GE Healthcare

Clinical Study Protocol:

Development Of Medical Ultrasound Systems, Accessories, And Components - GE Bangalore

(110.08-2015-GES-0004)

Version: 2.0; 15/Feb/2018

NCT Number: NCT02946242

Current contact information is

provided in Appendix A – Study Contacts

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

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/IRB 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.

Principal Investigator at study site:

Investigator Signature	Date
Print Name	
Site Name, Address	

Table of Contents

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	16/Jun/2016	[redacted]	Clinical Writer – Initial draft.
2.0	15/Feb/2018	[redacted]	Rev 2.0 changes include: Contact information for several sponsor contacts is moved from Appendix A to a Study Contact List [redacted]), • Title page, Study Synopsis, Sections 9.4 and 9,5 Definition of Device Deficiency is removed from Terminology Page 7 because the definition is repeated in the body of the protocol. Study duration extended from approximately 3 years to approximately 5 years. • Study Synopsis, Section 5,2 Exclusion criteria updated to exclude subjects with electronic medical devices. • Section 5.5 and 6.1.2 Clarification of requirements for monitoring, recording, and reporting AEs, SAEs, and USADEs. • Sections 9.3, 9.4, and 9.5

List of Abbreviations and Terms

Abbreviations

2D	Two-dimensional
3D	Three-dimensional
AE	Adverse event
ADE	Adverse Device Effect
AIUM	American Institute of Ultrasound in Medicine
ALARA	As Low As Reasonably Achievable
CFR	U.S. Code of Federal Regulation
CHF	Clinical History File
CPU	Computer processing unit
CRF	Case report form
DMP	Data management plan
DSP	Digital signal processors
EC	Ethics committee
ECG	Electrocardiogram
FDA	US Food and Drug Administration
FPGA	Field programmable gate arrays
GCP	Good Clinical Practice
GEHC	General Electric Healthcare
ICF	Informed Consent Form
IEC	International Electrotechnical Commission
IHSR	Internal Human Subject Research
[redacted]	
IQ	Image quality
ISO	International Standards Organization
IRB	Institutional Review Board
MI	Mechanical index
MR	Magnetic Resonance
NEMA	National Electrical Manufacturers Association
PI	Principal Investigator
PNDT	Pre-Natal Diagnostic Techniques (or “PNDT Act”)
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
[redacted]	
TI	Thermal index
TIB	Thermal index bone
TIS	Thermal index soft tissue
U/S	Ultrasound
USADE	Unanticipated Serious Adverse Device Effect
UI	User interface
WFUMB	World Federation for Ultrasound in Medicine and Biology
WI	GE Work Instruction

Terminology

Recruitment	Procedures conducted to identify potentially qualified subjects prior to signing the informed consent form
Study Visit	The total period where the subject is present at the ultrasound scanning site for the research, including time where the subject is in the research area but not directly exposed to the research device(s)

STUDY SYNOPSIS

Research Type:	This is a clinical (human) study designed as a prospective, open label, iterative, engineering evaluation without randomization, stratification, or block/quota grouping.

Brief Description of Study:

Ultrasound devices components and accessories are under continuous development in order to optimize, validate and improve the devices, including improving the quality of images. In this study, GEHC proposes to collect data in order to achieve the following

1) **Aim 1**: Perform iterative evaluations of the device (including features, accessories and components) to optimize device performance, assess feasibility of new features, and to perform testing necessary to support product and technology development;
2) **Aim 2**: Perform activities to support design validation and/or to confirm user requirements and specifications have been met, as per design controls and other applicable requirements;
3) **Aim 3**: Evaluate device complaints and analyze potential causes.

There is no animal or phantom model that is adequate to accomplish these aims; therefore human subjects are required.

Due to the inherently varied nature of study data, specific data points will be recorded on a per-case basis and the study final report will summarize at minimum number and type of study scans conducted. Electronic image data may be collected. The number and type of safety issues, including adverse events (AEs) and serious adverse events (SAEs) will be reported. Unexpected device issues that occur outside of expected and controlled engineering optimization will be reported.

Sponsor Name: General Electric Company, acting through its GE Healthcare Business	**Address:** GE Healthcare 3000 N Grandview Blvd [redacted] Waukesha, WI 53188
Principal Investigator: Site contact information is provided in Appendix A – Study Contacts.	**Sponsor Contacts:** Sponsor contacts are provided in Study Contact List [redacted]
Study Facility Name: GE Healthcare, Bangalore	**Address:** Wipro GE Healthcare Pvt. Ltd. Odyssey Building, No. 122, EPIP Phase 2, Whitefield Road Bangalore, Karnataka 560066, India

GEHC Modality:	Ultrasound (U/S)
Device Description:	Non-invasive ultrasound devices are under study, including hardware and software components and accessories. [redacted]
Regulatory Status:	This study will conduct procedures using non-invasive ultrasound devices, accessories, or components that are pre-market (investigational), post-market (commercially available), or commercial but modified with investigational hardware and/or software components. No therapeutic ultrasound devices will be used. These devices share a common and well-understood safety profile. All scanning conducted is for research purposes only, and all procedures are treated as investigational (not for use in medical management).

Procedures/ Methods:	Subjects will be considered enrolled that provide written informed consent to participate, and with thereafter be scheduled to attend up to up to five (5) ultrasound scans per day lasting up to 60 cumulative minutes each with approximately a 15 minute break before starting another study scan (limited to 15 cumulative minutes of scan time per eye, per day for ophthalmic scanning) as long as they remain eligible per the study inclusion and eligibility criteria. Vital sign information about subjects may be collected and subjects will be positioned for scanning of a variety of target anatomic areas using a variety of non-invasive, transcutaneous techniques, such as scanning abdominal, musculoskeletal, breast(s), peripleural, transcranial, cervical/neck, cardiac, ophthalmic, vascular, extremity, soft tissue, and other accessible anatomical regions. The subject will be monitored for adverse events throughout the research study scan. The resultant images and associated data will be recorded and stored as part of study data.
Sample Size and Sites:	This study will be conducted at a single site and will enroll up to 150 subjects over the approximate 5 year duration. Based on the Sponsor's prior research and engineering experience, this number of subjects represents the minimum needed to adequately evaluate each system, probe, feature and/or application setting in a sample of different subjects that sufficiently represents the intended population of device use. Only the minimum number of study scans necessary to accomplish research aims will be performed, which may be fewer than the total number allowable by this protocol.
Study duration:	The study is expected to last approximately 5 years. **Estimated start date**: 15/Aug/2016 **Estimated end date**: 15/Aug/2021

1. PRELIMINARY INVESTIGATION AND JUSTIFICATION

1.1 Literature Review and Background

Diagnostic ultrasound (U/S), also called ultrasonic imaging or sonography, is a non-invasive imaging modality that produces pictures of the inside of the body using acoustic energy, or sound waves. There are numerous contemporary applications for diagnostic ultrasound. These technologies are attractive because of their ease of use, noninvasive nature, low cost, and ability to generate clinically useful images without the use of ionizing radiation required by other imaging modalities, such as X-ray and tomography procedures. [1] Ultrasound images are collected using a simple procedure in which a small transducer (probe) is connected with the skin's surface using an ultrasound gel or other agent. High-frequency sound waves are then transmitted from the probe through the gel into the body, and the transducer collects sounds that bounce back, which are analyzed by a computer to create images of structures inside of the body. [2] Because ultrasound images are captured in real-time, they are particularly useful in showing movement of internal organs and blood flowing through vessels. [2] Continuing technological advances, including increased portability and versatility of ultrasound devices, have improved ultrasound images and increased adoption of these technologies worldwide.

Although diagnostic ultrasound has been in routine clinical use since the early 1980s, the machine cost and bulk generally limited early ultrasound devices to conventional clinical care facilitates in developed areas, [3] and more recent developments include compact portable ultrasound devices adopted by a wide array of obstetricians, surgeons, emergency medicine physicians, and others in clinical and less conventional emergency response settings. [4, 5, 6, 7, 8] Ultrasound technologies are now used in most branches of medicine for examining a variety of target anatomies for diagnostic imaging and screening purposes, including extensive clinical use of ultrasound in cardiovascular medicine, women's health, general abdominal imaging and numerous point of care applications in settings such as emergency departments, operating rooms, and field medicine. [9, 10, 11, 12, 13 , 14] Thus, ultrasound technologies provide an important and growing source of diagnostic care.

Continuous and diligent advancement of ultrasound technology, as conducted under the current study protocol, can contribute to technological improvements in ultrasound technology with potential to yield clinical benefits in the future.

1.1.1 Recommendations for Use of Ultrasound in Research

Acoustic energy is measured by thermal index (TI), mechanical index (MI) displayed on the instrument. 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, in Asia, in North America (American Institute of Ultrasound in Medicine or AIUM), in Latin America, in Australasia and in Africa and Mediterranean Countries. [15] WFUMB provides summary guidance and recommendations for ultrasound examinations for diagnostic purposes as well as for non-diagnostic research and training.

Furthermore, because the success of ultrasound procedures is highly reliant on the competence of clinicians performing the exams, there has been recent emphasis on training and competence assessment with ultrasound aimed at both physicians and other care providers, such as midwives. [12] The American Institute of Ultrasound in Medicine (AIUM) Consensus Conference (2005 and 2008) indicated that 3D volume acquisition was useful for improving diagnostic efficiency and patient throughput, and the most recent recommendations from the AIUM include future investigations related to the utility of volume sonography in obstetrics and gynecology as well as ongoing research related to the bioeffects of ultrasound. [16, 17] Ultrasound technologies are rapidly evolving, and this study considers the most current recommendations for research use of ultrasound to ensure subject safety and data integrity.

1.2 Preclinical (animal) Trials and Previous Clinical (human) Experience

The ultrasound devices, accessories, and components being investigated in this study are similar to the ultrasound devices that have been commercially available for more than 30 years. [9, 10, 11, 12, 13. 18] Ultrasound devices emit sound waves that are transmitted through tissues of different densities at different speeds, and reflect and refract from tissue boundaries to create an echo, which is measured by a transducer. Contemporary ultrasound devices use these principles to not only produce high quality still images of the body but also to project movement of organs and tissues such as the heart and blood. Prior to clinical evaluation, devices may be researched in animal and phantom (gel filled objects that are used to test the physical characteristics of sound transmission and reflectance) models.

1.3 Device Risk and Benefit Analysis

Diagnostic ultrasound devices, components, and accessories are generally considered non-significant risk devices that safely and effectively use reflection of sound waves from different tissues in the human body to generate images. Ultrasound devices have a consistent safety and bioeffect profile that has been studied and reported. [16, 17] Diagnostic ultrasound devices have been used since the 1950s and are considered one of the safest imaging modalities available. No confirmed adverse biological effects on humans have been reported, though it is possible that the short-term and long-term biological effects of ultrasound are not completely known. [13. 18]

The possibility of adverse health effects from the sound waves produced by diagnostic ultrasound systems is remote. Ultrasound imaging devices used in this study typically adhere to the exposure limits set forth in the *WFUMB Recommendations on Non-medical Use of Ultrasound* (2013) [19] and the *British Medical Society Guidelines for the Safe Use of Diagnostic Ultrasound Equipment* (2009), as detailed in the safety appendix. [20] These standards are employed extensively in other ultrasound studies conducted by the Sponsor. Factors involved in the dose of energy delivered to tissue include the ultrasonic power level and volume of tissue exposed. Prudent and widely accepted limitations are employed in this study to the exposure time and power level during use (as detailed in Appendix B: SAFETY GUIDELINE TRAINING MATERIALS).

1.3.1 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 U.S Food and Drug Administration (FDA) has issued guidelines that require manufacturers of diagnostic ultrasound devices to limit the acoustic output (energy) of the transducer for 510(k) marketing clearance, 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 device in the form of a thermal index (TI), including bone at focus thermal index (TIB), soft tissue thermal index (TIS) and bone at surface thermal index (TIC) and mechanical index (MI), in combination limiting 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. [16, 17] To reduce any potential risks in this study, the duration of ultrasound scan time 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, TIS, TIC, MI) will be carefully monitored and will be kept within the FDA recommended levels. All devices used in this study adhere to the limits for thermal index , mechanical index, and other factors set forth by the 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[a] Standards Publication (AIUM/NEMA 2004) and IEC[b] 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.

1.3.2 Safety Justification for Multiple or Prolonged Ultrasound Exposures

Based on extensive epidemiologic data available, many years of clinical use of ultrasound devices and current knowledge of interactive mechanisms, there is nothing that suggests any causal relationship between multiple ultrasound exposures and adverse effects in humans. Safety mechanisms built into the device and maintaining acoustic power within recommended levels and WFUMB recommendations serve to minimize any possible adverse effects. [19]

1.3.3 Medicinal/Biologic Products Administration

No additional medicinal or biologic agents, such as sedatives or contrast agents, will be administered for the purposes of this research study. As such, there is expected to be no additional risk associated with biologically active substance administration in this study.

1.3.4 Benefits

Subjects are not expected to benefit directly from study participation. The results may benefit future patients by helping to better understand and develop ultrasound technology.

1.4 Justification

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 involves the engineer and the Device Operator viewing images together and discussing the performance of the features and changes under development during the study scan. 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 Bangalore facility).

The expertise for the product development of the ultrasound devices in use under this study resides at the GEHC Bangalore 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 Bangalore site.

- Facility expertise for product development includes:
- Feasibility; new features and console-transducer 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 input 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 Bangalore site because the location contains:

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

1.5 Justification for Use of Human Subjects

While preliminary, controlled testing and exploration can be conducted in phantoms (simulations), *in vitro* models like cultured cell lines, and preclinical animal models, data obtained from studies on infrahuman models may not be extrapolated to humans due to the unique characteristics of *in vivo* human physiology and anatomy. [21] Because the diverse characteristics of the general intended use population cannot be fully demonstrated through nonhuman models without introducing biases that are difficult or impossible to characterize, *in vivo* human studies are necessary to optimize medical device hardware and software for best outcomes.

Specifically echogenic phantoms work well for verification of system focusing, geometric distortion and measurement of sound beam penetration. However, such phantoms cannot replicate speed-of-sound variations capable of reducing image contrast (defocusing) and geometry distortion (refraction) as observed in living tissues. Similarly, sound reverberations between layers inside the body lead to image artifacts (structural ghosts or even clouds or echoes) that are not detectable on phantoms. Moreover, the hemodynamics of laminar and turbulent flow seen in the human vasculature are not sufficiently simulated by Doppler frequency shifts in phantoms. Similarly, image quality (IQ) is can be altered by actual probe access and placement relative to anatomical structures, such as the ribs and other structures. Variability in body habitus and tissue type (fat, muscle, blood, other) may also cause changes in performance only demonstrable by examining a range of diverse human subjects.

Currently, the American Institute of Ultrasound in Medicine (AIUM) Official Statement on tissue models reports that "presently available models are limited in their ability to represent clinical conditions because of varying tissue paths during diagnostic ultrasound exposures and uncertainties in acoustical properties of soft tissues." [22]. Prior to testing devices or device modifications in humans, bench research is performed to the extent possible. No phantom sufficiently duplicates all human characteristics, thus requiring human subjects for research purposes.

2. RESEARCH DEVICE

This study employs Ultrasound devices and their software and hardware components and accessories. All devices are established as safe for human testing, by the Sponsor.

2.1 Identification and Description of Research Device/Product

Non-invasive ultrasound devices (no therapeutic grade ultrasound), including hardware and software components and accessories, will be utilized in this study. The *Device List* [redacted] contains a list of devices

included in this study. The *Device List* will be updated when a new device is added to the study. The central devices and components under study are detailed in the following sections.

2.1.1 Ultrasound Scanner

The ultrasound scanner is an ultrasonic imaging system. The real time ultrasonic images produced by the scanner are obtained non-invasively (no skin puncture) by placing a transducer (probe) on the subject's skin. The scanner uses the sound energy to image soft tissue structures such as muscle, organs, tendons, and blood vessels.

2.2 System and Component Identity, Mechanism, and Function

The central devices and components of the ultrasound system under study are detailed in the following sections:

2.2.1 Transducers

Transducers are comprised of piezoelectric elements and are central to producing high quality ultrasound images. Transducers have various configurations. New developments in transducer materials and technology are necessary for new product development.

2.2.2 System Hardware

Acoustic energy is generated by exciting the transducer with an electrical sequence. The acoustic energy is measured to display device compliance. [23] The transmit hardware also laterally focuses the sound beam to improve spatial and contrast resolution. The receiver hardware takes the small amplitude electronic signal from the transducer and compensates for the sound attenuation from the body tissue. In addition, the receiver hardware focuses the received sound to improve the signal to noise ratio and the spatial resolution of the image. The receiver hardware also performs apodization of the signals which reduces side lobe artifacts and thus improves the contrast resolution of the image.

2.2.3 Software Receive Processing

The software that performs receive processing allows the received ultrasound signals to be used for a variety of clinical benefits. These include the b-mode image formation in one, two, three and four dimensions, the 2D color blood velocity estimation, the 1D pulsed and continuous wave Doppler blood flow estimation, and qualitative tissue stiffness displays. The processing is often adjusted in an attempt to improve one of the above display techniques. Receive processing is contained both in traditional computer processing unit (CPU) based architecture and also distributed software units of field programmable gate arrays (FPGA) or digital signal processors (DSP).

2.2.4 System Software

Data processing software reconstructs images from the raw data, re-processes reconstructed image data, and/or enables improved visualization of the image data. Data processing software may also be used to calculate quantitative physiologic measurements, such as blood flow rates and tissue stiffness.

2.3 Accessory and Ancillary Devices

Accessory devices can be used optionally along with systems under study. Some accessories are intended to be included with the device system upon commercialization and others may be separately marketed. Accessories include devices such as gels/coupling agents and hardware/software components may be used, as described in the following sections. A variety of accessory devices and combinations of accessory devices not specifically listed in

this protocol may or may not be used, at the discretion of the study staff. Other routine ancillary equipment may be used as necessary to accomplish research objectives.

2.3.1 Coupling Agents (Gels, Lotions, and Water Baths)

When handheld probes and some automated probes are used, a layer of water based gel or lotion (i.e. coupling agent) is placed between the probe and the subject to eliminate air bubbles and aid in moving the probe along the subject. The gel transmits the sound beam from the probe to the subject without a significant loss of power. [redacted]

2.3.2 Accessory Hardware and Software

Development efforts will also be focused on other types of system accessory hardware and software components such as but not limited to the scanner user interface, tracking equipment, and physiologic monitoring tools (non-life supporting or sustaining) such as an electrocardiogram (ECG). In some cases, probes may be coupled with accessories as necessary for testing.

2.3.3 Intended Use/Purpose of the Research Device

In clinical settings, when prescribed by a medical doctor, the non-invasive ultrasound systems are intended to provide information to medically trained personnel to use during the diagnosis process. Diverse devices may be used in this study in accordance with their labeled indications or in new ways. The indications may vary between devices. The procedures conducted in this study are intended for research purposes and are not intended as a substitute for required medical care.

2.4 Regulatory Status

This study may include devices, components and accessories that are post-market (completely through the Quality System and approved for commercial use in India), pre-market (investigational and not completely through the entirety of the Quality System or not in accordance with labeled indications in India), and in some cases a combination of a post-market devices, accessories or components and an investigational device, accessory or component. All activities will be considered investigational.

2.5 Device Classification and Rationale

Indian medical device classifications distinguish low to medium risk devices such as diagnostic ultrasound devices as Class B devices on a Class A (low risk) – D (highest risk) scale. The regulatory procedures for medical devices vary according to their class. In general, higher-risk devices are subject to more regulation in India. Presently there are no Indian requirements for registration of diagnostic ultrasound products prior to commercialization. The Declaration of Helsinki and principles of ISO 14155:2011 and the India Ministry of Health and Family Welfare (MOHFW) will be employed in this study.

2.6 Device Accountability and Maintenance

2.6.1 Device Issuance, Installation, and Accountability

Verification and documentation of device safety, traceability of software versions, device labeling, and device installation/disposition will be recorded by the site. Unique identifying information (e.g. model, serial number, etc.) of each device used in this study will be recorded. Devices that are concurrently used in other product development or research activities will be qualified for use in this study prior to being used in subject procedures.

2.6.2 Device Security and Access

Devices for this study will be located at a GEHC facility. GEHC facilities are restricted to GEHC employees or GEHC contractors, or persons supervised by a GE employee or an authorized GE Contractor. The devices that are part of this study will be managed per specific local safety procedures.

2.6.3 Maintenance and Optimization of Study Devices

The devices are frequently upgraded and/or modified during the course of development.

2.6.4 Concurrent Use of Research Devices and Research Area

Research device(s) and their accessories and components as well as the research area containing these devices may be used for other concurrent research activities and other activities authorized by the Sponsor, in accordance with the Sponsor's procedures and applicable laws and regulation. Procedures conducted in this study are done to accomplish research objectives outlined in the aims of this protocol, and are not intended to provide diagnostic information. No study scans will be conducted in this study solely for commercial training or product demonstration purposes.

2.6.5 Labeling of Research Devices

Investigational systems used in this study will be clearly labeled as investigational devices, in accordance with applicable US FDA labeling and/or regional regulatory requirements in India. Device qualification history will be maintained by GE, including information such as when devices are installed for study use.

2.6.6 Disposition of Devices

Devices will be dispositioned by GE in accordance with applicable local laws and regulations.

3. OBJECTIVES OF RESEARCH STUDY

3.1 Purpose of the Study

Ultrasound device systems, accessories, and components can be used to successfully perform ultrasound scans resulting in data from human subjects. No efficacy tests will be performed for any clinical indication as part of this study, and no statistical hypothesis testing or other cohort-based statistical inferences are prospectively planned.

3.2 Study Objectives

This study includes a diverse series of iterative ultrasound scans performed to satisfy specific aims outlined in this protocol. These aims include a variety of scan evaluations such as usability, ergonomics, and workflow, from pre-

market and post-market device systems, accessories, and components, and combinations thereof. Information learned is primarily intended for engineering optimization and complaint investigations.

3.3 Study Endpoints

3.3.1 Primary Endpoint

The primary endpoint is number and type of ultrasound study scans (which may include one or more sets of data and/or image data), which does not include evaluation of any specific clinical condition or efficacy measures.

3.3.2 Safety Endpoints

The number and type of safety issues, including adverse events (AEs) and serious adverse events (SAEs) will be reported. The number and type of device complaints will be reported.

4. DESIGN OF RESEARCH STUDY

4.1 Type of Research Study

This is an open label, prospective research study involving human subjects. Due to the heterogeneous nature of these diverse study scans, there will be no cohort-based comparative efficacy or safety analysis and no assessment of missing data elements (it is not required that any study scan produce all exploratory elements) and therefore no randomization. Prospective subjects are enrolled and then undergo one or more study scans without randomization, stratification, block/quota, or other grouping.

4.2 Controls and Minimization of Bias

This study is open to the general population. All who respond to IRB/EC-approved recruitment materials and meet all of the inclusion criteria and none of the exclusion criteria are eligible to be enrolled. This minimized possible selection bias. Based on the study hypotheses and Aims, employing control or comparison groups and techniques to reduce potential source of bias are not indicated. The data derived from this study are not intended to yield any cohort-based safety or efficacy conclusions for regulatory purposes. Anonymized images resulting from this study may be used for regulatory support purposes if they are used as samples or examples to demonstrate image quality only.

5. SUBJECTS

5.1 Study Population

This population will consist of adult men and women that meet all inclusion criteria and do not meet any exclusion criteria. The term “adult” shall mean any individual 18 years of age or older.

Subjects in this study will generally reflect the desired population for the device use. Because different anatomical components of the human body have different acoustic properties, it is prospectively expected that the study will

enroll a diverse population with variant body habitus in order to assess performance in different sub-populations (such as different gender, age, or body type).

5.2 Number of Subjects

This study will be conducted at a single site and will enroll up to 150 subjects over the 5 year duration. Based on the Sponsor's prior research and engineering experience, this number of subjects represents the minimum needed to adequately evaluate each system, probe, feature and/or application setting in a sample of different subjects that sufficiently represents the intended population of device use. Only the minimum number of study scans necessary to accomplish research aims will be performed, which may be fewer than the total number allowable by this protocol.

5.3 Protection of Vulnerable Subjects

The study activities cannot otherwise be performed without the use of vulnerable populations. 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.

5.3.1 GE Employees

Direct employees of GE may participate as subjects in this study. These subjects will be protected from coercion or undue influence at all times, and participation in this study and study results will not be considered in any decisions related to education or employment. Information about research participation and outcomes will not be made available to the employee's manager/supervisor. Information about employees collected during the study will not be revealed to others within the company except as necessary to conduct the study. Employees may be asked for personal and corporate identification information as necessary to conduct and reimburse participants, in accordance with local laws and regulations. Identifiable information will be removed from any study data used or stored outside of the study for engineering development or other purposes as such that it cannot be reasonably linked the employee participant in the future.

5.3.2 Safeguards for GE Employees

General Electric (GE) Ultrasound employees and Ultrasound contractors are not eligible to participate in this study. Recruitment materials will state that there is no requirement for GE employees to participate in this research Study and there will be no consequences for anyone who does not volunteer.

5.3.3 Additional Study-Specific Risk Mitigations

Ultrasound scans conducted in this study will not require any medical or biologic administrations including intravenous contrast agent. Further, no study scans will require any invasive techniques and only transcutaneous scanning will be performed.

5.4 Inclusion Criteria

Subjects must meet all of the following:

1. Aged 18 years or older;
2. Able and willing to provide written informed consent in accordance with the PNDT Act in India;
3. Able to understand and respond in English;
4. General Electric (GE) employee or contractor at the John F. Welch Technology Centre (JFWTC) facility.

5.5 Exclusion Criteria

Subjects must not meet any of the following:

1. Direct employee or contractor of the General Electric (GE) Ultrasound business at the John F. Welch Technology Centre (JFWTC) facility;
2. If female, pregnant or unsure of her pregnancy status per self-report.
3. Is not able to or would be put at additional risk from completing study activities, in the opinion of the study staff;
4. Subjects who have an electronic medical device at the time of the study scan (such as pacemaker, implantable cardioverter/defibrillator, insulin pump, cochlear implant, or other implanted electronic medical device).

5.6 Recruitment and Scheduling

Potential subjects will be recruited from the GE facility using IRB/EC-approved methods detailed in the study Recruitment Plan, which may include electronic materials, paper materials, and/or word-of-mouth. To evaluate devices across different population sub-groups, some recruitment efforts may be focused on reaching specific population sub-groups, including but not limited to: gender, age, or body type. As allowable per IRB/EC policy, this study may also recruit from eligible subjects already participating in other research activities Sponsored by GEHC that have consented to be contacted by GEHC for future studies. Enrolled subjects who agree to be re-contacted will constitute a pool of individuals upon which to draw for future study scans. Subjects may be scheduled for additional visits in a non-randomized order to ensure an appropriately representative subset of subject characteristics is tested for each device under study.

5.7 Screening Subjects for Enrollment

Subjects may be pre-screened via telephone or email following IRB/EC-approved scripts to assess potential eligibility.

Informed consent will be obtained as described in the Informed Consent and Privacy Requirements section. Upon agreeing to participate in the Study, the subject will sign and date the ICF. The subject will be assigned an identification code unique to the subject (i.e. next sequential number on the enrollment log). A subject's enrollment in the study begins when he/she completes the above Informed Consent process and is assigned a unique study identification code.

After the subject has completed the informed consent process, Study Staff will verify that he or she meets all of the inclusion criteria and none of the exclusion criteria. Determination of eligibility relies on information reported by the subject. The Study Staff may or may not have necessary medical training or licensure to confirm subject self-reported health status and will not make independent assessments.

Subjects may participate more than once throughout the study's duration. Eligibility will be documented at the subject's first visit, and for any subsequent visits it will be confirmed that the subject remains eligible per the inclusion/exclusion criteria prior to the study scan.

5.8 Enrollment

Following recruitment, a subject will be considered enrolled (the point of enrollment) once he/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.

5.9 Screen Failures

Subjects that do not meet all inclusion and exclusion criteria will be considered screen failures. Subjects who leave the study should be counted as withdrawals per Section 6.8. Discontinuation and Withdrawal Criteria rather than screen failures.

5.10 Discontinuation/Withdrawal Criteria

5.10.1 Discontinuation of a Scan

Subjects may decide to discontinue (not participate or end participation) during any study scan without any negative repercussions. A subject may choose to discontinue or be discontinued by Study Staff from a study scan. If this occurs, all data and images collected prior to discontinuation will be used. If a subject discontinues a study scan, he or she will still be considered enrolled in the study and eligible for future study scans unless specifically documented as withdrawn from the study.

5.10.2 Study Withdrawal

The subject may withdraw from study participation at any time, for any reason without consequence. The Study Staff may withdraw a subject at any time for any reason. The reason for withdrawal for any subject will be recorded and reported to the Sponsor. The IRB/EC is to be notified per their notification of subject withdrawal policy. Withdrawn subjects may not participate in future study scans unless they are re-enrolled. Subjects should only be considered withdrawn if they do not wish to participate or are ineligible for all future study scans.

6. STUDY PROCEDURES

6.1 Protections and Safeguards

Participation in Multiple Study Visits – Enrolled subjects may be eligible for one or more research study visit. The Investigator or study staff may limit the number or duration of visits for any subject if it is suspected that the subject is under undue influence to participate, if participating could pose a risk to the subject's physical or mental

health, or for any other reason, in the opinion of the study staff. Subjects that have already been screened for enrollment, provided consent, and undergone necessary safety and eligibility screening to participate may participate in additional study visits if the subject:

- has provided written informed consent using the current IRB/EC-approved consent version (subjects should be re-consented if previously consented using an older version of the consent form).
- remains eligible according to the inclusion/exclusion criteria on the day of the procedure.

6.1.1 Handling of Requests for Physician Notification

Upon subject request, a notification form describing the subject's enrollment in this study will be sent to the subject's primary physician.

6.1.2 Activities prior to a Study Scan

For some ultrasound devices, there may be a risk of interference with electronic medical devices. Subjects will be asked if they have an electronic medical device (for example pacemakers, insulin pumps, defibrillators, hearing aids, among others). Subjects who report having a removable hearing aid may be asked to remove the hearing aid during the study scan.

Prior to scanning, subjects may be asked to move, remove, or change their clothing, or to change into a gown, in order to allow access to the target anatomical region(s) for scanning. A private area (enclosed room or curtained area) will be provided for subjects that are required to change clothes.

As necessary for the scanning procedures, subjects may be asked to perform conventional pre-scanning maneuvers or activities similar to those required for clinical ultrasound procedures, such as positioning themselves in certain ways or withholding urination in order to have a partially full bladder during scanning. None of these activities should cause discomfort. For subjects asked to have a partially full bladder, a break to empty the bladder will be provided at any time upon request, and subjects may still participate if they decline to have a partially full bladder. The skin surface may be cleaned before scanning.

6.1.3 Activities during a Study Scan

Each subject may elect to participate in up to five (5) study scans per day lasting up to 60 cumulative minutes each with approximately a 15 minute break before starting another study scan. Ophthalmic scanning will be limited to no more than 15 cumulative minutes of scan time per eye, per day.

The start time of a study scan begins when the device contacts the subject's skin and scanning begins; the stop time is when the study scan is complete. Pauses in active scanning are not counted towards the cumulative scan duration.

The study ultrasound scan will be performed while the subject is lying, sitting, or standing. Subjects may be asked to shift positions, to hold still, complete breath hold(s), bear down (Valsalva maneuver), or other maneuvers necessary for the scanning procedure. In some cases, device accessories (e.g. coupling agents, probe, land marking, tracking, monitoring, or other ultrasound device components) may be placed in direct contact with the subject's skin and/or superficial marks may be placed with a semi-permanent medical grade marker.

Scanning may be performed for target anatomic areas using a variety of non-invasive, transcutaneous techniques, such as scanning abdominal, musculoskeletal, breast(s), peripleural, transcranial, ophthalmic, cervical/neck, cardiac, vascular, extremity, soft tissue, and other accessible anatomical regions. More than one region may be scanned in a single study scan.

If a subject reports discomfort or wishes to stop the scan for any reason, the Study Staff will respond to subject's concerns and adjust the scanning procedures or, if the concern is not able to be resolved, discontinue the study scan. There will be no negative repercussions to the subject for reporting discomfort or deciding to stop the study scan, and he/she may still participate in future visits. Non-medical care will be provided to the subject to alleviate any discomfort, as needed.

6.1.4 Study Data Collection

All study scans will be performed to satisfy one or more aims of the study, as follows:

1) **Aim 1**: Perform iterative evaluations of the device (including features, accessories and components) to optimize device performance, assess feasibility of new features, and to perform testing in general support of product and technology development. Aim 1 is to perform evaluations necessary to enable scientists and engineers to establish appropriate design specifications; to optimize the device, accessories, and their various components; and to establish feasibility. Evaluations conducted using investigational devices; devices with regulatory clearance but have not met requirements for commercial release; and devices used off label are included within the scope of this study.
2) **Aim 2**: Perform activities to support design validation and/or to confirm user requirements and specifications have been met, as per design controls and other applicable requirements. This includes activities to test that human image quality and system features are acceptable for clinical use and that the system usability meets user needs.
3) **Aim 3**: Evaluate device complaints and analyze potential causes. Aim 3 is to reproduce and, when possible, determine root cause of non-safety related complaints (e.g. reports of degraded image quality) that can only be reproduced and investigated in vivo.

Comparator devices (a device used to compare ultrasound against another research device) may be used during the study scans for any aim. Information about the scan (including the resultant images/electronic files, scan aim, date, and relevant parameters of scanning) may be accessed for research purposes.

Study Staff will record information in source documentation about each study scan including:

- Study aim(s) satisfied
- Date of scanning
- Duration of scan exposure
- Device identification (including applicable software versions)
- Anatomical region(s) scanned
- Subject ID#

6.1.5 Subject Follow-Up

AEs will be collected throughout the scan duration (start to conclusion) of the investigational ultrasound exam. AEs unresolved upon completion of the investigational ultrasound exam will be followed until resolution. No other follow-up procedures will be conducted.

6.2 Incidental Finding Notification

The ultrasound procedures performed in this study are not for diagnostic use. The Device Operators may or may not be licensed to interpret the images for potential abnormalities. However, should the Device

Operators or Study Staff observe what they interpret to be a potential abnormality, the following procedures will be followed:

- An *Incidental Finding Notification* will be issued to the subject stating that a potential abnormality called an "Incidental Finding" has been observed, and a copy will be placed in the subject's study file.

All incidental findings will be reported and filed in the subject's study file, even if the incidental finding was identified during a previous visit.

7. TRAINING PLAN

7.1 GE Facility and Study Staff Roles

Study Staff – Individuals trained on the study protocol and, if necessary, device operation for this study. Records of study staff training will be retained as part of the Sponsor's Clinical History File (CHF).

The Sponsor may identify non-GEHC employees and other research partners (such as visiting physicians, consultants, Original Equipment Manufacturers (OEM), or other researchers) to provide engineering, clinical domain expertise, and feedback necessary to meet the study aims.

7.2 Training Plan for the Research Device

Device Operators will be provided with appropriate device training or will be qualified based on experience, such as by credentials or work experience in device engineering, clinical imaging, imaging science/physics, or other relevant disciplines. Device Operators may be employees or contractors of GE Healthcare or non-GE employees such as physicians, sonographers, or other researchers. All Device Operators will complete training and/or be qualified prior to being added as Study Staff.

7.3 Device Manuals

Device manuals may be accessed electronically at the Common Documentation Library [redacted] or will be made available at the site. Because devices used in this study are under continuous development, manuals may not be available for iterations of a device.

7.4 Training Plan for Protocol

The sponsor will ensure that study staff (including the PI, study staff, and device operators) are trained on the following as necessary for their roles in the study:

- Protocol Training – including training on study procedures and completion of Case Report Forms (CRFs)
- Good Clinical Practice (GCP) for medical devices per ISO 14155:2011
- Study-Specific Informed Consent

A record of training attendance and date conducted will be stored in the Site Regulatory Binder and included in the Sponsor's Clinical History File (CHF).

The PI is responsible for communicating with the Sponsor's Clinical Affairs representatives (Sponsor representative), maintaining the regulatory binder, delegating various study activities (i.e. informed consent, recruitment), ensuring that study staff are trained, ensuring that devices are correctly labeled, and ensuring that the protocol is followed, in accordance with IRB and regulatory requirements.

7.4.1 Observation of Study Scans

In some cases, observation by GE staff or third parties (such as engineers, research partners, or others) is necessary for technical evaluation and development of the devices under study. As authorized by GE Healthcare, observers may be present during scanning with subject approval.

8. DATA REPORTING, ANALYSIS, AND STATISTICS

There is no prospective plan to generate or utilize cohort-based clinical or efficacy data derived from this study for regulatory purposes, and no prospective cohort-based summary of study scan data collection is planned. Individual anonymized sample images may be used for regulatory submission, engineering development, publication and other purposes, as determined by the Sponsor. The Sponsor will generate the final report that summarizes the number and type of study scans, at minimum.

8.1 Data Reporting

A Final Clinical Study Report will be prepared by the Sponsor. This report will contain a report of the primary endpoint, and results from all study data collection activities will be stored at the investigational site (but are not prospectively planned to be summarized as part of the final study report for this study). Data collected from study scans in this study may be used for other engineering activities outside of the clinical report for this study, including activities such as retrospective analyses, meta-analysis, and other activities authorized by GE.

The final clinical report will contain a report of subject disposition and listing of AE/SAE by description, severity, and device relatedness of and unexpected device issues not anticipated based on engineering optimization activities. A summary of device complaints and resolution will be included in the final clinical report for this study. Individual narratives for each SAE and unexpected device issue will be summarized as part of the final report.

8.2 Statistical Analysis Methods

Descriptive statistics may be used to describe enrollment, subject disposition, and other parameters related to study conduct as part of the final clinical report.

8.3 Sample Size Justification

The sample size is not designed to test any statistically powered endpoint and is determined based on the engineering development needs of the Sponsor. Due to the heterogeneous nature of the study procedures, each subject will be allowed to participate multiple times, if he/she remains eligible per protocol requirements. As possible, the minimum number of study scans will be conducted to meet the internal engineering and optimization needs of the Sponsor, and it is prospectively planned that significantly fewer subjects (fewer study scans) than the maximum may be enrolled, if possible to achieve study aims.

8.4 Interim Reporting

No interim reporting is prospectively planned as part of this research study; however, the Sponsor may monitor the study and, at its discretion, complete formal interim reporting at any interval it deems necessary.

8.5 Handling of Missing Data

No interim reporting is planned as part of this research study; however, the Sponsor may monitor the study and, at its discretion, complete interim reporting at any interval it deems necessary**.**

9. SAFETY

9.1 Anticipated Adverse Events and Device Effects

The non-invasive ultrasound devices and their accessories under study share a common and well-understood safety profile. [19, 25, 26] According to the American Institute of Ultrasound in Medicine (AIUM) Safety in Training and Research (2012) statement, no hazard has been identified that would preclude the prudent and conservative use of such diagnostic ultrasound in research when exposure times and risk conditions are as low as reasonably achievable (ALARA) within the context of the research objectives. [25]

There are known risks associated with conventional ultrasound scanning. The risks of ultrasound scans performed in this study are not expected to be greater than those encountered in routine clinical practice using diagnostic ultrasound, which include:

- Transient tissue warming induced by acoustic energy used in ultrasound scanning, which can, in rare cases, lead to superficial burns.
- Formation of small pockets of gas in body fluids or tissues (known as “acoustic cavitation”) is a rare effect of ultrasound scanning. Because no contrast agents are used in this study, the likelihood of cavitation is remote. [26] The long-term effects of tissue heating and cavitation caused by ultrasound are not known.
- Local discomfort, superficial contact injury, and/or skin irritation due to contact with materials in the transducer, gel, disinfectant, or other device components.
- Direct contact with moving or stationary device components can lead to bruising, abrasions, and/or tears in the skin or, pinching, or in rare cases, more serious injury. Subjects and operators are able to immediately end scans in the event of discomfort.
- While standard cleaning procedures are followed, there is a remote possibility cross-contamination when multiple-use devices or components are used, which can lead to infection or other conditions possibly requiring medical intervention.
- As with any medical electrical equipment, there is a risk of electric shock if subjects or operators come into direct contact with electrically active elements. These risks are mitigated by design in ultrasound devices so that the chance or electrical shock is remote.

These effects are typically not very painful and resolve spontaneously after the scan ends without further medical intervention. Maneuvers during scanning, such as changing clothing, positioning, and/or having a partially full bladder are not expected to cause severe discomfort.

While there have been rare reports of chronic or severe bioeffects resulting from ophthalmic scanning (such as cataracts/vision impairment), [26, 27] the additional protections employed to minimize risks to subjects in this study are well within conservative ranges to mitigate the risk of possible serious or chronic effects of ultrasound. Within the scanning parameters set forth in this protocol, serious or chronic injury is not expected to result for any participating subject.

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

9.2 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].

Anticipated: Any adverse event and/or reaction, the specificity or severity of which is consistent with the IRB approved informed consent, protocol, investigator brochure, or product labeling.

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].

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].

9.3 Monitoring and Recording AEs and USADEs

All adverse events (AE), including all serious adverse events (SAE) and Unanticipated Serious Adverse Device Effects (USADEs), are required to be collected, investigated, and documented during the study reporting period, as defined in the study procedure set forth in this protocol. For the purposes of AE reporting, enrolled subjects will be monitored for AEs during the time between entering the research scanning area at the site for their research scan and the time that they exit the research scanning area. Subjects will not be followed for any potential or existing AEs after leaving the research scanning area, with the exception of SAEs that occur during scanning, which will be followed to resolution.

Any AEs will be recorded on the Adverse Event Case Report Form. 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/paused, withdrawn from study, or no action)
- Anticipated (yes/no): Anticipated is defined as events previously observed and documented in the Foreseeable Adverse Events and Adverse Device Effects section.

9.4 Reporting AEs and USADEs

All SAEs and USADEs will be documented as outlined above and reported in writing to the Sponsor within 72 hours of knowledge of the event. The Adverse Event Case Report Form [redacted] will also be submitted to the study Sponsor within 72 hours of knowledge of the event.

If the event resulted in the death of a subject, the event will be reported to the Sponsor within 24 hours of knowledge of the event.

The Sponsor Medical Monitor is the contact for SAEs and/or USADEs at the following E-mail: [redacted].

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. AEs and SAEs will be reported to the EC/IRB per their policy.

9.5 Device Deficiencies/Complaints Definitions and Reporting

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].

This study is intended as an iterative feasibility and optimization study, in which it is expected that devices may perform atypically in ways that do not pose safety issues during the course of optimization. Expected atypical function as a routine part of engineering investigation that does not pose a safety risk is not considered a device deficiency.

Device Complaints: Device complaints will be considered reports of unexpected atypical device function and device issues that are suspected by study staff to pose a safety risk. Device complaints will not include expected atypical function occurring as a routine part of engineering investigation, so long as such atypical function is not expected to pose a safety risk.

Study staff and/or authorized representatives of the Sponsor at the site should report complaints/deficiencies to the Clinical Affairs Project Manager, including:

- a brief description of the issue,
- date and time of occurrence,
- subject ID numbers of affected subject(s), and
- safety issue (Y/N)

The Principal Investigator is responsible for notifying the Sponsor within 72 hours in the event that there is any device issue that could potentially lead to a SAE.

9.6 Managing the Subject Transition from Scanning Area to Hospital

For cases that require hospitalization, there is an agreement with a hospital located close to the facility.

An ambulance will be available for the duration of scanning activity at the GEHC on-site medical center for emergencies. The medical center shall contact the medical service provider at the given emergency contact number in the hospital to inform them of any medical emergency at the facility.

The medical care of the participating subject will be provided at the Hospital noted in Appendix A: Study Contacts. The PI will be in contact with attending physician until the complete resolution of the issue and until the reporting requirements are met.

10. 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 14971:2012; and applicable requirements of the India Ministry of Health and Family Welfare (MOHFW).

The study will be conducted and reported in accordance with applicable policies of the 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 apply the principles of this International Standard to the greatest extent possible, irrespective of any lesser requirements, and shall record such efforts.

10.1 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 the 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.

Copies of all EC submissions, approval letters, Informed Consent Forms (ICF), and other correspondence shall be sent to the Sponsor, and originals shall be maintained in the Site Regulatory Binder.

10.2 Regulatory Agency Approval Requirements

Indian clinical trial requirements regarding a governmental licensing authority permission to conduct a clinical trial (in Drug and Cosmetics Rules, 1945 – Rule 122 DAC) are deemed not applicable to trials on low to medium risk devices not required to be registered for commercialization in India. Ethics committee approval is required prior to clinical trial initiation.

10.3 Management of Protocol Modifications and Amendments

Substantial amendments will only be implemented after approval of the EC, in accordance with their policy.

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, if applicable, the EC or competent authority (CA). Such deviations shall be documented and reported to the Sponsor and the IRB 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 per applicable laws, local site procedures, and to the EC per their policy.

10.4 Participant Information and Informed Consent

Written informed consent will be obtained from all subjects prior to participating in the study, per the determination of the IRB/EC. Signed copies of the informed consent form will be stored by the site. Trained Study

Staff will conduct the informed consent process per regulatory guidelines, which include: the subject will be allowed ample time to review the ICF and have all questions answered to their satisfaction; the subject may take the ICF home to review with family members or others prior to agreeing to participate in the study; upon agreeing to participate in the study, the subject will sign and date the informed consent; the person who obtained consent from the subject will also sign and date the document.

The subject will be given a copy of the signed informed consent form and the original will be retained with the study record.

Per the recommendation of the American Institution of Ultrasound in Medicine (AIUM) recommendation (2007), subjects having ultrasound scans for the purposes of training or research will be informed via the informed consent form that the anticipated exposure and conditions are not expected to expose the subject to greater risks compared with routine diagnostic ultrasound procedures commonly performed in clinical practice. [25]

If a study scan is performed on a subject without obtaining informed consent, this will be considered a critical deviation and reported to the Sponsor and the IRB/EC within 5 working days of the occurrence.

Study documents that contain personally identifiable private information will be maintained securely at the site. Study records will only be made accessible to third parties (such regulatory agencies) as necessary for the conduct of the study and as required by law. Authorized representatives of the Sponsor, including Study Monitor(s) and Quality Auditor(s), may review the study records as necessary to ensure the quality and conduct of the study. All reasonable efforts will be made to protect the confidentiality of each subject's personally identifiable private information obtained during the course of this study.

10.4.1 Additional Informed Consent and Privacy Requirements

Wipro GE Healthcare (WGE) is registered with Appropriate Authority, Bengaluru Urban District ("**Appropriate Authority**") in compliance with the Pre-conception and Pre-diagnostics Techniques (Prohibition of Sex Selection) Act, 1994 and Rules therein ("**PNDT Act**") and is required to provide monthly reports of all scans done to the Appropriate Authority in accordance with the PNDT Act.

Information collected and reported to the Appropriate Authority include but is not limited to each volunteer subjects name, age, sex/gender, father/husband's name, address, type and date of ultrasound scan, scan facility and scan operator's name.

An additional 'PNDT Consent Form' will be obtained from all volunteer scanning subjects prior to participation in the study.

10.5 Early Termination/Suspension 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.

The Sponsor will promptly notify the investigators of any determination to terminate the study outside of the protocol timeframe. The Sponsor will provide each investigator with written guidelines/instructions on termination processes and timelines.

The site is responsible for reporting the early termination to the responsible EC/IRB, per their policy.

11.QUALITY ASSURANCE AND CONTROL

11.1 Data Management

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

11.1.1 Completion of Case Report Forms (CRFs)

The data reported on the CRFs may serve in full or part as the source documents for the study, when no other source documents exist. Paper CRFs and/or electronic CRFs (eCRFs) 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, whether during monitoring or during data review by the study team, the site will make necessary corrections directly to the CRF(s). The Sponsor may request to review CRF data, at its discretion. The Sponsor may provide a Data Clarification Form (DCF) to the site to correct or clarify discrepancies.

11.1.2 Data Handling and Record Keeping

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

11.1.3 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. Elements should include:

- **Source data and documentation** relevant to data recorded for subject screening and CRF corroboration (CRFs may serve as source documentation)
- **Subject records** containing the completed ICFs and CRFs
- **Regulatory binder** containing the protocol and any subsequent amendments, IRB submissions and approvals, blank ICF(s), recruitment materials, correspondence, and site logs

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

11.1.4 Archiving

All study documents will be retained securely at the site with limited access.

Study records will be retained for a period no less than the period required by applicable laws and regulations, at present a minimum of 10 years per CFDA Order No. 25. Archived study records will be made available for inspection by authorized representatives of the Sponsor or to third parties, such as regulatory agencies, as required by local law. No study records will be destroyed without prior 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.

12.1 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. Anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing data in scientific journals.

Individual subject information obtained as a result of this study that contains information that identifies a subject will be considered confidential, and disclosure to third parties will be prohibited unless specific consent from the subject has been obtained.

Third parties, as authorized by the Sponsor, may be present during study procedures and have incidental access to subject information. To the extent possible, the study staff will ensure that risks to the subject's confidentiality are minimized.

Individual subject 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 Institutional Review Board (IRB) or Ethics Committee (EC) may require direct access to parts of the subject records and any other information, such as payment or financial information, collected during the course of the study, in accordance with applicable laws and regulations.

12.1.1 Storage and Use of Data and Images

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

12.1.2 Subject De-Identification

Subjects will be assigned a unique Subject Identification Number and study data, including electronic image files, provided to the study Sponsor or others at GE Healthcare not directly participating in the conduct of the study will not contain any personally identifiable information about subjects.

12.2 Publication Policy

No cohort-based results from this study are planned for publication. De-identified data, including images, may be stored and used indefinitely by GE Healthcare for unspecified future purposes, including but not limited to, future analysis for technology development, marketing materials, product brochures, training and educational materials, scientific presentations, and other public purposes.

13.ADDITIONAL STUDY MATERIALS/REFERENCES

13.1 Country-Specific Regulatory Requirements

This study will be conducted in accordance with the principles set forth in:

- ISO 14155:2011
- Ethical Guidelines for Biomedical Research on Human Participants - Indian Council of Medical Research, New Delhi, 2006 - http://icmr.nic.in/ethical_guidelines.pdf
- Good Clinical Practices for Clinical Research in India, Central Drugs Standard Control Organization (CDSCO) [written primarily for pharmaceutical trials] - http://cdsco.nic.in/html/GCP.htm
- Guidelines for Determining Quantum of Financial Compensation to be Paid in Case of Clinical Trial Related Injury or Death, CDSCO, August 3, 2012
- Pre-conception and Pre-diagnostics Techniques (Prohibition of Sex Selection) Act, 1994 and Rules therein ("PNDT Act").

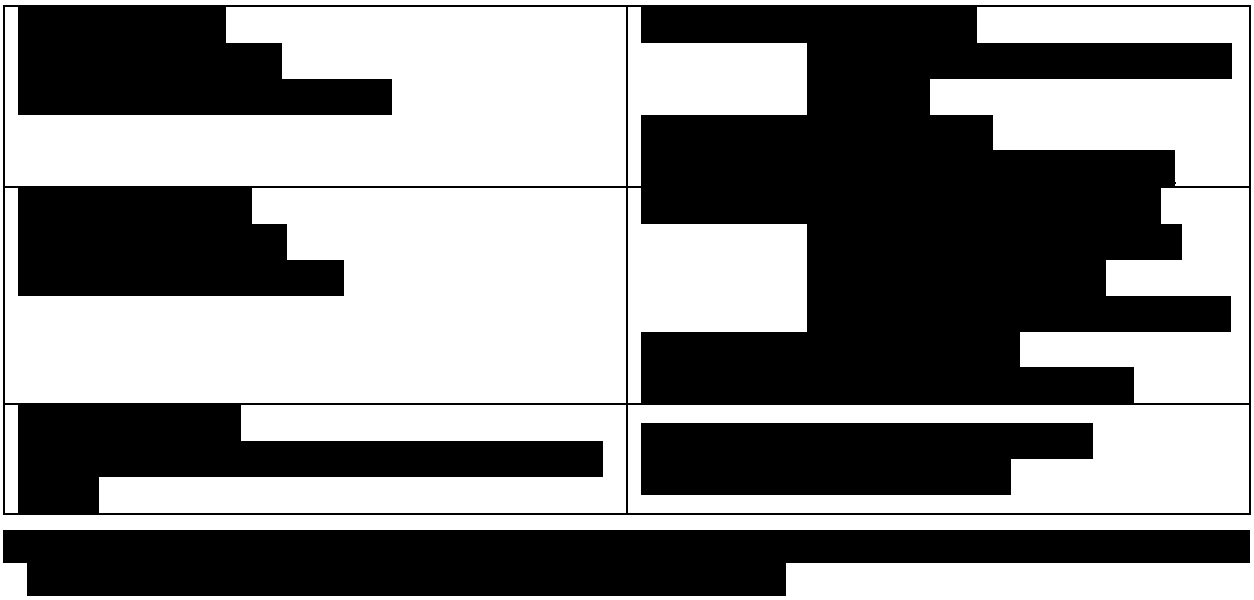
REFERENCES

1. Rhodes D, Bishop P. A review of diagnostic ultrasound of the spine and soft tissue. *J Manipulative Physiol Ther*. 1997;20(4):267-73.
2. RadiologyInfo.Org. What is General Ultrasound Imaging? *Ultrasound - General*. 2014. Available at: http://www.radiologyinfo.org/en/info.cfm?pg=genus. Accessed Aug 1, 2014.
3. Kendall J, Hoffenberg S, Smith CCM2, Suppl):S126–S130RS 3. History of emergency and critical care ultrasound: the evolution of a new imaging paradigm. *Crit Care Med*. 2007;35(5(5 Suppl)):S126–S130.
4. Nelson B, Chason K. Use of ultrasound by emergency medical services: a review. *Int J Emerg Med*. 2008;1(4):253–259.
5. Lapostolle F, Petrovic T, Lenoir G. Am J Emerg Med. *Usefulness of hand-held ultrasound devices in out-of-hospital diagnosis performed by emergency physicians*. 2006;24(237-242).
6. Heegaard W, Plummer D, Dries D. Ultrasound for the air medical clinician. *Air Med J*. 2004;23(2).
7. Walcher F, Weinlich M, Conrad G. Prehospital ultrasound imaging improves management of abdominal trauma. *Br J Surg*. 2006;93(2):238–242.
8. Walcher F, Patrovic T, Neri L, Heegaard W. Prehospital ultrasound. In: Ma O, Mateer J, Blaivas M, eds. *Emergency Ultrasound*. New York: McGraw-Hill; 2008.
9. Barnett S, Abramowicz J, Ziskin M, Marsal K, Claudon M. WFUMB Symposium on Safety of Nonmedical Use of Ultrasound. *Ultrasound in Med and Biol*. 2010;36(8):1209–1212.
10. Sikdar S, Shah J, Gebreab T, et al. Novel applications of ultrasound technology to visualize and characterize myofascial trigger points and surrounding soft tissue. *Arch Phys Med Rehabil*. 2009;90(11):1829-38.
11. Rhodes D, Bishop P. A review of diagnostic ultrasound of the spine and soft tissue. *J Manipulative Physiol Ther*. 1997;20(4):267-73.
12. Papp Z, Fekete T. The evolving role of ultrasound in obstetrics/gynecology practice. *Int J Gynaecol Obstet*. 2003;82(3):339-46.
13. Houstonm L, Odibo A, Macones G. The safety of obstetrical ultrasound: a review. *Prenat Diagn*. 2009;29(13):1204-12.
14. Sippel S, Muruganandan K, Levine A, Shah S. Review article: Use of ultrasound in the developing world. *Int J Emerg Med*. 2011;4(72).
15. World Federation for Ultrasound In Medicine (WFUMB). Affiliated Organizations. *World Federation for Ultrasound In Medicine*. 2014. Available at: http://www.wfumb.org/about/affiliatedOrgs.aspx. Accessed Aug 2014, 20.
16. Benacerraf B, Benson C, Abuhamad A, et al. Three- and 4-dimensional ultrasound in obstetrics and gynecology: proceedings of the American Institute of Ultrasound in Medicine Consensus Conference. *J Ultrasound Med*. 2005;24(12):1587-97.

17. Fowlkes J, Medicine BCotAIoUi. American Institute of Ultrasound in Medicine consensus report on potential bioeffects of diagnostic ultrasound: executive summary. *J Ultrasound Med*. 2008;27(4):503-15.
18. National Council on Radiation Protection and Measurements. Diagnostic Ultrasound Safety: Exposure Criteria for Medical Diagnostic Ultrasound: II. Criteria Based on all Known Mechanisms..
19. WFUMB. WFUMB Recommendations on Non-medical Use of Ultrasound. *Safety Statements*. 2013. Accessed Aug 2014, 20.
20. The Britich Medical Ultrasound Society. *Guidelines for the safe use of diagnostic ultrasound equipment* 2009.
21. Conn M. *Animal Models for the Study of Human Disease*. First ed ed. London, UK; Waltham, MA, USA: Elsevier Academic Press; 2013.
22. AIUM. *Statement Regarding Mathematical Tissue Models*. Laurel, MD 2012.
23. US FDA. *Guidance for Industry and FDA Staff: Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers* 2008.
24. Blaivas M, Lyon M, Brannam L, Duggal S, Sierzenski P. Water bath evaluation technique for emergency ultrasound of painful superficial structures. *Am J Emerg Med*. 2004;22(7):589-93.
25. AIUM. *Safety in Training and Research*. Laurel, MD: American Institute of Ultrasound Research; 2012. 4/1/2012.
26. Ter Haar G. Ultrasound bioeffects and safety. *Proc Inst Mech Eng H*. 2010;224(2):363-73.
27. O'Brian W. Ultrasound—biophysics mechanisms. *Prog Biophys Mol Biol. 2007*. 2007;93(103):212-255.

APPENDIX A: STUDY CONTACTS

If there are any changes to the study contact information, an updated version of this Appendix will be stored in the Sponsor's Clinical History File (CHF) and provided to the site and EC, in accordance with their policy.



APPENDIX B: SAFETY GUIDELINE TRAINING MATERIALS

Figure B.1 – Non-Obstetrical Scanning [20]

Application	Values to monitor (A)	Thermal Index value		Mechanical Index value	
		0 – 1.0	> 1.0	0 - 0.3	> 0.7
General abdominal Peripheral vascular Unlisted applications	Usually TIB and MI. [use TIC and MI if bone closer than 1 cm; TIS and MI only if bone does not come into the image]	✓	(B) restrict time to 1.0<TIB≤1.5 : 120 min 1.5<TIB≤2.0 : 60 min 2.0<TIB≤2.5 : 15 min 2.5<TIB≤3.0 : 4 min 3.0<TIB≤4.0 : 1 min 4.0<TIB≤5.0 : 15 sec 5.0<TIB≤6.0 : 5 sec TIB>6: **not recommended**	✓	(C) risk of cavitation with contrast agents
Eye	TIS and MI recommended	✓	**Scanning of the eye is not recommended**	✓	(C) risk of cavitation with contrast agents
Adult transcranial (imaging and stand-alone) (D)	TIC and MI	✓	(B) restrict time to 0.7<TIC≤1.0 : 60 min 1.0<TIC≤1.5 : 30 min 1.5<TIC≤2.0 : 15 min 2.0<TIC≤2.5 : 4 min 2.5<TIC≤3.0 : 1 min TIC>3: **not recommended**	✓	(C) risk of cavitation with contrast agents
Peripheral pulse monitoring	TI or MI are not usually available for dedicated peripheral pulse monitors.	The output from CW Doppler devices intended for monitoring peripheral pulses is sufficiently low that their use is not contra-indicated, on safety grounds			

✓: There is no known reason to restrict scanning times in this region.
A: Many scanners allow MI and one of the TI values to be displayed simultaneously: the most appropriate TI value depends on the clinical application.
B: TI > 1.0 - the overall exposure time (including pauses) should be restricted.
C: MI > 0.7 - there is a risk of cavitation if an ultrasound contrast agent containing gas micro-spheres is being used. There is a theoretical risk of cavitation without the presence of ultrasound contrast agents. The risk increases with MI values above this threshold.
D: Transcranial ultrasound investigations may require higher acoustic output or longer monitoring times than other applications. When times longer than those recommended here are required, it is recommended that monitoring is paused regularly to minimise exposure.

For ophthalmic applications, the maximum attainable value for the Thermal Index should be less than or equal to 1, the maximum attainable value of the Mechanical Index should be less than or equal to 0.23 and the maximum attainable value of the derated spatial peak time average intensity, $I_{spta.3}$ should be less than or equal to 50 mW/cm^2.

End of Document