

IN.PACT AV Access

Randomized Study of IN.PACT™ AV Access Paclitaxel-Coated  
Percutaneous Transluminal Angioplasty (PTA) Balloon vs. Standard PTA  
for the Treatment of Obstructive Lesions in the Native Arteriovenous  
Dialysis Fistulae (AVF)

Clinical Investigation Plan Version 3.0  
26/APR/2019

NCT03041467

<p><b>Medtronic</b></p> <p><b>Clinical Investigation Plan</b></p>	
<b>Clinical Investigation Plan/Study Title</b>	IN.PACT™ AV Access Study Randomized Study of IN.PACT™ AV Access Paclitaxel-Coated Percutaneous Transluminal Angioplasty (PTA) Balloon vs. Standard PTA for the Treatment of Obstructive Lesions in the Native Arteriovenous Dialysis Fistulae (AVF)
<b>Clinical Investigation Plan Identifier</b>	APV-IN.PACT AV Access
<b>Study Product Name</b>	IN.PACT™ AV Access Paclitaxel-Coated PTA Balloon Catheter (“IN.PACT™ AV Access DCB <sup>1</sup> ”)
<b>Global Sponsor</b>	Medtronic Vascular, Inc. 3576 Unocal Place Santa Rosa, CA 95403 USA
<b>Local Sponsors</b>	Medtronic Japan Co., Ltd 1-2-70 Konan, Minato-ku, Tokyo 108-0075 Japan Protocol No.: MDT2-16-16 Investigational Device No.: MDT-2116  Medtronic Australasia Pty Ltd 5 Alma Road Macquarie Park NSW 2113 Australia
<b>Document Version</b>	3.0; 26-APR-2019
<b>Lead Principal Investigators</b>	Lead Principal Investigator(s) information will be provided under a separate cover.
<p><b>Confidentiality Statement</b></p> <p>The information contained in this document is confidential and the proprietary property of Medtronic. Any distribution, copying, or disclosure without the prior written authorization of Medtronic is strictly prohibited. Persons to whom the information is disclosed must know that it is confidential and that it may not be further disclosed by them.</p>	

<sup>1</sup>IN.PACT AV Access DCB was the device name used during the clinical study. Medtronic has changed the name of the device to IN.PACT™ AV Paclitaxel-Coated Balloon Catheter (also referred as IN.PACT AV DCB).

## **1. Investigator Statement**

The Investigator Statement will be a separate document from the clinical investigation plan.

## Table of Contents

1.	Investigator Statement .....	2
	Table of Contents .....	3
2.	Glossary .....	6
3.	Synopsis .....	11
4.	Introduction .....	18
4.1.	Background .....	18
4.2.	Purpose .....	19
5.	Objectives and Endpoints .....	20
5.1.	Objectives .....	20
5.1.1.	Primary Objective .....	20
5.2.	Endpoints .....	20
5.2.1.	Primary Endpoints .....	20
5.2.2.	Secondary Endpoints .....	20
6.	Study Design .....	22
6.1.	Duration .....	22
6.2.	Rationale .....	23
6.3.	Blinding .....	23
7.	Product Description .....	24
7.1.	General .....	24
7.2.	Manufacturer .....	28
7.3.	Packaging .....	28
7.4.	Intended Population .....	28
7.5.	Equipment .....	28
7.6.	Product Training Requirements .....	28
7.7.	Product Receipt and Tracking .....	29
7.8.	Product Storage .....	30
7.9.	Product Return .....	30
8.	Selection of Subjects .....	30
8.1.	Study Population .....	30
8.2.	Subject Enrollment .....	30
8.3.	Inclusion Criteria .....	31
8.4.	Exclusion Criteria .....	32
9.	Study Procedures .....	33

9.1.	Schedule of Events.....	33
9.2.	Subject Screening.....	43
9.3.	Prior and Concomitant Medications.....	43
9.4.	Subject Consent .....	43
9.5.	Randomization and Treatment Assignment .....	45
9.6.	Assessment of Safety .....	45
9.7.	Recording Data .....	45
9.8.	Deviation Handling.....	46
9.9.	Subject Withdrawal or Discontinuation.....	47
10.	Risks and Benefits .....	48
10.1.	Potential Risks.....	48
10.2.	Potential Benefits.....	51
10.3.	Risk-Benefit Rationale.....	51
11.	Adverse Event Assessments.....	52
11.1.	Definitions/Classifications .....	52
11.2.	Reporting of Adverse Events .....	54
11.3.	Emergency Contact Details.....	56
12.	Data Review Committees and Core Laboratories .....	56
12.1.	Data Monitoring Committee.....	56
12.2.	Clinical Event Committee.....	57
12.3.	Duplex Ultrasound Core Laboratory .....	57
12.4.	Angiographic Core Laboratory .....	57
13.	Statistical Design and Methods.....	57
13.1.	Hypotheses and Sample Size Calculation .....	57
13.2.	Analysis Strategy .....	60
13.3.	Analysis Sets.....	61
13.3.1.	Primary Analysis Set .....	61
13.3.2.	Secondary Analysis Set .....	61
13.4.	Analysis of the Primary Endpoints .....	61
13.4.1.	Primary Analysis of the Primary Endpoints .....	61
13.4.2.	Additional Analysis of the Primary Endpoints .....	62
13.4.3.	Sensitivity Analysis of the Primary Endpoints .....	62
13.4.4.	Poolability Analysis of the Primary Endpoints.....	63
13.5.	Analysis of the Secondary Endpoints.....	63
13.6.	Subset Analyses .....	64
13.7.	Patient withdrawal and Missing Data.....	65
14.	Ethics.....	65
14.1.	Statement(s) of Compliance .....	65



15. Study Administration ..... 67

    15.1. Investigator and Investigational Site Selection..... 67

    15.2. Training of Investigational Sites..... 67

    15.3. Investigator Responsibility / Performance ..... 67

    15.4. Role of Sponsor Representatives..... 68

    15.5. Monitoring..... 68

    15.6. Audits / Inspections ..... 69

    15.7. Data Management..... 69

    15.8. Direct Access to Source Data/Documents..... 70

    15.9. Confidentiality..... 70

    15.10. CIP Amendments..... 71

    15.11. Record Retention ..... 71

    15.12. Investigator reports..... 72

    15.13. Sponsor Reports ..... 74

    15.14. Publication and Use of Information ..... 75

    15.15. Suspension or Early Termination ..... 76

    15.16. Liability ..... 77

16. References..... 78

17. Appendices..... 80

    17.1. Instructions for Use..... 80

    17.2. Investigator Brochure ..... 81

    17.3. Labeling..... 82

    17.4. Master Informed Consent Form ..... 83

    17.5. Site and Investigator List..... 84

    17.6. IRB/EC Committee List..... 85

    17.7. CRO/Core Laboratories..... 86

    17.8. Sample Case Report Forms..... 87

    17.9. EQ-5D..... 88

    17.10. Medicare Coverage ..... 89

    17.11. Recommended Guidelines for Re-interventions..... 90

18. Version History..... 91

## 2. Glossary

### Abbreviations

AE	Adverse Event
AVF	Arteriovenous “Dialysis” Fistula
CBC	Complete Blood Count
CD-TLR	Clinically Driven Target Lesion Revascularization
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRO	Clinical Research Organization
CTA	Clinical Trial Agreement
DCB	Drug Coated Balloon
DD	Device Deficiency
DMC	Data Monitoring Committee
DOA/DTL	Delegation of Authority/Delegated Tasks List
DUS	Duplex Ultrasound
EC	Ethical Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESRD	End-Stage Renal Disease
FDA	Food and Drug Administration
HD	Hemodialysis
IB	Investigator Brochure
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonization – Good Clinical Practice
IDE	Investigational Device Exemption
IFU	Instructions for Use
IMRS	Interactive Mobile Response System
IRB	Institutional Review Board
ITT	Intent to Treat
ISO	International Organization for Standardization
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
OTW	Over-the-Wire
PHI	Protected Health Information
PI	Principal Investigator
PMA	Premarket Approval

PTA	Percutaneous Transluminal Angioplasty
RA	Regulatory Affairs
RBP	Rated Burst Pressure
RVD	Reference Vessel Diameter
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SID	Subject Identification Number
TLR	Target Lesion Revascularization
UADE	Unanticipated Adverse Device Effect
U.S.	United States
USADE	Unanticipated Serious Adverse Device Effect

**Definitions**

<b>Term</b>	<b>Definition</b>
Access Circuit	The area from the AV access fistula arterial anastomosis to the axillosubclavian junction.
Access Thrombosis	A total occlusion within the AV access circuit due to thrombus formation which is rapidly evolving as confirmed by sudden onset of symptoms and documented by duplex ultrasound and/or angiography
Adverse Device Effect (ADE)	See section 11.1
Adverse Event (AE)	See section 11.1
Arteriovenous “Dialysis” Fistulae (AVF)	The joining of an artery and vein for the purpose of hemodialysis access
Clinical Success	Resumption of successful dialysis for at least one session after index procedure
<i>De Novo</i> Lesion	A lesion that has not been previously treated
Device Deficiency	See section 11.1
Device Malfunction	Unexpected change to the device that is contradictory to the IFU and may or may not affect device performance



Term	Definition
Device Success	Successful delivery, inflation, deflation and retrieval of the intact study balloon device without burst at or below rated burst pressure (RBP) at index procedure
Dissection Types A-F	<p>Intimal disruption of the vessel wall with or without medial or adventitial contrast staining, classified as per the NHLBI (National Heart, Lung, and Blood Institute) criteria as follows:</p> <p><b>A) Luminal Haziness:</b> Minor radiolucent areas in the lumen without impairment of flow or persistent dye staining after contrast runoff.</p> <p><b>B) Linear Dissection:</b> Luminal flap that is radiolucent and that runs parallel to the vessel wall with contrast injection but without impairment of flow or persistent dye staining after contrast runoff.</p> <p><b>C) Extraluminal Contrast (i.e., "cap dissection"):</b> Contrast appears outside of the vessel lumen as an "extraluminal cap." The staining appears even after contrast clears the lumen.</p> <p><b>D) Spiral Dissection:</b> Spiral radiolucent luminal filling defects; often persistent staining after contrast clears from the vessel.</p> <p><b>E) Dissection with Reduced Flow:</b> New and persistent filling defects in the vessel lumen</p> <p><b>F) Dissection with Total Occlusion:</b> Lesions that progress to impaired flow or total occlusion</p>
Embolism	The obstruction of a blood vessel by a foreign substance or a blood clot that travels through the bloodstream, lodging in a blood vessel or plugging the vessel.
Enrollment	The time of randomization

Term	Definition
EQ-5D	EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal*
Geographic Miss	Balloon dilatation (or stent placement) at an unintended area of the vessel wall.
Optimal PTA	Repeated and prolonged balloon inflations aimed to achieve <50% residual stenosis (visual estimate) without stenting.
Procedural Success	Maintenance of patency ( $\leq 30\%$ residual stenosis) in the absence of peri-procedural serious adverse device effect (SADE)
Provisional Stenting	Placement of a stent due to sub-optimal PTA resulting in either of the following conditions: <ul style="list-style-type: none"> <li>• Residual stenosis of <math>\geq 50\%</math> (by visual estimate);</li> <li>• Major (<math>\geq</math> Grade D) flow-limiting dissection</li> </ul>
Serious Adverse Event (SAE)	See section 11.1
Spot Stenting	Utilization of a single, shortest stent which minimal length is sufficient to cover the residual stenosis
Steal Syndrome** Dialysis-associated steal syndrome (DASS)	Ischemic signs and symptoms (pain, diminished radial pulse, coldness, cyanosis, necrosis) produced by an access device as a result of the diversion of arterial blood flow into the AV fistula
Successful Dialysis	A complete dialysis session includes: <ul style="list-style-type: none"> <li>• Normal cannulation <i>and</i></li> <li>• Is not stopped prematurely</li> </ul>
Target Lesion Revascularization (TLR)	Any repeat invasive procedure, including angioplasty, stenting, or thrombolysis, performed to open or increase the lumen diameter within the previously treated lesion.  <i>Clinically-Driven Target Lesion Revascularization (CD-TLR):</i> Any re-intervention involving the target lesion in which:

Term	Definition
	<ul style="list-style-type: none"> <li>• The subject has a <math>\geq 50\%</math> diameter stenosis (per angiographic core lab assessment) <b>in the presence of</b> clinical or physiologic abnormalities that indicate dialysis access dysfunction <i>OR</i></li> <li>• <math>\geq 70\%</math> stenosis with or without the presence of clinical or physiologic abnormalities indicating dialysis access dysfunction</li> </ul> <p><i>Non-Clinically-Driven Target Lesion Revascularization: any re-intervention involving the target lesion which does not meet the criteria for CD-TLR.</i></p>

\* EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208

\*\* Defined by National Kidney Foundation KDOQI Guidelines

### 3. Synopsis

<b>Title</b>	<p><b>IN.PACT™ AV Access</b></p> <p>Randomized Study of IN.PACT™ AV Access Paclitaxel-Coated Percutaneous Transluminal Angioplasty (PTA) Balloon vs. Standard PTA for the Treatment of Obstructive Lesions in the Native Arteriovenous Dialysis Fistulae (AVF)</p>
<b>Clinical Study Type</b>	Pivotal
<b>Investigational Device</b>	IN.PACT™ AV Access Paclitaxel-Coated PTA Balloon Catheter (“IN.PACT™ AV Access DCB”)
<b>Global Sponsor</b>	<p>Medtronic Vascular, Inc.                      3576 Unocal Place                      Santa Rosa                      California 95403, United States</p>
<b>Local Sponsor(s)</b>	<p>Medtronic Japan Co., Ltd                      1-2-70 Konan, Minato-ku, Tokyo 108-0075 Japan                      Protocol No.: MDT2-16-16                      Investigational Device No.: MDT-2116</p> <p>Medtronic Australasia Pty Ltd                      5 Alma Road                      Macquarie Park NSW 2113                      Australia</p>
<b>Indication Under Investigation</b>	The IN.PACT™ AV Access Paclitaxel-Coated PTA balloon catheter is indicated for percutaneous transluminal angioplasty, after pre-dilatation, for the treatment of obstructive lesions up to 100 mm in length in the native arteriovenous dialysis fistulae with reference vessel diameters of 4 to 12 mm.
<b>Investigation Purpose</b>	To evaluate the safety and efficacy of the IN.PACT™ AV Access Drug Coated Balloon (DCB) compared to percutaneous transluminal angioplasty (PTA) for treatment of subjects presenting with <i>de novo</i> or

	non-stented restenotic obstructive lesion of native arteriovenous dialysis fistulae (AVF) in the upper extremity.
<b>Product Status</b>	The IN.PACT™ AV Access DCB is investigational in the United States, Japan, and New Zealand.
<b>Primary Efficacy Endpoint</b>	<p><b>Target Lesion Primary Patency Rate through 6 Months</b></p> <p>Defined as freedom from clinically-driven target lesion revascularization (CD-TLR) or access circuit thrombosis measured through 6 months post-procedure.</p>
<b>Primary Safety Endpoint</b>	<p><b>Serious Adverse Event Rate within 30 Days</b></p> <p>Defined as the Serious Adverse Event (SAE) rate involving the AV access circuit through 30 days post-procedure.</p>
<b>Secondary Endpoints</b>	<p>Secondary endpoints assessed through 24-month for the study are as follows:</p> <p><b>Access Circuit Primary Patency through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure</b></p> <p>Defined as freedom from re-intervention in the access circuit or access circuit thrombosis through 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.</p> <p><b>Target Lesion Primary Patency through 3 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure</b></p> <p>Defined as freedom from CD-TLR or access thrombosis occurring in the target lesion through 3 months, 9 months, 12 months, 18 months, and 24 months post-procedure.</p> <p><b>Cumulative Target Lesion Revascularizations Measured through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure</b></p> <p>Defined as proportion of subjects with TLR through 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.</p>

	<p><b>Number of Interventions Required to Maintain Target Lesion Patency through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure</b></p> <p>Defined as number of TLR through 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.</p> <p><b>Number of Interventions Required to Maintain Access Circuit Patency through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure</b></p> <p>Defined as number of reinterventions in the target lesion and/or access circuit through 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.</p> <p><b>Cumulative Access Circuit Thromboses Measured through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure</b></p> <p>Defined as proportion of subjects with access circuit thrombosis through 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.</p> <p><b>Device, Procedure, and Clinical Success</b></p> <p>Device Success: Defined as successful delivery, inflation, deflation and retrieval of the intact study balloon device without burst at or below rated burst pressure (RBP) at index procedure</p> <p>Procedural Success: defined as maintenance of patency (<math>\leq 30\%</math> residual stenosis) in the absence of peri-procedural serious adverse device effect (SADE)</p> <p>Clinical Success: defined as resumption of successful dialysis for at least one session after index procedure</p> <p><b>Rate of Device and Procedure Related Adverse Events Reported through 30 Days, 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure</b></p> <p>Device Related Adverse Event Rate: defined as proportion of subjects with device related Adverse Events reported through 30 days, 3 months,</p>
--	---

	<p>6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.</p> <p>Procedure Related Adverse Event Rate: defined as proportion of subjects with procedure related Adverse Events reported post-index procedure until the first successful dialysis session.</p> <p>The following endpoints will be assessed annually up to 60 months in addition to the assessment through 24 months where applicable:</p> <p><b>Target Lesion Revascularizations</b></p> <p>Defined as proportion of subjects with TLR up to 60 months post-index procedure</p> <p><b>Clinically-Driven Target Lesion Revascularizations</b></p> <p>Defined as proportion of subjects with CD-TLR up to 60 months post-index procedure</p> <p><b>Re-interventions in the access circuit</b></p> <p>Defined as proportion of subjects with reinterventions occurring within the access circuit up to 60 months post-index procedure</p> <p><b>Abandonment of Target AVF</b></p> <p>Defined as proportion of subjects with abandonment of the target AV abandonment up to 60 months post-index procedure</p> <p><b>Serious Adverse Events</b></p> <p>Defined as the Serious Adverse Event (SAE) rate up to 60 months post-index procedure.</p>
<p><b>Study Design</b></p>	<p>A prospective, global, multicenter, single-blinded, randomized (1:1) clinical study evaluating the IN.PACT™ AV Access DCB (study arm) vs standard PTA (control arm) for the treatment of obstructive lesions up to 100 mm in length in the native arteriovenous dialysis fistulae.</p>
<p><b>Randomization</b></p>	<p>Subjects will be randomized in a ratio of 1:1 to either the IN.PACT™ AV Access DCB (study arm) or a standard PTA balloon (control arm).</p>

	Randomization will be stratified based on lesion status: <i>de novo</i> or restenotic within study sites.
<b>Sample Size</b>	330 Subjects
<b>Number of Sites</b>	Up to 30 global investigational sites in the United States, New Zealand and Japan.
<b>Study Population</b>	Subjects with a <i>de novo</i> or non-stented restenotic obstructive lesion up to 100 mm in length, located in the native arteriovenous dialysis fistulae.
<b>Inclusion/Exclusion Criteria</b>	<p><b>Inclusion</b></p> <ol style="list-style-type: none"> <li>1. Patient is <math>\geq 21</math> years of age</li> <li>2. Patient has a life expectancy of <math>\geq 12</math> months</li> <li>3. Patient has a native AV fistula created <math>\geq 60</math> days prior to the index procedure</li> <li>4. The target AV fistula has undergone successful dialysis for at least 8 of 12 sessions during a four week period</li> <li>5. Patient has a <i>de novo</i> and/or non-stented restenotic lesion located between the arteriovenous anastomosis and axillosubclavian junction with <math>\geq 50\%</math> stenosis</li> </ol> <p><i>Note:</i> If the lesion is located in the anastomosis, the treatment may be delivered up to 2 cm upstream on the arterial side</p> <p><i>Note:</i> If the lesion is located in the cephalic arch, the treatment may be delivered up to 2 cm into the subclavian vein</p> <ol style="list-style-type: none"> <li>6. Patient has a target lesion or a tandem lesion that is <math>\leq 100</math> mm in length (by visual estimate)</li> </ol> <p><i>Note:</i> Tandem lesions may be enrolled provided they meet <u>all</u> of the following criteria:</p>



- Separated by a gap of  $\leq 30\text{mm}$  (3 cm)
  - Total combined lesion length, including 30 mm gap,  $\leq 100$  mm
  - Able to be treated as a single lesion
7. Patient has a target vessel diameter of 4.0 – 12.0 mm (by visual estimate)
  8. Patient underwent successful crossing of the target lesion with the guide wire and pre-dilatation with a high pressure PTA balloon defined as:
    - Residual stenosis of  $\leq 30\%$  AND
    - Absence of a flow limiting dissection (Grade  $\geq C$ ) or perforation
  9. Patient provides written informed consent prior to enrollment in the study
  10. Patient is willing to comply with all follow-up evaluations at specified times

**Exclusion Criteria:**

1. Women who are breastfeeding, pregnant, or are intending to become pregnant, or men intending to father children
2. Patient is receiving immunosuppressive therapy
3. Patient is anticipating a kidney transplant within 6 months of enrollment into the study
4. Patient has undergone prior intervention of access site within 30 days of index procedure
5. Patient with anticipated conversion to peritoneal dialysis
6. Patient has an infected AV access or systemic infection
7. Patient has planned surgical revision of access site
8. Patient with secondary non-target lesion requiring treatment within 30-days post index procedure
9. Patient with hemodynamically significant central venous stenoses that cannot be successfully treated prior to treatment of the target lesion
10. Patient with target AVF or access circuit which previously had or currently has a thrombosis

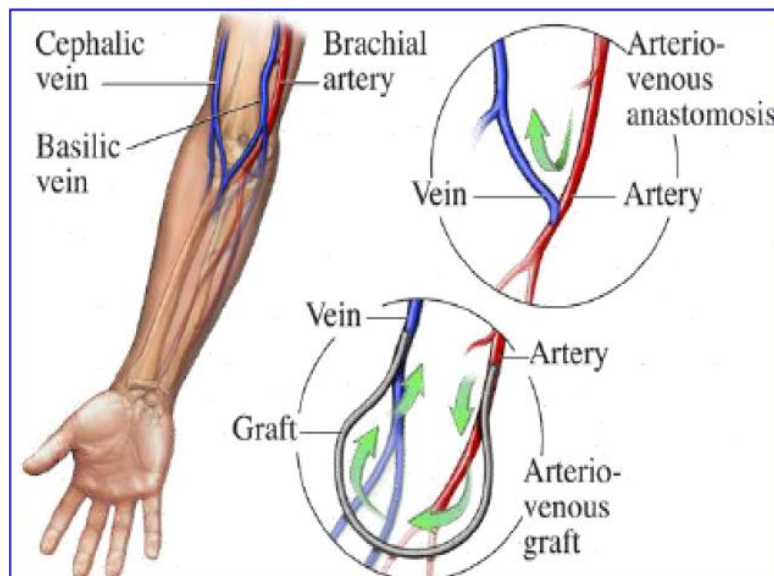


	<ol style="list-style-type: none"> <li>11. Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system</li> <li>12. Patient with target lesion located central to the axillosubclavian junction</li> <li>13. Patient has significant arterial inflow lesion requiring treatment more than 2 cm upstream from the anastomosis in the AV access</li> <li>14. Patient has presence of pseudoaneurysm or aneurysm requiring treatment at the lesion site</li> <li>15. Patient has presence of a stent located in the target AV access circuit</li> <li>16. Patients with known allergies or sensitivities to paclitaxel</li> <li>17. Patient with known contraindication, including allergic reaction, or sensitivity to contrast material that cannot be adequately pre-treated</li> <li>18. Patient who cannot receive recommended antiplatelet and/or anticoagulant therapy</li> <li>19. Patient with clinically significant Steal Syndrome requiring treatment</li> <li>20. Patient is enrolled in another investigational drug, device, or biologic study and has not completed the primary endpoint, or was previously enrolled in this study</li> <li>21. Patient has a co-morbid condition that, in the judgment of the Investigator, may cause him/her to be non-compliant with the protocol or confound the data interpretation.</li> </ol>
<p><b>Subject Follow-up</b></p>	<p>Subjects randomized and enrolled in the study will be followed up to 5 years. Follow-up assessments are scheduled for 30-day, 3, 6, 9, 12, 18, 24, 36, 48, and 60-months post index procedure.</p>
<p><b>Time Course</b></p>	<p>Start of enrollment: 25-APR-2017                  Enrollment completed: 10-MAY-2018                  Planned study close-out: approximately October 2023</p>

## 4. Introduction

### 4.1. Background

The incidence of end-stage renal disease (ESRD) has been escalating and the creation of the hemodialysis (HD) access has become a common vascular procedure in the form of either an autologous arteriovenous dialysis fistula (AVF) or prosthetic graft (AVG), see Figure 1<sup>1</sup>. In the United States and Japan, according to the United States Renal Data System (USRDS), the incidence rates of ESRD in 2010 were 369 per million and 288 per million, respectively, with a prevalence rate in the U.S. of 1,870 per million and 2,260 per million in Japan<sup>2</sup>. In Europe, there are an estimated 65,000 new ESRD patients/year, ~80% of which received HD treatment<sup>3</sup>.



**Figure 1: Hemodialysis Access by Arteriovenous Fistula or Arteriovenous Graft**

Dysfunction of the dialysis circuit is a significant cause of morbidity and mortality in patients undergoing HD which can eventually lead to loss of vascular access<sup>4,5</sup>. At 12 months, primary patency rates of 49% and 14% for forearm AVFs and AVGs, respectively, have been reported by Turmel-Rodrigues et al.<sup>6</sup> These conduits have a high rate of failure mainly because of the development of a neointimal hyperplasia response after endothelial and smooth muscle injury that results in the formation of stenotic lesions at the anastomotic site and/or along the venous outflow tract.<sup>7</sup> Mortality rates vary depending on the ESRD treatment. After one year of treatment, those on dialysis have a 20-25% mortality rate, with a 5-year survival rate of 35%<sup>8</sup>.

PTA is the current standard for the treatment of flow limiting stenotic lesions within the dialysis circuit, however, angioplasty itself results in vessel trauma that can further drive the intimal hyperplasia and the subsequent development of restenosis that necessitates repeat procedures. Balloon angioplasty of vascular access is characterized by poor midterm patency and high rate of reintervention.<sup>9</sup>

Acceptable secondary patency rates require multiple repeated reinterventions which adds to the patient hospitalization time and contributes to the economic burden of maintaining functioning dialysis access.

Localized delivery of antiproliferative drugs, such as paclitaxel, have been proven safe and effective in inhibition of neointimal hyperplasia and effective reduction of vascular restenosis after PTA in coronary and peripheral arteries.<sup>10,11,12</sup>

Initial clinical data following treatment of failing AV access with IN.PACT™ DCB reports improved primary patency of the target lesion and a reduction in the need for future revascularizations. In addition, no new safety concerns were identified in this patient population with limited options who represents a significantly unmet clinical need.

Therefore, Medtronic is seeking to obtain an indication for use for the IN.PACT™ AV Access DCB.

For further literature review, pre-clinical testing and previous clinical experience refer to the Investigator Brochure.

## **4.2. Purpose**

The purpose of this study is to collect and evaluate safety and efficacy data of the IN.PACT™ AV Access DCB in order to support regulatory applications in seeking market approval with the following indication in the U.S./Japan and possibly other geographies:

*The IN.PACT™ AV Access Paclitaxel-Coated PTA balloon catheter is indicated for percutaneous transluminal angioplasty, after pre-dilatation, for the treatment of obstructive lesions up to 100 mm in length in the native arteriovenous dialysis fistulae with reference vessel diameters of 4 to 12 mm.*

## 5. Objectives and Endpoints

### 5.1. Objectives

#### 5.1.1. Primary Objective

To evaluate the safety and efficacy of the IN.PACT™ AV Access Drug Coated Balloon (DCB) compared to PTA for treatment of subjects presenting with obstructive lesions of native arteriovenous dialysis fistulae (AVF) in the upper extremity.

### 5.2. Endpoints

#### 5.2.1. Primary Endpoints

Primary endpoints for the study are as follows:

**Primary Efficacy Endpoint: Target Lesion Primary Patency Rate through 6 Months**

Defined as freedom from clinically-driven target lesion revascularization (CD-TLR) or access circuit thrombosis measured through 6 months post-procedure.

**Primary Safety Endpoint: Serious Adverse Event Rate within 30 Days**

Defined as the Serious Adverse Event (SAE) rate involving the AV access circuit through 30 days post-procedure.

#### 5.2.2. Secondary Endpoints

Secondary endpoints assessed through 24-month for the study are as follows:

**Access Circuit Primary Patency through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure**

Defined as freedom from re-intervention in the access circuit or access circuit thrombosis through 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.

**Target Lesion Primary Patency through 3 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure**

Defined as freedom from CD-TLR or access thrombosis occurring in the target lesion through 3 months, 9 months, 12 months, 18 months, and 24 months post-procedure.

**Cumulative Target Lesion Revascularizations Measured through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure**

Defined as proportion of subjects with TLR through 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.

**Number of Interventions Required to Maintain Target Lesion Patency through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure**

Defined as number of TLR through 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.

**Number of Interventions Required to Maintain Access Circuit Patency through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure**

Defined as number of reinterventions in the target lesion and/or access circuit through 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.

**Cumulative Access Circuit Thromboses Measured through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure**

Defined as proportion of subjects with access circuit thrombosis through 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.

**Device, Procedure, and Clinical Success**

Device Success: Defined as successful delivery, inflation, deflation and retrieval of the intact study balloon device without burst at or below rated burst pressure (RBP) at index procedure

Procedural Success: defined as maintenance of patency ( $\leq 30\%$  residual stenosis) in the absence of periprocedural serious adverse device effect (SADE)

Clinical Success: defined as resumption of successful dialysis for at least one session after index procedure

**Rate of Device and Procedure Related Adverse Events Reported through 30 Days, 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure.**

Device Related Adverse Event Rate: defined as proportion of subjects with device related Adverse Events reported through 30 days, 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.

Procedure Related Adverse Event Rate: defined as proportion of subjects with procedure related Adverse Events reported post-index procedure until the first successful dialysis session.

The following endpoints will be assessed annually up to 60 months in addition to the assessment through 24 months where applicable:

**Target Lesion Revascularizations**

Defined as proportion of subjects with TLR up to 60 months post-index procedure

**Clinically-Driven Target Lesion Revascularizations**

Defined as proportion of subjects with CD-TLR up to 60 months post-index procedure

**Re-interventions in the access circuit**

Defined as proportion of subjects with reinterventions occurring within the access circuit up to 60 months post-index procedure

**Abandonment of Target AVF**

Defined as proportion of subjects with abandonment of the target AV abandonment up to 60 months post-index procedure

**Serious Adverse Events**

Defined as the Serious Adverse Event (SAE) rate up to 60 months post-index procedure.

## 6. Study Design

This is a prospective, global, multicenter, single-blinded, randomized (1:1) clinical study evaluating the IN.PACT™ AV Access DCB (study arm) vs. standard PTA (control arm) for the treatment of *de novo* or non-stented restenotic obstructive lesions up to 100 mm in length in the arteriovenous dialysis fistulae. All eligible subjects who provide informed consent and meet all inclusion/exclusion criteria will be randomized 1:1 based upon lesion type (*de novo*, restenotic) to the control or study arm. Total enrollment will be 330 subjects at up to 30 global sites, with a minimum of 50% (165) of subjects coming from the U.S. sites, and a minimum of 30% (99) of subjects coming from the Japan sites. There is no minimum enrollment requirement at each site; however, individual sites may enroll no more than 20% of the total study subjects. Approximately 165 study devices will be used in this study.

### 6.1. Duration

Once enrolled, subjects will remain in the study through completion of the required follow-up duration unless the subject withdraws consent, the investigator withdraws the subject, or Medtronic terminates

the study for any reason. The enrollment phase is expected to take 15 months. The follow-up duration for each subject is up to 60 months. The total expected duration of the study is approximately 6 years.

## 6.2. Rationale

The clinical performance of the IN.PACT™ AV Access DCB will be evaluated through a prospective, global, multicenter, single-blinded, randomized (1:1) clinical study in a total of 330 subjects with a hypothesis-based 30-day primary safety endpoint and a 6-month primary efficacy endpoint. The study has been designed with the assumption of a target lesion primary patency rate of 60% for the study arm and 40% for the control arm. The safety endpoint composite rate is assumed 5% for both study arms. The assumptions for endpoint rates were based upon publicly available information from currently marketed devices and the literature. See Section 14.1 for further details on the statistical method.

PTA is the current standard for treatment of flow limiting stenotic lesions within the dialysis circuit. PTA may cause vessel trauma leading to neointimal hyperplasia resulting in poor midterm patency, and therefore, an increased rate of reinterventions. The addition of the antiproliferative drug, paclitaxel, has been proven in other vessel beds to be safe and effective in the inhibition of neointimal hyperplasia and reduction of vascular restenosis.<sup>8</sup>

## 6.3. Blinding

The study subjects will remain blinded through completion of the 6-month primary efficacy endpoint, including completion of all associated evaluations. Independent Core Laboratories and the Clinical Events Committee (CEC) will be blinded to the treatment assigned through the entire study duration.

Study site staff (implanting physicians, catheterization lab staff, and other research staff) will not be blinded to treatment assignment due to the macroscopic visual differences between the investigational device and the control device. As study investigators are not blinded to the subject's treatment assignment, no procedures to break the blind in the case of an emergency are required.

Medtronic representatives whose responsibilities require knowledge of treatment assignment to perform their respective roles will not be blinded. Designated individuals within the IN.PACT™ AV Access study team, Data Solutions, Safety, Customer Service (responsible for device shipment and accountability), and Regulatory will not be blinded. Clinical Customer Service, a small group of individuals who will be responsible for device shipment and reconciliation, will be unblinded, as will the team of monitors assigned to the study.



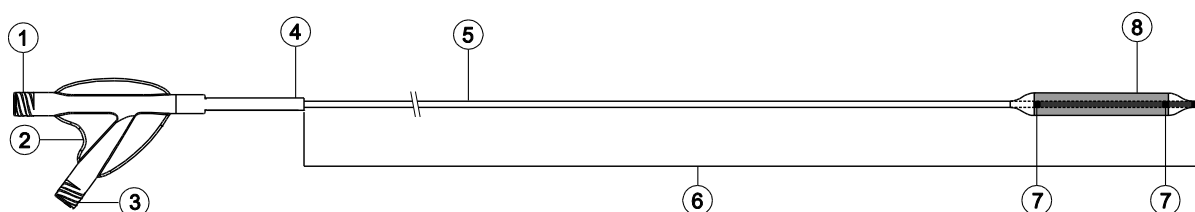
Unblinded individuals within Medtronic and at the study sites will receive guidance on preserving the blind as required.

## 7. Product Description

### 7.1. General

#### Device Description

The investigational device being evaluated in this study is the IN.PACT™ AV Access Paclitaxel-Coated PTA Balloon Catheter (“IN.PACT™ AV Access DCB”) and is not currently commercially available in the U.S., Japan, or New Zealand, see Figure 2. The IN.PACT™ AV Access DCB is an over-the-wire (OTW) balloon catheter with a drug coated balloon at the distal tip. The drug component consists of paclitaxel and the excipient, urea. IN.PACT™ AV Access DCB catheter is dual-lumen shaft which is branched at the proximal end so that one tube forms the entrance to the central lumen for the guide wire, while the other tube is used to inflate and deflate the dilation balloon with a mixture of contrast medium and saline solution. The catheter construction and the balloon material are designed so that a specific balloon diameter can be reached, depending on the balloon size and defined pressure.



**Figure 2: Schematic of the IN.PACT™ AV Access Paclitaxel-coated PTA Balloon Catheter**

1. Guidewire Port
2. Hub
3. Inflation Port
4. Strain Relief
5. Shaft
6. Usable Catheter Length
7. Radiopaque Marker
8. Balloon

The device has two modes of action: the balloon’s PTA mechanical dilatation of the vessel lumen and drug delivery to the vessel wall intended to inhibit the restenosis normally caused by the proliferative

response to the PTA. IN.PACT™ AV Access DCB is based on the design of the currently FDA- approved IN.PACT™ Admiral DCB indicated for treatment of *de novo*, restenotic, or in-stent restenotic lesions in the superficial femoral (SFA) or popliteal arteries (PA).

The investigational *Instructions for Use* (IFU), see Section 17.1- Instructions for Use, will be the primary source of information for the device and will be packaged with the investigational device or provided to the study sites as needed throughout the study. Table 1 summarizes the IN.PACT™ AV Access DCB balloon and catheter working lengths characteristics including available sizes, nominal pressures, rated burst pressures, and sheath compatibility. Table 2 lists the IN.PACT™ AV Access model numbers for all geographies.

**Table 1: IN.PACT™ AV Access DCB Characteristics**

	Balloon Diameter (mm)	Balloon Length (mm)				
		40	60	80	120	150
<b>Available Balloon Diameters (mm) and Lengths (mm)</b>	4.0	X	X	X	X	X
	5.0	X	X	X	X	X
	6.0	X	X	X	X	X
	7.0	X	X	X	---	---
	8.0	X	X	X	---	---
	9.0	X	X	X	---	---
	10.0	X	---	---	---	---
	12.0	X	---	---	---	---
	<b>Note:</b> "—" indicates size not offered; "x" indicates sizes offered					
<b>Usable Catheter Lengths</b>	40 cm, 80 cm and 130 cm*					
<b>Balloon Inflation Pressure</b>	Balloon Diameter (mm)	Nominal Pressure (atm)		Rated Burst Pressure (atm)		
	4.0	8		14		
	5.0					
	6.0					
	7.0					
	8.0	6		10		
	9.0					
	10.0	6		9		
	12.0					
<b>Minimum Introducer Sheath Compatibility</b>	Balloon Diameter (mm)	Max Crossing Profile (mm)		Introducer Sheath		
	4.0	1.88		5 Fr		
	5.0	2.00		6 Fr		
	6.0	2.10				
	7.0	2.33		7 Fr		
	8.0					
	9.0					
	10.0					
	12.0	3.00		9 Fr		
<b>Guidewire Compatibility</b>	The catheter is compatible with a guidewire diameter of 0.035 in (0.89 mm).					

\* For the clinical trial only the 40 cm and 80 cm catheter lengths will be made available

**Table 2: Study Device Model Numbers (All Geographies)**

Balloon Diameter (mm)	Balloon Length (mm)	Model Number (40 cm Catheter)	Model Number (80 cm Catheter)	Model Number (130 cm Catheter*)
4.0	40	AVC 040 040 04P	AVC 040 040 08P	AVC 040 040 13P
4.0	60	AVC 040 060 04P	AVC 040 060 08P	AVC 040 060 13P
4.0	80	AVC 040 080 04P	AVC 040 080 08P	AVC 040 080 13P
4.0	120	AVC 040 120 04P	AVC 040 120 08P	AVC 040 120 13P
4.0	150	AVC 040 150 04P	AVC 040 150 08P	AVC 040 150 13P
5.0	40	AVC 050 040 04P	AVC 050 040 08P	AVC 050 040 13P
5.0	60	AVC 050 060 04P	AVC 050 060 08P	AVC 050 060 13P
5.0	80	AVC 050 080 04P	AVC 050 080 08P	AVC 050 080 13P
5.0	120	AVC 050 120 04P	AVC 050 120 08P	AVC 050 120 13P
5.0	150	AVC 050 150 04P	AVC 050 150 08P	AVC 050 150 13P
6.0	40	AVC 060 040 04P	AVC 060 040 08P	AVC 060 040 13P
6.0	60	AVC 060 060 04P	AVC 060 060 08P	AVC 060 060 13P
6.0	80	AVC 060 080 04P	AVC 060 080 08P	AVC 060 080 13P
6.0	120	AVC 060 120 04P	AVC 060 120 08P	AVC 060 120 13P
6.0	150	AVC 060 150 04P	AVC 060 150 08P	AVC 060 150 13P
7.0	40	AVC 070 040 04P	AVC 070 040 08P	AVC 070 040 13P
7.0	60	AVC 070 060 04P	AVC 070 060 08P	AVC 070 060 13P
7.0	80	AVC 070 080 04P	AVC 070 080 08P	AVC 070 080 13P
8.0	40	AVC 080 040 04P	AVC 080 040 08P	AVC 080 040 13P
8.0	60	AVC 080 060 04P	AVC 080 060 08P	AVC 080 060 13P
8.0	80	AVC 080 080 04P	AVC 080 080 08P	AVC 080 080 13P
9.0	40	AVC 090 040 04P	AVC 090 040 08P	AVC 090 040 13P
9.0	60	AVC 090 060 04P	AVC 090 060 08P	AVC 090 060 13P
9.0	80	AVC 090 080 04P	AVC 090 080 08P	AVC 090 080 13P
10.0	40	AVC 100 040 04P	AVC 100 040 08P	AVC 100 040 13P
12.0	40	AVC 120 040 04P	AVC 120 040 08P	AVC 120 040 13P

\* For the clinical trial only the 40 cm and 80 cm catheter lengths will be made available

## 7.2. Manufacturer

The IN.PACT™ AV Access DCB will be manufactured in accordance with standard procedures and specifications under 21 CFR 820 and EN ISO13485. The manufacturer is listed below:

Medtronic, Inc.  
710 Medtronic Parkway  
Minneapolis, MN  
55432 USA

## 7.3. Packaging

The IN.PACT™ AV Access DCB is delivered in a sterile package for single use only. See Section 17.3 – Labeling, for specific language on the device label.

## 7.4. Intended Population

Subjects will be 21 years of age or older with a *de novo* or non-stented restenotic lesion in the AVF in the upper extremity with a reference vessel diameter (RVD) between 4.0 - 12.0 mm which is amenable to PTA.

The IN.PACT™ AV Access Paclitaxel-Coated PTA balloon catheter is indicated for percutaneous transluminal angioplasty, after pre-dilatation, for the treatment of obstructive lesions up to 100 mm in length in the native arteriovenous dialysis fistulae with reference vessel diameters of 4 to 12 mm.

## 7.5. Equipment

Any test equipment critical to be used for assessing endpoints (e.g., Duplex Ultrasound, angiography, etc.) will be maintained/calibrated according to the site's standard protocol. Maintenance and calibration reports will be monitored periodically.

## 7.6. Product Training Requirements

The treating investigator will be evaluated to ensure that he/she is qualified by training, education, and experience in PTA. The treating investigators will be trained on the IN.PACT™ AV Access CIP prior to performing study related procedures.

## 7.7. Product Receipt and Tracking

Medtronic will provide study sites with Investigational devices per the site specific Clinical Trial Agreement (CTA) terms. Investigational devices will not be shipped to the study sites until they have received approval from their corresponding regulatory agency and IRB/EC, and an executed CTA is in place. The investigational device must be used only in the IN.PACT™ AV Access Study.

All sites will be trained on device accountability, including the return of opened or unopened devices (for defect, damage, malfunction, expired inventory). Device accountability should be captured on the Product Accountability Log if the site does not perform direct data entry into the Device Tracking eCRF.

The Principal Investigator (PI) is responsible for maintaining adequate records of the receipt and disposition of all IN.PACT™ AV Access DCB systems. All sites are required to maintain investigational device records that contain the following information on all components shipped to the site for the study:

- Subject ID
- Party Responsible (upon receipt)
- Product Received by (name)
- Receipt Date
- Model/Reference Identifier
- Serial Number
- Expiration Date
- Date Used
- State of the device (unused, returned, disposed, in use)
- Date of Return or Disposal
- Method of Return or Disposal
- Product Disposal By (name)
- Reason for Tracking/ Disposition Event
- Quantity of Tracked Device

For devices that are returned to Medtronic or disposed of, sites are required to document the following additional information:

- The reason for the device being returned to Medtronic or disposed of
- Name of the person who returned or disposed of each device
- Date shipped to Medtronic, if returned
- If device is disposed of, the method of disposal

The monitor will check the device storage/management conditions.

In Japan, the procedures for managing the study device will be provided by the sponsor.

## 7.8. Product Storage

The investigational device, IN.PACT™ AV Access DCB, must be stored per the investigational IFU at the site in a secure area that is accessible and controlled only by the assigned, trained study personnel.

## 7.9. Product Return

In the event of a device deficiency of the IN.PACT™ AV Access DCB system prior to, during, or after device use, the device should be returned to Medtronic, if possible. Sites should contact their Medtronic clinical study representative to obtain further instruction on device return procedures. All returned devices will be analyzed by Medtronic. At the end of the study enrollment period, all remaining investigational devices must be returned to Medtronic.

# 8. Selection of Subjects

## 8.1. Study Population

This study will enroll subjects with a *de novo* or non-stented restenotic obstructive lesions up to 100 mm in length, located in the native arteriovenous dialysis fistulae. The complete lists of eligibility criteria can be found in Section 8.3 - Inclusion Criteria and Section 1 - Exclusion Criteria.

## 8.2. Subject Enrollment

A subject will be enrolled in the study after he/she has signed the informed consent, it has been determined that he/she meets all of the inclusion criteria and none of the exclusion criteria, and successful pre-dilatation has been performed.

**The point of enrollment is defined as the moment randomization occurs.**

See Section 10.5 - Randomization and Treatment Assignment, for further information.

### 8.3. Inclusion Criteria

1. Patient is  $\geq 21$  years of age
2. Patient has a life expectancy of  $\geq 12$  months
3. Patient has a native AV fistula created  $\geq 60$  days prior to the index procedure
4. The target AV fistula has undergone successful dialysis for at least 8 of 12 sessions during a four week period
5. Patient has a *de novo* and/or non-stented restenotic lesion located between the arteriovenous anastomosis and axillosubclavian junction with  $\geq 50\%$  stenosis

*Note:* If the lesion is located in the anastomosis, the treatment may be delivered up to 2 cm upstream on the arterial side

*Note:* If the lesion is located in the cephalic arch, the treatment may be delivered up to 2 cm into the subclavian vein

6. Patient has a target lesion or a tandem lesion that is  $\leq 100$  mm in length (by visual estimate)

*Note:* Tandem lesions may be enrolled provided they meet all of the following criteria:

- Separated by a gap of  $\leq 30$ mm (3 cm)
  - Total combined lesion length, including 30 mm gap,  $\leq 100$  mm
  - Able to be treated as a single lesion
7. Patient has a target vessel diameter of 4.0 – 12.0 mm (by visual estimate)
  8. Patient underwent successful crossing of the target lesion with the guide wire and pre-dilatation with a high pressure PTA balloon defined as:
    - Residual stenosis of  $\leq 30\%$  AND
    - Absence of a flow limiting dissection (Grade  $\geq C$ ) or perforation
  9. Patient provides written informed consent prior to enrollment in the study
  10. Patient is willing to comply with all follow-up evaluations at specified times



## 8.4. Exclusion Criteria

1. Women who are breastfeeding, pregnant, or are intending to become pregnant, or men intending to father children
2. Patient is receiving immunosuppressive therapy
3. Patient is anticipating a kidney transplant within 6 months of enrollment into the study
4. Patient has undergone prior intervention of access site within 30 days of index procedure
5. Patient with anticipated conversion to peritoneal dialysis
6. Patient has an infected AV access or systemic infection
7. Patient has planned surgical revision of access site
8. Patient with secondary non-target lesion requiring treatment within 30 days post index procedure
9. Patient with hemodynamically significant central venous stenoses that cannot be successfully treated prior to treatment of the target lesion
10. Patient with target AVF or access circuit which previously had or currently has a thrombosis
11. Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the delivery system
12. Patient with target lesion located central to the axillosubclavian junction
13. Patient has significant arterial inflow lesion requiring treatment more than 2 cm upstream from the anastomosis in the AV access
14. Patient has presence of pseudoaneurysm or aneurysm requiring treatment at the lesion site
15. Patient has presence of a stent located in the target AV access circuit
16. Patients with known allergies or sensitivities to paclitaxel
17. Patient with known contraindication, including allergic reaction, or sensitivity to contrast material that cannot be adequately pre-treated
18. Patient who cannot receive recommended antiplatelet and/or anticoagulant therapy
19. Patient with clinically significant Steal Syndrome requiring treatment
20. Patient is enrolled in another investigational drug, device, or biologic study and has not completed the primary endpoint, or was previously enrolled in this study
21. Patient has a co-morbid condition that, in the judgment of the Investigator, may cause him/her to be non-compliant with the protocol or confound the data interpretation

## 9. Study Procedures

### 9.1. Schedule of Events

Figure 3 provides a flow diagram from the point of subject screening through the follow-up visits. Table 3 provides an overview of the assessment requirements for the study, and Tables 4-10 provide specific requirements at each stage of the study.

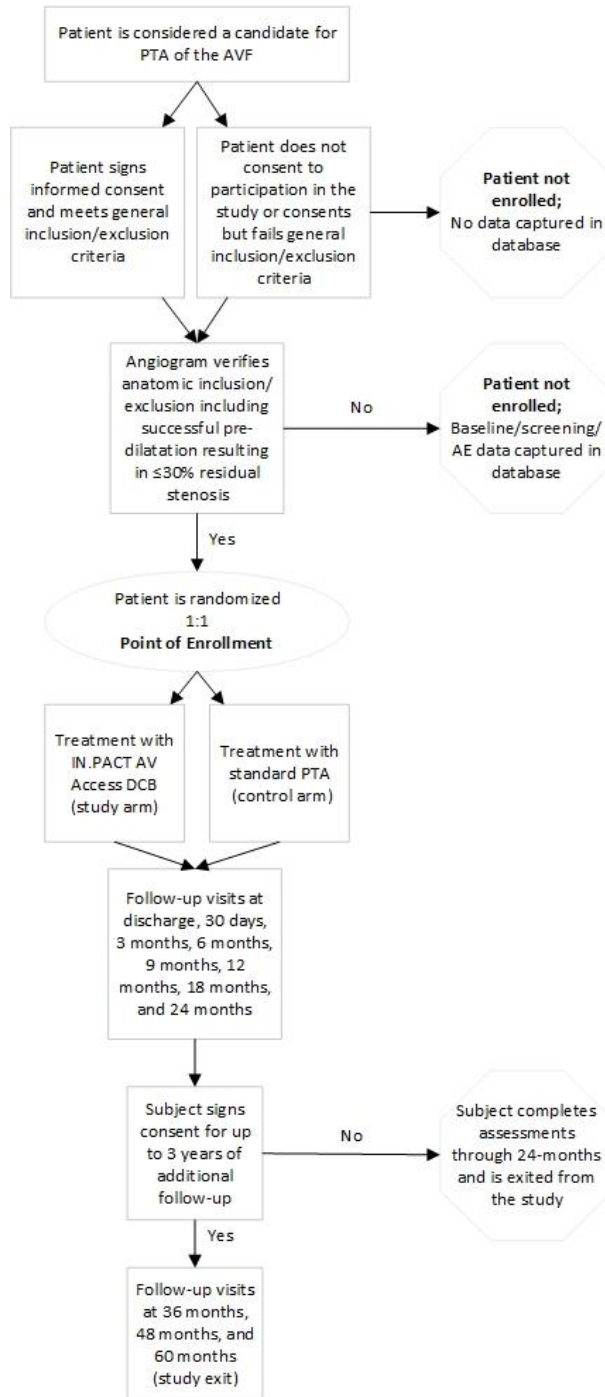


Figure 3: Study Flow Diagram



**Table 3: Study Assessment Requirements†**

Assessments/ Procedure	Baseline/ Screening	Index Procedure	Discharge (within 7 days post- procedure)	30 Days (± 7 days)	3 Months* (90 ± 15 days)	6 Months (180 ± 30 days)	9 Months* (270 ± 30 days)	12 Months (360 ± 30 days)	18 Months* (540 ± 30 days)	24 Months (720 days ± 30 days) 36 Months (1,080 days ± 30 days) 48 Months (1,440 days ± 30 days) 60 Months†† (1,800 days ± 30 days)	Unscheduled Visit**	Target AVF Abandonment
Informed Consent	X <sup>1</sup>											
Medical History	X <sup>2</sup>											
Physical Exam	X <sup>2</sup>										X <sup>4</sup>	
Medication Assessment	X <sup>2</sup>	X	X	X	X	X	X	X	X	X		
EQ-5D	X <sup>2</sup>			X		X		X		X		
Duplex Ultrasound				X		X		X			X <sup>6</sup>	
Angiography‡		X <sup>3</sup>									X <sup>4</sup>	
Randomization		X										
Adverse Event	X	X	X	X	X	X	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>
Abandonment eCRF												X

†Follow-up dates are calculated based on 30-day months

\*Subjects will be contacted by telephone 3 months, 9 months, and 18 months post index procedure to assess adverse events and medications

††After assessments for the 60 month visit are completed, the subject will be exited from the study

\*\*See Appendix 17.11 Recommended Guidelines for Re-interventions

‡Angiograms performed outside of the index procedure and unscheduled visits (e.g. standard of care angiograms at 6 months post index-procedure) should be submitted to the angiographic core laboratory.

<sup>1</sup> Consent process may occur within 14 days prior to enrollment. Signing on the same day as procedure is allowed if allowed by the IRB/EC and source records document that the consent process was conducted and consent was signed pre-procedure

<sup>2</sup> Within 14 days prior to enrollment

<sup>3</sup> Angiogram must include all pre- and post-procedure images. Refer to the Angiographic Core Laboratory guidelines for full requirements.

<sup>4</sup> Repeat at unscheduled visit only if clinically warranted or institutional standard

<sup>5</sup> After the primary endpoints are met (6 months), only SAEs, TLRs, and/or device related events will be collected

<sup>6</sup> Duplex Ultrasounds conducted within 2 years of index procedure should be submitted to the Core Laboratory; after the 24 month assessment DUS exams should no longer be submitted for evaluation

### **Baseline Requirements**

Baseline data collection requirements are identified in Table 4. Baseline assessment results will be submitted to the sponsor. The subjects will undergo a standard physical exam including a physical examination of the target limb, and medical history (review of symptoms, pre-existing conditions, and medications). The baseline review will also capture information on the target AVF (location, age, and previous revascularizations). *Although not required by the protocol, the treating physician should obtain and evaluate laboratory tests, e.g. CBC/creatinine/coagulation profile, per their institution's standard of care prior to the index procedure.*

**Table 4: Baseline Requirements**

Baseline Requirements	Timeframe Window
Informed Consent	Within 14 days of the index procedure*
Medical History	
Physical Exam	
Medication Use Documentation	
EQ-5D	

\* Ensure ICF is signed prior to conducting study specific assessments or procedures

### **Index Procedure Requirements**

The Investigator performing the study index procedure must be both approved by Medtronic and delegated by the study site's Principal Investigator (as documented on the Delegation of Authority/Delegated Tasks List Form).

The treating Investigator must use the study device in accordance with the investigational IFU. The corresponding manufacturer's IFU should be followed for all ancillary devices (e.g., guide wires, sheath/guiding catheters, pre-dilatation balloons, etc.) used during the index procedure.

The following describes required assessments and procedures associated with the index procedure. All activities should be documented.

**Target Lesion:** only one target lesion per subject is eligible for study treatment. Tandem lesions may be treated provided they meet all requirements for a single lesion (as defined in the Inclusion Criteria) and can be treated as a single lesion.

### **Preparation / Medications**

Single antiplatelet therapy, at a minimum, (e.g. aspirin, clopidogrel, ticlopidine or Prasugrel) should be administered before the procedure and for a minimum of 4 weeks after the intervention as stated in the

investigational IFU. If antiplatelet therapy is not standard of care at the study site, ensure the informed consent form has been reviewed and signed by the patient prior to administering antiplatelet medications

Access will be gained at the appropriate vascular site utilizing a sheath with a hemostatic valve.

### **Angiogram**

Angiography should be performed according to the Angiographic Imaging Protocol provided by the Angiographic Core Lab.

During pre-enrollment angiography the Investigator will assess the subject for the anatomic eligibility criteria including verifying the target lesion or tandem lesions are up to 100 mm in length.

Angiograms of the AV access circuit will be obtained immediately prior to and after the index procedure to document pre- and post-treatment results. Copies of all angiograms must be sent to the angiographic core lab.

The angiographic core lab values will supersede the physician's measurement assessments for data analysis purposes; however, the physician's assessment will be used to determine subject eligibility at the time of enrollment.

### **Pre-Dilatation**

In both treatment groups, pre-dilatation is required for all target lesions and *must be performed successfully before a subject can be randomized (inclusion criteria 8)*. Pre-dilatation must be performed with a high pressure PTA balloon (no other devices, such as cutting/scoring balloons, or DCBs are allowed). The pre-dilatation balloon must have a diameter matching the RVD distal to the target lesion. Patients must be excluded from enrolling in the study if pre-dilatation is unsuccessful. Up to two balloons may be used to achieve successful pre-dilatation prior to considering the patient a screen failure. Pre-dilatation is considered *unsuccessful* if any of the following occur:

- The tip of the guide wire or PTA balloon is unable to cross and extend beyond the target lesion
- A flow-limiting dissection (Grade  $\geq$ C) or perforation occurs
- Inability to pre-dilate
- Residual stenosis > 30%

If pre-dilatation is successful, the patient will be randomized to receive either standard PTA (control arm) or IN.PACT™ AV Access DCB (study arm), see Section 9.5 – Randomization and Treatment Assignment. Subjects randomized to the standard PTA arm will receive additional PTA treatment with a low pressure balloon.

## Drug Coated Balloon Angioplasty and Post-Dilatation

**Balloon Sizing:** Balloon size must match the RVD and fully cover and extend beyond the lesion length:

- Nominal **balloon diameter** must match the inner diameter of the reference vessel distal to the target lesion.
- Nominal **balloon length** must exceed the total target lesion length by approximately 1 cm at the proximal and distal edge in order to ensure full lesion coverage and prevent geographic miss.

**Inflation Pressure:** Balloon inflation pressure should be at the nominal pressure and should never exceed rated burst pressure.

**Inflation Time:** Balloon inflation must be at least 180 seconds (3 minutes). The IN.PACT™ AV Access DCB releases the drug into the vessel wall on first expansion and adequate drug transfer occurs in the first 60 seconds of inflation. The additional 120 seconds is intended solely for mechanical dilatation purposes to fulfill optimal PTA requirements.

**Prolonged and Repeat Inflations:** Longer inflation times are possible at the discretion of the Investigator for the purpose of optimizing lesion dilatation.

A second dilatation must be performed with a non-DCB when the initial dilation results in any of the following:

- Residual stenosis > 30% (by visual estimate);
- Presence of flow-limiting dissection

**Use of Multiple Study Balloons:** In subjects with a total target lesion length that is longer than the longest available balloon, two or more IN.PACT™ AV Access DCBs may be used and they should overlap by approximately 1 cm.

The use of a second IN.PACT™ AV Access DCB to complete treatment is allowed only under either of the following circumstances:

- The first IN.PACT™ AV Access DCB bursts prior to 60 seconds of inflation time
- The total length of the eligible target lesion requires more than one IN.PACT™ AV Access DCB to fully cover the lesion and extend about 1 cm beyond the lesion at the proximal and distal edges

If a second IN.PACT™ AV Access DCB is required under the circumstances described above, the second IN.PACT™ AV Access DCB must be a newly opened device, and may be of a different diameter.

**Post-dilatation:** Post-dilatation should be completed according to the investigator's discretion. It is important to provide drug delivery to the entire length of the treated vessel prior to post-dilatation or provisional stenting. If adequate PTA results are not obtained after the IN.PACT™ AV Access DCB(s) inflation, post-dilatation using a non-drug-coated PTA balloon of shorter length than the previously

used IN.PACT™ AV Access DCB is recommended. For both treatment arms, all balloon dilatations in enrolled subjects, including the pre-randomization dilatation, must be documented with angiographic images and submitted to the angiographic core lab.

**Only** study subjects randomized to treatment with the IN.PACT™ AV Access DCB may be treated with the investigational product.

No **alternative therapies** are allowed (DES, grafts, laser, atherectomy, cryoplasty, brachytherapy, etc.). Intention to use such alternative therapies to treat the target lesion either pre- or peri-procedure constitutes a violation of exclusion criterion.

### **Provisional Stenting**

Provisional stenting should be avoided unless required for subject safety. *Only non-drug-coated stents that are approved in country of the study site and for this indication may be used in this study.*

Since the purpose of this study is to evaluate the safety and efficacy of the IN.PACT™ AV Access DCB investigational device, provisional stenting should be avoided, if possible. Provisional stenting should be performed only after repeated and prolonged balloon inflations result in either of the following conditions:

- Residual stenosis of  $\geq 50\%$  (by visual estimate);
- Major ( $\geq$  Grade D) flow-limiting dissection

All subjects who undergo a provisional stenting are required to be followed per the protocol-required follow-up schedule. These subjects will be analyzed in the Intent-to-Treat (ITT) population.



**Follow-Up Requirements**

**Discharge**

All subjects will be assessed pre-discharge. At this time, an evaluation for adverse events (AEs) per protocol requirements will be completed and documented and medications will be recorded. Discharge assessment requirements are listed in Table 5.

**Table 5: Discharge Requirements**

Discharge Requirements	Timeframe Window
Adverse Event Documentation	Prior to discharge (within 7 days post-procedure)
Documentation of Medication Use	

**30-Day Follow-up Requirements**

All subjects are required to have a follow-up visit 30-days post-procedure. At this time, an evaluation for AEs per protocol requirements will be completed and documented. A duplex ultrasound will be performed, medication use will be documented and the EQ-5D questionnaire will be administered. Table 6 lists the 30-day follow-up requirements.

**Table 6: 30-Day Follow-up Requirements**

30-Day Follow-up Requirements	Target	Follow-up Window
Adverse Event Documentation	30 days post-procedure	23-37 days post-procedure
Documentation of Medication Use		
EQ-5D		
Duplex Ultrasound		

**3-Month, 9-Month, 18-Month Follow-up Requirements**

All subjects will be contacted *by telephone* at 3-months, 9-months, and 18-months post-procedure. At this time, an evaluation for AEs per protocol requirements will be completed and documented and medication use will be documented. The physician may choose to perform an in-office visit to meet the study follow-up requirement.

Table 7 lists the 3-, 9-, and 18-month follow-up requirements.

**Table 7: 3-Month, 9-Month, 18-Month Follow-up Requirements**

<b>3-Month, 9-Month, 18-Month Follow-up Requirements</b>	<b>Target</b>	<b>Follow-up Window</b>
Adverse Event Documentation	3-month follow-up: 90 days post-procedure	3-month: 75-105 days post-procedure
Documentation of Medication Use	9-month follow-up: 270 days post-procedure 18-month follow-up: 540 days post-procedure	9-month: 240-300 days post-procedure 18-month: 510-570 days post-procedure

**6-Month and 12-Month Follow-up Requirements**

All subjects are required to have a follow-up visit 6-months and 12-months post-procedure. At this time, an evaluation for AEs per protocol requirements will be completed and documented. A duplex ultrasound will be performed, medication use will be documented and the EQ-5D questionnaire will be administered. Subjects should be unblinded at the 6-month visit *after* completing follow-up requirements. Table 8 lists the 6-month and 12-month follow-up requirements.

**Table 8: 6-Month and 12-Month Follow-up Requirements**

<b>6-Month and 12-Month Follow-up Requirements</b>	<b>Target</b>	<b>Follow-up Window</b>
Adverse Event Documentation	6-month follow-up: 180 days post-procedure	6-month: 150-210 days post-procedure
Documentation of Medication Use	12-month follow-up: 360 days post-procedure	12-month: 330-390 days post-procedure
EQ-5D		
Duplex Ultrasound		

**24-Month, 36-Month, 48-Month and 60-Month Follow-up Requirements**

All subjects are required to have annual visits up to 5 years post-procedure. At these times, an evaluation for AEs per protocol requirements will be completed and documented. Medication use will be documented and the EQ-5D questionnaire will be administered. After completion of the required

assessments at the 60-month follow-up, the subject will be exited from the study. Table 9 lists the 24-month, 36-month, 48-month and 60-month follow-up requirements.

**Table 9: 24-Month, 36-Month, 48-Month and 60-Month Follow-up Requirements**

24-Month, 36-Month, 48-Month and 60 Month Follow-up Requirements	Target	Follow-up Window
Informed Consent*	24-month follow-up: 720 days post-procedure	24-month: 690-750 days post-procedure
Adverse Event Documentation	36-month follow-up: 1,080 days post-procedure	36-month: 1,050 - 1,110 days post-procedure
Documentation of Medication Use	48-month follow-up: 1,440 days post-procedure	48-month: 1,410 - 1,470 days post-procedure
EQ-5D	60-month follow-up: 1,800 days post-procedure	60-month: 1,770 – 1,830 days post-procedure

\* Ensure subject is re-consented prior to conducting any study specific assessments after 24-months

**Unscheduled Visit**

A subject who returns to the investigational site between protocol-required visits *for a clinical event in the target limb* is considered to have an Unscheduled Visit, and all appropriate assessments must be completed and captured in the appropriate electronic case report forms (eCRFs). Appendix 18.11 details the recommended guidelines for re-interventions.

Angiography and/or duplex ultrasound should be repeated if clinically indicated and/or within the institution’s standard of care. As much as possible, imaging studies performed during an Unscheduled Visit should be performed in accordance with the Core Lab imaging protocols. Angiographic and/or duplex ultrasound and/or arterial flow studies results must be submitted to the appropriate core lab with the Core Lab Technician Worksheet.

If the subject refuses an angiogram, duplex ultrasound or re-intervention at an unscheduled visit, it will not be considered a deviation from the protocol. Table 10 lists the assessments to be performed if clinically indicated at unscheduled and re-intervention visits.

**Table 10: Unscheduled Visit**

Assessments to be Performed if Clinically Indicated
Physical Exam

Adverse Event Documentation
Angiogram
Duplex Ultrasound

## 9.2. Subject Screening

It is expected that all potentially eligible patients be approached for enrollment in the study and be screened at the site. Eligible patients will be given an explanation of the study, educated on the possible risks and benefits of participating, and be asked to provide written informed consent prior to any study-specific screening or testing. Patients will be informed that, despite signing the informed consent document, screening procedures outlined in Table 3 may demonstrate the patient is not a suitable candidate for the study.

During the course of the study, Medtronic may limit enrollment to a specific IN.PACT™ AV Access balloon size if needed in order to achieve an acceptable distribution of sizes. Investigators would be notified of what balloon sizes are needed for enrollment, and patients who are not candidates for treatment with those sizes would no longer be considered for enrollment. This determination may be made during the procedure after the initial angiogram, at which point the patient would become a screen failure.

## 9.3. Prior and Concomitant Medications

Single antiplatelet therapy, at a minimum, (e.g. aspirin, clopidogrel, ticlopidine or Prasugrel) should be administered before the procedure and for a minimum of 4 weeks after the intervention as stated in the investigational IFU. If antiplatelet therapy is not standard of care at the study site, ensure the informed consent form has been reviewed and signed by the patient prior to administering antiplatelet medications.

Use of anticoagulant and antiplatelet medications will be documented on the Concomitant Medication eCRF. Use of medications other than antiplatelet and anticoagulants will not be collected.

Note: medications and dose as market approved in geography

## 9.4. Subject Consent

All subjects must undergo the consent process, possess the mental capacity to provide Informed Consent, and sign the ICF prior to enrollment and prior to undergoing any assessments or procedures that are study-specific (defined as those that would not be conducted if the subject was not participating in the study). Some general inclusion/exclusion criteria that are standard of care may be

evaluated prior to the subject signing the Informed Consent Form. An exam previously conducted, but repeated solely for the study (for example, to determine eligibility) is considered a study-specific assessment.

The subject must personally sign and date the site's current Institutional Review Board (IRB)/Ethics Committee (EC) – approved version of the Informed Consent to be eligible for the study. A legally appointed representative may sign the consent form in cases where a subject has mental capacity but cannot sign due to physical inability. If a patient is illiterate, an impartial witness must be present during the entire informed consent discussion. All items addressed in the patient informed consent must be explained.

The study site Principal Investigator and/or his/her delegated designee must conduct the informed consent process. The content of the ICF must be explained to the subject in a language that is as non-technical as possible and is understandable to the subject (and witness, if required/applicable). The patient must be given ample opportunity to ask questions and will be informed about their rights to withdraw from the study at any time, for any reason, and without any disadvantage.

When the patient has thoroughly understood this information, he/she will be asked if he/she is willing to sign or seal (with printed name) and date consent form. A subject may participate in the study when he/she consents to do so of their own free will and signs the informed consent form.

After all required parties have signed and dated the ICF, the subject must be provided with a copy of the signed and dated ICF. The original signed ICF should be retained in the Investigator Site File or medical record.

The informed consent process for all subjects must be documented in the source records.

The ICF and other written explanatory information will be revised if significant new information that may be relevant to the subject's consent becomes available, or there is an amendment to the protocol which necessitates a change to the ICF. The subjects should be re-consented in a timely manner and will be asked to confirm willingness to continue his/her participation in the study and obtain his/her signature or seal (with printed name) on the revised consent form. All revisions to the consent form and information sheet must be approved in advance by the IRB/EC.

Medtronic revised the written informed consent template to include the extension of follow-up from the originally planned 24 months up to 5 years post index procedure. Subjects who are currently participating in the clinical study shall be asked to sign the updated informed consent to confirm their continuing informed consent in writing for up to 5 years of follow-up. The revised informed consent documents will be provided to the investigational sites for approval by the local EC/IRB.

Enrolled subjects who decline to continue to participate in follow-up beyond 24-months shall exit the study upon the completion of their 24-month visit.

## 9.5. Randomization and Treatment Assignment

After a patient has signed informed consent, the eligibility criteria has been verified and undergone successful pre-dilatation, the patient will be enrolled via randomization to one of two treatment arms in a 1:1 ratio:

1. IN.PACT™ AV Access DCB (study arm)
2. Standard PTA Balloon (control arm)

Randomization will be accomplished using an Interactive Voice Response System (IVRS), or Interactive Web Response System (IWRS) or Interactive Mobile Response System (IMRS). Randomization should occur as closely as possible to the time of index procedure. Randomization will be stratified based on lesion status: *de novo* vs. restenotic and with pre-specified block sizes within study sites. A separate protocol for instructions on how to randomize subjects will be provided to the study sites.

Confirmation of randomization reports will be provided to the site immediately after randomization occurs. These reports must be maintained in the site files.

Once randomized (enrolled), a subject must be followed per protocol, regardless of whether or not a subject ultimately receives study treatment.

If a subject inadvertently undergoes the wrong treatment (e.g. randomized to the control arm but undergoes PTA with the study device), the subject will be analyzed in accordance with the treatment assignment, not the treatment actually administered.

If a subject is inadvertently randomized more than once, the subject must be treated in accordance with the first treatment assignment and the subject will be followed per protocol and will be analyzed in the intent-to-treat (ITT) data set.

## 9.6. Assessment of Safety

The primary safety endpoint is based on the Adverse Event data collected. Further information on collection of Adverse Events is discussed in Section 11 – Adverse Event Assessments.

## 9.7. Recording Data

### Source Documents

Data entered into the electronic database must be traceable to source documents. Source documentation is defined as the first time data appear and may include original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, or evaluation checklists, pharmacy records, recorded data from automated instruments, copies or transcriptions

certified after verification of accuracy and other documents/records required by geographies regulation where required).

In general, eCRFs (or paper copies/worksheets) may not serve as source documents. An exception is the quality of life questionnaire or for data elements not routinely captured in medical records. This should be documented as being the source documents, printed out, signed and dated by a delegated member from the study site.

Copies of source documents will be requested to support event adjudication by the Clinical Events Committee. Any private health information (PHI) in source document copies provided to the CEC should be masked. In Japan, availability of source documentation may be limited due to hospital policies. If a specific source document is not available, necessary information may be transcribed onto the relevant CRF page.

The Investigator must ensure the availability of source documents as outlined in Section 15.8 - Direct Access to Source Data/Documents.

## **9.8. Deviation Handling**

A deviation is any event in which the study is not conducted according to the CIP, applicable laws or regulations or the Investigator Agreement. Deviations may include, but are not limited to the following:

- Failure to obtain informed consent prior to participation
- Incorrect version of the informed consent form used
- Failure to obtain IRB/EC approval before the start of enrolling subjects in the study
- Included subject did not meet inclusion/exclusion criteria
- Required testing and/or measurements not done or incorrectly done
- Subject did not attend follow-up visit
- Follow-up visit was completed outside window
- Unauthorized use of IN.PACT™ AV Access DCB(s)
- Adverse events/UADE or device deficiencies not reported in the required timeframe by country regulation or as specified in the CIP
- Control of study devices not maintained
- Source data permanently lost
- Enrollment of subjects during lapse of IRB/EC approval
- Enrollment limits exceeded

Investigators are required, whenever possible, to obtain prior approval from Medtronic before initiating changes in or deviations from the investigational plan, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval will be documented in writing and

maintained in the study files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g., subject did not attend scheduled follow-up visit), the event, however, is still considered a deviation.

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 from the date of the deviation occurrence.

Reporting of all deviations should comply with IRB/EC policies and/or local laws and/or regulatory agencies and must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation. Subject specific deviations will be reported on the Protocol Deviation eCRF; all non-subject specific deviations (e.g. unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator Agreement, etc.) will be reported to Medtronic in writing.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions which may include amending the CIP, conducting additional training, terminating the investigation, etc. Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment at that site 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.

## **9.9. Subject Withdrawal or Discontinuation**

Every subject should be encouraged to remain in the study until they have completed the required follow-up per the CIP. Subjects will be included in the analyses up to the time that consent was withdrawn, unless a subject specifically instructs Medtronic that none of their data may be used. Subjects who discontinue participation prior to study completion will be included in the analysis of results, but will not be replaced in the inclusion of total study subjects.

### **Loss to Follow-Up**

Every attempt must be made to have all subjects complete the follow up visit schedule. A subject will be considered lost-to-follow-up if efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information must include three documented attempts to make contact (e.g. phone, email, text), followed by a certified letter from the Principal Investigator. Once deemed lost-to-follow-up, the subject will be exited from the study.



## Subject Withdrawal

All study subjects have the right to withdraw their consent to participate at any time during the study. Whenever possible, the site staff should obtain written documentation from the subject of his/her request to withdraw his/her consent. If the site is unable to obtain written documentation, all information regarding the subject's withdrawal must be recorded in the subject's medical record. In addition, the appropriate eCRFs must be completed.

Withdrawal of a subject from the study can also occur at the direction of the Principal Investigator without the subject's consent. Reasons for physician-directed subject withdrawal include, but are not exclusive to: protocol requirements, the subject has enrolled in another study that conflicts with the primary outcome, or the physician deems it in the best interest for the safety or welfare of the subject to withdraw.

## Medical Care after Study Exit

After study exit, the subjects may be followed as per routine standard of care by the investigational site or a treating physician. Relevant medical records may be made available by the investigational sites for the treating physician per local laws and regulations if needed for further subject treatment. As per local law and regulation the investigator may be contacted by the treating physician in case of questions related to the study device and treatment.

# 10. Risks and Benefits

## 10.1. Potential Risks

Potential risks or complications anticipated with the use of the IN.PACT™ AV Access DCB in PTA are similar to those associated with standard PTA and drug-eluting stent procedures. Such risks, as listed in the IN.PACT™ AV Access DCB investigational IFU, include but may not be limited to those listed below (in alphabetical order). Table 11 below also includes potential risks and complications that may occur.

**Table 11: Potential Risks Associated with the Study Procedure**

Potential adverse effects which may be associated with balloon catheterization may include, but are not limited to:

- abrupt vessel closure
- access site pain

- allergic reaction to contrast medium, antiplatelet therapy, or catheter system components (materials, drugs, and excipients)
- arrhythmias
- arm edema
- arterial or venous aneurysm
- arterial or venous thrombosis
- arteriovenous (AV) fistula
- death
- dissection
- embolization
- fever
- hematoma
- hemorrhage
- hypotension/hypertension
- inflammation
- ischemia or infarction of tissue/organ
- local infection at access site
- local or distal embolic events
- perforation or rupture of the artery or vein
- pseudoaneurysm
- pulmonary embolism
- renal insufficiency or failure
- restenosis of the dilated artery or vein
- sepsis or systemic infection
- shock
- stroke
- systemic embolization
- vessel spasms or recoil
- vessel trauma which requires surgical repair

Potential complications of peripheral balloon catheterization include, but are not limited to:

- balloon rupture
- detachment of a component of the balloon and/or catheter system
- failure of the balloon to perform as intended
- failure to cross the lesion

As with any device requiring mechanical deployment and retraction, there exists a risk of mechanical failure of the device resulting in potential surgical intervention to remove the balloon or delivery system.

It is expected that the fluoroscopy time during the procedure may be minimally longer (in order to confirm inclusion and exclusion criteria) than the time required for standard PTA procedures using other devices. Following the fluoroscopic procedure, the skin area exposed to the x-rays could react to produce an effect similar to a sun burn.

All of the above could cause prolonged illness, permanent impairment of daily function or, in rare cases, death. Possible treatments could include, but are not limited to medication, surgery, medical monitoring or other applicable treatments, and will be provided at the discretion of the Investigator.

#### **Potential Side Effects of Paclitaxel**

Paclitaxel is a drug commonly used in the treatment of oncology patients; particularly in patients with breast cancer. In that setting, paclitaxel is usually administered as an intravenous infusion and side effects associated with this systemic administration are known.

High systemic safety margins were reported in the IN.PACT™ SFA II Pharmacokinetic Report. Paclitaxel systemic exposures in 24 study subjects was brief, declining in one hour by over 87% from the peak of 7.9 ng/mL to 1.0 ng/mL, followed by a continued decline to very low concentration levels of 0.1ng/mL at day 7.

Some of the common side effects known to occur in cancer patients treated with paclitaxel include, but are not limited to, the side effects listed in Table 12.

**Table 12: Potential Risks Associated with Paclitaxel**

- allergic/immunologic reaction
- alopecia
- anemia
- gastrointestinal symptoms
- hematologic dyscrasia (including leucopenia, neutropenia, thrombocytopenia)
- hepatic enzyme changes
- histologic changes in vessel wall, including inflammation, cellular damage, or necrosis
- myalgia/arthralgia
- myelosuppression
- peripheral neuropathy

Refer to the Physician's Desk Reference for more information on the potential adverse events observed with paclitaxel.

As with the use of any investigational product, there may be other potential adverse events that are unforeseen at this time.

## **10.2. Potential Benefits**

There are no guaranteed benefits from participation in the study. It is possible that treatment with IN.PACT™ AV Access DCB may improve and maintain blood flow through the treated AVF, resulting in the need for fewer treatments. This may allow for continued/resumption of AV access for the purpose of hemodialysis. Information gained from the conduct of this study may be of benefit to other persons with the same medical condition.

## **10.3. Risk-Benefit Rationale**

It has been demonstrated that standard PTA for obstructive lesions in the native AVF can be performed safely and that these devices are effective in restoring and maintaining AVF patency. The risks associated with the IN.PACT™ AV Access DCB or the participation in this study are not anticipated to be worse than the risks normally associated with the use of other commercially available devices.

Potential risks with this study are minimized by selecting Investigators who are trained in the use of the study device and trained to the study protocol, by clearly defining inclusion/exclusion criteria to ensure only appropriate subjects are enrolled. In addition, the investigator performs a continuous monitoring, assessment, and documentation of any risks.

Medtronic will establish a CEC and DMC to independently review and evaluate subject health status, device performance, and identify any safety concerns regarding subjects' wellbeing. Medtronic has further minimized the possibility of risks by completing product testing prior to the use of the IN.PACT™ AV Access DCB in this clinical study, implementing quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling.

Risk management for IN.PACT™ AV Access is performed in accordance with EN ISO 14971:2012. The Indication, warnings, and contraindications are provided in the investigational IFU.

## 11. Adverse Event Assessments

### 11.1. Definitions/Classifications

#### Definitions

For the purpose of this clinical study, Medtronic will define and classify the following events per EN ISO14155:2011 and Title 21 CFR 812.3. Definitions are provided in Table 13.

**Table 13: Definitions of Adverse Events**

Event Type	Definition
<p><b>Adverse Event (AE)</b>  (EN ISO14155:2011 3.2)</p>	<p>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.</p> <p><i>NOTE 1: This definition includes events related to the investigational medical device or the comparator.</i></p> <p><i>NOTE 2: This definition includes events related to the procedures involved.</i></p> <p><i>NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.</i></p>
<p><b>Serious Adverse Event (SAE)</b>  (EN ISO14155:2011 3.37)</p>	<p>Adverse event that</p> <ul style="list-style-type: none"> <li>a) led to death,</li> <li>b) led to a serious deterioration in the health of the subject, resulting in                             <ul style="list-style-type: none"> <li>1) a life-threatening illness or injury, or</li> <li>2) a permanent impairment of a body structure or a body function, or</li> <li>3) in-patient or prolonged hospitalization, or</li> <li>4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,</li> </ul> </li> </ul>

	<p>c) led to foetal distress, foetal death or a congenital abnormality or birth defect.</p> <p><i>NOTE: 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.</i></p>
<p><b>Adverse Device Effect (ADE)</b>  (EN ISO14155:2011 3.1)</p>	<p>Adverse event related to the use of an investigational medical device.</p> <p><i>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.</i></p> <p><i>NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device.</i></p>
<p><b>Serious Adverse Device Effect (SADE)</b>  (EN ISO14155:2011 3.36)</p>	<p>Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.</p>
<p><b>Unanticipated Adverse Device Effect (UADE)</b>  (21 CFR 812.3)</p>	<p>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 nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.</p>
<p><b>Unanticipated Serious Adverse Device Effect (USADE)</b>  (EN ISO14155:2011 3.42)</p>	<p>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.</p> <p><i>NOTE: 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.</i></p>
<p><b>Device Deficiency</b>  (EN ISO14155:2011 3.15)</p>	<p>Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.</p>

*NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.*

### Classification of Causal Relationships

For each reported AE, the causal relationship between the AE and the study device, interventional procedure, and therapy will be classified as not related, unlikely, possible, probable, or causal relationship by the Investigator and Sponsor.

In the case where the AE may not be adequately assessed because of insufficient data, data cannot be verified, or if data is contradictory, Medtronic will classify the relatedness as 'possible'.

The causal relationships are defined in Table 14, and should be collected for subjects randomized to either the control arm or study arm.

**Table 14: Causal Relationship Definitions**

Related To	Definition
<b>Study Procedure</b>	Complication associated with the initial use of the device or any necessary secondary interventions after the point of enrollment through the resumption of successful dialysis for one session. This includes morbidity associated with either anesthesia or surgical procedure. This also includes inappropriate subject selection and errors attributed to inappropriate operator techniques, measurements or judgment.
<b>Device</b>	Complication associated with the device design as it relates to placement, efficacy or durability, (these may involve the delivery system).
<b>Therapy</b>	Complication associated with a subject's physiological response to the paclitaxel drug.

## 11.2. Reporting of Adverse Events

The investigator is required to assess and document in the medical record all Adverse Events (AEs) and Device Deficiencies (DDs) (per the definitions in Table 13) observed in subjects from the time of consent. All AEs (except those listed in Table 16) regardless of relatedness, seriousness, expectedness or outcome, must be reported through the primary endpoint after which only SAEs, ADEs, SADEs, and UADEs will be collected. AEs will be followed until the event has resolved or until study exit. In case of permanent impairment, the event will be followed until the event stabilizes and the overall clinical outcome has been ascertained. Reporting of AEs and DDs will end once the subject exits the study. In case AEs are unresolved at the time of study exit, this will be documented on the eCRF.

The investigator is responsible for reporting AEs to Medtronic as outlined in Table 15 by completing the Adverse Event eCRF and/or Device Deficiency eCRF. For the purposes of this CIP, planned/elective procedures for pre-existing conditions will not be considered or reported as adverse events (AE). A list of AEs that may be associated with the device and/or the interventional procedure is provided in Section 10.1 – Potential Risks.

**Table 15: Adverse Event Reporting Guidelines (Site Reporting to Medtronic)\***

Type of Event	Reporting Time Frame	Reported Through Study Visit
Adverse Event	At time of procedure and follow-up visits	6 Month Follow-up Visit <sup>‡</sup>
Serious Adverse Event (SAE)	As soon as possible, but <b>within 10 working days</b> after Principal Investigator** is first aware of the event.	60-Month Follow-up Visit
Adverse Device Effect (ADE)		
Serious Adverse Device Effect (SADE)		
Unanticipated Adverse Device Effect (UADE)		
Device Deficiency		

\* Study sites are responsible for reporting AEs/Device Deficiencies to the IRB/EC per the IRB/EC reporting policy; where applicable, Medtronic will perform expedited reporting to Medsafe in New Zealand where required under the regulatory guidelines

\*\* Principal Investigator also includes all designated study personnel at the site

<sup>‡</sup>AEs associated with a TLR and not considered an SAE should be reported up to the 60-month follow-up visit

**Non-Reportable Medical Occurrences**

Documented pre-existing conditions are not considered AEs and should not be reported unless there is a change in the nature or severity of the condition. Pre-existing events should be reported as Adverse Events in the situation where a new treatment has to be started or an existing treatment has to be changed to treat the adverse event and the event is accompanied with signs and symptoms.

Clinical events that are inherent to a surgical procedure and expected to occur in the majority of subjects for a projected duration may be considered unavoidable. Such events include, but are not



limited to, those listed in Table 16. These events should not be reported as adverse events during this study.

**Table 16: Expected and Unavoidable Adverse Events Related to the Procedure**

Description of the Event	Time Frame from the Index Procedure
Anesthesia-related nausea and/or vomiting	Within 24 hours
Access site bleeding controlled by usual means	Within 24 hours
Low-grade fever (< 100° F or < 37.8° C)	Within 48 hours
Back pain related to laying on OR table	Within 72 hours
Incisional pain (pain at access site)	Within 72 hours
Sleep problems or insomnia	Within 72 hours
Mild to moderate bruising or ecchymosis	Within 168 hours
Suture irritation	After suture removal

### 11.3. Emergency Contact Details

For any study related emergency, the investigators can contact the Medtronic Clinical Research Specialist assigned to the site. Contact information for the Clinical Research Specialist and the Medical Expert are listed on the Study Contact List.

## 12. Data Review Committees and Core Laboratories

### 12.1. Data Monitoring Committee

An independent Data Monitoring Committee (DMC), will be established with the responsibility to assess the progress of the clinical investigation, the safety data, and the critical performance endpoints and to recommend to Medtronic whether to continue, modify, or stop the investigation. All final decisions regarding study modifications or termination will be made by Medtronic. Detailed information, such as the DMC member selection, composition, duties, procedures, and deliberation rules are detailed and documented in the DMC Charter.

## 12.2. Clinical Event Committee

An independent Clinical Events Committee (CEC) will be responsible for the adjudication of selected adverse events and clinical endpoints in the study, using criteria established at the outset of the study and specified by the CIP, the CEC Charter and relevant societal reporting standards. The CEC Charter will specify explicit rules outlining the minimum amount of data required and the algorithm followed in order to classify an event. Detailed information such as the CEC member selection, composition, duties, procedures, and deliberation rules are detailed and documented in the CEC Charter.

## 12.3. Duplex Ultrasound Core Laboratory

The Duplex Ultrasonography Core Laboratory (DUS Core lab) is responsible for developing protocol requirements, reviewing DUS exams, interpreting subject DUS data, and providing feedback on the quality of the DUS exams to participating sites. The DUS Core lab will review, analyze, and record data on the Duplex Core laboratory Assessment eCRF. The DUS Core laboratory's interpretation of all DUS exams will be used for the data analyses through 24-months post index procedure.

## 12.4. Angiographic Core Laboratory

The Angiographic Core Laboratory is responsible for review of the index procedural angiograms to assess lesion characteristics as well as procedural outcomes. The Angiographic Core Laboratory will also review any angiograms performed during the follow-up period and any re-interventions. The Angiographic Core laboratory's interpretation of all angiograms will be used for the data analyses.

## 13. Statistical Design and Methods

This is a prospective, global, multi-center, single-blinded, randomized (1:1) study of balloon dilatation with IN.PACT™ AV Access DCB (study arm) vs. standard non-coated PTA balloons (control arm) for the treatment of *de novo* and non-stented restenotic lesions in the AVF. The study will enroll in three geographies: U.S., Japan, and New Zealand. Further details on the statistical methods, including justification, timing of interim analysis can be found in the Statistical Analysis Plan.

### 13.1. Hypotheses and Sample Size Calculation

There are two primary hypotheses for the study. One is for the primary efficacy endpoint – target lesion primary patency through 6 months, and one is for the primary safety endpoint – SAE rate involving the AV access circuit through 30 days post-procedure.

For the primary efficacy endpoint – target lesion primary patency through 6 months, the treatment ( $p_T$ ) and control ( $p_C$ ) groups will be compared in a superiority format under the following hypothesis.

$$H_0: p_T \leq p_C$$

$$H_A: p_T > p_C$$

For the primary safety endpoint - SAE rate involving the AV access circuit through 30 days, the treatment ( $\pi_T$ ) and control ( $\pi_C$ ) groups will be compared in a non-inferiority format under the following hypothesis.

$$H_0: \pi_T \geq \pi_C + 0.075$$

$$H_A: \pi_T < \pi_C + 0.075$$

For primary efficacy endpoint, with one-sided alpha of 0.025 and assuming 60% primary patency rate in treatment and 40% in control, a Z-test of proportions will provide at least 92% statistical power to test for superiority, when the effective sample size is 140 in each arm. After accounting for 15% of attrition rate through 6 months, the total sample size will be 330.

For primary safety endpoint, an effective sample size of 161 in each arm provides at least 80% power using a Farrington-Manning test based on a one-sided alpha of 0.025, with the assumed event rate of 5% in each arm and a non-inferiority margin of 7.5%<sup>15</sup>. After accounting for 2% of attrition at 30-day follow-up, the total sample size will be 330.

According to above the consideration of both primary endpoints, the total sample size is therefore 330. The power and sample size calculations were performed by using PASS v14.0.7 (NCSS LLC, Kaysville, Utah). The establishment of the assumptions for endpoint rates was based upon publicly available information from currently marketed devices and the literature.

Device Name	Source (SSED, Literature)	Target Lesion Patency Definition	Results
IN.PACT DCB, PTA	NCT01174472 Kitrou, P. M., et al. (2015). Eur J Radiol 84(3): 418-423. Katsanos, K., et al. (2012). J Endovasc Ther 19(2): 263-272.	Angiographic visualization of a lesion with <50% restenosis and no need for any additional repeat interventional procedure within the previously treated lesion, due to failing access.	70% [50%, 90%] in DCB vs 25% [6%, 44%] in PTA
IN.PACT DCB	Patanè D et al. (2014). J Vasc Access 15(5):338-43	The absence of dysfunction of the vascular access, patent lesion or residual stenosis <30% and no need for further reintervention of the TL;	92.3% [82%, 100%] in DCB



GORE VIABAHN Endoprosthesis, PTA	Vesely, REVISE Clinical Trial presented at Scientific Meeting, 2014. SSED	time interval of uninterrupted patency from initial study treatment to the next access thrombosis or intervention performed on the target lesion.	52.9% [43.8%, 61.6%] in stent graft vs 35.5% [27.4%, 43.6%] in PTA
FLAIR Endovascular Stent Graft, PTA	Haskal et. al. NEJM 362, 6, 494-503, 2010. SSED	patency (open to blood flow) after the study index procedure until reintervention in the treatment area (within 5 mm proximal or 5 mm distal to the study device or index balloon angioplasty treated area), or thrombotic occlusion that involved the treatment area.	KM rate: 50.6%[40.0%, 60.8%] in stent graft vs 23.3% [14.3%, 32.2%] in PTA
Bard Fluency Stent Graft, PTA	Dolmatch et. al. J Vasc Interv Radiology, 23, 4, 479-487, 2012. SSED	Interval after the index intervention until the next re-intervention at the original treatment site or until the extremity (access) is abandoned for permanent access	KM rate: 65.2%[55.6%, 74.9%] in stent graft vs 10.4% [4.3%, 16.6%] in PTA

Device Name	Source	Primary Safety Endpoint	Results
Bard Fluency Stent Graft, PTA	Dolmatch et. al. J Vasc Interv Radiology, 23, 4, 479-487, 2012. SSED	Freedom through 30 days from any localized or systemic adverse events, which reasonably suggests the involvement of the AV access circuit (not including stenosis or thrombosis) that require or result in any of the following alone or in combination: additional interventions (including surgery); inpatient hospitalization or prolongation	96.6% (114/118) in stent graft vs 96.8% (122/126) in PTA group

		of an existing hospitalization; or death.	
FLAIR Endovascular Stent Graft, PTA*	Haskal et. al. NEJM 362, 6, 494-503, 2010. SSED	Incidence of adverse events at 6 months	No significant difference in two arms, except for restenosis which was higher in control PTA group
GORE VIABAHN Endoprosthesis, PTA	Vesely, REVISE Clinical Trial presented at Scientific Meeting, 2014. SSED	Freedom from major device-, procedure-, and treatment site-related adverse events through 30 days post-procedure	0% in stent graft group vs 1.4% in the PTA group

\*The key adverse events reported include death (5%), CVA (2%), CHF (4%), edema of arm/hand (3%), vessel rupture (3%), and pseudoaneurysm (5%) in the stent graft arm at 6 months

### 13.2. Analysis Strategy

The primary efficacy endpoint will be tested for superiority of treatment to control using a one-sided Z-test and the primary safety endpoint will be tested for non-inferiority of treatment to control using the Farrington Manning Method and a predefined non-inferiority margin of 7.5%. The study will be claimed successful if both primary efficacy and primary safety tests showed significance at 0.025. The family-wise type I error will therefore be controlled at 0.025.

Once the hypothesis tests succeed for both primary endpoints, key secondary endpoints will be compared between treatments sequentially in a superiority manner as detailed in Section 14.5. If all of the selected key secondary endpoints pass the test, an exact test of superiority of the IN.PACT™ AV Access DCB compared to PTA in 30-day primary safety endpoint will follow; this sequential approach does not inflate the Type I error for superiority.

Any deviation(s) and change(s) from the original statistical plan and justifications will be documented in the CIP amendment and in the Statistical Analysis Plan (SAP).

## 13.3. Analysis Sets

### 13.3.1. Primary Analysis Set

#### Intent-to-treat (ITT) Analysis Set

All primary analyses will be performed using Intent-to-treat (ITT) Analysis Set which includes all randomized subjects. The ITT subjects will be analyzed according to their randomized group assignment irrespective of the treatment actually delivered and subject follow-up time, and all events post-randomization will be counted toward study endpoints. In general, all analyses will be performed on evaluable subjects in ITT analysis set. For Primary efficacy endpoint, the evaluable subjects include all ITT subjects that had a patency-related event (i.e., CD-TLR or access circuit thrombosis) within 210 days post procedure or had no patency-related event but followed up for at least 150 days. For primary safety endpoint, the evaluable subjects include all ITT subjects that had AV-access-circuit-related-SAE within 30 days post-procedure or had no AV-access-circuit-related-SAE but were followed up for at least 23 days.

### 13.3.2. Secondary Analysis Set

#### As treated analysis set

As treated analysis set include randomized subjects who received a DCB or PTA. The as treated subjects will be analyzed according to the device they actually received. If the as treated analysis set is different from ITT analysis set, the primary and secondary endpoints will be analyzed on as treated analysis set to assess the sensitivity.

#### Per-Protocol Analysis set

Per-Protocol Analysis set include subjects who have: (a) received the randomized treatment as assigned without provisional stenting or other potential bailout procedure; (b) no pre-specified inclusion/exclusion violation(s); and (c) available endpoint data post-index procedure. Per-Protocol Analysis set will be applied to primary and key secondary endpoint analyses.

## 13.4. Analysis of the Primary Endpoints

### 13.4.1. Primary Analysis of the Primary Endpoints

Both the primary efficacy outcome and primary safety outcome will be analyzed as observed. The count and percentage of subjects with each outcome will be presented by treatment. The percentage of the efficacy endpoint will be based on the subjects who had non-patency event (i.e., CD-TLR or access circuit

thrombosis) within 210 days post procedure or had no non-patency event but followed up for at least 150 days. The efficacy endpoint will be compared between treatments using the Z-test as the primary analysis method.

The percentage of the primary safety endpoint will be based on subjects who had AV-access-circuit-related-SAE within 30 days post-procedure or had no AV-access-circuit-related-SAEs but were followed up for at least 23 days. Non-inferiority on the safety endpoint will be tested using the Farrington-Manning method. The differences between treatments and the corresponding 95% confidence interval (CI) will be calculated.

To control the overall Type I error (one-sided  $P=0.025$  superiority and one-sided  $P=0.025$  non-inferiority) the following sequential analysis approach will be taken:

- Primary efficacy superiority; if significant at one-sided  $\alpha=0.025$ , and
  - Primary safety non-inferiority; if significant at one-sided  $\alpha=0.025$ ,
- then proceed to key secondary endpoints detailed in section 14.5.

The study will be deemed a success if both the superiority of efficacy and non-inferiority of safety are demonstrated.

### **13.4.2. Additional Analysis of the Primary Endpoints**

The time to the events will be evaluated according to Kaplan-Meier method, and the log-rank tests will be applied to compare the survival curves over time between the treatments for each primary endpoint respectively.

Primary endpoints will also be analyzed using per-protocol analysis set and as treated analysis set respectively when applicable.

### **13.4.3. Sensitivity Analysis of the Primary Endpoints**

- Multiple Imputation: ITT subjects with missing clinical follow-up data will be imputed using multiple imputation procedure.
- Tipping point analyses in which the number of successes or failures amongst missing data necessary to reverse the study conclusion are determined;
- Worst case analysis in which all missing endpoint in the treatment arm will be imputed as failures and all missing endpoint in the control arm will be imputed as successes.

Multiple Imputation will be conducted for primary efficacy endpoint. Tipping point analysis and worst case analysis will be conducted for both primary efficacy and primary safety endpoints.

#### 13.4.4. Poolability Analysis of the Primary Endpoints

Poolability of subjects across clinical sites for the primary efficacy and safety endpoint analysis will be tested using Cox proportional hazards regression. Included as independent variables in the Cox models will be treatment, site and the treatment-by-site interaction effect; if the interaction effect is not statistically significant (defined as  $p > 0.15$  on the interaction test) or the interaction effect is significant but not qualitative in nature, all data irrespective of site will be collected in a single analysis cohort. It may be necessary to combine two or more low enrolling study sites into pseudo-sites to allow these analyses. Sites with fewer than 10 subjects will be ranked by enrollment from low to high, then starting from the lowest enrollment site, sites will be combined into a pseudo site until the combined size reaches the median enrollment among all sites. This process will be repeated until all resulting sites have enrollment equal to or greater than 10 subjects. This will be done in a manner to preserve the structure of the study and prevent bias. Similar poolability analyses will be conducted to assess treatment-by- geography (U.S. vs. Japan vs. New Zealand) interaction and treatment-by-lesion status (*de novo* vs. restenotic) interaction.

#### 13.5. Analysis of the Secondary Endpoints

Descriptive statistics for the secondary endpoints will be provided. Unless otherwise specified, for categorical variables, the count and percentage of subjects with each outcome will be presented. They will be evaluated by using chi-square tests or Fisher's exact tests depending on the event counts. Continuous variables will be compared with t-tests. The differences between treatments together with the corresponding 95% confidence interval will be calculated. Additional time to event survival analysis will be employed when applicable. Secondary endpoints will be analyzed using ITT analysis set, per-protocol analysis set and as treated analysis set respectively when applicable.

The following key secondary endpoints will be compared between treatments sequentially by using ITT analysis set in a superiority manner if the two primary endpoint tests pass, each at a one sided significance level of 0.025, for potential inclusion in the label, in the following order:

- (1) Cumulative target lesion revascularizations(TLR) measured through 6 months post-procedure;

$$H_0: t_T \geq t_C$$

$$H_A: t_T < t_C$$

$t_x$  refer to the expected cumulative TLR rate through 6 month ( $x=T$  for DCB  $x=C$  for PTA). One-sided Z-test will be performed at a significance level of 0.025.

- (2) Number of interventions required to maintain target lesion patency through 6 months post-procedure;



$$H_0: I_T \geq I_C$$

$$H_A: I_T < I_C$$

$I_x$  refer to the expected number of interventions to maintain target lesion patency through 6 months ( $x=T$  for DCB  $x=C$  for PTA). The comparison will be performed at one-sided significance level of 0.025 using Wilcoxon Rank Sum Test.

(3) Number of interventions required to maintain access circuit patency through 6 months post-procedure

$$H_0: C_T \geq C_C$$

$$H_A: C_T < C_C$$

$c_x$  refer to the expected number of interventions to maintain access circuit patency through 6 months ( $x=T$  for DCB  $x=C$  for PTA). The comparison will be performed at one-sided significance level of 0.025 using Wilcoxon Rank Sum Test.

(4) Access circuit primary patency through 6 months post-procedure;

$$H_0: a_T \leq a_C$$

$$H_A: a_T > a_C$$

$a_x$  refer to the expected access circuit primary patency rate through 6 month ( $x=T$  for DCB  $x=C$  for PTA). One-sided Z-test will be performed at a significance level of 0.025.

If (1) – (4) all pass the test, the superiority test of primary safety endpoint will be performed

$$H_0: \pi_T \geq \pi_C$$

$$H_A: \pi_T < \pi_C$$

$\pi_x$  refer to the expected event rate of primary safety endpoint at 30-day ( $x=T$  for DCB  $x=C$  for PTA).

Exact test will be performed to compare DCB and PTA.

The testing procedure will stop at the first rejection failure. This fixed sequence preserves overall type I error.

## 13.6. Subset Analyses

The following subset analyses of primary and key secondary endpoints will be performed:

- Lesion Type (*de novo*, restenotic)
- AVF type
- Lesion location
- Single and multiple balloon use
- Gender
- Age ( $\leq$  Median,  $>$  Median)
- Diabetics
- Subjects without provisional stenting or other bailout procedure

Subset analysis based on Race and Ethnicity will be performed if applicable. There will be no formal hypothesis testing on these subsets due to insufficient power. The primary purpose of this subset analysis is to assess consistency of results across subgroups.

### 13.7. Patient withdrawal and Missing Data

In general, all analyses will be performed using the ITT analysis set, which constitutes all available (or observed) cases. Imputation of missing data will not be performed unless otherwise specified.

For primary endpoints, sensitivity analyses such as Multiple imputation tipping point analysis and worst case analysis will be performed as specified in 14.4.2.

## 14. Ethics

### 14.1. Statement(s) of Compliance

The IN.PACT™ AV Access Study will be conducted under an FDA Investigational Device Exemption (IDE) in compliance with EN ISO 14155:2011 3.1, 3.15, 3.2, 3.36, 3.37, 3.42, laws and regulations of the countries in which the clinical study is conducted, including data protection laws, the Clinical Investigation Agreement and the Clinical Investigation Plan. 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 Medtronic and investigators.

The study will be conducted according to the study protocol, federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted.

- In the US, the study will be conducted under an FDA Investigational Device Exemption (IDE) in compliance with 21 CFR Parts 11, 50, 54, 56, and 812 and 45 CFR part 46.
- In Japan, the study will be conducted in accordance with the ethical principles of the Japan GCP Ordinance and the Pharmaceutical and Medical Device Act.
- In New Zealand, the study will be conducted in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).
- In addition, the study will be conducted in compliance with 21 CFR Part 11 and 54 in all participating geographies.

The study will also be conducted in accordance with the Declaration of Helsinki. The principles of the Declaration of Helsinki are implemented in this study by means of the patient informed consent (IC) process, IRB/EC approval, study training, clinical study registration, pre-clinical testing, risk benefit assessment, and publication policy.

Where applicable, regulatory authority notification/approval will be done/obtained. Investigational sites will not be activated, nor begin enrolling subjects until the required approval/favorable opinion from the respective regulatory agency and IRB/EC has been obtained (as appropriate).

Additionally, any requirements imposed by a local regulatory agency or IRB/EC shall be followed, as appropriate.

Each site must provide Medtronic with a copy of the investigational site's IRB/EC approval letter and the IRB/EC-approved Informed Consent Form. IRB/EC approval letters must contain the following elements:

- Study Title and the Medtronic Protocol Number;
- Medtronic's Protocol Version (revision letter and/or date of issue);
- A list of the documents reviewed at the meeting covered by the approval letter;
- If applicable, the required interval for the site's continuing review by the IRB/EC; and
- Expiration date, if applicable and/or allowed by the site's system, of the current approval.

If applicable, approvals for the continuation of the study at each investigational site must be kept current in accordance with the IRB/EC's review schedule, but at a minimum, the study must be re-reviewed by the IRB/EC regularly based on local requirements. All site communications to and from the IRB/EC must be forwarded to Medtronic as they are sent/received.

Medtronic will be informed by the IRB/EC and/or the investigator in case any action is taken by an IRB/EC with respect to this investigation.

This study was publicly registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki.

## 15. Study Administration

### 15.1. Investigator and Investigational Site Selection

The primary requirements of Investigator selection for this study are relevant experience, adequate institutional facilities and equipment, appropriate site research staff to support the conduct of the study, commitment to safety and adherence to the investigational plan, and patient volume.

Throughout the conduct of the study, Medtronic and/or its designees will closely monitor compliance with the investigational plan, the applicable laws and regulations, the requirements of the IRB, and the terms of the Clinical Trial Agreement. Medtronic may suspend or terminate the study prematurely at any site with repeated occurrences of significant non-compliance.

### 15.2. Training of Investigational Sites

Medtronic and/or its designees are responsible for the training of appropriate clinical site personnel. Medtronic or its designees will present a formal training session to review proper reporting of adverse events, device usage, uniform data collection and compliance with the Clinical Investigation Plan (i.e., protocol and consent processes), the device IFU, techniques for the identification of eligible subjects, instructions on data collection, schedules for follow-up, and applicable regulatory requirements. The site Principal Investigator is responsible for key center personnel to be appropriately trained to the tasks they have been delegated. Ongoing assistance regarding completion and submission of eCRFs as well as retraining (if necessary) will be provided by Medtronic and/or its designee.

### 15.3. Investigator Responsibility / Performance

The Investigator is responsible to ensure that all work and services related to this study described herein, or incidental to those described herein, are conducted in accordance with the highest standards of medical and clinical research practice, the requirements of the IRB/EC, the clinical investigation plan, and the terms of the Investigator Agreement, and all applicable local laws and regulations, U.S.

Investigational Device Exemption regulations, including:

- 21 CFR 812: Investigational Device Exemptions
- 21 CFR 50 (Subpart B): Informed Consent of Human Subjects (21 CFR 50.20 General requirements for informed consent)
- 21 CFR 54 (Part 54): Financial Disclosure by Clinical Investigators

Upon completion or termination of the study, the Investigator will submit a final written report to Medtronic and the IRB/EC as required by the IDE regulations in 21 CFR 812.150. The report will be

submitted to Medtronic within three (3) months of completion or termination of the study and to the local IRB/EC in accordance with the IRB/EC policies and procedures.

The Investigator must maintain a DOA/DTL of appropriately qualified persons to whom the Investigator has delegated significant study related duties.

## **15.4. Role of Sponsor Representatives**

Sponsor's representatives may provide support as required for the clinical study, including technical support during the index procedure. The sponsor representative is an experienced expert of device sizing, placement and the technical features of the device and will advise the investigator during the index procedure if needed.

## **15.5. Monitoring**

Monitoring and monitoring oversight will be provided by Medtronic and detailed in a Monitoring Plan separate from this CIP. Representatives of Medtronic (i.e. contractors and authorized designees) may also act as the study monitors to the site. A list of the study monitors will be kept separate from the Monitoring Plan and provided under a separate cover.

Medtronic will be responsible for ensuring adequate monitoring, including site initiation and study closure, at each study site is completed to ensure the protection of the rights of subjects, the safety of the subjects, and the quality and integrity of the data collected and submitted. Appropriately trained personnel appointed by Medtronic will conduct site visits to ensure accuracy of data, timeliness of data submissions, adequate subject enrollment, investigational device accountability, as well as compliance with the protocol, IRB/EC conditions and guidelines. Any non-compliance with these items that is not adequately addressed by the principal investigator/site staff may be cause for the sponsor to put the investigator/site staff on probation or withdraw the investigator/site staff from the study. Frequency of monitoring will be based upon enrollment, study duration, compliance, and any suspected inconsistency in data that requires investigation. After each monitoring visit, the monitor will send the principal investigator a letter summarizing the monitoring visit. The principal investigator will be responsible for ensuring that follow-up actions needed to resolve issues are completed in an accurate and timely manner.

See Section 15.8- Direct Access to Source Data/Documents, for further details on source data verification.

## 15.6. Audits / Inspections

Medtronic initiated audits or regulatory authority initiated inspections at the investigational sites may occur during the course or after completion of the study. In the event that an audit is initiated by Medtronic or a designee (only in geographies where approved), the Investigator shall allow access to the original medical records and provide all requested information. In the event that an inspection is initiated by a regulatory authority, the Investigator shall immediately notify Medtronic of the impending inspection and allow the regulatory body access to the medical records and other information as required by applicable laws and regulations.

## 15.7. Data Management

Study sites will designate a unique subject ID number (SID) at the point of subject enrollment, which is assigned by Medtronic in the EDC system. Records of the subject/SID relationship will be maintained by the study site.

### Electronic Data Capture

Medtronic will use the Oracle Clinical Remote Data Capture database system for data collection. The database is located on a secure server at a Medtronic facility located in the US. All users will be trained on the use of the database prior to obtaining access. Once access is granted, users will have a unique User ID and will create their own password. Data stored electronically shall be maintained in compliance with 21CFR Part 11. The database for this study will be maintained according to corporate policy and record retention schedule.

### Data Validation

Medtronic and/or assigned designee will be responsible for the processing and quality control of the data (data management) per the Data Management Plan, which describes the procedures for data review, database cleaning and issue/resolution of data queries. Data will be collected and stored in a validated, password protected database. Data analysis will be conducted utilizing validated software and analysis programs by qualified biostatisticians.

Study data collected will be monitored and verified against source documents in accordance with EN ISO 14155:2011 sections 3.1, 3.15, 3.2, 3.36, 3.37, 3.42 and international standards. Any data discrepancies will be addressed through queries posted within the EDC system.

### Data Collection

It is the responsibility of the participating investigator to ensure the quality of the data being collected.

Required data will be recorded on electronic case report forms (eCRFs) by authorized site personnel as indicated on the Delegation of Authority/Delegated Task List. The eCRFs must be completed and/or updated to reflect the latest observations on the subjects participating in the study. It is recommended that all data is entered into the database/eCRF within 10 business days of the completion of the protocol-specified assessments or sooner as requested by the sponsor.

The investigator (or authorized sub-investigator) will electronically approve each eCRF. The EDC system maintains an audit trail on entries, changes or corrections in eCRFs, once the eCRF is saved. If changes are made to an already signed eCRF, the investigator shall re-sign this eCRF.

### **Data Queries**

During the review of source documents and eCRFs at the monitoring visits, any discrepancies noted will be queried by Medtronic or its designee (only in geographies where approved), and must be resolved by the investigational site staff and investigator in a timely manner. In addition, Medtronic or its designee may also generate data queries during routine or remote review of the data. These queries will be sent to the site and must also be resolved in a timely manner.

## **15.8. Direct Access to Source Data/Documents**

When source data verification is performed, the monitor must be granted direct access to original source documentation or certified copies of the original source must be provided. Direct access must also be permitted for individuals conducting audits, IRB/EC review and regulatory inspections.

If electronic source documentation is used at the site, the site must provide to the monitor:

- Direct access to the electronic medical record (e.g. the monitor is given a guest password to directly access the system) or
- Direct access to the electronic medical record by reviewing alongside appropriate study staff (e.g. a research coordinator) or
- Certified copies of the electronic medical record. The monitor shall verify that he/she has complete access to all original source required for the study (e.g. the monitor does not have a lower level of access to the original source documentation than the research coordinator or principal investigator necessary for the study).

## **15.9. Confidentiality**

Subject confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique subject identification code consisting of the unique Site Number and Subject Number will be assigned and used to allow identification of all data reported for each subject.

To maintain confidentiality, the subject's name or any other (PHI) should not be recorded on any study document other than the informed consent form. This scenario will be covered in the Patient Information-Informed Consent Form. In the event a subject's name/PHI is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel.

Study data may be made available to third parties, e.g., in the case of an audit performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event that study data are published.

The study sites in the US must comply with applicable subject confidentiality provisions of the Health Insurance Portability and Accountability Act (HIPAA) issued by the U.S. Department of Health and Human Services (HHS). All sites should maintain subject privacy in accordance to federal regulations (45 CFR Parts 160 and 164), local regulations, and institutional requirements.

### **15.10. CIP Amendments**

Any revisions or amendments to the CIP or Informed Consent document, along with a statement of justification for the changes, will be submitted to all affected Regulatory Authorities (FDA, PMDA (per GCP, *if needed*, these documents will be submitted to PMDA, and Medsafe, if needed), Competent Authority) and governing IRBs/ECs, according to applicable regulations. All amendments to the CIP shall be agreed between Medtronic and the principal investigator(s). Approval by regulatory agencies and IRB/EC (where applicable) must be obtained prior to implementing a CIP revision at the site.

### **15.11. Record Retention**

The investigator must retain the Investigator Site File, subject medical files, including images (angiograms and duplex ultrasound), and CRFs in accordance with local law and regulations for a minimum period of 2 year (or longer if local laws require) after market-release in his/her region. The investigator should take measures to prevent accidental or early destruction of the clinical study related materials.

Medtronic will retain the study records according to Medtronic corporate policy and record retention schedule.



## **15.12. Investigator reports**

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the clinical investigation plan. If any action is taken by an IRB/EC with respect to this 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.

Safety data investigator reporting requirements are listed in Section 11.2 – Reporting of Adverse Events. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

If any action is taken by an IRB/EC with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner.

**Table 17: Investigator Reports per Medtronic Requirements**

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Sponsor and Relevant Authorities, if applicable	The investigator must report a withdrawal of approval by the reviewing IRB/EC of the investigator’s part of the investigation within 5 working days.
Study Deviations	Sponsor and IRB/EC	Notice of deviations from the CIP to protect the life or physical wellbeing 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. If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be approved by Medtronic, the IRB/EC, and the FDA/applicable regulatory authorities. If the deviation does not affect these issues then only Medtronic must approve it. <i>(21 CFR 812.150(a)(4))</i>
Withdrawal of IRB/EC approval (either suspension or termination)	Sponsor	The investigator must report a withdrawal of approval by the reviewing IRB/EC of the investigator’s part of the investigation within 5 working days. <i>(21 CFR 812.150(a)(2))</i>
Progress report	Sponsor and IRB/EC	The investigator must submit this report to the sponsor and IRB/EC at regular intervals, but in no event less than yearly. <i>(21 CFR 812.150 (a)(3))</i> .
Failure to obtain informed consent prior to investigational device use	Sponsor and IRBs/ECs	If an investigator uses a device without obtaining informed consent, the investigator shall report such use within 5 working days after device use. <i>(21 CFR 812.150(a)(5))</i>
Final report	Sponsor and IRBs/ECs	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator’s part of the investigation. <i>(21 CFR 812.150(a)(6))</i>

### 15.13. Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the table below. In addition to the reports listed below, Medtronic shall, upon request of reviewing IRB/EC and/or regulatory agency, provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in Section 11.2 – Reporting of Adverse Events.

**Table 18: Sponsor Reports**

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, IRB/EC, and relevant authorities	Provide prompt notification of termination or suspension and reason(s).
Withdrawal of IRB/EC approval	Investigators, IRB/EC, FDA and relevant Authorities	Notification within 5 working days. (21 CFR 812.150(b)(2))
Withdrawal of FDA approval	Investigators, IRB/EC, and relevant Authorities	Notification within 5 working days. (21 CFR 812.150(b)(3))
Progress Reports	IRB/EC and FDA,	Progress reports will be submitted at least annually. (21 CFR 812.150(b)(5), 812.36(f))
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))
Recall and device disposition	Investigators, IRB/EC, FDA, and relevant Authorities	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 and relevant Authorities	Investigator's report will be submitted to FDA within 5 working days of notification. (21 CFR 812.150(b)(8))

Report	Submit to	Description/Constraints
Final report	Investigators, IRB/EC, FDA, and relevant Authorities	<p>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/ECs within six months after completion or termination of this study. <i>(21 CFR 812.150(b)(7))</i></p> <p>Medtronic shall prepare, according to the procedure, a clinical study report that summarizes the results, etc., of a clinical study when it is completed or discontinued. <i>(MHLW Ordinance 36, Article)</i></p>
Study deviation	Investigators	<p>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.</p> <p>Medtronic may provide center-specific reports to investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.</p>
Other	IRB/EC and FDA	<p>Accurate, complete, and current information about any aspect of the investigation. <i>(21 CFR 812.150(b)(10))</i></p>

Medtronic records and reports will be stored in a password-protected document management system.

The sponsor and principal investigator shall maintain the clinical investigation documents as required by the applicable regulatory requirement(s). They shall take measures to prevent accidental or premature destruction of these documents. The principal investigator or sponsor may transfer custody of records to another person/party and document the transfer at the investigation site or at the sponsor's facility.

**15.14. Publication and Use of Information**

Publications and presentations referring to this clinical study will be coordinated by Medtronic to allow the use of all available data. The following publication policy will have to be adhered to by all participating investigation sites:

Medtronic may use the study data for Regulatory Authority submission results, may publish the results in peer reviewed scientific journal(s) and present the data at major congresses.

Authorship on any publication(s) resulting from this clinical study will be assigned according to substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published. This is in accordance with the Vancouver principles (The Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, ICMJE, October 2008), as agreed upon by the editors of all major medical journals.

The number of authors will be dependent on the regulations of the concerning journal. Names of all participating investigators will appear in the Acknowledgment of the paper.

Based on the principle that Medtronic owns the data of this clinical study, a single investigation site may access and use the data provided by itself for scientific publications following prior approval by Medtronic.

Pooling data from several investigation sites for publication purposes, national projects and international projects all require prior approval from Medtronic.

Medtronic as the owner of the data can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research and development of devices or educational use.

The study sponsor will collect data in such way that no subject can be identified, and monitor study records.

Participating subjects will not be identified by name in any published reports about the clinical study.

## **15.15. Suspension or Early Termination**

### **Early Study Suspension or Termination**

Medtronic or Regulatory Authority may decide to suspend or prematurely terminate the clinical study (e.g. if information becomes available that the risk to study subject is higher than initially indicated, if interim analysis indicates that the results significantly differ from the clinical study objectives or statistical endpoints). If the clinical study is terminated prematurely or suspended, Medtronic shall promptly inform the investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB/EC and the study subjects.

### **Early Site Suspension or Termination**

Medtronic, IRB/EC or Regulatory Authority may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing IRB/EC, non-compliance to the Clinical Investigation Plan or lack of enrollment).

If an investigation site is suspended or prematurely terminated:

- Medtronic shall promptly inform the clinical investigator(s) of the termination or suspension and the reason(s) for this
- The investigator shall then promptly inform the reviewing IRB/EC
- The investigator shall then promptly inform study subjects
- The investigator agreement will be terminated
- The investigator will inform the institution (where required by applicable regulatory requirements)
- Medtronic will inform the Regulatory Authority(ies) (where required by applicable regulatory requirements)

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify or immediately stop the clinical study in the respective investigation site and immediately inform the sponsor and IRB/EC, if applicable.

### **15.16. Liability**

Medtronic, Inc. (including all wholly owned subsidiaries) 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 study insurance statement/certificate will be provided to the IRB/EC.

## 16. References

1. Bittl JA. Catheter interventions for hemodialysis fistulas and grafts. *JACC Cardiovasc Interv* 2010;3:1-11.
2. United States Renal Data System. 2010 Annual Data Report: Volume Two. *American Journal of Kidney Diseases*. 2011; 57(Suppl 1):192.
3. Patane D (2011) Superior patency with DEB in stenotic arteriovenous fistulae. *Inerventional News Educational Supplement* (September):1-3.
4. Schwartz CI, McBrayer CV, Sloan JH, et al. Thrombosed dialysis grafts: comparison of treatment with transluminal angioplasty and surgical revision. *Radiology*. 1995;194:337–341.
5. Rodriguez JA, Armadans L, Ferrer E, et al. The function of permanent vascular access. *Nephrol Dial Transplant*. 2000;15:402–408.
6. Turmel-Rodrigues L, Pengloan J, Rodrigue H, Brillet G, Lataste A, Pierre D, Jourdan JL, Blanchard D. *Kidney Int*. 2000;57(3):1124-40.
7. Diskin CJ. Novel insights into the pathobiology of the vascular access - do they translate into improved care? *Blood Purif*. 2010;29:216–229.
8. United States Renal Data System, *USRDS 2013 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2014.
9. Schwab SJ. Hemodialysis vascular access: the Achilles' heel remains. *Kidney Int*. 2007;72:665–666.
10. Manzi M, Cester G, Palena LM. Paclitaxel located balloon angioplasty for lower extremity revascularization: a new way to fight in-stent restenosis. *J Cardiovasc Surg (Torino)*. 2010;51:567–571.
11. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter vs. paclitaxelcoated stent for the treatment of coronary in-stent restenosis. *Circulation*. 2009;119:2986–2994.
12. Scheller B, Hehrlein C, Bocksch W, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl JMed*. 2006;355:2113–2124.
13. National Kidney Foundation KDOQI Guidelines: Clinical Practice Guidelines and Clinical Practice Recommendations 2006 Updates.
14. Ohira S, Naito H, Amano I, et al. 2005 Japanese Society for Dialysis Therapy Guidelines for Vascular Access Construction and Repair for Chronic Hemodialysis. *Ther Apher Dial*. 2006 Oct;10(5):449-62.

15. Farrington, C. P., and Manning, G. Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-zero Risk Difference or Non-unity Relative Risk. *Statistics in Medicine* 9:1447–1454. 1990.



## **17. Appendices**

### **17.1. Instructions for Use**

IN.PACT™ AV Access DCB Instructions for Use will be provided under separate cover.

## **17.2. Investigator Brochure**

The IN.PACT™ AV Access DCB Investigator Brochure will be provided under separate cover.

### **17.3. Labeling**

Labeling for IN.PACT™ AV Access DCB will be provided under separate cover. Labeling for all other market approved system components can be found with each package insert.

## **17.4. Master Informed Consent Form**

Patient Informed Consent Form will be provided under separate cover.

## **17.5. Site and Investigator List**

This information will be updated throughout the course of the study. The updated list will be maintained at Medtronic and will be available upon request.

## **17.6. IRB/EC Committee List**

This information will be updated throughout the course of the study. The updated list will be maintained at Medtronic and will be available upon request.

## **17.7. CRO/Core Laboratories**

A complete list of selected CROs and core laboratories will be distributed under a separated cover.

## **17.8. Sample Case Report Forms**

Draft Case Report Forms for the IN.PACT™ AV Access Study will be provided under a separate cover. Final CRFs will be provided to sites via the electronic data management system after the site has fulfilled all requirements for database access.



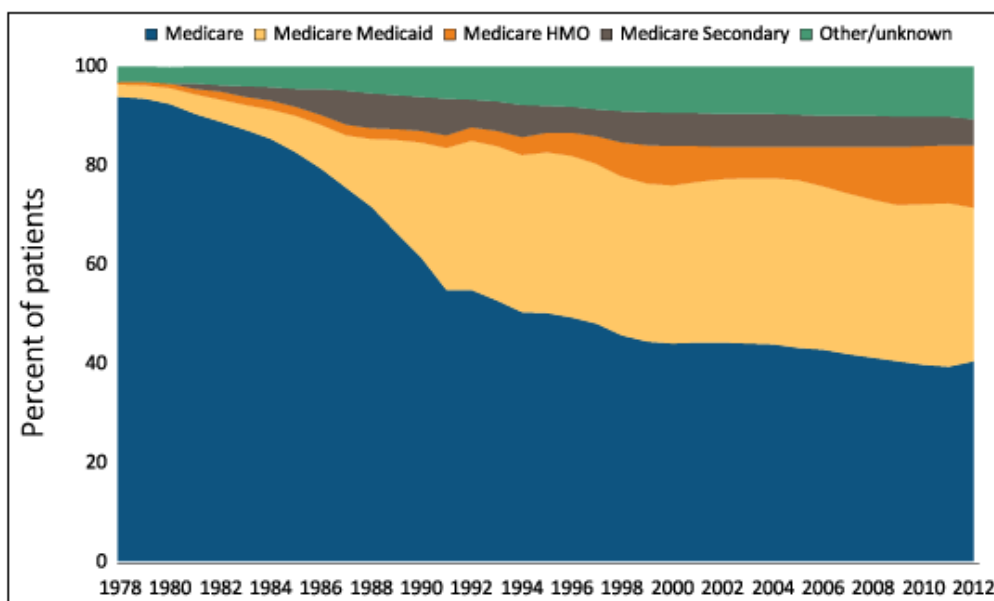
## **17.9. EQ-5D**

The EQ-5D-5L will be provided under a separate cover.

### 17.10. Medicare Coverage

It is anticipated that Medicare beneficiaries would be affected by this device because a predominant proportion of ESRD patients undergoing hemodialysis requiring the need for a dialysis access fistula, are covered by Medicare as shown in Figure A, below, from the 2014 USRDS Annual Data Report-Vol 2, found at: [https://www.usrds.org/2014/view/v2\\_01.aspx](https://www.usrds.org/2014/view/v2_01.aspx).

**Figure A: Trend in Distribution of Payer Type, by Modality, Among Prevalent ESRD Patients, 1978-2012 (Hemodialysis)**



In addition, claims data analysis including Medicare and commercial populations showed that 80% or more cases of dialysis vessel PTAs were performed in Medicare beneficiaries. The results of the IN.PACT™ AV Access IDE Study are therefore expected to be applicable to and generalizable to the Medicare beneficiary population since Medicare is the predominant payer of services for ESRD patients, including treatment of dialysis vessels with PTA.

### **17.11. Recommended Guidelines for Re-interventions**

Significant stenosis requiring treatment based on US KDOQI Guidelines<sup>13</sup> and Japanese Society for Dialysis Therapy Guidelines<sup>14</sup>: Significant stenosis defined as a decrease 50% or greater of normal vessel diameter accompanied by hemodynamic or clinical abnormality, including but not limited to:

- Decreased blood flow
- Elevated venous pressures
- Unexplained reduction in Kt/V
- Abnormal recirculation values\*
- Swollen extremity or Aneurysm formation
- Elevated negative arterial prepump pressures
- Unexplained reduction of dialysis efficiency
- Abnormal physical findings (thrill, murmur, arm swelling, etc.)
- Abnormally high BUN

\*Japanese guidelines state that it is possible to use recirculation rates for AVF surveillance



## 18. Version History

Version	Summary of Changes	Author(s)/Title
1.0	<ul style="list-style-type: none"> <li>Not applicable, new document</li> </ul>	Stephanie Cihlar, Sr. Clinical Research Specialist
2.0	<ul style="list-style-type: none"> <li>Minor administrative, language, grammatical and punctuation changes for clarity throughout CIP</li> <li>Definitions table: added “successful dialysis” for standardization of reporting successful dialysis</li> <li>Section 5.2: Updated the indication statement per FDA</li> <li>Section 8.1: added a footnote stating that for the clinical trial only the 40 cm and 80 cm catheter lengths will be made available</li> <li>Section 10 and throughout: replaced the KD-QOL questionnaire with the EQ-5D questionnaire for healthcare economic analysis purposes</li> <li>Section 14:                             <ul style="list-style-type: none"> <li>Changed the statement of “two-sided Chi-square test at <math>\alpha=0.05</math>” to “one-sided Z-test at <math>\alpha=0.025</math>” for primary efficacy endpoint per FDA recommendation to be consistent with the alternative hypothesis</li> <li>Added worst case analysis per FDA recommendation to assess the sensitivity of the primary endpoints</li> <li>Explicitly expressed the hypotheses of key secondary endpoints in mathematical form per FDA recommendation</li> </ul> </li> </ul>	Stephanie Cihlar, Sr. Clinical Research Specialist  [REDACTED] [REDACTED]



	<ul style="list-style-type: none"> <li>• Clearly distinguished the “secondary analysis” and “sensitivity analysis” per FDA recommendation. Specified the additional analysis on primary endpoints, including time-to-event analysis, analysis on as-treated subjects and per-protocol subjects. The sensitivity analysis, including multiple imputation, Tipping Point and Worst Case analysis were added.</li> <li>• Added “As-Treated Analysis Set” and “Per-Protocol Analysis Set” and reworded the “as-treated analysis” and “per-protocol analysis” by applying pre-defined analysis set for clarification.</li> <li>• Changed the test method of evaluating the primary safety endpoint from Z-test to Farrington-Manning test per FDA recommendation. The exact test provides a stronger control on type I error for the small event rates.</li> <li>• Changed the cutoff day for the 6 month target lesion primary patency from 180 days to 210 days. The Target lesion primary patency is a composite endpoint that has two component events- a clinical endpoint of CD-TLR and an imaging based endpoint of thrombosis, using upper limit of clinical visit window (180+30 days) helps to maximize the assessment of imaging data.</li> <li>• Added Appendix 17.11 Recommended Guidelines for Re-interventions, per FDA and PMDA recommendations, to provide investigators with guidelines for when to intervene on subjects if there is suspicion of recurrent stenosis</li> </ul>	
--	---	--



<p>3.0</p>	<ul style="list-style-type: none"> <li>• Update template version to v A:             <ul style="list-style-type: none"> <li>▪ Moved version history to end of document – sections numbers updated accordingly</li> <li>▪ Moved “Study Insurance/Subject Indemnification” language to “Liability” section 15.16. No changes to the technical content.</li> </ul> </li> <li>• Extension of follow-up period for up to 5 years (60 months) to collect data on long-term safety and effectiveness:</li> <li>• Section 3.0: Synopsis “follow-up” and “time course” updated to extend the study up to 5 years in order to collect long term safety and effectiveness data; long term assessments added to the secondary endpoints</li> <li>• Section 5.0: Long term assessment measures added</li> <li>• Section 6.1: Follow-up and total expected duration updated to account for up to 5 year follow-up</li> <li>• Section 10.1: Updated to account for up to 5 year follow-up and to capture abandoned target fistula data</li> <li>• Section 9.1: Updated study flow diagram to reflect reconsenting and extended follow-up; updated table 3 to reflect extension and collection of abandonment data; updated follow-up tables to extend for up to 5 years</li> <li>• Section 9.4: updated with language regarding reconsenting subjects willing to participate in the study for up to 5 years</li> <li>• Section 11.2: updated the site reporting timeframe of SAEs, ADE, SADE, UADE, Device Deficiency to 10 working days to align with 21 CFR 812.150 a(1)</li> <li>• Section 12.3: updated to state DUS exam should be submitted to core laboratory only through 24- months</li> </ul>	<p>Stephanie Cihlar, Prin. Clinical Research Specialist</p>
------------	--	---