



GE Healthcare

Clinical Study Protocol:

Evaluation of Feasibility and Accuracy of Assisted Fetal Heart Rate (FHR) feature of the GE Vscan Access R2 Ultrasound System (110.05-2017-GES-0001)

Version: 1.0; 26/Jul/2017

Sponsor: General Electric Company, acting through its GE Healthcare Business
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Investigational Device/Product: Vscan Access R2 with Assisted Fetal Heart Rate Measurement **Modality:** Ultrasound (U/S)

FOR QUALIFIED INVESTIGATORS, STUDY STAFF, AND THEIR ETHICS COMMITTEE(S) ONLY

CONFIDENTIALITY STATEMENT

Information in this RESEARCH STUDY PROTOCOL is for investigators, site personnel involved with the study, ethics committee(s), and/or their authorized representative(s) except as required to obtain consent from study participants or as otherwise required by law. Once signed, the terms of the protocol are binding for all parties.

Study Title: Evaluation of Feasibility and Accuracy of Assisted Fetal Heart Rate (FHR) feature of the GE Vscan Access R2 Ultrasound System

Study No: 110.05-2017-GES-0001



The Sponsor and Investigator have approved this protocol version, and I confirm hereby to conduct the study according to the protocol and in accordance with applicable principles of the World Medical Association Declaration of Helsinki and Good Clinical Practice (GCP) guidelines as per ISO 14155:2011, any conditions of approval imposed by the reviewing EC or governing regulatory body, and applicable laws and regulations. The investigator should not deviate from this protocol except for emergency use. I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Local Principal Investigator at study site:

Investigator Signature

Date

Print Name

Site Name, Department, Address



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DOCUMENT AND VERSION CONTROL

This section records all changes made to the protocol for a specific study. In the table below, record every relevant change by indicating what changes were made.

Revision	Date	Revision Author	Comments/Changes
1.0	26/Jul/2017	Aneysha Bhat	Clinical Writer - This is the initial version.



LIST OF ABBREVIATIONS AND TERMS

AE	Adverse Event
ADE	Adverse Device Effect
ALARP	As Low as Reasonably Possible
AMA	American Medical Association
BPM	Beats per Minute
CA	Competent Authority
CAPM	GE Clinical Affairs Project Manager
CCG	Case Report Form Completion Guidelines
CFR	Code of Federal Regulations
CHF	Clinical History File (synonymous with e-Trial Master File)
CRF	Case Report Form
DCF	Data Clarification Form
EC	Ethics Committee
EU	European Union
FDA	United States Food and Drug Administration
FHR	Fetal Heart Rate
GCP	Good Clinical Practice (see ISO 14155:2011) ¹
GE	General Electric
GEHC	General Electric Healthcare
ICF	Informed Consent Form
ISO	International Standards Organization
MWS	GE MyWorkshop Internal Documentation System
PRTS	Protocol synopsis
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SPR	System Problem Report
US	United States
U/S	Ultrasound
USADE	Unexpected Serious Adverse Device Effect



STUDY SYNOPSIS	
Sponsor:	General Electric Company, acting through its GE Healthcare Business
Research Type:	This is a clinical, open label, non-randomized, prospective, single-site, non-blinded research study, that will enroll from the accessible women (aged >18 years) in the 2nd and 3rd trimesters of pregnancy. The study will be conducted in two parts, including an initial pilot for determination of parameters (Part 1) and continued testing (Part 2).
Regulatory Status:	This is a pre-market research study of the following products: <i>Pre-market:</i> Vscan Access R2 Ultrasound System <i>Post-market:</i> GE Corometrics* 170 Series Fetal Monitor
Background and Rationale:	Fetal heart rate (FHR) estimation is an important tool for assessment of fetal well-being and development during pregnancy that is traditionally measured using M-mode or Doppler methods on ultrasound systems. The Vscan Access Ultrasound system is a diagnostic ultrasound imaging system manufactured by the study Sponsor, GE Healthcare (GEHC) and equipped with Assisted FHR, a novel investigational feature that enables visualization and measurement of fetal heart rate. This feature visually maps obstetrical and abdominal anatomical structures and fluid and is intended to be used by qualified and trained primary and specialty health care professionals, including midwives, other paraprofessionals and general physicians. The built-in preset workflows and protocols, particularly enable novice users to scan efficiently and conduct basic screening exams. This technology provides an innovative way of assessing FHR that is semi-automated and does not involve any manual measurements once the fetal heart is scanned. This study is being conducted to validate procedural accuracy of the Vscan Access R2 Ultrasound System with Assisted FHR Measurement in users of all experience levels.



<p>Procedures/ Methods:</p>	<p>Subjects in the initial pilot period (Part 1) and validation testing (Part 2) will undergo up to 45 minutes of ultrasound scanning, including up to 8 test scans on the Vscan Access R2 Ultrasound System with Assisted FHR (research device) and a conventional commercially available ultrasound device. Subjects will also undergo routine commercially available noninvasive FHR monitoring as a reference. All procedures will be conducted at a Sponsor, GE Healthcare (GEHC), facility. All members of the study staff will be qualified based on experience and trained prior to participation.</p> <p>The study population will consist of asymptomatic women ages 18 or older in the second (2nd) and third (3rd) trimesters of pregnancy. Users will be instructed to use the VScan Access R2 device to take a 3 second video of the volunteer, which will result in a calculated fetal heart rate measurement from the monitor. Volunteers will also undergo routine commercially available FHR monitoring using the current standard of care.</p> <p>The first session (Part 1) will be a run-in session, in which the parameters and procedures will be a replica of the study but these results will not count towards the documented results. There will be four (4) sessions following this run-in session (Part 2). Each of these sessions will be approximately 3-4 hours in length over a period of 1-2 weeks.</p> <p>In each session, there will be 1-2 users and 3 volunteers. The users will be instructed to take as many measurements as possible during the allotted time. Finalization of the procedure to calculate accuracy is to be determined based on the run-in procedures executed in Part 1. The specific procedures for the measurement of accuracy which will be used for validation will be performed by the team during Part 1 of the study.</p>
<p>Objectives:</p>	<p>Data from Part 1 and Part 2 may be pooled or analyzed as separate subgroups, as determined necessary by the sponsor.</p> <p>The primary objective is to validate the accuracy of the VScan Access R2 ultrasound assisted FHR measurement compared to the reference standard in a pregnant population.</p> <p>The exploratory objective is to collect usability data for further user experience optimization.</p> <p>The safety objective is to collect safety information, including type and number of AEs, SAEs, and other device issues.</p>
<p>Endpoints:</p>	<p>The primary endpoint is FHR data from the investigational and comparator devices on a per-sample basis in bpm (beats per minute).</p> <p>The exploratory endpoint is the number of subject cases containing scan parameters will be reported and descriptively summarized as necessary to assist in evaluation of usability of the Vscan Access R2 Ultrasound System.</p> <p>The safety endpoint is the type and number of AEs, SAEs, and device issues.</p>



<p>Eligibility criteria:</p>	<p>Inclusion criteria: All included subjects will be:</p> <ol style="list-style-type: none"> 1. Women aged 18 years or older at the time of consent; 2. By self-report, are in the 2nd or 3rd trimester of pregnancy; <p>AND</p> <ol style="list-style-type: none"> 3. Able and willing to provide written informed consent for participation. 	<p>Exclusion criteria: Subjects will be excluded that:</p> <ol style="list-style-type: none"> 1. Are direct employees/contractors of General Electric (GE); 2. Have anatomical characteristics or comorbid medical conditions that prevent completion of ultrasound scanning using the study device; <p>OR</p> <ol style="list-style-type: none"> 3. Are potentially put at additional risk by participating, in the opinion of study staff.
<p>Sample size and Sites:</p>	<p>Up to 25 subjects will be included as part of this study to achieve the targeted number of complete and evaluable subjects. The target sample size for this study is 15 subjects. This includes testing up to 5 subjects in Part 1 and 20 subjects in Part 2 of the study. The sample size for both study parts is based on estimation necessary for study device evaluation and validation requirements. This study is not statistically powered for any measure.</p>	
<p>Study duration:</p>	<p>The study is expected to last approximately 6 weeks. Estimated start date: 01/Sep/2017 Estimated end date: 30/Oct/2017</p>	



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1. BACKGROUND AND JUSTIFICATION

FHR estimation is an important tool for assessment of fetal well-being and development during pregnancy that is traditionally measured using M-mode or Doppler methods on ultrasound systems or with conventional acoustic systems. The Vscan Access R2 Assisted FHR method is an innovative way of assessing FHR that is semi-automated and does not involve any manual measurements once fetal heart is scanned. Assisted FHR method may have clinical benefits, such as improved ease of training and utilization in real clinical cases.

FHR monitoring is important for prenatal care and can be used to indicate a variety of clinically relevant conditions in the mother and fetus, which is the subject of extensive research collaborations worldwide.¹ Training clinicians to perform accurate FHR measurements can be challenging due to various discrepancies in both practice and the acceptable standards for routine FHR measurement.

FHR measurement is important to clinical practice and widely considered safe and effective. A study by Ruma et al.² found that appropriate maternal-fetal care, including FHR determination via obstetric ultrasound improves the outcomes of mothers and their infants, in part due to improved accuracy using advanced ultrasound techniques. This has been demonstrated in large clinical trials, including the Eurofetus study which examined second trimester ultrasounds prospectively.³ American Institute of Ultrasound in Medicine (AIUM) recommends medically necessary fetal ultrasound in the 2nd and 3rd trimester, which are widely considered to be safe for mother and fetus.^{4,5}

The Vscan Access R2 Ultrasound System with its Assisted FHR feature has the potential to improve the accuracy and reproducibility assessment of FHRs for second and third trimester scans, and it also may reduce the variability between clinicians performing similar procedures. Results from this study may be useful for the evaluation of procedural accuracy of the Vscan Access R2 Ultrasound System with Assisted FHR compared to the conventional methods of measuring FHR on ultrasound or Doppler devices.

Justification for Use of GE-Operated Facility

Diagnostic ultrasound device development is an iterative process that involves engineers making changes and adjustments and then evaluating those updates using human subjects. The process listed above is repeated until the product is functioning optimally. One of the key aspects of this process involved the engineer and the device operator viewing images together and discussing the performance of the features and changes under development during the human subject scanning session. In order for this cycle to function both efficiently and economically, it is critical that the human scanning occur in the same location as the Research and Development teams (i.e., onsite at Research Park facility).

The expertise for the product development of the Ultrasound Devices in use under this Study resides at the GEHC Research Park, Wauwatosa, Wisconsin, USA site. In particular, not only the personnel expertise, but certain specialized testing hardware and software to enable development of these Ultrasound Devices, components and accessories are located at the Research Park site.

Facility expertise for product development includes:

- Feasibility; new feature pairings need to be evaluated.
- Verification and Validation; necessary components of the design control cycle.
- Image Quality; the primary determinant of the commercial success of an Ultrasound Device; and determined by a complex matrix of inputs.
- Complaint Resolution; replication of Device complaints in a laboratory controlled setting is an essential part of post-market surveillance.
- Usability testing; to fulfill the requirement for products to have usability testing prior to completion of design output requirements.



- System performance with new hardware and software features.
- Ergonomics and Human Factors; essential part of safe, efficient, and successful product design.

In summary, this study needs to be performed at the Research Park development site because the location contains:

1. Engineering expertise;
2. Clinical domain expertise;
3. User preferences (image quality, presets, knobology) expertise;
4. Competitive benchmarks; and
5. Clinical marketing teams.

1.1 Recommendations for Use of Ultrasound in Research

The World Federation for Ultrasound in Medicine and Biology (WFUMB) includes over 51,155 members in the Regional Federations including the National Societies of Ultrasound in Europe (EFSUMB), in Asia (AFSUMB), in North America (AIUM), in Latin America (FLAUS), in Australasia (ASUM) and in Africa and Mediterranean Countries (MASU).⁴ The study is informed by the WFUMB summary guidance and recommendations for ultrasound examinations for diagnostic purposes as well as for non-diagnostic research and training. Because the exam is performed on a commercially available ultrasound system with exposure not exceeding that normally encountered in clinical practice, the study is considered to pose minimal risk to subjects and adhere to responsible use of ultrasound for research.

1.2 Device Risk and Benefit Analysis

Diagnostic ultrasound devices, components, and accessories are generally considered non-significant risk, and generate images through the use of sound waves rather than ionizing radiation. Diagnostic ultrasound devices share a well-understood safety profile.^{6,7} These devices have been used since the 1950s and are considered one of the safest imaging modalities available with no confirmed adverse biological effects on humans.^{8,9}

This study involves having an ultrasound exam not required for the subject's clinical care. All ultrasound exams done for the study are performed on the the Vscan Access R2 Ultrasound System in a similar manner as routine non-invasive clinical ultrasound exams. Duration and exposure in this study do not exceed those typically encountered in clinical practice and thus involve similar risks as routine clinical ultrasound exams.

Participating in this study does not directly benefit subjects, but will provide images and case data that may benefit others in the future by helping to develop and improve new ultrasound technologies.

1.2.1 Established Safety Measures

In order to minimize the risk of potential adverse biological events, known or unknown, as a result of exposure to ultrasound, the FDA has issued guidelines that require manufacturers of diagnostic Ultrasound devices for 510(k) to limit the acoustic output (energy) of the transducer, the Guidance for Industry and FDA Staff - Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers (2008). These limits, which are displayed on the instrument in the form of a thermal index (TI), both thermal index bone (TIB) and thermal index soft tissue (TIS) and mechanical index (MI), in combination with guidance to the sonographer to limit the scan duration according to the ALARA principle (As Low As Reasonably Achievable) minimizes the risk of a significant adverse biological events.

With these safety measures in place, extensive use of ultrasound in the past 30 years has been shown to be well tolerated in humans.^{6,10} To reduce any potential risks, the duration of Ultrasound scan time in this Study



including the dwell time (i.e. the length of time that the Ultrasound beam is fixed on a specific tissue target), and the acoustic output (TIB, TIC, MI) will be carefully monitored and will be kept within the FDA cleared/approved/recommended levels. All devices used in this study adhere to the limits for thermal index (TI), mechanical index (MI), and other factors set forth by the US Food and Drug Administration (FDA) Guidance for Industry and FDA Staff - Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers (2008), which references the “Standard for real-time display of thermal and mechanical acoustic output indices on diagnostic ultrasound equipment Revision 1,” AIUM/NEMA Standards Publication (AIUM/NEMA 2004a) and IEC 60601-2-37 “Medical electrical equipment - Part 2-37: Particular requirements for the safety of ultrasonic medical diagnostic and monitoring equipment” (IEC 2007). Biological effects of ultrasound are rare within these limits, and ultrasound scanning in this study is thus considered to pose minimal risk of adverse effects in research subjects.

Concern over the bio effects of the acoustic output in vulnerable tissues, such as those of a developing fetus in utero; have been investigated since the 1970s.^{6, 10, 11, 12, 13} To date, obstetric scanning poses minimal risk to mother and fetus if the sonographer abides by the recommended guidelines for scanning obstetric patients set forth in the WFUMB Recommendations on Non-medical Use of Ultrasound (2013).¹⁴

1.3 Controls and Minimization of Bias

The following bias control method will be implemented during the course of this study: selection bias will be limited by consecutively enrolling eligible subjects.

2. DEVICE/PRODUCT DESCRIPTION

2.1 Identity, Mechanism, and Function

Name: Vscan Access R2 Ultrasound with **Assisted Fetal Heart Rate Measurement**

Modality/Type: Ultrasound (U/S)

Manufacturer: GE

Software version: Verified software version cleared for study use

Regulatory Status: Pre-market

Note: A record of number of devices issued, along with applicable identification numbers (e.g. serial/lot/batch) and components/accessories used in this study, will be retained by the Sponsor as part of the clinical history file (CHF), as required by applicable laws and regulations.

The Vscan Access Ultrasound system is a diagnostic ultrasound imaging system manufactured by the study Sponsor, GE Healthcare (GEHC) and equipped with Assisted FHR. It enables visualization and measurement of obstetrical and abdominal anatomical structures and fluid and is intended to be used by qualified and trained primary and specialty health care professionals, including midwives, other paraprofessionals and general physicians. The built-in preset workflows and protocols, particularly enable novice users to scan efficiently and conduct basic screening exams.

The system consists primarily of the core components:

- **Transducer/Probe:** Convert ultrasound waves to electrical signals or vice versa. Vscan Access only supports a convex probe that is part of the Vscan Access device and cannot be detached.
- **Image Quality (IQ) Optimization:** Auto-optimization to image quality for challenging cases.



- Clinical Software tools: Software features like ScanCoach, Clinical protocols, touch screen user interface, patient education videos to enhance clinical efficacy and workflow.
- Applications: Imaging and analysis for OB and Abdominal applications

Routine commercially available ultrasound accessories and components (lubricating gels) may be used during study procedures at the discretion of the study staff. The device will be used for research purposes in this study in accordance with applicable sections of US FDA 21 CFR and other applicable laws and regulations. This study uses the device with a software that is verified but is yet to be commercially available.

Vscan Access Ultrasound system is CE marked to meet CE marked to European Medical Devices Directive (MDD) 93/42/EEC. Vscan Access is not available in the USA.

The Vscan Access Ultrasound System and its accessories and components under study are considered Class II in the United States per 21 CFR §892.1550 (Ultrasonic pulsed-Doppler imaging system), 21 CFR §892.1560 (Ultrasonic pulsed echo imaging system), and 21 CFR §892.1570 (Diagnostic ultrasonic transducer).

The results of this study are intended for future use in clinical engineering and development next generation ultrasound technologies and de-identified information may be in the United States and other countries.

2.2 Intended Use

The Vscan Access Ultrasound system is intended to be used to support diagnostic decision-making when used by trained medical personnel. Personnel operating the devices in this study may or may not have medical training, and results of research scans are not intended for diagnosis. The procedures conducted in this study are intended primarily for research purposes and are not intended as a substitute or replacement for required medical care required outside of this study.

2.3 Comparator/Reference Standard

The comparator/reference standards used for comparison with the investigational product will be the commercially available FHR monitor using the M-mode ultrasound device. All commercially available devices used in this study will be documented on the device listing for the study.

2.4 Concomitant/Ancillary Administrations

2.4.1 Medications and Biologic Products

No medications or biologic products will be administered as part of study procedures.

2.4.2 Laboratory Tests and Sample Processing

No laboratory tests or sample processing is planned as part of the study procedures.

2.5 Accountability

Accurate and adequate records will be maintained for all devices, from time of shipment to the sites until return or disposal of all devices issued by the Sponsor as part of this study, as required by applicable laws and regulations.

GE Healthcare (GEHC) will provide the research Vscan Access R2 Ultrasound with Assisted Fetal Heart Rate Measurement and commercial devices used as the reference standard for study use, which may be used concurrently in other commercial and research activities. Site procedures for verification and documentation of device safety, traceability of software versions, device labeling, and device disposition will be followed. The



Principal Investigator will be ultimately responsible for the security and integrity of research devices at the site during the course of the study.

2.5.1 Issuance

Device will be provided by the Sponsor site. There is no additional calibration or maintenance of study devices planned. The Sponsor may provide maintenance and monitoring of devices as necessary to maintain the integrity of study data.

2.5.2 Disposition

The device(s) will be dispositioned after the study by returning the device to the Sponsor, in accordance with applicable laws and regulations. Identifiable health information will be removed prior to the device disposition.

2.6 Anticipated Risks and Benefits

The device under study has undergone risk assessment, in accordance with International Standards Organization (ISO) 14971, and risks have been mitigated to levels as low as reasonably possible (ALARP).

The risks of study participation are not expected to be greater than those of similar procedures routinely conducted in clinical practice. Post-trial care or follow-up is not required by this study. FHR measurement has been performed for over 20 years and shown to have an excellent safety profile for trained users, because it is non-interventional and does not impact maternal growth or fetal development.

It is also noteworthy that continuous electronic FHR monitoring has been linked to increases in cesarean sections and instrumental births, and therefore costs, without an associated improvement in perinatal outcomes.^{15, 16, 17}

There are no expected risks to subjects, operators, or others in this study beyond those of routine devices in clinical care. Stresses induced on the fetus are minimal and are widely accepted to be well below harmful levels in clinical practice.¹⁸

There are no expected risks to subjects, operators, or others in this study beyond those of similar devices already used in clinical care.

2.6.1 Risk Category and Rationale

The Vscan Access R2 Ultrasound with Assisted Fetal Heart Rate Measurement, as used in this study, is not considered a significant risk device per the 21 CFR §812.3 definition:

- 1) it is not intended as an implant;
- 2) is not purported or represented to be for a use in supporting or sustaining human life;
- 3) is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health;
- 4) and it does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Purpose of the Study

The purpose of the study is to evaluate the procedural accuracy of the Vscan Access R2 Ultrasound System with Assisted FHR feature, versus the use of a conventional FHR monitoring device, such as GE Corometrics* 170 Series Fetal Monitor, for measuring FHR in pregnant women in the 2nd and 3rd trimesters. The Vscan Access R2 Assisted FHR method is an innovative way of assessing FHR that is semi-automated and does not involve any



manual measurements once the fetal heart is scanned, unlike conventional methods of measuring FHR with M-mode ultrasound.

3.1.1 Primary Objective:

- To validate the accuracy of the Vscan Access R2 Ultrasound System Assisted FHR measurement compared to the reference standard in a pregnant population.

3.1.2 Exploratory Objective(s):

- To collect usability data for further user experience optimization.

3.1.3 Safety Objective(s):

- To collect safety information, including type and number of AEs, SAEs, and device issues.

3.2 Study Endpoints

3.2.1 Primary Endpoints:

- FHR data from the investigational and comparator devices on a per-sample basis in bpm (beats per minute)

3.2.2 Exploratory Endpoints:

- The number of subject cases containing scan parameters will be reported and descriptively summarized as necessary to assist in evaluation and optimization of the Vscan Access R2 Ultrasound System.

3.2.3 Safety Endpoints(s):

- Type and number of AEs, SAEs, and device issues.

3.3 Summary of Study Design

This is a Clinical, pre-market open label, non-randomized, prospective, single-site, non-blinded, research study, that will enroll from the accessible adult (aged >18 years) female population in the 2nd and 3rd trimesters of pregnancy. The study will be conducted in two stages, beginning with a run-in study (Part 1), followed by a clinical study (Part 2). The results of the run-in pilot study will not be included in the results and data analysis; rather, Part 1 of this study will be used to test procedures and determine any experimental factors that have yet to be defined. The study will be conducted at a GE-operated facility. The study is expected to last approximately 6 weeks. The study is not statistically powered for any measure, and is intended to evaluate procedural accuracy of the Vscan Access R2 Ultrasound System Assisted FHR versus use of a conventional FHR monitor (reference): GE Corometrics* 170 Series Fetal Monitor.

4. STUDY DESIGN

4.1 Study Population

Adult women (aged >18 years) in their 2nd or 3rd trimesters of pregnancy based on self-report, will be enrolled. A normal FHR usually ranges from 120 to 160 beats per minute (bpm). FHR rises through early pregnancy, peaking at 170 bpm (10 weeks), and then, decreases through the 2nd trimester (~140 bpm by 20 weeks), until the end of the 3rd trimester (130 bpm at term).¹⁹ This population of subject selected are feasible for the collection of representative FHR ultrasound scans, within a range suitable for validating the feasibility and accuracy of the



Vscan Access R2 Ultrasound System, with Assisted FHR versus the conventional, commercially available GE Corometrics* 170 Series Fetal Monitor.

4.2 Number Subjects

Up to 25 subjects will be included as part of this study to achieve the targeted number of complete and evaluable subjects. The target sample size for this study is 15 subjects. This includes testing up to 5 subjects in Part 1 and 20 subjects in Part 2 of the study. The sample size for both study parts is based on estimation necessary for study device evaluation and validation requirements. This study is not statistically powered for any measure.

There is only a single population under study, which is intended to include a range of clinical cases representative of FHR exams conducted at a typical site. This protocol does not prospectively specify any quotas based on scan type or anatomy. However, the site should attempt to enroll a diverse range of subjects including race, ethnicities, and anatomies in order to test a range of features on the study device.

4.3 Protection of Vulnerable Subjects

Vulnerable subjects are individuals whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate.

The Sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s), or other parties participating in, or contributing to, the clinical investigation.

All investigators shall avoid improper influence on, or inducement of, the subject, Sponsor, monitor, other investigator(s), or other parties participating in, or contributing to, the clinical investigation.

The study activities cannot otherwise be performed without the use of vulnerable populations because FHR can only be measured in pregnant women with viable fetuses.

Pregnant women/fetuses/neonates: Pregnant women, fetuses, and/or neonates will be subjects in this study. The purpose of this study involves meeting the health needs of these populations. The mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, and risk to the fetus will be minimal.

4.4 Eligibility Criteria

4.4.1 Inclusion Criteria

All included subjects will be:

1. Women aged 18 years or older at the time of consent;
 2. By self-report, are in the 2nd or 3rd trimester of pregnancy;
- AND
3. Able and willing to provide written informed consent for participation.

4.4.2 Exclusion Criteria

Subjects will be excluded that:

1. Are direct employees/contractors of General Electric (GE);



2. Have anatomical characteristics or comorbid medical conditions that prevent completion of ultrasound scanning using the study device;
- OR
3. Are potentially put at additional risk by participating, in the opinion of study staff.

4.5 Recruiting and Screening

Subjects will be recruited for potential enrollment in this study according to the standard procedures of the investigational site, unless otherwise specified by the Sponsor in this study protocol. All participation will be voluntary. During subject recruitment, efforts will be made to identify subjects with variety of gestational age and number, race and ethnicity, age, and body type. Recruiting materials may target necessary subpopulations.

Subjects will be screened for enrollment in this study against the inclusion and exclusion criteria according to the standard procedures of the investigational site.

Following recruitment, a subject will be considered enrolled (the point of enrollment) once she signs and dates the informed consent form (ICF). Once enrolled, the subject will be assigned a unique subject number, which will not contain information that could identify the subject (such as subject name or date of birth). The unique subject number will be used to label case report form (CRF) data for the subject throughout his/her participation in the study.

4.6 Criteria for Withdrawal/Discontinuation

A subject may withdraw from study participation at any time, for any reason. The study staff may withdraw a subject at any time, for any reason. The reasons for withdrawal and discontinuation for any subject shall be recorded to the Sponsor-provided case report form (CRF). Subjects may be withdrawn if they require medications (such as sedatives) that could interfere with study participation. These will be reported to the Sponsor. The IRB should be notified per their notification of subject withdrawal policy.



5. STUDY PROCEDURES

5.6 Study Parts

The study will be conducted in two parts, including a initial pilot run-in period (Part 1) and testing period (Part 2), as described in Table 1. Patients in both parts of the study will undergo the same procedure and have a similar experience in the study; however, results will not be collected or recorded for analysis from Part 1 of the study

Table 1 - Description of Study Parts

Study Part	Maximum enrollment	Operator Experience Level	Description
Part 1	5	Any experience level	Pilot for determining
Part 2	15	Approx. 4 Novice and 1 Experienced	Scanning with fixed parameters

5.7 Subject Procedure

Subjects will be asked basic demographic and pregnancy status questions. Subjects will be screened for eligibility and no other preparations are required to participate. Following consent, eligible subjects will be fitted with a conventional FHR Monitor while simultaneously undergoing a non-invasive abdominal ultrasound scan using the Vscan Access R2 system with Assisted FHR and a commercially available ultrasound device (reference standard). FHRs will be collected using both devices.

Eight (8) paired ultrasound scans with FHR Monitor determination will be attempted for each subject participating in the study (a total of 16 scans each, 8 with the research device and 8 with the reference device). Each paired scan will last approximately 5 minutes for both determinations, for a total of approximately 40 minutes of total ultrasound exposure. Breaks may be provided between scans based on operator availability or requests by the subject. At least 2 operators will perform scanning for each subject.

A prospective blocked schedule detailing the order in which scanning will be conducted for each operator and subject will be prepared before the start of subject scanning.

Up to 5 clinicians (Experienced sonographers, Novice users e.g. newly qualified sonographers, nurses/midwives, etc.) - with an approximate 80-20 split of novice vs. experienced - with respect to ultrasound familiarity & scanning experience will be aspired for.

The resultant ultrasound and case data (including basic demographics; self-reported pregnancy status; and information about when and how the ultrasound exam was conducted) will be collected for each subject.

All procedures will be conducted at a Sponsor, GE Healthcare (GEHC), facility. All members of the study staff will be qualified based on experience and trained prior to participation.

5.8 Scan Operators

Approximately 5 clinician ultrasound operators may participate in the study at two skill levels:

- **Novice:** Nurse, midwife, medical residents, or technologist with <3 years' experience with obstetric ultrasonography
- **Experienced:** Physicians or technologists with ≥3 years of experience



5.9 Follow-up

No follow-up will be conducted. The subject will be followed for AEs from the time they enter the GE facility to the time they leave the GE facility.

Any data, including images, collected for the subject, up until the time of withdrawal or discontinuation, may still be included in the study results and provided to the Sponsor, unless the subject requests that their data not be used. The site shall document all requests by subjects regarding their data use.

6. STUDY DATA COLLECTION AND ASSESSMENTS

6.6 Primary Assessment

The operator will record FHR values estimated from the reference and research ultrasound devices to the CRF. Relevant demographics and clinical information will also be recorded to the CRF.

6.7 Exploratory Assessments

The device operator will save the ultrasound images, which includes information about the parameter of scanning, for each subject than completes an ultrasound scan in the study. Additional information will be recorded to the CRF as follows:

- Subject ID
- Date of scan
- Duration of scanning
- Patient demographics (age, height, weight, race/ethnicity)
- Gestational age and number, self reported or by LMP or EDD from previous scans
- Trimester (2nd or 3rd)

6.8 Safety Assessments

The description, severity, and device relatedness of any AE or SAE during the study will be recorded. Subjects will, if necessary, be provided with emergency care. In the event of any device issues, the event will be recorded. Safety reporting will be conducted as described in this protocol.

7. QUALIFICATION AND TRAINING PLAN

7.6 Staff Qualifications

All members of the study staff participating in the conduct of the clinical investigation shall be qualified by education, training and/or experience to perform their tasks, and this shall be documented appropriately, as per ISO 14155:2011 for clinical studies.

All members of the study staff participating in the conduct of the investigation shall be qualified by education, training and/or experience to perform their tasks, and this shall be documented appropriately, as per United States Food and Drug Administration (FDA) requirements and ISO 14155:2011.

7.7 Training Plan for the Protocol and Research Device/Product



Before starting the study, the study staff will be trained based on their role in the study on the clinical investigation requirements set forth in this study protocol according to the training plan, as follows:

- *Protocol Training* – All study staff will be trained on the study protocol and, as applicable, on devices. Documentation of such training will be retained at the site as part of the regulatory binder and by the Sponsor as part of the study Clinical History File (CHF).
- *Training objectives* – Objectives will be recorded in each training session.
- *Training logistics* – A qualified trainer authorized by the study Sponsor will conduct training sessions.
- *Target audience* – All site personnel involved with the conduct of the study will be trained on the protocol and, as necessary, on device use.
- *Device Training* – All users will be trained on the VScan Access R2 and Assisted FHR feature per the user manual.

Study staff directly operating or maintaining the research device will be trained based by the Sponsor or qualified based on experience, such as being an imaging scientist, engineer, sonographer, or other medical professional qualified by the site policy.

The Principal Investigator will be ultimately responsible for execution of this study in accordance with the protocol and for device/product use in this study by members of the study staff.

8. SAFETY

The description, severity, and study device relatedness of any AE or SAE during the study will be recorded. Subjects will, if necessary, be provided with emergency care. In the event of any study device issues, the issues will be recorded. Safety reporting will be conducted as described in this protocol.

8.6 Anticipated Adverse Events

FHR determination with ultrasound is widely considered safe for 2nd and 3rd trimester pregnancies without significant comorbidities.^{15, 16, 17} Because no subjects will be enrolled that are in active labor or exhibit significant medical conditions that could pose risk of harm to mother or developing fetus, the risks of this study are expected to be the same as for conventional commercially available ultrasound devices for prenatal scanning.

Diagnostic ultrasound exams involve minimal risk because they use acoustic energy rather than X-rays or other types of ionizing radiation. Ultrasound is commonly used in populations of pregnant women and is not expected to pose additional risks to subjects.^{20, 21} This study enrolls from a population of pregnant women that may foreseeably experience adverse events not related to the study device during the course of this study. In the event that the study staff observed any medical issues that could pose additional risk to the mother or



developing fetus, the subject will be immediately withdrawn and referred for appropriate medical care outside of the study.

Even though manifestation of risks during cardiac, pulmonary, and/or abdominal ultrasound exams is rare, ultrasound can produce effects on the body. Having an ultrasound exam involves some foreseeable risks that are not different from those routinely encountered in routine clinical ultrasound exams, which include:

- Tissue warming
- Discomfort
- Skin irritation
- Bruising
- Abrasions or tears in the skin
- In rare cases, formation of small pockets of gas in body fluids or tissues (cavitation) can occur. The long-term effects of tissue heating and cavitation caused by ultrasound are not known.

As part of this study, subjects will have an ultrasound exam as part of this study that is not required for clinical care. All study scans are completed using non-invasive methods on a commercially available ultrasound device. All exams are performed in a similar manner as routine clinical exams. Thus, study participation is not expected to pose additional risks to subjects beyond those of routine ultrasound scanning.

There is always a chance of unexpected risks. Throughout the study, the Sponsor will evaluate and update safety information in study documents.

8.7 Adverse Event Definitions

Adverse Event (AE): any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device [ISO 14155:2011 3.2]. This includes events related to the investigational device or the comparator and to the procedures involved. For users or other persons, this is restricted to events related to the investigational medical device.

Serious Adverse Event (SAE): an adverse event that led to death; led to a serious deterioration in the health of the subject, that either resulted in a life-threatening illness or injury, a permanent impairment of a body structure or a body function, or in-patient or prolonged hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function; or led to fetal distress, fetal death or a congenital abnormality or birth defect. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol without serious deterioration in health, is not considered a SAE [ISO 14155:2011 3.37].

Adverse Device Effect (ADE): an adverse event related to the use of an investigational medical device [ISO 14155:2011 3.1]. This includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This includes any event that is a result of a user error or intentional misuse of the investigational device [ISO 14155:2011 3.43].

Serious Adverse Device Effect (SADE): an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event [ISO 14155:2011 3.36].

Device deficiency: an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, such as malfunctions, use errors, and inadequate labelling [ISO 14155:2011 3.15].

Unanticipated serious adverse device effect (USADE): a 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 [ISO 14155:2011 3.42]. In the United States, 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 study documents, will be reported in accordance with 21 CFR §812.3 and applicable laws and regulations.



8.8 Documentation of Safety Events

All adverse events (AE), including all serious adverse events (SAE), are required to be collected, investigated, and documented during the study reporting period, as defined in the study procedure set forth in this protocol. Documentation will include:

- Description of Event
- Date of onset and resolution
- Severity (mild, moderate, or severe)
 - *Mild:* Symptom(s) barely noticeable to the subject or does not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
 - *Moderate:* Symptom(s) of a sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.
 - *Severe:* Symptom(s) of a sufficient severity to cause the subject severe discomfort. Treatment for symptom(s) may be given.
- Serious (yes/no)
- Causal relationship to investigational medical device? (not related, possibly related, or related)
 - *Not related:* The adverse event is reasonably expected to be related to (or caused by) a concurrent illness, effect of another device/drug or other cause, and is unlikely related to the investigational product.
 - *Possibly related:* The adverse event is reasonably expected to be related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product.
 - *Related:* There is a strong relationship to investigational product or recurs on re-challenge, and another etiology is unlikely or there is no other reasonable medical explanation for the event.
- Treatment given and/or action taken (procedure stopped, withdrawn from study, or no action)
- Anticipated (yes/no)

8.9 Reporting of Safety Events and Device Deficiencies/Complaints

The following events are to be reported to the Sponsor within 72 hours of the event occurrence and to the EC per their policy:

- All SAEs and USADEs
- All device issues that could possibly lead to an SAE

Additional follow-up information may be requested by the Sponsor. In addition, safety information may be shared with regulatory agencies and other participating sites, as required by applicable law and regulation.

8.10 Device Deficiencies/Complaints

Device deficiencies/complaints should be reported to the study Sponsor contact identified on the cover page of this protocol. All device deficiencies/complaints will to be collected, fully investigated, and documented in the source document and appropriate case report form (CRF) during the study reporting period. The Principal Investigator is responsible for notifying the Sponsor in the event that there is any device issue that could potentially lead to a SAE.

9. ETHICAL CONDUCT OF THE STUDY

The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki; the guidelines of Good Clinical Practice (GCP) for medical devices, as set



forth by ISO 14155:2011 and ISO 14971:2010; applicable sections of US FDA 21 Code of Federal Regulations (CFR), and applicable regulatory authority's requirements in the United States.

The study will be conducted and reported in accordance with applicable policies of the governing Ethics Committee (EC) and governing regulatory authorities.

If national or regional EC requirements are less strict than the requirements of GCP, such as ISO 14155:2011 for medical devices, the Sponsor shall make attempts to apply the requirements of this International Standard to the greatest extent possible, irrespective of any lesser requirements, and shall record such efforts.

9.6 Ethics Committee

The responsible Principal Investigator at each site will ensure that approval from an appropriately constituted EC is attained for the clinical study prior to enrolling subjects, and Principal Investigator will ensure that documentation of approval is maintained for the duration of the study.

The Principal Investigator will ensure that the Sponsor is notified of any withdrawal of EC approval within 5 working days of such occurrence. If approval is terminated or suspended, the Principal Investigator will promptly notify the Sponsor and provide written explanation.

9.7 Regulatory Agencies and Competent Authority(ies)

This trial is considered non-significant risk and IDE exempt. As such, prospective US FDA review is not required prior to the start of the study. Any additional requirements imposed by the EC or regulatory authority shall be followed, when applicable.

9.8 Management of Protocol Modifications and Amendments

Substantial amendments will only be implemented after approval of the EC.

A deviation is any instance(s) of failure to follow, intentionally or unintentionally, the requirements of the protocol. Under emergency circumstances, deviations from the protocol to protect the rights, safety, and wellbeing of human subjects may proceed without prior approval of the Sponsor and the EC/competent authority (CA). Such deviations shall be documented and reported to the Sponsor and the EC as soon as possible. Deviations will be reported as:

- **Critical Deviations:** Deviations that significantly affect the safety, efficacy, integrity, or conduct of the study. These deviations must be reported to the Sponsor no later than 5 working days from awareness of occurrence and reported to the EC per the deviation reporting policy.
- **Non-Critical Deviations:** Protocol deviations that do not significantly affect the safety, efficacy, integrity, or conduct of the trial. These deviations must be documented on the CRF Protocol Deviation page and will be reviewed by the study monitor.

Non-substantial modifications may be made during the normal course of device optimization, maintenance, and feasibility testing. Non-substantial modifications will be communicated to the CA as soon as possible, if applicable, and to the EC per their policy.

9.9 Participant Information and Informed Consent

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration of exposure to the investigational device (if applicable), the potential risks and benefits, and any potential discomforts. Each participant will be informed that participation in the study is voluntary, that she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. The participant must be informed that his/her medical records may be examined by authorized individuals other than their treating physician.



All participants for the study will be provided an ICF describing the study and providing sufficient information to allow the participant to make an informed decision about his/her participation in the study. Informed consent documents will be subject to approval by the EC prior to enrolling subjects in the study.

The participant should read and consider the statement before signing and dating the ICF, and shall be given a copy of the signed document. The ICF must also be signed and dated by the investigator (or his/her designee), and it shall be retained as part of the study records.

9.10 Early Termination of the Study

The Sponsor may terminate the study prematurely according to certain circumstances. Examples of such circumstances include ethical concerns, insufficient participant recruitment, participant safety concerns, alterations in accepted clinical practice that make the continuation of a clinical trial unwise, early evidence of benefit or harm of the research product, or for any other reason.

10. STATISTICAL METHODS

10.6 Statistical Hypothesis

No statistical hypothesis is being tested in this study.

10.7 Sample Size Determination

Up to 25 subjects will be included as part of this study to achieve the targeted number of complete and evaluable subjects. The target sample size for this study is 15 subjects. This includes testing up to 5 subjects in Part 1 and 20 subjects in Part 2 of the study. The sample size for both study parts is based on estimation necessary for study device evaluation and validation requirements. This study is not statistically powered for any measure.

Fewer subjects may be enrolled, at the discretion of the Sponsor, if it is determined that necessary engineering development targets can be completed with a lesser number of subjects than the maximum enrollment of 25. In such cases, the site will be notified in writing to discontinue enrollment.

10.8 Statistical Analysis

No statistical hypothesis testing is prospectively planned. Gestational age/number and other variables or subgroups determined necessary by the Sponsor, at its discretion, will be summarized as tables and listings, which may include appropriate descriptive statistics when applicable. Subject disposition and number of image sets collected will be summarized in the final report.

10.8.1 Interim Analysis

No interim analyses are intended to be conducted as part of this study. The Sponsor may access the study data at any time during the study, as necessary for engineering purposes.

10.9 Handling of Missing Data

No imputation will be done for missing data.



11. QUALITY ASSURANCE AND CONTROL

11.6 Data Management

Data management processes for handling study data will be maintained by the Sponsor.

11.6.1 Completion of Case Report Forms (CRFs)

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents. Paper CRFs will be used to collect data. The Sponsor will provide CRFs and train study staff on completion of CRFs using Good Documentation Practices (GDP). CRF Completion Guidelines (CCG) may be provided by the Sponsor to help facilitate training.

CRFs are to be completed as information becomes available at the site. CRFs should be signed by indicated parties, in indicated area(s), to certify the contents of the form. The Principal Investigator is ultimately responsible for ensuring completion of CRFs.

If discrepancies are discovered on paper CRFs during monitoring, the Sponsor's representative will ensure that the study staff makes necessary corrections directly to the CRF(s) prior to collection.

Following CRF collection, the Sponsor will review the data. A Data Clarification Form (DCF) may be provided to the site to correct or clarify discrepancies.

If a site discovers discrepancies after CRF collection, the site may notify the Sponsor and request data modification.

11.6.2 Data Handling and Record Keeping

All documents and data shall be produced and maintained in a manner that assures control and traceability.

11.6.3 Source Data and Documents

Source data includes information in original records, certified copies of original records of clinical findings, observations, or other activities for the study. Source documents for each subject must be retained throughout the investigation, including printed or electronic documents containing source data.

The Principal Investigator or institution shall provide direct access to source data during and after the clinical investigation for monitoring, audits, EC review, and regulatory authority inspections.

11.6.4 Archiving

All study data must be archived for a minimum of 3 years after study termination (or as required by local law) or premature termination of the clinical trial. No source documents or study records will be destroyed without Sponsor notification and approval.

12. MONITORING PLAN

In collaboration with the site, the Sponsor will ensure proper monitoring of the study to confirm that all the research requirements are met. Monitoring visits will oversee the progress of a clinical investigation and ensure that it is conducted, recorded, and reported in accordance with the protocol, written procedures, Good Clinical Practice (GCP) ISO 14155:2011, and the applicable regulatory requirements.



12.6 Confidentiality and Data Protection

The investigator affirms and upholds the principle of the participant's right to privacy, and the investigator shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing data in scientific journals.

Individual subject medical information obtained as a result of this study will be considered confidential, and disclosure to third parties will be prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers. For data verification purposes, authorized representatives of the Sponsor, a competent authority (CA), or an ethics committee (EC) may require direct access to parts of the medical records relevant to the study, including subject medical history.

12.6.1 Storage of Images and Associated Health Data

Research images and associated data will be collected and disclosed to the Sponsor as part of this study. Fully de-identified data, which has had all personal identifying information removed, may be stored and used by the Sponsor indefinitely. The Sponsor and/or its authorized representatives may use any de-identified data collected in this study for future technology and engineering development, marketing purposes, education, regulatory claims, or other possible uses.

12.7 Publication Policy

The results of this study may be used in future publications, at the discretion of the Sponsor. The conditions of publication are described in a separate contractual agreement. The investigator should in good faith make the Sponsor aware of any possible public scientific contributions, such as publications or presentations. The Sponsor may request modifications or to delay presentations at its discretion.



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APPENDIX A – STUDY SITE AND INVESTIGATOR LIST

The following investigators at each study site will be responsible for the conduct of this study:

Investigator(s):¹	Anand Bherwani, DNB, MBBS <i>Tel:</i> 1-262-212-9786 <i>e-mail:</i> dr.anand.bherwani@ge.com	GE Healthcare (GEHC) <i>Address:</i> 9900 Innovation Drive, Wauwatosa, WI 53226
	Janette F Strasburger, MD <i>Tel:</i> 1-414-266-2000 <i>e-mail:</i> investigator@ge.com	Children's Hospital of Wisconsin-Milwaukee Campus <i>Address:</i> 8915 W. Connell Ct. Milwaukee, WI 53226

¹The role of the **Principal Investigator** is to implement and manage the conduct of the investigation as well as ensure data integrity and the rights, safety, and well-being of humans involved in the study [ISO 14155:2011 9.1]. **Co-Investigators** share all responsibilities of the **Principal Investigator**, and **Sub-investigators** share only those responsibilities designated by the **Principal Investigator**.