests and data collection must be completed:

Lead Impedance

- Obtain LV Lead Impedance Test for the final programmed vector
- Perform a manual test for a missing value
- NOTE: Retain printouts at the site

Pacing Capture Thresholds (PCT)

- Obtain a PCT at 0.5ms pulse width using Vector Express on the final programmed vector
- Perform a manual test for a missing value
- NOTE: A one time manual reprogramming the pulse width to 0.5ms will be required (Out of the box pulse width is set at 0.4ms)
- NOTE: Retain printouts at the site

Phrenic Nerve Stimulation (PNS)

- Test for presence of PNS at 8.0V at 0.5ms on final programmed vector
- NOTE: If PNS is present at 8.0V at 0.5ms, measure the PNS threshold at 0.5ms
- NOTE: PNS observed during this testing will not be considered an AE

Other Data Collection

- Record the reason why the final configuration was selected for final programming
- Record any programming changes to the LV lead apart from the LV lead pacing vector since the last visit and provide rationale for the change(s)

Attain Stability Quad MRI SureScan LV Lead (Model 4798) capped or explanted without replacement with another Attain Stability Quad MRI SureScan LV Lead (Model 4798)

If the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is capped or explanted without replacement while the subject is in the study, subjects will continue to be followed per their original follow-up schedule for safety monitoring until study closure. LV lead electrical testing and interrogation files will not be required at follow-ups for subjects without the full protocol required system implanted.

Explant of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the Medtronic CRT-P or CRT-D device without replacement with another Attain Stability Quad MRI SureScan LV Lead (Model 4798) and Medtronic CRT-P or CRT-D device

Subjects who have their Attain Stability Quad MRI SureScan LV Lead (Model 4798) and Medtronic CRT-P or CRT-D device explanted without replacement during a system modification procedure should be exited from the study as soon as all system related and/or system modification procedure related AEs are resolved. If no system or procedure related AEs are present at the conclusion of such a system modification procedure, the subject should be exited immediately.

Medtronic CRT-P or CRT-D device explanted without replacement, Attain Stability Quad MRI SureScan LV Lead (Model 4798) remains implanted

If the Medtronic CRT-P or CRT-D device is explanted and a replacement device will be implanted, all attempts should be made to replace with another Medtronic CRT-P or CRT-D device. In the event that an explanted Medtronic CRT-P or CRT-D device cannot be replaced with a new Medtronic CRT-P or CRT-D device, subjects who still have an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted will continued to be followed for safety monitoring in person per their original follow-up schedule until study closure. Events related to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) should be reported. Left ventricular lead electrical testing will not be required at follow-ups for subjects without the full protocol required system implanted. In an event that a second Attain Stability Quad MRI SureScan LV Lead (Model 4798) was implanted as a result of an Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complication, the subject will be followed for safety, however the second implanted Attain Stability Quad MRI SureScan LV Lead (Model 4798) will not be included for the analyses of study objectives except reportable system related adverse events.

15.15. Study Exit

Study Exit is defined as the moment when a subject officially stops participating in the study. Date and reason for subject exit must be reported to Medtronic at the earliest opportunity.

Subjects will be exited from the study for any of the following situations:

- Study completed
- Subject lost to follow-up
- Subject did not meet eligibility criteria and was not yet implanted with an Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- Subject did not have a successful implant and no attempt at re-implant is made
- Subject did not provide consent or data protection authorization, as required by law
- Subject chooses to exit (i.e. revokes consent)
- Investigator withdraws subject

Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing system- and procedure-related AEs are resolved, unresolved with no further actions planned, or 30 days post the 6 month visit, whichever occurs first. Following exit, subjects will continue to receive standard medical care. There will be no further required study-related follow-up visits for these subjects. All data through the time of the subject's exit will be available for data analyses.

If possible, the following procedures should be performed / data collected at the exit visit:

- Report the reason for exit
- Final interrogation file (or CareLink transmission) for exits occurring prior to the 6 month visit
- Study deviations
- AEs and device deficiencies (as applicable)

After subjects are exited from the study they should receive standard medical care and should be managed and followed per physician discretion.

15.15.1. Study Completed

All subjects will be followed until FDA Pre-Market Approval (PMA) of the Attain Stability Quad MRI SureScan LV Lead (Model 4798). Medtronic will notify sites when the study is complete. Upon exiting subjects, if the current follow-up visit and exit visit are combined, then both the follow-up CRF and a Study Exit CRF need to be completed but only one device interrogation/save-to-media needs to be completed and collected. If AEs are unresolved at time of exit, it should be noted on the AE CRF that the AE is unresolved at time of study exit.

15.15.2. Lost to Follow-up

In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be recorded. In addition, follow the regulations set forth by the governing IRB or EC.

15.15.3. Study Exit Upon Sponsor Request

A subject must be exited from the study if the sponsor suspends study enrollment and a subject has signed the ICF but no implant attempt of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) has occurred (see Section 15.8.2.2).

15.16. Subject Withdrawal or Discontinuation

15.16.1. Subject Chooses to Exit (i.e. revokes consent)

A subject can withdraw from the study at any time. If the subject wishes to exit from the study (i.e. the subject revokes consent), the site is required to document the reason for exit on the Exit CRF. In addition, study sites shall follow the regulations set forth by the governing Ethics Committee. For countries following ISO 14155, permission may be requested to follow up with the patient outside of the study due to withdrawal based on problems related to the investigational feature safety or performance. If possible, the following data should be collected prior to subject withdrawal:

- Report the reason for subject withdrawal
- Final device interrogation/save-to-media
- Study deviations
- AEs and device deficiencies (as applicable)

15.16.2. Investigator Withdraws Subject

No subjects should be withdrawn by investigators unless compelling medical justification is present. It is recommended investigators discuss any withdrawals with the study sponsor prior to exiting subjects. If

an Investigator withdrawal is necessary, the following data should be collected prior to subject withdrawal if possible:

- Report the reason for subject withdrawal
- Final device interrogation/save-to-media
- Study deviations
- AEs and device deficiencies (as applicable)

The following are reasons for investigator-initiated subject withdrawal;

Medical Necessity

A subject may be exited from the study if an investigator feels it is necessary to withdraw the subject from the study due to a medical condition or other reason. In such cases, the subject will be notified and provided an explanation regarding the reasons for the study exit.

Explant of Medtronic CRT-P or CRT-D Device and Attain Stability Quad MRI SureScan LV Lead (Model 4798)

Subjects in which the Attain Stability Quad MRI SureScan LV Lead (Model 4798) and the Medtronic CRT-P or CRT-D device are explanted without replacement (i.e., subject no longer has a Medtronic CRT-P or CRT-D device and an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted) shall be exited from the study (refer to Section 15.8.2.2). Subjects exposed to an Attain Stability Quad MRI SureScan LV Lead (Model 4798) through a lead attempt must be followed through at least one month or until all implant related AEs (system-, and/or procedure-related) have resolved or are unresolved with no further actions planned. Subjects who have either an Attain Stability Quad MRI SureScan LV Lead (Model 4798) (active or not active) or a Medtronic CRT-P or CRT-D device implanted will continued to be followed for safety until study completion.

Attain Stability Quad MRI SureScan LV Lead (Model 4798) Not Implanted

Subjects that are not anticipated to have an implant attempt (e.g. do not meet inclusion/exclusion criteria) must be exited from the study. Subjects that have a CRT system implant attempt, but who do not have an Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempted (See Section 15.8.2.2 for definition) will be exited from the study following their procedure unless an Attain Stability Quad MRI SureScan LV Lead (Model 4798) attempt is scheduled. If this attempt is more than 30 days from the baseline assessment, verification of the baseline data must be completed prior to a subsequent implant attempt.

Subjects with an unsuccessful Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt will be followed at pre hospital discharge and one month unless there are ongoing implant related AEs (system- and/or procedure related), in which case they will be followed beyond one month until the implant related (i.e., system-, and/or procedure related) AEs have been resolved or are considered unresolved with no further actions planned. The subjects may be followed via a clinic visit or by phone contact. In geographies where the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is market-released, subjects will be exited from the study after the assessment of implant procedure or CRT system related AEs if the initial attempt of one Attain Stability Quad MRI SureScan LV Lead (Model 4798) model was unsuccessful. The subject may undergo implant attempts with any market released LV lead that provides the best benefit to the patient, but data collection on these subsequent attempts will not be required as these subjects will be considered exited from the study.

15.17. Assessment of Efficacy

The primary efficacy objective is based on the pacing capture threshold data collected as discussed in Section 19.1.

15.18. Assessment of Safety

The primary safety objective is based on the Adverse Event data collected. Further information on the collection of Adverse Events is discussed in Section 17.1.1.

15.19. Recording Data

The study will collect data using Oracle Clinical, an electronic data management system for clinical studies. Sites will enter data onto CRFs within the Oracle Clinical database.

Data reported on the CRFs shall be derived from source documents, which may include worksheets, patient medical records, programmer printouts and device interrogation/save-to-media files. These source documents must be created and maintained by the investigational site team. Further detail on data management is provided in Section 21.2.

15.20. Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the Clinical Investigation Plan or the Clinical Trial Agreement.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. In all geographies, prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported to Medtronic regardless of whether they are medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The deviation must be recorded in Oracle Clinical with an explanation for the deviations. In the occurrence of a corrupted device interrogation/save-to-media file, Medtronic will request a deviation to document that a readable device interrogation/save-to-media file is unavailable.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB/EC as well as Medtronic as soon as possible but no later than five (5) working days, or according to local requirements. Reporting of all other study deviations should comply with IRB/EC policies and/or local laws and deviations must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, and terminate the study). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic may provide site-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

16. Risks and Benefits

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of the product, from the research and development phase through the study phase and market release. The risk analysis process for the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is being performed in accordance with ISO 14971, and will ensure that the level of risk has been reduced as low as possible and is acceptable prior to starting the Attain Stability Quad Clinical Study.

Potential Risks

Standard risks associated with the medical device used in this study, an analysis of Adverse Device Effects and a history of modification or recall of device under investigation or equivalent devices are listed in the Instruction for Use Manual or Clinical Manual.

The potential adverse events (listed in alphabetical order) related to the use of transvenous leads inlcude, but are not limited to, the following conditions:

- Air embolism
- Avulsion or other damage to the endocardium, valve, or vein (particularly in fragile hearts)
- Cardiac dissection or perforation
- Cardiac tamponade
- Coronary sinus dissection
- Death
- Endocarditis or pericarditis
- Erosion through the skin
- Extracardiac muscle or nerve stimulation
- Fibrillation or other arrhythmias
- Heart Block
- Heart wall or vein wall rupture
- Hematoma/seroma
- Infection
- Lead conductor fracture or insulation failure
- Lead dislodgement
- Myocardial irritability
- Myopotential sensing
- Pericardial effusion or rub
- Pneumothorax
- Rejection phenomena (local tissue reaction, fibrotic tissue formation)
- Threshold elevation or exit block
- Thrombosis
- Thrombotic embolism

Additional potential adverse events related to the lead and the programmed paramenters include, but are not limited to, the following:

Table 10: Additional adverse events related to the lead and programmed parameters

Potential adverse event	Indicator of potential adverse event	Corrective actions to consider
Lead dislodgement[i]	Intermittent or continuous loss of capture or LV EGM signal integrity (including sensing)[i]	Reprogram the LV pacing polarity. Reposition the lead.
Lead dislodgement[i]	Intermittent or continuous oversensing	Reprogram the LV pacing polarity. Reposition the lead.
Lead conductor fracture	Intermittent or continuous loss of capture or LV EGM signal integrity (including sensing)[i]	Replace the lead. Reprogram the LV pacing polarity.
Lead conductor insulation failure	Intermittent or continuous loss of capture or LV EGM signal integrity (including sensing)[i]	Replace the lead. Reprogram the LV pacing polarity.
Threshold elevation or exit block	Loss of capture[i]	Adjust the implantable device output. Reprogram the LV pacing polarity. Replace or reposition the lead.

[I] Transient loss of capture or LV EGM signal integrity (including sensing) may occur following surgery until lead stabilization takes place. If stabilization does not occur, lead dislodgement may be suspected.

Implant techniques that may damage the lead include, but are not limited to, the following techniques:

Table 11: Implant Techniques that may damage the lead

Implant techniques that may damage the lead	Possible effects on the lead	Corrective action to consider
Forcing the lead through the introducer/delivery system	Electrode, conductor coil, or insulation damage	Replace the lead.
Use of too medial of an approach with venous introducer resulting in clavicle and first rib binding	Conductor coil fracture, insulation damage	Replace the lead.
Using too stiff a stylet	Conductor coil/insulation perforation	Replace the lead.
Puncturing the periosteum or tendon when using subclavian introducer approach resulting in binding	Conductor coil fracture, insulation damage	Replace the lead.
Advancing the lead through the non-coronary central access veins without the stylet or guide wire fully inserted	Tip distortion or insulation perforation	Replace the lead.
Inserting the proximal end of the guide wire through the lead tip seal without using the guide wire insertion tool	Lead tip seal damage or conductor coil/insulation damage	Replace the lead.

Subjects who are pregnant may be at increased risk (e.g., radiation exposure, and other unforeseen risk to the fetus), and are excluded from participation in the study. If a subject becomes pregnant during the study, she must notify the physician immediately. The subject will remain in the study for intention to treat analysis, but the investigator will avoid any procedures that may be determined harmful.

There may be other discomforts and risks related to the CRT-P or CRT-D device, the Attain Stability Quad MRI SureScan LV Lead (Model 4798), and/or this study that are not foreseen at this time. Interactions with concomitant medical treatment are not expected.

The adverse event collection requirements in this study will ensure that risks associated with the study device and the Attain Stability Quad MRI SureScan LV Lead (Model 4798) are adequately monitored.

16.2. Risk Minimization

Medtronic has minimized the risks to the subject by the following:

- Performing required laboratory and pre-clinical testing prior to the Attain Stability Quad Clinical Study; this information is available under separate cover in the RPI with the FDA IDE submission and the CER with the CE-Mark
- Implementing quality control measures into development and production processes
- Providing guidelines for subject selection and evaluation, and subject inclusion and exclusion criteria
- Providing adequate instructions via the Attain Stability Quad MRI SureScan LV Lead (Model 4798) User Manual, training, and labeling

- Selecting implanters that have demonstrated previous experience with implanting CRT-P or CRT-D devices and specifically LV leads
- Selecting investigators that have demonstrated previous experience with the programming, interrogating, and monitoring of CRT-P or CRT-D devices
- After enrollment in the Attain Stability Quad Clinical Study, at each protocol required follow-up, the investigator must interrogate the study device to verify appropriate study device function and to evaluate the subject's health and assess for any AEs

16.3. Potential Benefits

The potential benefits of having the Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted are similar to other LV leads currently available to the public. The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is expected to increase lead stability and reduce the need for patients to undergo an additional procedure to replace a dislodged/displaced lead. Due to the active fixation helix, it may be possible to place the lead in veins of various sizes. There is a possibility that the Attain Stability Quad MRI SureScan LV Lead (Model 4798) may offer no additional benefit over similar LV leads. The information gained from this study could result in the improved management of other CRT patients.

16.4. Risk-Benefit Rationale

The risk-benefit analysis has shown that there are no major additional risks associated with the Attain Stability Quad MRI SureScan LV Lead (Model 4798), other than those associated with the implant, while benefits to the patient are possible. Any residual risk associated with this study is considered low and acceptable.

17. Adverse Event Assessments

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Medtronic has established procedures in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information. This study is conducted in accordance with these procedures and regulations.

Data collected in this study may be used in support of global regulatory approvals. Since the safety reporting requirements and classification systems vary for each regulatory agency, requirements from all geographies are taken into account for the collection and reporting of safety information. Adverse Events and Device Deficiencies will be reported in all geographies.

17.1. Adverse Event and Device Deficiency Assessment

17.1.1. Adverse Events

Adverse Event definitions are provided in Table 12. The following AEs will be collected throughout the study duration, starting at the time the informed consent form is signed:

- All procedure related AEs
- All system related AEs
- All accessory related AEs
- All cardiovascular related AEs
- All Serious Adverse Events (SAEs), regardless of relatedness

Reporting of these events to Medtronic will occur on an AE Form, including date of AE, treatment, resolution, assessment of both the seriousness of the AE and the relatedness to the investigational device or procedure. Each AE must be recorded on a separate AE eCRF. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. In addition, AEs impacting users or other persons, Non-subject Adverse Events, (reportable per ISO 14155) will be collected.

In all geographies, Unavoidable AEs, listed in Table 12, need not be reported unless the AE worsens or is present outside the stated timeframe post-implant.

For AEs that require immediate reporting (see Table 14), initial reporting may be done by contacting the study sponsor per the sponsor contact information. The original completed AE CRF must be submitted to Medtronic as soon as possible.

Any medication, whether cardiovascular or not, associated with the treatment of an AE must be reported. Medication changes that are not related to adverse events will not be collected.

Subject deaths are also required to be reported. Refer to Section 17.4 for Subject Death collection and reporting requirements.

17.1.2. Device Deficiencies

Device deficiency (DD) information will be collected throughout the study and reported to Medtronic. Note that DDs that result in an Adverse Device Effect (ADE) to the subject should be captured as an AE only. Device Deficiencies that did not lead to an AE but could have led to a Serious Adverse Device Effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting (see Table 14). For DDs that require immediate reporting, initial reporting may be done by contacting the study sponsor per the sponsor contact information.

17.1.3. Event Updates and Resolution

For any changes in status of a previously reported AE (i.e. change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE form. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject dies or exits the study, or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to their 6 month visit, all efforts should be made to continue following the subject until all unresolved system or procedure related adverse events, as classified by the investigator, are resolved or unresolved with no further actions planned.

At the time of study exit, all collected AEs with an outcome of ”Unresolved” must be reviewed and an update to the original AE must be reported. At a minimum, if there are no changes to the description, relatedness, test and procedures or actions taken, the outcome must be updated to reflect “Unresolved at time of study exit”.

17.2. Definitions/Classifications

Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system, and includes but is not restricted to: the CRT-P or CRT-D device, the RA, RV or LV leads, the programmer, and implant tools.

Table 12: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. (ISO 14155:2011, 3.2)
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. (ISO 14155:2011, 3.1)
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors and inadequate labeling (ISO 14155:2011, 3.15)
Relatedness	
Procedure Related	An Adverse Event that is directly related to the implantation or surgical modification of the system. NOTE: In general, this excludes events that are inherent to any surgical procedure (e.g. anesthesia complications) as well as indirect subsequent consequences of the procedure (e.g. reaction to pain medication).

System Related (includes all implantable components and features, associated introduction tools, operational and installed software and programmers as defined in the Clinical Investigation Plan)	An adverse event that results from the presence or performance of any component of the system. Device-related: An adverse event that results from the presence or performance (intended or otherwise) of the device. RA lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the RA lead. RV lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the RV lead. LV lead-related: An adverse event that results from the presence or performance (intended or otherwise) of the LV lead. a) LV Lead Fixation-related: An adverse event that results from the presence or performance of the side-helix.
Accessory Related	Programmer Related: An adverse event that results from the presence or performance (intended or otherwise) of the programmer Implant tool-related: An adverse event that results from the presence or performance (intended or otherwise) of the implant tool.
Cardiovascular Related	An Adverse Event relating to the heart and the blood vessels or the circulation (e.g. Atrial Fibrillation, Myocardial Infarction, stroke, perivascular disease)
Heart Failure Related	An adverse event related to worsening heart failure signs and symptoms such as hypervolemic and hypovolemic status requiring the administration, alteration, adjustment or augmentation of HF therapy (diuretics, inotropes and/or vasodilators etc.) or the utilization of ultrafiltration devices.
MRI Related	An adverse event which is caused by the interaction between the pacing system and the MRI system that occurs during the MRI procedure and up through the one-month post-MRI/waiting period follow-up visit.

Not Related	Relationship to the device or procedures can be excluded when: ▪ The event is not a known side effect of the product category the device belongs to or of similar devices and procedures; ▪ The event has no temporal relationship with the use of the device or the procedures; ▪ The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; ▪ The discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure) do not impact the serious event; ▪ The event involves a body-site or an organ not expected to be affected by the device or procedure; ▪ The serious event can be attributed to another cause (e.g., an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors); ▪ The event does not depend on a false result given by the device used for diagnosis (when applicable); ▪ Harms to the subject are not clearly due to use error; ▪ In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The event is associated with the device or study procedures beyond reasonable doubt when: ▪ The event is a known side effect of the product category the device belongs to or of similar devices and procedures; ▪ The event has a temporal relationship with device use/application or procedures; ▪ The event involves a body-site or organ that the device or procedures are applied to or the device or procedures have an effect on; ▪ The serious event follows a known response pattern to the medical device (if the response pattern is previously known); ▪ The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure) impact on the serious event (when clinically feasible); ▪ Other possible causes (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug, or treatment) have been adequately ruled out; ▪ Harm to the subject is due to error in use; ▪ The event depends on a false result given by the device used for diagnosis (when applicable); ▪ In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Seriousness	
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. (ISO 14155:2011, 3.37)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011, 3.36)
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. (ISO 14155:2011, 3.42)

Complication	An adverse event that includes the following is considered a complication: • Results in death, • Involves any termination of significant device function, or • Requires an invasive intervention Non-invasive (21 CFR 812.3 (k)): when applied to a diagnostic device or procedure, means one that does not by design or intention: Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os *Note* (FDA): Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive. *** Only system or procedure related AEs will be classified as complication or observation
Observation	Any Adverse Event that is not a complication. *** Only system or procedure related AEs will be classified as complication or observation

<table>
<tr><th colspan="2">Other</th></tr>
<tr><td>Unavoidable Adverse Event</td><td>An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator's opinion, including, but not limited to:
<table>
<tr><th>Event Description</th><th>Timeframe (hours) from the Surgical Procedure</th></tr>
<tr><td>Anesthesia related nausea / vomiting</td><td>24</td></tr>
<tr><td>Low-grade fever (<100°F or 37.8°C)</td><td>48</td></tr>
<tr><td>Pocket site / Incisional pain</td><td>72</td></tr>
<tr><td>Mild to moderate bruising / ecchymosis</td><td>168</td></tr>
<tr><td>Sleep problems (insomnia)</td><td>72</td></tr>
<tr><td>Back pain related to laying on table</td><td>72</td></tr>
<tr><td>Shoulder pain/discomfort/stiffness related to shoulder immobilization during procedure</td><td>72</td></tr>
</table></td></tr>
</table>

17.3. Reporting of Adverse Events

17.3.1. Adverse Events and Device Deficiency Classification

All reported AEs and DDs will be reviewed by a Medtronic representative. Adverse Events will be classified according to the definitions provided.

Upon receipt of AEs at Medtronic, a Medtronic representative will review the AE/DD for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize the Medical Dictionary for Regulatory Activities (MedDRA), to assign a MedDRA term for each AE based on the information provided by the investigator.

Regulatory reporting of AEs and DDs that could have led to an SADE will be completed according to local regulatory requirements. Refer to Table 14 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the investigator to abide by any additional AE reporting requirements stipulated by the IRB/EC responsible for oversight of the study.

APPENDIX 1 contains the Foreseeable Adverse Event List (FAL), which is a list of adverse events related to the system or procedure that have been observed in previous studies and may be experienced by subjects. This list may help to assess if an AE is unanticipated in nature.

For emergency contact regarding a UADE, SAE and/or SADE, contact a Attain Stability Quad Clinical Study representative immediately (refer to the study contact list provided in the site's study documents binder/investigator site file or refer to the Sponsor Contact Information section provided in the CIP).

Adverse Events and Deaths will be classified according to the standard definitions as outlined below:

Table 13: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Device, RA Lead, RV Lead, LV Lead, Implant Tool(s), Programmer, Procedure, Cardiovascular, Heart Failure, MRI
	Sponsor	Device, RA Lead, RV Lead, LV Lead, Implant Tool(s), Programmer, Procedure
Seriousness	Investigator	SAE
	Sponsor	SAE, UADE/USADE, Device Deficiency with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

An independent Clinical Events Committee (CEC) will review and adjudicate, at a minimum, all events classified by the investigator or Medtronic as procedure or system related to determine relatedness and complication or observation classifications. In addition, the CEC will also review and adjudicate all Adverse Events resulting in death.

17.3.2. Adverse Events and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and device deficiencies will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator to abide by the adverse event reporting requirements stipulated by local law and the site's IRB/EC.

Table 14: Reporting Requirements

Serious Adverse Events (SAEs)	
Investigator submit to:	
Medtronic	**Canada:** Investigators are required to report SAEs to the sponsor immediately except for those SAEs that the protocol or other document (e.g. Investigator's Brochure (IB)) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. Medical Devices Regulations, sections 59-61. *A guidance for "immediately" is within 72 hours of the investigator becoming aware of the event; Report to sponsor, without unjustified delay ISO 14155:2011, sec 9.8.b).* **EMEA:** Immediately after the investigator first learns of the event or new information in relation with an already reported event. **All geographies:** Report to the sponsor, without unjustified delay, all serious adverse events.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.

Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Adverse Device Effects (ADEs),	
Investigator submit to:	
Medtronic	**EMEA:** Immediately after the investigator first learns of the event or new information in relation with an already reported event. **All geographies:** Submit in a timely manner after the investigator first learns of the effect.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Serious Adverse Device Effects (SADEs), Unanticipated Adverse Device Effects (UADEs), Unanticipated Serious Adverse Device Effects (USADEs),	
Investigator submit to:	
Medtronic	**US:** Submit as soon as possible, but no later than within 10 working days after the investigator first learns of the event. (21 CFR 812.150(a)(1)) **Canada:** SADEs on the patient, the user or any other person must be reported to the Sponsor within 72 hours after it comes to the attention of the qualified investigator. It is recommended for the investigator to report safety events as soon as possible but no longer than 15 calendar days." **All geographies:** Immediately after the investigator learns of the event or of new information in relation to an already reported event.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement
Ethics Committee	**All geographies:** Submit to Ethics Committees per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Investigators	**All geographies:** Submit per local reporting requirement.

All other reportable Adverse Events	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the event.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Device Deficiencies with SADE potential	
Investigator submit to:	
Medtronic	**Canada:** DDs that have resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person or could do so were it to reoccur must be reported to the Sponsor within 72 hours after it comes to the attention of the qualified investigator **EMEA:** Immediately after the investigator first learns of the deficiency or of new information in relation with an already reported deficiency. **All other geographies:** Submit or report as required per local reporting requirements.
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
Sponsor submit to:	
Regulatory authorities	**All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	**All geographies:** Submit in a timely manner after the investigator first learns of the deficiency.
Regulatory authorities	**Canada:** any DD that: a. has resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person; These must be reported by Medtronic to the Regulator within 10 days from the date Medtronic becomes aware. or b. could do so were it to reoccur. These must be reported by Medtronic to the Regulator within 30 days from the date Medtronic becomes aware. **All geographies:** Submit to regulatory authority per local reporting requirement.
Ethics Committee	**All geographies:** Submit to Ethics Committee per local reporting requirement.

17.4. Subject Death

17.4.1. Death Data Collection

All subject deaths must be reported by the investigator to Medtronic on an AE form (AE with outcome of death) as soon as possible after the investigator first learns of the death. In case of death, there should be one SAE with the outcome of death reported.

In the event of a subject's death, it is recommended that the implanted system be explanted and returned to Medtronic for analysis whenever possible per local process. Local laws and procedures must be followed where applicable.

System Interrogation Data Recommendations:

- After the subject has died but prior to explant, it is strongly recommended that the system be interrogated and a full summary interrogation (Interrogate All) performed when possible, and saved in a digital format (Save-to-Media). Store one copy of the save-to-media at the site and send a copy to Medtronic.
- Make the device interrogation/save-to-media file before any programming to prevent overwriting information in the device's memory and/or distinguishing between events detected during versus before the explant procedure.
- Recommend obtaining the exact date and time of death as lower temperatures after death can cause ERI and other "event flags" to be stored in the device memory.

If the system is not interrogated, an explanation must be entered on the AE form. For ICD systems, the ventricular tachycardia (VT) and ventricular fibrillation (VF) detection capabilities must be disabled to avoid inadvertent shocks. If any system component is returned to Medtronic, internal return product reporting systems may be used to gather additional information about the returned device/component.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic Attain Stability Quad Clinical Study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records should be sent to the Medtronic Attain Stability Quad Clinical Study team, if available. If an autopsy is conducted, the autopsy report should also be sent to the Medtronic Attain Stability Quad Clinical Study team if available and allowed by state/local law. When the death occurs at a remote site, it is the investigative site's responsibility to attempt retrieval of information about the death. Additionally, device disposition information should be updated. In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to system and/or procedure
- Device interrogation and Save-to-Media (if available)
- Device disposition information
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and allowed by state/local law)

17.4.2. Death Classification and Reporting

Sufficient information will be required in order to properly classify the subject's death. The Investigator shall classify each subject death per the following definitions:

Cardiac Death: A death directly related to the electrical or mechanical dysfunction of the heart.

Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be determined, SCD will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival.

Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support.

Non-cardiac Death: A death not classified as a cardiac death.

Unknown Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

Table 15: Subject Death Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-cardiac, Unknown

The Clinical Events Committee will review all deaths and provide a final adjudication of the death classification.

Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements.

17.5. Product Complaint Reporting

Product complaint reporting and vigilance reporting are applicable and AEs related to any market-released device during the study must be reported. The reporting of product complaints is not part of the Attain Stability Quad Clinical Study and should be done in addition to the AE reporting requirements. Refer to local regulations for reporting requirements.

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

- Abuse: Abnormal use (definition acc. #4.1 of Meddev 2.12-1 rev8)
- Misuse: Use error (definition acc. #4.20 of Meddev 2.12-1 rev8)

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the regulatory authorities (e.g. Competent Authority) as applicable for the following incidents immediately upon learning of them:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
    - Life-threatening illness or injury
    - Permanent impairment of a body function or permanent damage to a body structure
    - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

18. Data Review Committees

18.1. Clinical Events Committee

The study will utilize a Clinical Events Committee (CEC). At regular intervals, an independent CEC will review events and adjudicate at a minimum all system, and procedure-related events. Additionally, the CEC will provide an adjudication of the death classification for all reported deaths.

The CEC will consist of a minimum of three (3) non-Medtronic-employed physicians that are not participating investigators for the study, including a CEC chairperson.

Medtronic personnel may facilitate and participate in CEC meetings but will be non-voting members.

For AEs and deaths reviewed by the CEC, Medtronic will provide the CEC with the Investigator's description and classification and supportive documentation (when available). The CEC is responsible for reviewing the Investigator's assessment and supportive documentation (when available), reviewing applicable definitions, and determining final classifications for all adjudication parameters. For AEs, classification includes system/procedure relatedness and complication or observation. Additionally, the CEC will provide an adjudication for all reported deaths, including system/procedure relatedness and cardiac relatedness.

If the CEC disagrees with the investigator's classification of the event, the difference will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the CRF documenting the AE will be updated accordingly.

If the investigator does not agree with the CEC's adjudication classification, both determinations will be provided within the final report; however the CEC's adjudication will be used for data analysis. The disagreement will also be included in reporting to ethics committees and regulatory authorities, if required.

18.2. Data Monitoring Committee

A Data Monitoring Committee (DMC) will not be utilized for this study considering:

- An independent CEC will be formed to adjudicate at minimum all system and procedure related events and all deaths.
- This study does not meet FDA's recommended criteria (Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees) for when a study should use a DMC, primarily because the study is not evaluating the effectiveness of a treatment intended to prolong life or reduce the risk of a major adverse health outcome.
- As a result of risk analysis and mitigation efforts as outlined in Section 16, any residual risk associated with this study is considered low and acceptable.
- The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is a modification of the currently market approved Attain Performa lead Models 4298, 4398, and 4598 is a modification of the currently market approved Model 4396 LV lead. The Attain Stability Quad lead Model 4798 has a similar electrode spacing as the Attain Performa lead Models 4298, 4398, and 4598.
- Study will be conducted under FDA oversight via an investigational device exemption (IDE).

19. Statistical Design and Methods

This section presents statistical considerations for the study design and provides a high-level description of planned analysis and reporting. More details will be given in a separate Statistical Analysis Plan (SAP) that will be completed before data freeze for the primary objective analysis. Any deviation to the pre-specified statistical analyses will be noted in the study report. The analysis of the study objectives will be completed when the sample size requirements (see Table 18) for all the study primary and secondary objectives are met. An interim analysis will be conducted when 360 subjects are enrolled in the study. This interim analysis is specifically designed for one of the secondary objectives (details in Section 19.2.2).

19.1. Primary Objectives

19.1.1. Primary Safety Objective

Objective

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be considered safe if the probability of subjects free of Model 4798 lead-related complications at 6 months post-implant is greater than 87% (i.e., the lower bound of a one-sided 97.5% confidence interval must be greater than 87%).

Hypothesis:
H_0: $S_{(6\text{-month})} \leq 87\%$
H_1: $S_{(6\text{-month})} > 87\%$

where $S_{6\text{-month}}$ is the probability that a subject remains free from Model 4798 lead related complications through 6 months since implant.

Endpoint Justification

The study primary safety endpoint is Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complications. All reported system and procedure-related AEs will be reviewed by an event review committee for LV lead relatedness and severity (see Section 18.1).

Utilizing lead related complication free survival probability to evaluate lead safety performance is widely accepted across cardiac device manufacturers and in the medical literature. Current already market-released Quadripolar LV lead 6-month safety performance is summarized in Table 16. The population performance of the Attain Stability Quad MRI SureScan LV Lead (Model 4798) is expected to be similar to the Medtronic Attain Performa Model 4298 lead.

Table 16: Safety Performance of Market Released Quadripolar Lead

	Medtronic Attain Performa	St. Jude Medical Quartet[22]	Boston Scientific ACUITY X4[23]
6-month LV Lead Complication Free Survival Probability Estimate	Model 4298 (Canted): 96.0% Model 4398 (Straight): 98.8% Model 4598 (S-shape): 96.2%	96% at 3 months	Straight: 96.5% Spiral: 98.5%

Statistical Analysis Methods

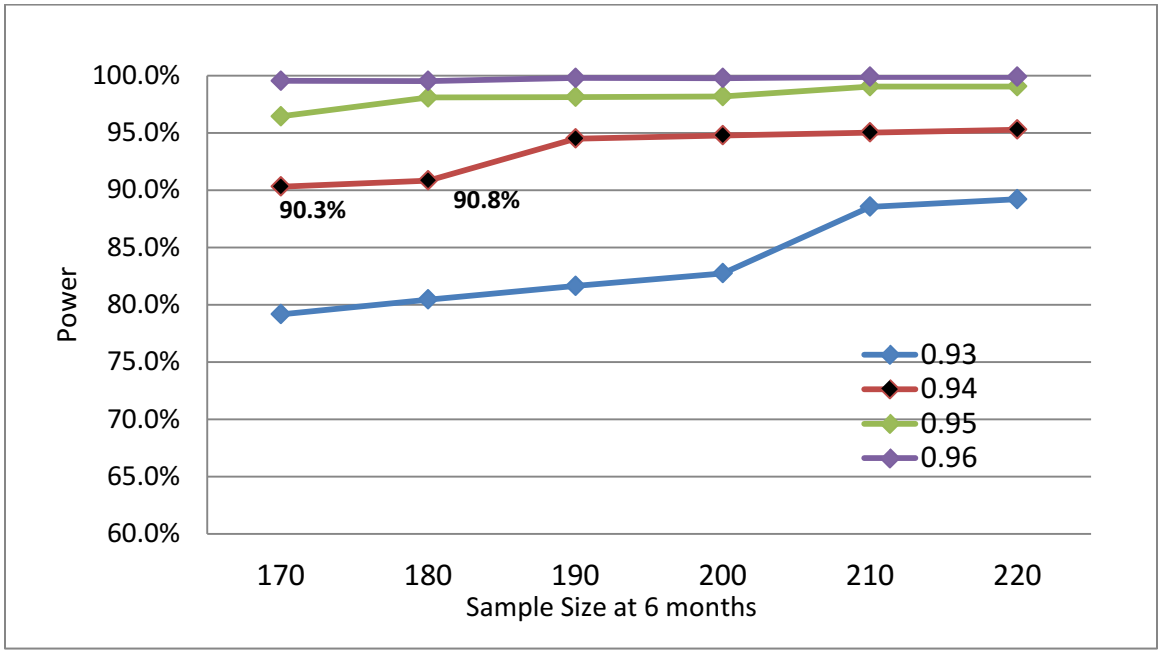
The primary objective will be analyzed using the time-to-first event Kaplan-Meier survival analysis method. Time 0 will be the day a subject undergoes the implant procedure of a Attain Stability Quad MRI SureScan LV Lead (Model 4798), which will be independent of success status of this implant procedure. Event date is the onset date of a subject's first complication that is related to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) according to CEC adjudication. Subjects who undergo an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt and do not experience any LV lead related complications will be censored at the time of their last known exposure to the Attain Stability Quad MRI SureScan LV Lead (Model 4798) for the survival analysis. For any lost-to-follow up subject, the last contact date will be used as the censor date. The 1-sided 97.5% confidence limit lower bound for the survival probability at 6 months (183 days) will be calculated using the log-log survival function approach (Kalbfleisch and Prentice 2002).

Sample Size Consideration

The primary safety objective performance criterion is set to be identical to Medtronic's Attain Performa Clinical Study (IDE Number: G120213). Therefore, the sample size calculation assumptions are derived based on the Model 4298 lead study results. The Attain Performa Model 4298 lead reported a 6-month complication free survival probably of 96.0%, with 97.5% Confidence Lower Limit of 94.3% (PMA-s clinical report).

The binomial calculation (Z-test) is used for initial sample size estimation. In order to preserve the overall study power, a type II error less than 10% was used for the sample size calculation. A sample size of 170 subjects completing their 6-month visit achieves greater than 90% power to detect a difference of 7% using the one-sided binomial test. The target significance level is 0.025. These results assume that the population proportion under the null hypothesis is 87% with an expected value of 94% (Figure 5). To account for 15% attrition, the enrollment size for this objective is 200.

Figure 5: Primary Safety Objective Sample Size Consideration by Difference Performance Assumption



Determination of Patients / Data for Analysis

All consented subjects who undergo an Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt will be included in the analysis cohort. If a patient experiences multiple Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant procedures during the study, the analysis cohort will only consider the first procedure. In the event multiple complications occur, the survival analysis endpoint is reached when the first Attain Stability Quad MRI SureScan LV Lead (Model 4798) related complication occurs.

19.1.2. Primary Efficacy Objective #1

Objective

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) will meet the first primary efficacy objective if the proportion of subjects with at least one Attain Stability Quad MRI SureScan LV Lead (Model 4798) pacing vector having a pacing capture threshold (PCT) less than or equal to 2.5 V at 0.5ms pulse width at 6 months post-implant is greater than 80% (i.e., the lower bound of the one-sided 97.5% confidence interval must be greater than 80%).

Hypothesis
H_0: $P1_{6\text{-month}} \leq 80\%$
H_A: $P1_{6\text{-month}} > 80\%$,

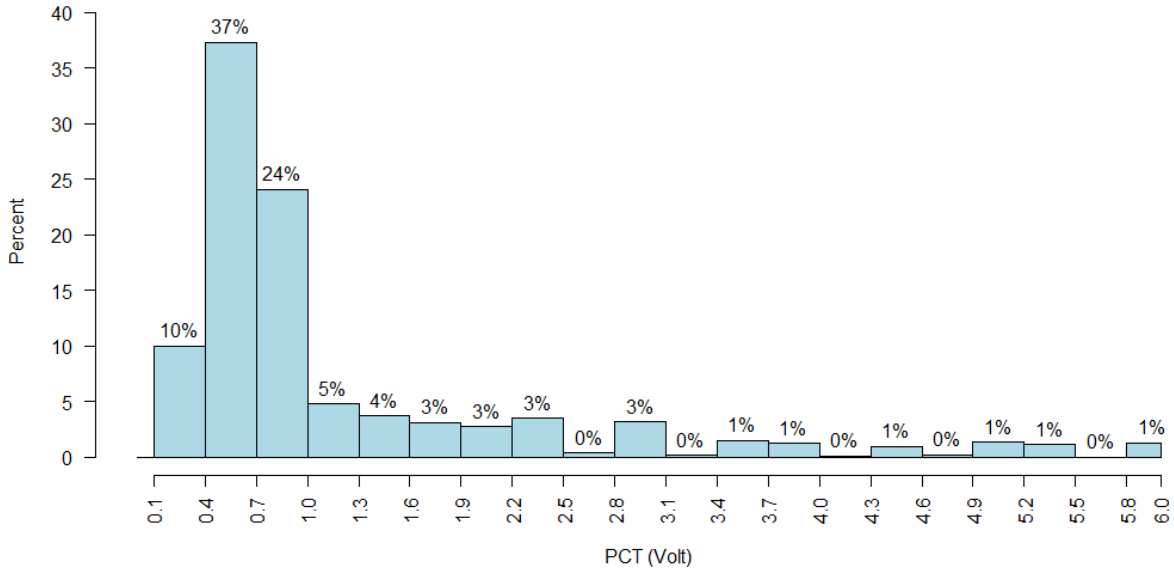
where $P1_{6\text{-month}}$ is the proportion of subjects with pacing voltage thresholds ≤ 2.5V at 0.5ms at 6 months follow-up visit post-implant for at least one LV lead pacing vector.

Endpoint Justification

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is equipped with the identical four electrodes to the Attain Performa LV leads. At the same time, the unique fixation mechanism may cause the distal end of the lead (tip) to be implanted away from the apical region of the heart, and therefore

the PCT may be slightly higher than the values observed in other Quadripolar LV leads. Therefore, we simulated the lead pacing threshold values based on the Attain Performa IDE study data, but excluding the PCT values collected at the most distal electrode. The simulation estimated that 89% of the subjects will achieve this endpoint (Figure 6).

Figure 6: Simulated PCT Distribution



Statistical Analysis Methods

All subjects with valid pacing thresholds measured at the 6 month follow-up visit will be included in this analysis. The proportion of subjects having at least one LV lead pacing vector with voltage thresholds less than or equal to 2.5V will be calculated. The lower bound of the 1-sided 97.5% Confidence Interval will be calculated using the Exact binomial method. Any subject in which no valid pacing threshold value is measured or who has an unable-to-capture result via all LV lead pacing vectors will be reviewed and adjudicated for a possible lead related AE but will not be included for this evaluation if the occurrence is deemed to be a system related event (e.g. lead dislodgement). However, this event may be counted against the safety primary endpoint based on the CEC's final classification.

Sample Size

The primary efficacy endpoint will be analyzed using the Exact binomial method. In order to preserve the overall study power, a type II error less than 10% was used for the sample size calculation. A sample size of 145 subjects achieves 91% power to detect a difference of 0.1 using a one-sided binomial test at a target significance level of 0.025. These results assume that the population proportion under the null hypothesis is 80%, with an expected proportion of 90%.

Determination of Patients / Data for Analysis

All subjects enrolled into this study satisfying the following conditions will be included in this analysis:

- Successfully implanted with a Medtronic Quad CRT-P or CRT-D device and Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- Completed 6-month follow-up visit
- Initially implanted Attain Stability Quad MRI SureScan LV Lead (Model 4798) is active at the 6–month follow-up visit
- At least one available and valid pacing threshold at the 6-month follow-up visit

19.1.3. Primary Efficacy Objective # 2

Objective

The Attain Stability Quad lead will meet the second primary efficacy objective if the proportion of subjects with at least one additional (or second) LV lead pacing vector having a pacing capture threshold less than or equal to 4.0 V at 0.5ms pulse width at 6 months post-implant is greater than 80% (i.e., the one-sided 97.5% lower confidence bound must be greater than 80%).

Hypothesis
H_0: $P2_{6\text{-month}} \leq 80\%$
H_A: $P2_{6\text{-month}} > 80\%$,

where $P2_{6\text{-month}}$ is the proportion of subjects with at least one additional LV lead pacing vector with pacing voltage thresholds ≤ 4.0V at 0.5ms at 6 months post-implant follow-up visit.

Endpoint Justification

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) has 16 LV programmable pacing vectors . Subjects may have the pacing configuration programmed or reprogrammed at each clinic visit. A pacing threshold of 4.0 V will allow an adequate safety margin for programming LV pacing output. The maximum pacing amplitude of the CRT-P or CRT-D devices capable of programming pacing output to any LV lead pacing vector is 8.0V. In actual clinical practice, a less than 3V safety margin is used for the programmed LV lead pacing output in 99% of the patients.

Statistical Analysis Methods

The efficacy endpoint #2 will be analyzed using the Exact binomial method. The proportion of subjects with at least 2 LV lead pacing vectors having voltage thresholds less than or equal to 4.0V at 0.5ms will be calculated. The lower bound of the 1-sided 97.5% Confidence Interval will be calculated using the Exact binomial method. Any subject in which no valid pacing threshold values are measured or with an Unable-to-capture result via all LV lead pacing vectors will be reviewed and adjudicated for possible lead related complications, and therefore may be counted against the study safety endpoint. However, it will be counted as a failure if there is not any additional LV lead pacing vectors (excluding the vector that is already include for the efficacy endpoint #1) are unable to capture with no lead related events reported.

Sample Size

The Attain Performa Model 4298 LV lead observed 97.7% subjects who were able to obtain a non-programmed pacing vector with PCT less than or equal to 4 volts. A sample size of 50 subjects completing the 6 month visit achieves 98% power to detect a difference of 0.18 using a one-sided binomial test at a target significance level of 0.025. These results assume that the population proportion under the null hypothesis is 80%, with the expected proportion of 97%.

Determination of Patients / Data for Analysis

All subjects enrolled into this study satisfying the following conditions will be included in this analysis:

- Successfully implanted with a Medtronic Quad CRT-P or CRT-D device and Attain Stability Quad MRI SureScan LV Lead (Model 4798)
- Completed 6-month follow-up visit
- Initially implanted Attain Stability Quad MRI SureScan LV Lead (Model 4798) lead is active at the 6–month follow-up visit
- At least one available and valid pacing threshold at the 6-month follow-up visit. In the event a subject failed to provide more than one valid pacing threshold value, that subject will be considered as not having at least one additional LV lead pacing with PCT ≤ 4.0V at 0.5ms at 6 months post-implant follow-up visit

19.2. Secondary Objectives

19.2.1. Secondary Objective # 1

Objective - Implant procedure related information: success rate, implant related times

The Attain Stability Quad LV lead implant success rate will be estimated as the number of subjects with Attain Stability Quad MRI SureScan LV Lead (Model 4798) successfully implanted divided by the total number of subjects who had a Attain Stability Quad MRI SureScan LV Lead (Model 4798) implant attempt. A 2-sided 95% Confidence Interval will be calculated using the Exact Binomial method.

The distribution of implant related times will be summarized through statistical summaries such as mean, standard deviation, minimum, median and maximum. Only subjects with the Attain Stability Quad MRI SureScan LV Lead (Model 4798) successfully implanted will be included in this calculation. The total implant time is defined as time from initial incision to final skin closure. Fluoroscopy time is defined as the total time the fluoroscope is imaging. Cannulation time is defined as the time from insertion of the first CS cannulation catheter to the first successful CS cannulation. Successful lead placement time is defined as the time from lead insertion of the successfully placed lead to the time when the lead is placed in its first acceptable pacing location.

19.2.2. Secondary Objective # 2

Objective - 6-month reliability: post implant lead failure modes

The Attain Stability Quad MRI SureScan LV Lead (Model 4798) is a composite of two existing market released Medtronic products. The helix fixation is identical to the Attain Stability LV Lead Model 20066/4796 (market released outside of the US). The remainder of the lead is similar to the Attain Performa LV Lead Model 4298, released worldwide.

Historical datasets will be used as informative priors for lead related complications. More specifically, analysis of all complications related to fixation (helix performance) will use data from the Attain Stability (Model 20066/4796) research study, conducted outside of the US. Analysis of all other lead related complications will use data from the Attain Performa clinical study, conducted globally. Credible intervals will be constructed for each individual failure mode within the two groups.

Historical Data (for secondary endpoints only)

- Fixation-related LV lead complications - Data from the 37 patients who completed 6-month follow up with a successfully implanted 20066 lead in the Attain Stability study will be used as an informative prior.
- All other LV lead-related complications - Data from the 401 patients who completed 6-month follow up in the Attain Performa 4298 study will be used as an informative prior.

These historical datasets will be downweighted such that their effective sample size will not exceed the 9% of the total sample size (i.e at most 37 subjects at 6 months).

Statistical Analysis Methods

The weighted historical data will be incorporated using the power prior method[24]. The weight of the historical data will be adjusted using a loss function[25], which scales from 0 to 1 according to the similarity of the historical and observed data. This loss function adjusts the amount of weight the prior receives. The comparison between historical and observed data will be performed twice, once for each group of complications (fixation-related and all other). The objective of using a loss function with the power prior method is to reduce the influence of an informative prior in the parameter estimation, when the historical data does not agree with the current study data.

If analysis of failure rate shows a high level of agreement between historical and current study data or there is better performance for Attain Stability Quad MRI SureScan LV Lead (Model 4798) compared to historical data, the historical data will be weighted at or near a maximum level (9% of total effective sample size). If the Attain Stability Quad MRI SureScan LV Lead (Model 4798) performs worse than historical data, the historical data will receive very little or zero weight. Note that there will be two loss function weights, one for fixation-related complications and one for all other complications. Credible interval calculations will be done separately for individual failure modes within the two groups of complications (fixation and all other).

Denote by θ_c and θ_h the probabilities of lead complication for the current and historical studies respectively. The posterior distributions of θ_c and θ_h respectively, both with minimally informative priors are:

$$\theta_c = beta(y_c + 1, n_c - y_c + 1)$$
$$\theta_h = beta(y_h + 1, n_h - y_h + 1)$$

These posterior distributions are then stochastically compared using a posterior Bayesian p-value[26] as:

$$p = P(\theta_c \leq \theta_h)$$

The desired characteristics for the loss function are:

1. For $p \geq \sim 0.5$, there is a high level of agreement between current and historical data, therefore the loss function should allow a_0 to be close to 1, allowing for full weight of historical data.

2. Conversely, for $p < \sim 0.5$, there begins to be evidence of disagreement between current and historical data, and a_0 should start to down-weight the prior, i.e. a_0 approaches zero as p approaches zero.

The Weibull cumulative distribution function (CDF) meets these criteria:

$$a_0 = 1 - e^{-(p*5)^2}$$

Note that for the case where the number of samples in the prior is different than the effective number, a scaling factor will be applied, where n_h is the desired effective number of prior samples and N_h is the actual number of prior samples:

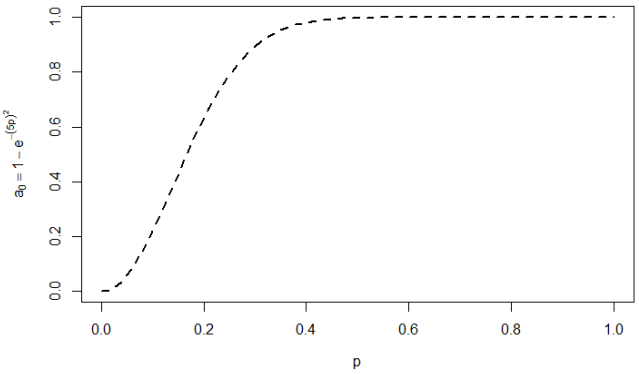
$$a_0 = \frac{n_h}{N_h}\left[1 - e^{-(p*5)^2}\right]$$

Sample values are listed in Table 17 below and illustrated in Figure 7. The comparison between current and historical data will be performed for all LV lead fixation related complications using Attain Stability (Model 20066) historical data and for all other LV lead related complications using Attain Performa historical data.

Table 17: Prior weight from Attain Stability (Model 20066) and prior weight from Attain Performa as a function of the posterior Bayesian p-value (p)

	Prior weight from Attain Stability (Model 20066)	Prior weight from Attain Performa
$\boldsymbol{p}$	$a_0 = 1 - e^{-(p*5)^2}$	$a_0 = \frac{37}{401}\left[1 - e^{-(p*5)^2}\right]$
0.01	0.002	0.000
0.05	0.061	0.006
0.1	0.221	0.020
0.2	0.632	0.058
0.5	0.998	0.092

Figure 7: Loss Function $a_0 = 1 - e^{-(p*5)^2}$

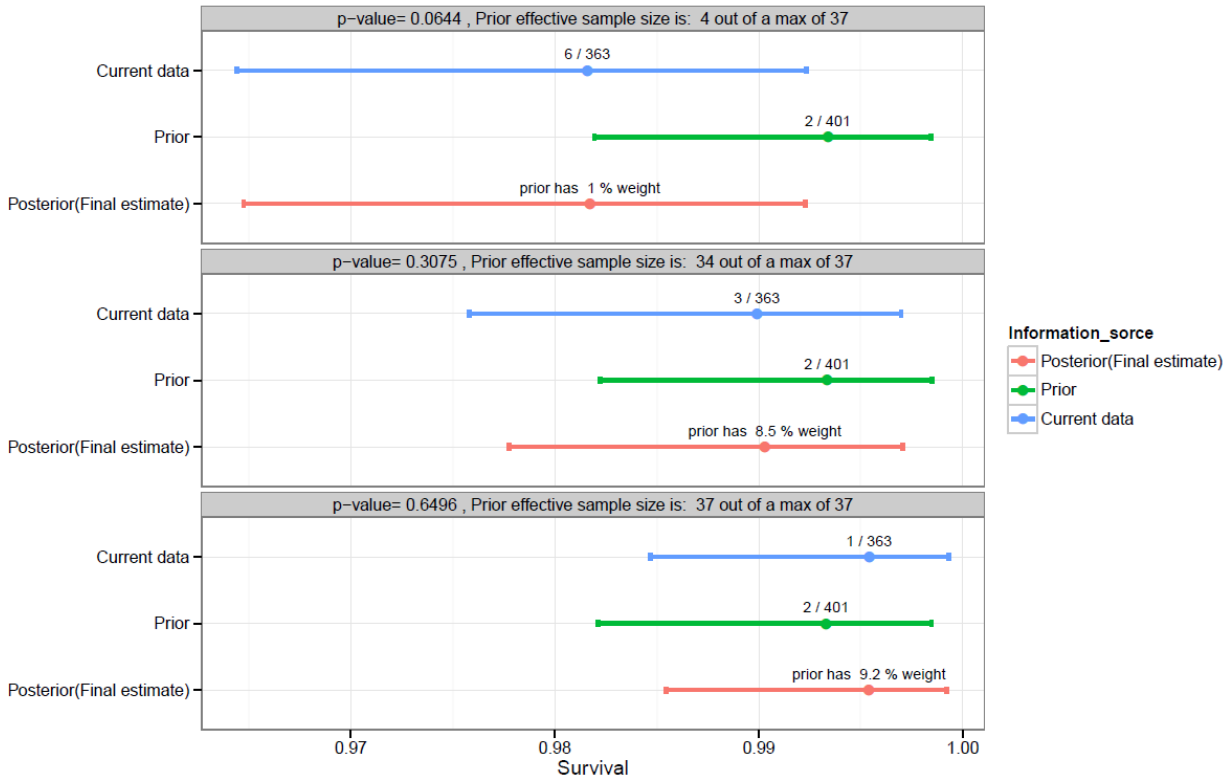


Note that the loss function proposed here does not reduce the strength of the prior when the current study outperforms the historical data. This implementation of the loss function is only concerned with negative impacts to patients, i.e. it penalizes an optimistic prior while not penalizing a pessimistic prior.

Also, note that this function is selected for the shape of the CDF rather than due to conventional statistical properties of the Weibull distribution.

Figure 8 illustrates the effect of the power prior coupled with the loss function. The figure shows credible intervals in scenarios where the prior is optimistic (better performance than current study), in agreement (similar performance to the current study), and pessimistic (worse performance than the clinical study). Note that the prior data source in Figure 8 is the Attain Performa study, with 401 patients. As will be discussed later, these data are scaled to represent a maximum of 37 patients (i.e. 9% weight).

Figure 8: Credible Intervals for Scenarios of Agreement Between Historical and Current Data



The prior data set in Figure 8 has 401 samples. However, the maximum effective historical data sample size is $n_h = 37$, for a maximum weight of 9%. Therefore, the prior will be scaled by a factor of (37/401). As an example, illustrated in the middle panel above, if the effective sample size is 34 out of 37, the prior has received 89% of the maximum weight, or 8.5%.

The panels in Figure 8 can be interpreted as follows:

- Top panel: The current data shows lower performance than the prior. The loss function produces a substantial penalty resulting in almost no weight to the prior (1%). The posterior (final estimate) is essentially the same as the current study.
- Middle panel: The current data is very similar to the prior. The loss function penalty is small, resulting in a prior weight of 8.5% (recall that the maximum weight is 9.2%). Because the agreement is good, the posterior(final estimate) is similar to both the prior and current study.
- Bottom panel: The current data is very similar, with slightly better performance than the prior. The loss function produces a weight very close to the maximum of 9.2%. The posterior (final estimate) is a balance between the prior and current study.

Sample Size

A Bayesian adaptive design is set up to enroll patients until a sufficient sample size is achieved to have high probability of meeting the required effective sample size of $n_e = 400$. The number of enrolled patients in the study may vary from 363 to 400 subjects due to the adaptations to the trial. This study follows methods from Berry, et.al.[27]

The interim analysis will take place after 360 subjects have been enrolled into the study.

The Adaptive Bayesian sample size algorithm will stop or continue enrollment accordingly to the following:

1.) If the predictive probability of $n_e \geq 400$ is larger than 80% then enrollment will stop.
2.) If the predictive probability of $n_e \geq 400$ is less than 80%, enroll sufficient additional patients to make the probability of $n_e \geq 400$ at least 80%.

At the time of the interim analysis, some patients will not have completed the full evaluation period. A longitudinal model will be employed to enable final observations to be imputed for those subjects with incomplete information.

There are 3 types of subjects at a given interim analysis:

1.) Subjects that have complete data
2.) Subjects that have partial data (censored value at a particular time)
3.) Subjects that have no information (subjects that have not been enrolled)

Predictive probabilities for types 2 and 3 will have to be computed. The predictive probability model that will be used is a piecewise exponential. This will allow the final outcomes for the subjects who have not had an event and have not completed 6 month follow up to be simulated.

Note this Bayesian approach to borrow information from historical datasets will only be used for the secondary objective #2.

19.2.3. Secondary Objective # 3

Objective – Electrical measurements (PCT and Impedance) at follow-ups

Pacing Capture Threshold (PCT) and impedance data will be collected using VectorExpress™. Pacing vector changes will be monitored for all implanted patients at follow-up visits.

Summary statistics for PCT and impedance at each time point (i.e. Implant, 6 months, etc.). The distribution of the electrical measurements at the final programmed pacing vector will be presented as n, mean, standard deviation, minimum, median and maximum. In the event of a replacement of a Medtronic Quad CRT-P or CRT-D device and/or the implanted LV lead, only measurements from the

Attain Stability Quad MRI SureScan LV Lead (Model 4798) implanted at the initial implant procedure will be included in the analysis cohort for this objective.

19.3. Additional Analysis

19.3.1. Poolability Analysis

Additional analysis will be conducted to summarize study primary objectives by patient characteristics, such as gender, age group, race and study site geography. The purpose of the poolability analysis is to identify if there is any clinical meaningful difference in a subgroup of patients. These analyses will not be statistically powered, and there is no pre-specified statistical significance level for these analyses.

19.3.2. Sensitivity Analysis

All subjects enrolled into this study and successfully implanted with a Medtronic Quad CRT-P or CRT-D device and Attain Stability Quad MRI SureScan LV Lead (Model 4798) will be included in the primary efficacy analysis datasets (efficacy objectives #1 and #2). Sensitivity analysis such as the Tipping Point method or similar will be conducted to investigate the influence of subjects who were successfully implanted with the required system however missed a 6 month post implant follow-up test(s) (due to reasons such as missing in-office visit, subject exit, death and/or the initial implanted lead was deactivated). For this purpose, all subjects with successful implant who do not meet analysis cohort requirements, will be considered as the worst case scenario (i.e. failure to meet the efficacy endpoints).The results will be submitted as part of the clinical reports.

19.3.3. Additional Data Collection

Heart failure clinical outcomes will be assessed. The measurements, including NYHA classification, death, heart failure related hospitalization, heart failure related study exits and subject self-reported global assessment for each subject will be obtained at 6 months post-implant. Summary statistics will be provided.

19.3.3. Overall Study Sample Size Requirements

The sample size requirement at 6-months for each of the study objectives is displayed in Table 18. The first row does not account for attrition, while the second row is inflated by 15% attrition. The sample size for Secondary Objective #2 assumes the conservative case that the interim look results in, no borrowing of historical data. Therefore, the overall sample size for the study is 471.

Table 18: Required Sample Size by Study Objective

	Primary Safety Objective	Primary Efficacy Objective #1	Primary Efficacy Objective #2	Secondary Objective #1	Secondary Objective #2 (post-implant failure modes)	Secondary Objective #3	Overall
Number needed at 6-months	170	145	50	NA	400	NA	400
Number of enrollments	200	171	59	NA	471	NA	471

20. Ethics

20.1. Statement(s) of Compliance

This study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). Good Clinical Practice includes review and approval by an independent IRB/EC before initiating a study, continuing review of an ongoing study by an IRB/EC, and obtaining and documenting the freely given IC of a subject before initiating the study.

The clinical investigation shall not begin until all required approvals and documents from the IRB/EC and a regulatory authority, if needed, have been received. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

The Attain Stability Quad Clinical Study was designed to reflect the GCP principles outlined in ISO 14155:2011 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In accordance with ISO 14155:2011, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation. Adverse Event and Device Deficiency handling in the Attain Stability Quad Clinical Study is ISO 14155:2011 compliant for all participating geographies with the exception that only those AEs which are related to the subject's system, procedure, accessory, or are cardiovascular-related, and all Serious AEs, will be collected. This ensures any AEs which could potentially be relevant will be collected. The scope and duration of the Attain Stability Quad Clinical Study would make collection of all AEs to be a significant burden for investigators and investigative sites. Therefore, only a subset of AEs will be collected in this study, including any that could be potentially relevant.

The principles of the Declaration of Helsinki have been implemented through the IC process, IRB/EC approval, study training, clinical trial registration, pre-clinical testing, risk-benefit assessment and publication policy.

Ultimately, all sites in all geographies will follow and comply with:

- Principles of Declaration of Helsinki
- 21 CFR Part 11 (Electronic Records, Electronic Signatures) (per local law)
- 21 CFR Part 54 (Financial Disclosure by Clinical Investigators)
- The Clinical Trial Agreement
- The procedures described within this CIP
- Local Ethics Board Requirements

In addition to the regulatory requirements outlined above, the study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. These include but are not limited to:

- In the United States, the study will be conducted under an FDA IDE in compliance with 21 CFR Parts:
  - 50: Protection of Human Subjects
  - 56: Institutional Review Boards
  - 812: Investigational Device Exemptions
- In Canada, SOR/98-282, Section 59-88 will be followed and Mandatory Problem Reporting 59(1), 59(2), 60 (1)).
- In EMEA the study will be conducted in compliance with the Active Implantable Medical Device Directive (AIMDD) and Declaration of Helsinki version 2013.
- In Hong Kong and Malaysia, the study will be conducted in compliance with the Declaration of Helsinki version 2013.
- In EMEA, an IB is not required for this study as it is a post market study

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act FDAAA and Declaration of Helsinki on http://clinicaltrials.gov (PL 110-85, section 810(a)). In addition, the study may be registered in local regulatory databases where required by local law.

Approval of the CIP and CIP amendments is required from the following groups prior to any study procedures at a study site:

- Medtronic
- Principal Investigators (where required by local law/regulations)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent medical ethics committee or institutional review board.

Similarly, approval of subsequent revisions to the CIP is required at each study site from the above mentioned groups prior to implementation of the revised CIP at the site.

21. Study Administration

21.1. Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this Attain Stability Quad Clinical Study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the CTA, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the Subject IC, Data Protection Authorization (where applicable) and CTA. The principal investigator should also be available during monitoring visits.

Monitoring for the study, including site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

Monitoring visits may be conducted periodically to assess site study progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to IRB/EC approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs. Monitors review site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to site personnel. Monitors may work with study personnel to determine appropriate corrective action

recommendations and to identify trends within the study or at a particular site. Regulatory documents may be reviewed at each study site.

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of adverse events, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation.

21.2. Data Management

Data will be collected using Oracle Clinical, an electronic data management system for clinical studies. CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

Only authorized persons can complete CRFs. CRFs shall be signed by the Principle Investigator. The Principle Investigator can delegate the CRF sign off task to Sub-Investigators only. Delegation of authority will be specified on the appropriate documentation.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to make it anonymous, for instance, where the subject's name cannot be removed from the data carrier.

Procedures in the CIP require source documentation. Source documentation will be maintained at the site. Source documents, which may include worksheets, patient medical records, programmer printouts and device interrogation files, must be created and maintained by the investigational site team. For source documentation, the investigational site study team must sign and date any copies or printouts of original source documents with a statement that this is a complete and true reproduction of the original source document.

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. The CRF may be considered source for the following data collection elements recorded directly on the CRFs:

- Enrollment Notification
    - Site assigned patient reference
- Baseline
    - Administrative information
- Adverse Event eCRF
    - Date study site became aware of event
    - Relatedness of adverse event
- Device Deficiency eCRF
    - Date study site became aware of event
- Subject Death
    - Date study site became aware of death
    - Relatedness of death
- System Modification
    - Justification for explanted product not being returned to Medtronic
- Deviations

    - Reason for deviation
- Investigational product Disposition Log
    - Date the Investigational Attain Stability Quad lead was implanted/explanted

Even when the CRF may be considered as source, an alternate method of source documentation is always strongly encouraged.

Save-to-media data collected at office visits will be sent to Medtronic. Upon receipt, device data will be maintained within a Medtronic device database and retrieved for analysis and reporting.

21.3. Direct Access to Source Data/Documents

The sponsor or a regulatory authority may audit or inspect the study site to evaluate the conduct of the study. The clinical investigator(s)/institution(s) shall allow study related monitoring, audits, IRB/EC review and regulatory inspection.

21.4. Confidentiality

All records and other information about subjects participating in this study will be treated as confidential.

21.5. CIP Amendments

Approval of subsequent revisions to the CIP is required at each study site from the following groups prior to implementation of the revised CIP at the site:

- Medtronic
- Principal Investigators (where required by local law)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent medical ethics committee or institutional review board.

If a CIP amendment occurs, site personnel will need to be re-trained as necessary, and will need to submit any changes to their IRB/EC as required by the committee. Protocol amendments will also be reported to and approved by the FDA, or regulatory authority.

21.6. Warranty/Insurance Information

21.6.1. Warranty

Warranty information is provided in the product packaging for the commercially released CRT-P or CRT-D devices and leads, and additional copies are available upon request.

21.6.2. Insurance (EMEA)

Medtronic Bakken Research Center B.V. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the EC and/or Competent Authority (CA).

21.6.3. Insurance (Canada)

Medtronic of Canada is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate general liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a General Liability insurance statement/certificate will be provided to the Ethics Committee.

21.6.4. Insurance (Malaysia)

Medtronic International Ltd. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

21.6.5. Insurance (Hong Kong)

Medtronic Hong Kong Medical Ltd. Ltd. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee.

21.7. Record Retention

21.7.1. Investigator Records

The investigator is responsible for the preparation and retention of the records including, but not limited to, those cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (e.g., the study binder provided to the investigator) or Subject Study Binder. Case Report Forms must be maintained and signed electronically by an investigator within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law/regulation or hospital administration requires) after product approval. Measures shall be taken to avoid loss or premature destruction.

- All correspondence between the IRB/EC, sponsor, monitor, regulatory authority and/or the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
    - Signed and dated informed consent form, in accordance with local requirements
    - Observations of adverse events/adverse device effects/device deficiencies
    - Medical history
    - Baseline, Implant and follow-up data (if applicable)
    - Documentation of the dates and rationale for any deviation from the protocol
- Electronically signed and dated eCRFs and a blank set of CRFs where required by local law
- All approved versions of the CIP, IC
- Fully executed Clinical Trial Agreement
- Ethics Committee approval documentation. Written information that the investigator or other study staff, when member of the Ethics Committee, did not participate in the approval process.

Approval documentation must include the Ethics Board composition, where required per local law.
- Regulatory authority notification, correspondence and approval, where required per local law.
- List of investigation sites: This list is not yet final at the time of CIP development. The list will be provided under separate cover and will be maintained by the sponsor.
- Financial disclosure (investigators)
- Enrollment Log (for sites following ISO 14155)
- For sites where the Attain Stability Quad lead is considered investigational, device disposition logs containing Model and serial numbers of devices implanted, subject IDs of the subjects implanted, implant/used dates, explant dates, returned-to-sponsor dates and reasons and method of disposal/destruction
- Current curriculum vitae (signed and dated in EMEA only) of principal investigators and key members of investigation site team (as required by local law)
- Documentation of delegated tasks
- Study training records for investigation site team
- Assurance certificates (EMEA, Hong Kong, and Malaysia)
- Any other records that FDA and local regulatory agencies require to be maintained (e.g. Ethics Committee Roster, study equipment calibration information)
- Final Study Report including the statistical analysis

21.7.2. Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all CRFs, AEs and ADEs (reported per the country-specific collection requirements), DDs, deaths, crossovers and any deviations from the CIP. If any action is taken by an IRB/EC with respect to this Attain Stability Quad Clinical Study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Investigator reporting requirements for safety data are listed in Section 17.3).

Table 19: Investigator Reports Applicable for All Geographies per Medtronic Requirements

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing Ethics Committee of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and Ethics Committee	Any deviation from the clinical investigation plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Failure to obtain informed consent	Sponsor and Ethics Committee	Informed consent shall be obtained in writing and documented before a subject is enrolled into the Attain Stability Quad Clinical Study
Final Report	Ethics Committee and Relevant Authorities	This report must be submitted within 3 months of study completion or termination.

21.7.3. Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records that includes, but is not limited to:

- All correspondence which pertains to the Attain Stability Quad Clinical Study
- Executed Clinical Trial Agreement
- Financial disclosures (investigators)
- Current curriculum vitae (signed and dated in EMEA only) of principal investigators and key members of investigation site team (as required by local law)
- Device Disposition Logs containing Model and serial numbers of devices implanted, subject IDs of the subjects implanted, implant/used dates, explant dates, returned-to-sponsor dates and reasons and method of disposal/destruction
- Electronically signed and dated eCRFs
- All approved informed consent templates, and other information provided to the subjects and advertisements, including translations
- Copies of all Ethics Committee approval letters and relevant Ethics Committee correspondence and Ethics Committee voting list/roster/letter of assurance
- List of names, addresses, and professional position of the clinical investigators and coordinating clinical, if appointed.
- Names and addresses of the institutions in which the Attain Stability Quad Clinical Study will be conducted: This list is not yet final at the time of CIP development. The list will be provided under separate cover and will be maintained by the sponsor.
- Regulatory authorities correspondence, notification and approval as required by national legislation
- Insurance certificates (EMEA, Hong Kong, and Malaysia)
- Names/contact addresses of monitors
- Monitoring reports (interim monitoring visit reports, follow-up letters and close-out visit reports)
- Site qualification visit reports
- Statistical analyses and underlying supporting data
- Final report of the Attain Stability Quad Clinical Study
- The approved Clinical Investigation Plan and study related reports, and revisions
- Documentation of delegated tasks
- Study training records for site personnel and Medtronic personnel involved in the study
- Sample of CRFs
- Any other records that local regulatory agencies require to be maintained

21.7.4. Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of reviewing Ethics Committee, regulatory agency or FDA, provide accurate, complete and current information about any aspect of the Attain Stability Quad Clinical Study. Safety data Medtronic reporting requirements are listed in Section 17.3).

Table 20: Sponsor Reports for Canada

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, Ethics Committee, Relevant authorities, and Head of the Institution	Provide prompt notification of termination or suspension and reason(s).
Recall and device disposition	Investigators, Ethics Committee	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices.
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically.

Table 21: Sponsor Reports for EMEA, Malaysia, Hong Kong

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, Ethics Committee, Relevant authorities and Head of the Institution	Provide prompt notification of termination or suspension and reason(s) per local law. *(ISO 14155:2011)*
Withdrawal of Ethics Committee approval	Investigators, Ethics Committee and relevant authorities	Investigators and other Ethics Committees will be notified only if required by local laws or by the Ethics Committee.
Withdrawal of CA approval	Investigators, Ethics Committee, and relevant authorities	Investigators, Ethics Committees and relevant authorities will be notified only if required by local laws or by the Ethics Committee.
Progress Reports	Ethics Committee and regulatory authorities	This will be submitted to the Ethics Committee and regulatory authorities only if required by local law.
Final report	Investigators, Ethics Committee, and Regulatory authorities upon request	• The investigator shall have the opportunity to review and comment on the final report. • If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). • The signature of the principal Investigator in each site should be obtained.
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. *(ISO 14155:2011)* Site specific study deviations will be submitted to investigators periodically.

Table 22: Sponsor Reports for the United States

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Investigators, Ethics Committee, FDA, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(2))*
Withdrawal of FDA approval	Investigators, Ethics Committee, and relevant authorities	Notification within five working days. *(21 CFR 812.150(b)(3))*
Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. *(21 CFR 812.150(b)(4))*
Progress Reports	Ethics Committee and FDA	Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(5), 812.36(f)*
Recall and device disposition	Investigators, Head of Institution, Ethics Committee, relevant authorities, and FDA	Notification within 30 working days and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6))*
Failure to obtain informed consent	FDA	Investigator's report will be submitted to FDA within five working days of notification. *(21 CFR 812.150(b)(8))*
Final report	Investigators, Ethics Committee, Regulatory authorities upon request, and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, investigators, and IRBs/MECs within six months after completion or termination of this study. *(21 CFR 812.150(b)(7))*
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically.
Other	IRB, FDA	Accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(b)(10))*

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in secured file cabinets at Medtronic during the course of this study. After closure of the study Medtronic will archive records and reports as required by applicable regulations.

21.8. Publication and Use of Information

Publications from the Attain Stability Quad Clinical Study will be handled according to Medtronic Policies and Standard Operating Procedures and as indicated in the CTA.

21.8.1. Publication Committee

The Attain Stability Quad Clinical Study will utilize a Publication Committee which will include the Steering Committee members as well as Medtronic personnel. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to:

- Manage elements addressed in the publication plan as outlined in this section
- Develop the final Publication Plan under separate cover
- Execute the Publication Plan
- Oversee the publication of primary, secondary and ancillary study results
- Review and prioritize publication proposals
- Provide input on publication content, and
- Determine authorship

In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan. Membership in the Publication Committee does not guarantee authorship. The committee will meet as needed.

21.8.2. Management of Primary, Secondary, and Ancillary Publications

The Publication Committee reviews, prioritizes and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary/ancillary objectives, respectively, as specified in the Clinical Investigation Plan. An ancillary publication is any publication that does not address the study objectives identified in the Clinical Investigation Plan. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this Attain Stability Quad Clinical Study and clinicians not participating in this Attain Stability Quad Clinical Study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual site data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

21.8.3. Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE), Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Medtronic personnel, must at a minimum meet all of the conditions below:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published

Decisions regarding authorship and contributor-ship will be made by the publication committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the

authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All investigators not listed as co-authors will be acknowledged as the "Medtronic Attain Stability Quad Clinical Study Investigators" and will be individually listed according to the guidelines of the applicable scientific journal when possible. Any other contributors will be acknowledged by name with their specific contribution indicated.

21.8.4. Transparency

Transparency of study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to all investigators, IRB/ECs and Competent Authorities of participating countries when required by local law
- Registering and posting the study results on ClinicalTrials.gov based on the posting rules stipulated
- Submitting for publication the primary study results after the study ends
- Disclosing conflicts of interest (e.g. financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- Making an individual sites study data accessible to the corresponding investigator after the completion of the study, if requested

21.9. Suspension or Early Termination

21.9.1. Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a clinical study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or regulatory authority, whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing IRB/EC oversight is required until the overall study closure process is complete. Upon study closure, subjects should be managed and followed per physician discretion.

21.9.2. Early Termination or Suspension

Early Termination of the Study is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single site. Study Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single site. In the event the whole study or a single site is terminated, subjects will be exited.

Study-Wide Termination or Suspension

Possible reasons for considering study suspension or termination of the study include but are not limited to:

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)

- Technical issues during the manufacturing process

Investigator/Site Termination or Suspension

Possible reasons for clinical investigator or site termination or suspension include but are not limited to:

- Failure to obtain initial IRB/EC approval or annual renewal of the study
- Persistent non-compliance to the clinical investigation (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment
- Noncompliance to regulations and the terms of the CTA (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.)
- Institutional Review Board/Ethics Committee suspension of the site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

21.9.3. Procedures for Termination or Suspension

Medtronic-Initiated and Regulatory Authority-Initiated

- Medtronic will promptly inform the clinical investigators of the (early) termination or suspension and the reasons and inform the regulatory authority(s) where required
- In the case of study termination or suspension for reasons other than a temporary IRB/EC approval lapse, the investigator will promptly inform the IRB/EC
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

Investigator-Initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the IRB/EC
- The investigator will promptly inform the regulatory authorities (for regions following ISO only)
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

Institutional Review Board Ethics Committee-Initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with IRB/EC policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)

- The investigator will promptly inform the subjects, and/or the personal physician of the subjects, with the rationale for the study termination or suspension
- The investigator will promptly inform the regulatory authorities (for regions following ISO 14155 only)

22. Appendices

APPENDIX 1: Foreseeable Adverse Event List

The information provided in this section pertains to foreseeable AEs that may be observed in study subjects and may collectively assist in identifying those events that are unexpected in nature. The foreseeable adverse events information consists of three parts: (1) listing of potential adverse events associated with implantation of CRT system and transvenous leads, (2) rates of AEs reported from previous Medtronic studies evaluating CRT systems and transvenous leads, and (3) AEs rates reported in published literature for procedures similar to the CRT system implant procedure. This information will be used in combination with device labeling, current event reporting information, and other published data to assess for an unexpected occurrence.

The implantation of the study device, CRT-P or CRT-D, involves surgery, therefore, standard AEs associated with a surgical procedure may be experienced (e.g. anesthesia complications, injury, infections, bleeding, exacerbation of pre-existing conditions, healing complications, etc.). The focus of this section is to specifically address in more detail, those events that are foreseeable due to the use, performance, and/or presence of the system under investigation.

Additional potential risks associated with the implantation of the CRT system and the Attain Stability Quad MRI SureScan LV Lead (Model 4798), as well as risk minimization are discussed within Section 16.

Treatment required for procedure and/or system related adverse events that are experienced may include medication, device reprogramming, device modification (e.g. repositioning, surgical abandonment, surgical removal), or other surgical and medical remedies. The AEs associated with the use of transvenous leads, pacing and defibrillation systems include, but are not limited to, the following:

Table 23: Listing of Potential Adverse Events Associated with System Implant

- acceleration of tachyarrhythmias (caused by device)
- air embolism
- bleeding
- body rejection phenomena, including local tissue reaction
- cardiac dissection
- cardiac perforation
- cardiac tamponade
- chronic nerve damage
- constrictive pericarditis
- death
- device migration
- endocarditis
- erosion
- excessive fibrotic tissue growth
- extrusion
- fibrillation or other arrhythmias
- fluid accumulation
- formation of hematomas/seromas or cysts
- heart block
- heart wall or vein wall rupture
- hemothorax
- infection
- keloid formation
- lead abrasion and discontinuity
- lead migration/dislodgment
- complications and mortality due to inability to deliver appropriate and intended therapy
- muscle and/or nerve stimulation
- myocardial damage
- myocardial irritability
- myopotential sensing
- pericardial effusion
- pericardial rub
- pneumothorax
- poor connection of the lead to the device, which may lead to oversensing, undersensing, or a loss of therapy
- stroke
- threshold elevation
- thrombotic embolism
- thrombosis
- tissue necrosis
- valve damage (particularly in fragile hearts)
- venous occlusion
- venous perforation

An additional potential AE associated with the use of transvenous left ventricular pacing leads is coronary sinus dissection.

Additional potential AEs associated with the use of ICD systems include, but are not limited to, the following events:

- inappropriate shocks
- potential mortality due to inability to defibrillate
- shunting current or insulating myocardium during defibrillation

Patients susceptible to frequent shocks despite medical management could develop psychological intolerance to an ICD system that might include the following conditions:

- dependency
- depression
- fear of premature battery depletion
- fear of shocking while conscious
- fear that shocking capability may be lost
- imagined shocking (phantom shock)

Adverse Events Reported in Previous Medtronic Studies

The listing below provides an example of reported system and procedure related AEs in recent Medtronic studies. This table includes a summary of combined system or procedure related AEs as reported in the Concerto-AT, Insync III US, 4194, 4195, 4196, 4396, Adaptive CRT, and Attain Performa studies along with their incidence. The observed rate is based on the study populations that included a total of 3,246 subjects. In total, there were 1749 system or procedure related events. This includes both serious and non-serious events. The rate is calculated as number of subjects that experience the event, not accounting for duration of follow-up.

Table 24: System or procedure-related adverse events from previous clinical studies

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Abdominal pain	1	1	0.03%	(0.00%, 0.17%)
Acidosis	1	1	0.03%	(0.00%, 0.17%)
Acute respiratory failure	4	4	0.12%	(0.03%, 0.32%)
Adverse drug reaction	1	1	0.03%	(0.00%, 0.17%)
Air embolism	1	1	0.03%	(0.00%, 0.17%)
Alcohol withdrawal syndrome	1	1	0.03%	(0.00%, 0.17%)
Alpha haemolytic streptococcal infection	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Anaemia	7	7	0.22%	(0.09%, 0.44%)
Anaemia postoperative	1	1	0.03%	(0.00%, 0.17%)
Anaphylactic shock	1	1	0.03%	(0.00%, 0.17%)
Anticoagulation drug level below therapeutic	1	1	0.03%	(0.00%, 0.17%)
Anxiety	3	3	0.09%	(0.02%, 0.27%)
Application site rash	2	2	0.06%	(0.01%, 0.22%)
Arterial haemorrhage	1	1	0.03%	(0.00%, 0.17%)
Arteriovenous fistula	1	1	0.03%	(0.00%, 0.17%)
Arteriovenous fistula operation	1	1	0.03%	(0.00%, 0.17%)
Arthralgia	1	1	0.03%	(0.00%, 0.17%)
Arthritis bacterial	1	1	0.03%	(0.00%, 0.17%)
Ascites	1	1	0.03%	(0.00%, 0.17%)
Atelectasis	2	2	0.06%	(0.01%, 0.22%)
Atrial fibrillation	19	19	0.59%	(0.35%, 0.91%)
Atrial flutter	4	4	0.12%	(0.03%, 0.32%)
Atrial tachycardia	5	4	0.12%	(0.03%, 0.32%)
Atrioventricular block	16	16	0.49%	(0.28%, 0.80%)
Back pain	3	3	0.09%	(0.02%, 0.27%)
Bacteraemia	1	1	0.03%	(0.00%, 0.17%)
Cardiac arrest	8	8	0.25%	(0.11%, 0.49%)
Cardiac failure	46	43	1.32%	(0.96%, 1.78%)
Cardiac failure chronic	5	5	0.15%	(0.05%, 0.36%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Cardiac pacemaker battery replacement	1	1	0.03%	(0.00%, 0.17%)
Cardiac perforation	8	8	0.25%	(0.11%, 0.49%)
Cardiac sarcoidosis	1	1	0.03%	(0.00%, 0.17%)
Cardiac tamponade	3	3	0.09%	(0.02%, 0.27%)
Cardiac vein dissection	38	37	1.14%	(0.80%, 1.57%)
Cardiac vein perforation	5	5	0.15%	(0.05%, 0.36%)
Cardiogenic shock	3	3	0.09%	(0.02%, 0.27%)
Cardiomyopathy	1	1	0.03%	(0.00%, 0.17%)
Cardiovascular disorder	1	1	0.03%	(0.00%, 0.17%)
Cellulitis	2	2	0.06%	(0.01%, 0.22%)
Cerebral infarction	1	1	0.03%	(0.00%, 0.17%)
Cerebrovascular accident	3	3	0.09%	(0.02%, 0.27%)
Chest discomfort	4	4	0.12%	(0.03%, 0.32%)
Chest pain	8	8	0.25%	(0.11%, 0.49%)
Chronic obstructive pulmonary disease	3	3	0.09%	(0.02%, 0.27%)
Circulatory collapse	1	1	0.03%	(0.00%, 0.17%)
Colitis	1	1	0.03%	(0.00%, 0.17%)
Complication of device insertion	1	1	0.03%	(0.00%, 0.17%)
Complication of device removal	4	4	0.12%	(0.03%, 0.32%)
Constipation	1	1	0.03%	(0.00%, 0.17%)
Contusion	2	2	0.06%	(0.01%, 0.22%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Cough	1	1	0.03%	(0.00%, 0.17%)
Cystitis	1	1	0.03%	(0.00%, 0.17%)
Decubitus ulcer	1	1	0.03%	(0.00%, 0.17%)
Deep vein thrombosis	14	14	0.43%	(0.24%, 0.72%)
Dehydration	1	1	0.03%	(0.00%, 0.17%)
Delirium	1	1	0.03%	(0.00%, 0.17%)
Device alarm issue	1	1	0.03%	(0.00%, 0.17%)
Device battery issue	1	1	0.03%	(0.00%, 0.17%)
Device capturing issue	30	29	0.89%	(0.60%, 1.28%)
Device computer issue	19	19	0.59%	(0.35%, 0.91%)
Device connection issue	19	19	0.59%	(0.35%, 0.91%)
Device damage	1	1	0.03%	(0.00%, 0.17%)
Device dislocation	125	107	3.30%	(2.71%, 3.97%)
Device electrical impedance issue	12	12	0.37%	(0.19%, 0.64%)
Device extrusion	2	1	0.03%	(0.00%, 0.17%)
Device failure	1	1	0.03%	(0.00%, 0.17%)
Device lead damage	13	13	0.40%	(0.21%, 0.68%)
Device lead issue	1	1	0.03%	(0.00%, 0.17%)
Device misuse	9	9	0.28%	(0.13%, 0.53%)
Device pacing issue	69	67	2.06%	(1.60%, 2.61%)
Device psychogenic complication	7	7	0.22%	(0.09%, 0.44%)
Device related infection	3	3	0.09%	(0.02%, 0.27%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Device signal detection issue	2	2	0.06%	(0.01%, 0.22%)
Device stimulation issue	443	349	10.75%	(9.71%, 11.87%)
Diabetes	1	1	0.03%	(0.00%, 0.17%)
Diarrhea	1	1	0.03%	(0.00%, 0.17%)
Dizziness	1	1	0.03%	(0.00%, 0.17%)
Dressler's syndrome	1	1	0.03%	(0.00%, 0.17%)
Drug hypersensitivity	3	3	0.09%	(0.02%, 0.27%)
Dysarthria	1	1	0.03%	(0.00%, 0.17%)
Dyspnoea	2	2	0.06%	(0.01%, 0.22%)
Dyspnoea exertional	1	1	0.03%	(0.00%, 0.17%)
Dyspnoea paroxysmal nocturnal	1	1	0.03%	(0.00%, 0.17%)
Ecchymosis	2	2	0.06%	(0.01%, 0.22%)
Electromagnetic interference	1	1	0.03%	(0.00%, 0.17%)
Endocarditis	1	1	0.03%	(0.00%, 0.17%)
Endocarditis staphylococcal	1	1	0.03%	(0.00%, 0.17%)
Erythema multiforme	1	1	0.03%	(0.00%, 0.17%)
Fatigue	5	5	0.15%	(0.05%, 0.36%)
Fluid overload	1	1	0.03%	(0.00%, 0.17%)
Gastroenteritis	1	1	0.03%	(0.00%, 0.17%)
Gastrointestinal haemorrhage	1	1	0.03%	(0.00%, 0.17%)
Haematoma	2	2	0.06%	(0.01%, 0.22%)
Haematuria	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Haemoptysis	2	2	0.06%	(0.01%, 0.22%)
Haemothorax	4	4	0.12%	(0.03%, 0.32%)
Hot flush	1	1	0.03%	(0.00%, 0.17%)
Hydrothorax	1	1	0.03%	(0.00%, 0.17%)
Hyperglycaemia	1	1	0.03%	(0.00%, 0.17%)
Hyperkalaemia	4	4	0.12%	(0.03%, 0.32%)
Hypersensitivity	1	1	0.03%	(0.00%, 0.17%)
Hypertension	1	1	0.03%	(0.00%, 0.17%)
Hyponatraemia	2	2	0.06%	(0.01%, 0.22%)
Hypotension	20	20	0.62%	(0.38%, 0.95%)
Hypovolaemia	1	1	0.03%	(0.00%, 0.17%)
Ileus	1	1	0.03%	(0.00%, 0.17%)
Impaired healing	2	2	0.06%	(0.01%, 0.22%)
Implant site bruising	2	2	0.06%	(0.01%, 0.22%)
Implant site cellulitis	1	1	0.03%	(0.00%, 0.17%)
Implant site effusion	1	1	0.03%	(0.00%, 0.17%)
Implant site erosion	1	1	0.03%	(0.00%, 0.17%)
Implant site erythema	6	6	0.18%	(0.07%, 0.40%)
Implant site haematoma	98	96	2.96%	(2.40%, 3.60%)
Implant site haemorrhage	6	6	0.18%	(0.07%, 0.40%)
Implant site hypoaesthesia	1	1	0.03%	(0.00%, 0.17%)
Implant site infection	44	44	1.36%	(0.99%, 1.82%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Implant site inflammation	3	3	0.09%	(0.02%, 0.27%)
Implant site irritation	5	5	0.15%	(0.05%, 0.36%)
Implant site oedema	3	3	0.09%	(0.02%, 0.27%)
Implant site pain	72	64	1.97%	(1.52%, 2.51%)
Implant site rash	3	3	0.09%	(0.02%, 0.27%)
Implant site swelling	4	4	0.12%	(0.03%, 0.32%)
Implant site warmth	1	1	0.03%	(0.00%, 0.17%)
Incision site complication	1	1	0.03%	(0.00%, 0.17%)
Incision site haemorrhage	5	5	0.15%	(0.05%, 0.36%)
Incision site pain	4	4	0.12%	(0.03%, 0.32%)
Incisional drainage	1	1	0.03%	(0.00%, 0.17%)
Infection	2	2	0.06%	(0.01%, 0.22%)
Infusion site extravasation	1	1	0.03%	(0.00%, 0.17%)
Intracardiac thrombus	6	6	0.18%	(0.07%, 0.40%)
Lead dislodgement	33	30	0.92%	(0.62%, 1.32%)
Leukocytosis	2	2	0.06%	(0.01%, 0.22%)
Localized oedema	1	1	0.03%	(0.00%, 0.17%)
Mediastinal effusion	1	1	0.03%	(0.00%, 0.17%)
Medical device discomfort	3	3	0.09%	(0.02%, 0.27%)
Medical device site reaction	1	1	0.03%	(0.00%, 0.17%)
Monoparesis	1	1	0.03%	(0.00%, 0.17%)
Muscle spasms	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Muscle twitching	1	1	0.03%	(0.00%, 0.17%)
Musculoskeletal chest pain	2	2	0.06%	(0.01%, 0.22%)
Musculoskeletal pain	42	40	1.23%	(0.88%, 1.67%)
Musculoskeletal stiffness	1	1	0.03%	(0.00%, 0.17%)
Myocardial infarction	1	1	0.03%	(0.00%, 0.17%)
Nausea	1	1	0.03%	(0.00%, 0.17%)
Neck pain	1	1	0.03%	(0.00%, 0.17%)
Nephrosclerosis	1	1	0.03%	(0.00%, 0.17%)
Neuropathy peripheral	1	1	0.03%	(0.00%, 0.17%)
Nodal rhythm	2	2	0.06%	(0.01%, 0.22%)
Non-cardiac chest pain	1	1	0.03%	(0.00%, 0.17%)
Oedema peripheral	12	12	0.37%	(0.19%, 0.64%)
Oliguria	1	1	0.03%	(0.00%, 0.17%)
Operative haemorrhage	1	1	0.03%	(0.00%, 0.17%)
Orthostatic hypotension	2	2	0.06%	(0.01%, 0.22%)
Oversensing	34	33	1.02%	(0.70%, 1.42%)
Oxygen saturation decreased	1	1	0.03%	(0.00%, 0.17%)
Pacemaker generated arrhythmia	6	6	0.18%	(0.07%, 0.40%)
Pain	1	1	0.03%	(0.00%, 0.17%)
Pain in extremity	1	1	0.03%	(0.00%, 0.17%)
Palpitations	9	9	0.28%	(0.13%, 0.53%)
Paraesthesia	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Pericardial effusion	16	15	0.46%	(0.26%, 0.76%)
Pericarditis	4	4	0.12%	(0.03%, 0.32%)
Phantom shocks	4	3	0.09%	(0.02%, 0.27%)
Phlebitis	2	2	0.06%	(0.01%, 0.22%)
Pleural effusion	21	21	0.65%	(0.40%, 0.99%)
Pneumonia	9	9	0.28%	(0.13%, 0.53%)
Pneumothorax	43	43	1.32%	(0.96%, 1.78%)
Pocket erosion	4	4	0.12%	(0.03%, 0.32%)
Post procedural haemorrhage	2	2	0.06%	(0.01%, 0.22%)
Presyncope	3	3	0.09%	(0.02%, 0.27%)
Procedural haemorrhage	1	1	0.03%	(0.00%, 0.17%)
Procedural headache	2	2	0.06%	(0.01%, 0.22%)
Procedural pain	1	1	0.03%	(0.00%, 0.17%)
Pruritus	1	1	0.03%	(0.00%, 0.17%)
Pruritus generalized	1	1	0.03%	(0.00%, 0.17%)
Pulmonary embolism	1	1	0.03%	(0.00%, 0.17%)
Pulmonary oedema	3	3	0.09%	(0.02%, 0.27%)
Pulmonary sepsis	1	1	0.03%	(0.00%, 0.17%)
Pulseless electrical activity	2	2	0.06%	(0.01%, 0.22%)
Pyrexia	5	5	0.15%	(0.05%, 0.36%)
Rash	8	8	0.25%	(0.11%, 0.49%)
Rash generalized	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Renal failure	8	8	0.25%	(0.11%, 0.49%)
Renal failure acute	2	2	0.06%	(0.01%, 0.22%)
Renal impairment	1	1	0.03%	(0.00%, 0.17%)
Respiratory acidosis	1	1	0.03%	(0.00%, 0.17%)
Respiratory distress	1	1	0.03%	(0.00%, 0.17%)
Respiratory failure	1	1	0.03%	(0.00%, 0.17%)
Sepsis	3	3	0.09%	(0.02%, 0.27%)
Sepsis syndrome	1	1	0.03%	(0.00%, 0.17%)
Septic shock	4	4	0.12%	(0.03%, 0.32%)
Sinus arrest	1	1	0.03%	(0.00%, 0.17%)
Sinus bradycardia	1	1	0.03%	(0.00%, 0.17%)
Sinus tachycardia	2	2	0.06%	(0.01%, 0.22%)
Staphylococcal infection	2	2	0.06%	(0.01%, 0.22%)
Stitch abscess	1	1	0.03%	(0.00%, 0.17%)
Subclavian vein thrombosis	2	2	0.06%	(0.01%, 0.22%)
Subcutaneous emphysema	1	1	0.03%	(0.00%, 0.17%)
Subcutaneous haematoma	1	1	0.03%	(0.00%, 0.17%)
Sudden cardiac death	10	10	0.31%	(0.15%, 0.57%)
Superior vena cava stenosis	1	1	0.03%	(0.00%, 0.17%)
Supraventricular extrasystoles	1	1	0.03%	(0.00%, 0.17%)
Supraventricular tachycardia	2	2	0.06%	(0.01%, 0.22%)
Syncope	1	1	0.03%	(0.00%, 0.17%)

MedDRA Preferred Term	Number of Occurrences	Number of Subjects	Event Rate	95% Confidence Interval
Tachycardia	1	1	0.03%	(0.00%, 0.17%)
Thrombophlebitis	2	2	0.06%	(0.01%, 0.22%)
Thrombosis	8	8	0.25%	(0.11%, 0.49%)
Thrombotic stroke	1	1	0.03%	(0.00%, 0.17%)
Toxicity to various agents	1	1	0.03%	(0.00%, 0.17%)
Twiddler's syndrome	5	5	0.15%	(0.05%, 0.36%)
Undersensing	7	7	0.22%	(0.09%, 0.44%)
Urinary retention	2	2	0.06%	(0.01%, 0.22%)
Vena cava thrombosis	1	1	0.03%	(0.00%, 0.17%)
Venous occlusion	1	1	0.03%	(0.00%, 0.17%)
Ventricular dyssynchrony	1	1	0.03%	(0.00%, 0.17%)
Ventricular extrasystoles	2	2	0.06%	(0.01%, 0.22%)
Ventricular fibrillation	1	1	0.03%	(0.00%, 0.17%)
Ventricular tachycardia	11	11	0.34%	(0.17%, 0.61%)
Vomiting	3	3	0.09%	(0.02%, 0.27%)
Weaning failure	1	1	0.03%	(0.00%, 0.17%)
Weight decreased	1	1	0.03%	(0.00%, 0.17%)
Wound dehiscence	1	1	0.03%	(0.00%, 0.17%)

Adverse Events in Literature

The potential AEs associated with the implantation of CRT-P or CRT-D systems have been documented in various articles in medical scientific literature. A summary of those events and their published incidence are included below.

1. Ahsan SY, Saberwal B, Lambiase PD, Chaubey S, Segal OR, Gopalamurugan AB, McCready J, Rogers DP, Lowe MD, and Chow AWC. An 8-year single-centre experience of cardiac

resynchronization therapy: procedural success, early and late complications, and left ventricular lead performance. Europace 2013;15:711-717.

Retrospective data were analyzed for all acute and chronic complications occurring over 490 consecutive CRT device procedures in 402 patients, from 2000 through 2008. Associated complications were reported by timeframe.

Table 25: Complications reported in Ahsan et al.

Table 3 Early and late complications by complication type[a]

Complication type	Early (<90 days) (*n*)	Late (>90 days) (*n*)	Mean time to late complication (months)
Death	1	0	–
Pneumothorax	2	0	–
Phrenic nerve stimulation requiring revision	3	4	11.4 (±8)
Infection	7	7	14.9 (±11)
Noise on RV/RA lead	1	3	17.0 (±22)
Box migration	2	1	15.0
RV/RA/LV lead fracture	1	4	33.1
Lead erosion	3	0	–
RV/RA lead displacement	6	6	4.9 (±2)
Inability to implant LV lead	13	–	–
LV lead displacement	5	5	6.8 (±4)
Total	44 (9.4%)	30 (6.1%)	

[a]This table shows all early and late complications and the mean time to their occurrence.

2. Dickstein K, Bogale N, Priori S, Auricchio A, Cleland JG, Gitt A, Limbourg T, Linde C, van Veldhuisen DJ, Brugada J; Scientific Committee; National Coordinators. The European Cardiac Resynchronization Therapy Survey. European Heart Journal 2009; 30:2450–2460.

The primary aim of this survey was to describe current European practice associated with CRT implantations. A total of 140 centers from 13 European countries contributed data from consecutive patients successfully implanted with a CRT device with or without an ICD between November 2008 and June 2009. The total number of patients enrolled was 2438.

Table 26: Complications reported in Dickstein et al.

Event	Incidence (%)
Peri-procedural complications	10
Bleeding	1
Pocket haematoma	3
Pneumothorax	1
Pericardial tamponade	0.3
Coronary sinus dissection	1
Phrenic nerve pacing	2
Lead dislocation	3

Post–implantation device related complications	4
Lead displacement	2
Lead malfunction	0
Phrenic nerve stimulation	2

3. Kirkfeldt R.E., Johansen J.B., Nohr E.A., Jorgensen O.D., Nielsen J.C. Complications after cardiac implantable electronic device implantations: An analysis of a complete, nationwide cohort in Denmark. European Heart Journal 2014 35:18 1186-1194.

This was a population-based cohort study in all Danish patients who underwent a Cardiac Implantable Electronic Device (CIED) procedure from May 2010 to April 2011. The study population consisted of 5918 consecutive patients. Total of 562 patients (9.5%) experienced at least one complication.

Table 27: Complications reported by Kirkfeldt et al. shows cumulative incidence of complications at 6 months[a].

Table 27: Complications reported by Kirkfeldt et al.

Complication type	**All (n=5918)**	**New Implant (n=4335)**	**Generator replacement (n=1136)**	**Upgrade/Lead revision (n=427)**
Any complication	562 (9.5; 8.7–10.2)	432 (9.9; 9.0–10.8)	67 (5.9; 4.5–7.3)	63 (14.8; 11.4–18.1)
Any major complication[b]	329 (5.6; 5.0–6.1)	253 (5.8; 5.1–6.5)	40 (3.5; 2.4–4.6)	36 (8.4; 5.8–11.1)
Any minor complication[c]	250 (4.2; 3.7–4.7)	189 (4.3; 3.7–4.9)	30 (2.6; 1.7–3.6)	31 (7.3; 4.8–9.7)
Major complications				
Lead related re-intervention	143 (2.4; 2.0–2.8)	120 (2.8; 2.3–3.2)	10 (0.9; 0.3–1.4)	13 (3.0; 1.4–4.7)
Infection	49 (0.8; 0.6–1.1)	24 (0.6; 0.3–0.8)	17 (1.5; 0.8–2.2)	8 (1.9; 0.6–3.2)
Local infection	22 (0.4; 0.2–0.5)	10 (0.2; 0.1–0.4)	8 (0.7; 0.2–1.1)	4 (1.0; 0.0–1.9)
Systemic infection/endocarditis	27 (0.5; 0.3–0.6)	14 (0.3; 0.2–0.5)	9 (0.8; 0.3–1.3)	4 (0.9; 0.0–1.9)
Pneumothorax requiring drainage	51 (0.9; 0.6–1.1)	45 (1.0; 0.7–1.3)	0	6 (1.4; 0.3–2.5)
Cardiac perforation	38 (0.6; 0.4–0.8)	35 (0.8; 0.5–1.1)	0	3 (0.7; 0.0–1.5)

Cardiac perforation (No intervention)	21 (0.4; 0.2–0.5)	18 (0.4; 0.2–0.6)	0	3 (0.7; 0.0–1.5)
Cardiac perforation (Intervention)	17 (0.3; 0.2–0.4)	17 (0.4; 0.2–0.6)	0	0
Pocket revision because of pain	25 (0.4; 0.3–0.6)	10 (0.2; 0.1–0.4)	9 (0.8; 0.3–1.3)	6 (1.4; 0.3–2.5)
Generator-lead interface problem with re-intervention	7 (0.1; 0.0–0.2)	3 (0.1; 0.0–0.1)	4 (0.4; 0.0–0.7)	0
Haematoma requiring re-intervention	10 (0.2; 0.1–0.3)	9 (0.2; 0.1–0.3)	1 (0.1; 0.0–0.3)	0
Other[d]	16 (0.3; 0.1–0.4)	16 (0.4; 0.2–0.5)	0	0
Minor complications				
Haematoma[e]	138 (2.3; 1.9–2.7)	104 (2.4; 1.9–2.8)	20 (1.8; 1.0–2.5)	14 (3.3; 1.6–5.0)
Wound infection treated with antibiotics	69 (1.2; 0.9–1.4)	47 (1.1; 0.8–1.4)	12 (1.0; 0.5–1.7)	10 (2.3; 0.9–3.8)
Pneumothorax conservatively treated	39 (0.7; 0.5–0.9)	32 (0.7; 0.5–1.0)	0	7 (1.6; 0.4–2.8)
Lead dislodgement without re-intervention	10 (0.2; 0.1–0.3)	9 (0.2; 0.1–0.3)	0	1 (0.2; 0.0–0.7)

[a]Reported as absolute frequencies and percentages with 95% CIs in parenthesis.

[b]All re-interventions were categorized as major complications due to their inherently higher risk of infections e.g. local CIED infections requiring re-intervention, systemic infections, pocket revisions etc.

[c]Minor complications included haematomas resulting in a prolonged hospital stay, hospital re-admissions, or additional out-patient visits, wound infections treated with antibiotics, pneumothorax conservatively treated, and lead dislodgements without re-intervention.

[d]Deep venous thrombosis (n=8), Twiddler's syndrome (n=3), wound revision (n=3), stroke (n=1), myocardial infarction (n=1)

[e]Resulting in prolonged hospital stay, hospital re-admission, or additional out-patient visit.

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