Clinical Study Protocol

Study Title: GE Cardiovascular Ultrasound Device Evaluation

Study Number: 217021760

Version: 2.0; 14/Apr/2022

NCT Number: NCT05340244

Sponsor: General Electric Company, acting through its GE Precision Healthcare LLC business
3000 N. Grandview Blvd
Waukesha, WI 53188

Sponsor Contact: See Appendix B – Administrative Structure of Investigation

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 per applicable principles of the World Medical Association Declaration of Helsinki and Good Clinical Practice (GCP) guidelines as per ISO 14155, any conditions of approval imposed by the reviewing ethics committee (EC) or governing regulatory body, and applicable local and federal 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 have been made.

Version	Date	Author	Comments/Changes
1.0	23/Aug/2021	[redacted]	Lead Medical Writer – Initial version.
2.0	14/Apr/2022	[redacted]	Lead Research Program Integrator, Ultrasound During review of the IDE application for this study, FDA requested modifications to the eligibility criteria, which are detailed in Appendix C (Amendment of Protocol Version 1.0 to 2.0)

LIST OF ABBREVIATIONS AND TERMS

AE	Adverse Event
ADE	Adverse Device Effect
AFAP	As Far As Possible
AMA	American Medical Association
CA	Competent Authority
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
DMP	Data Management Plan
EC	Ethics Committee
EDC	Electronic Data Capture
EU	European Union
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice (see ISO 14155)
GDP	Good Documentation Practices
GE	General Electric
HCP	Health Care Provider
IB	Investigator Brochure
ICF	Informed Consent Form
IFU	Instructions for use
ISO	International Standards Organization
IQ	Image quality
LAR	Legally authorized representative
[redacted]	
PI	Principal Investigator
RPI	Research Program Integrator
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SPR	System Problem Report
UADE	Unanticipated Adverse Device Effect
US	United States
USADE	Unexpected Serious Adverse Device Effect

SYNOPSIS

Sponsor:	General Electric Company, acting through its GE Healthcare (GE Healthcare) Business
Research Type:	This is an open label, prospective, non-randomized clinical research study at a single site.
Regulatory Status:	This is a pre-market – pilot stage research study of the following devices/products: *Pre-market*: Vivid E95 [redacted] ultrasound system; [redacted] transesophageal echocardiography (TEE) probe
Background and Rationale:	GE Healthcare (GEHC) manufactures the Vivid E95 – a general purpose ultrasound system, specialized for use in cardiac imaging. Feedback from real clinical use cases is required to optimize medical devices prior to device finalization and commercialization. The goal of this study is to collect user feedback and de-identified images from the investigational Vivid E95 [redacted] system and probes during transthoracic echocardiogram (TTE) and TEE exams. The results of this study are intended primarily for use in engineering evaluation and optimization of the device.
Procedures/ Methods:	Eligible subjects will be enrolled into the study and positioned for their ultrasound exam. Standard clinical practice procedures will be followed using the standard of care device at the site to complete the clinically indicated exams. After the clinically indicated exam, portions of the TTE and/or TEE exam will be repeated with the investigational Vivid E95 ultrasound device. Ultrasound scans in this study will take a similar amount of time and be performed in a similar manner as standard of care ultrasound exams at the site. The device operator will store images from both ultrasound exams conducted with the standard of care device and the investigational device. Images collected with the investigational device will not be used for patient management.
Objectives:	The primary objective of this study is to collect user feedback and de-identified images from the Vivid E95 [redacted] ultrasound system and probes in TTE and TEE exams in a clinical setting. User feedback will include workflow, performance, user preference, image quality (IQ), device features, and open-ended feedback. The safety objective of this study is to collect safety information, including type and number of AEs, SAEs, and device issues. No clinical efficacy endpoints will be assessed.

Eligibility Criteria:	**Inclusion criteria:** 1) Has a clinical indication for a TEE and/or TTE procedure with an ultrasound device; 2) Has a weight of at least 5kg; 3) Is able and willing to comply with study procedures; 4) If less than 7 years old, has two parents or legally authorized representatives able and willing to provide written consent to participate. 5) If 7-17 years old, is able and willing to provide written assent to participate AND has two parents or legally authorized representatives able and willing to provide written consent to participate. 6) If 18 years old or older, is able and willing to provide written consent to participate.	**Exclusion criteria:** 1) Pregnant or suspected to be pregnant based on the opinion of a clinician investigator; 2) Expected to be at increased risk due to study participation (e.g. due to sensitivities, relative or absolute contraindication to TEE), in the opinion of a clinician investigator; 3) Previously participated in this study or are enrolled in another research study that could be expected to interfere with participation in study procedures; 4) History of esophageal surgery or known vascular ring; OR 5) Experiences any complications or difficulty with the initial TEE procedure performed using the standard device.
Sample Size and Sites:	Up to 100 subjects from one site will be included. This number is based on prior engineering development and testing experience of the Sponsor. This study will enroll the minimum number of subjects necessary to complete Sponsor engineering requirements for this stage of development and optimization of the device, which may be less than the maximum enrollment set forth in this protocol.	
Expected Subject Participation Duration:	The duration of subject participation is the time it takes to complete the ultrasound exam(s) (less than one day).	
Study Duration:	The study is expected to last approximately 6 months. Estimated start date (first subject in): January 2022 Estimated end date (last subject out): June 2022	
Study Completion:	The study will be considered complete when subject enrollment requirements are met per the Sponsor's determination.	

1. BACKGROUND AND JUSTIFICATION

[redacted]

The goal of this study is to collect user feedback and de-identified images from investigational Vivid E95 [redacted] system and probes during TTE and TEE exams. The results of this study are intended primarily for use in engineering evaluation and optimization of the device and may be used for augmenting design verification and design validation. [redacted] Funding for this study will be provided by GE Healthcare.

2. DEVICE DESCRIPTION

2.1 Identity, Mechanism, and Function

Name: Vivid E95 [redacted], [redacted] TEE probe

Modality/Type: Cardiovascular Ultrasound

Manufacturer: GE Healthcare

Software version: The most current version available will be used.

Regulatory Status: Pre-market – pilot stage

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.

[redacted]

[redacted]

The research device, instructions for use, or packaging shall indicate that the research device is for use in a research investigation, per FDA 21 CFR §812.5 and other applicable laws and regulations.

The investigational device will be exclusively used for research purposes. Routine accessories necessary to perform ultrasound, such as ultrasound gels, may be provided by the site and used according to the site standard of care during this study. Additionally, software may be used for post processing of images. [redacted]

2.2 Intended Use

The Vivid E95 ultrasound system is intended to be used for a variety of diagnostic cardiovascular procedures on pediatric and adult patients. Vivid E95 is a general purpose ultrasound system, specialized for use in cardiac imaging. It is intended for use by, or under the direction of a qualified physician for ultrasound imaging, measurement, display and analysis of the human body and fluid. [redacted]

The procedures conducted in this study are intended for device development purposes.

2.3 Concomitant / Ancillary Administrations

2.3.1 Medications and Biologic Products

No medications or biologic products will be administered as part of study procedures. As part of the standard of care at the site, subjects may receive anesthesia. Clinically necessary medications for the subjects' prescribed medical procedure shall be administered per the site standard care and participation in this study will not alter their standard care.

2.3.2 Laboratory Tests and Sample Processing

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

2.4 Accountability

Accurate and adequate records will be maintained for all devices, from time of shipment to the site until return or disposal of all devices issued by the Sponsor as part of this study, as required by applicable laws and regulations. The Principal Investigator will be responsible for the security and integrity of research devices at the investigational site during the study.

2.4.1 Issuance

The research device will be provided by the Sponsor. No calibration/maintenance procedures are planned for this study. Software updates may be made during the study.

2.4.2 Disposition

The device will be dispositioned after the study and returned to the Sponsor, per applicable laws and regulations.

2.5 Anticipated Risks and Benefits

The device under study has undergone risk assessment, per International Standards Organization (ISO) 14971, and risks have been mitigated to levels as far as possible (AFAP). Verification of the system will be completed, including mitigation of hazards and functional changes impacting the study, and that the system device features operate as expected. Additionally, electromagnetic interference testing will have been completed to ensure the investigational device does not impact other electronic medical devices, and acoustic output verification testing will be completed to ensure that the energy output from the system is within acceptable ranges. The measures ensure that the devices used in the study are equivalent to systems that already meet the requirements for CE mark and are used for diagnosis outside of the USA. Validation of user requirements and expectations will be completed for the device.

The risks associated with the investigational device are not expected to be greater than those of similar procedures routinely conducted in clinical practice. Subjects will undergo procedures with both the standard of care device and the investigational device, so there may be an incremental risk associated with the double procedure. Post-trial care or follow-up is not required by this study.

Subjects are not expected to benefit directly from study participation. The results may benefit future patients by helping to optimize the device, accessories, and software. This may provide better imaging for pediatric patients in the future.

2.5.1 Risk Category and Rationale

The [redacted] TEE probe, as used in this study, is considered a significant risk device per 21 CFR §812.3(m) because it does present a potential for serious risk to the health, safety, or welfare of a subject.

3. OBJECTIVES

3.1 Purpose of the Study

The purpose of the study is to collect user feedback on the Vivid E95 [redacted] ultrasound system and probes during clinical procedures on the device's intended population in order to optimize the device.

3.1.1 Primary Objective

The primary objective of this study is to collect user feedback and de-identified images from the Vivid E95 [redacted] ultrasound system and probes in TTE and TEE exams in a clinical setting. User feedback will include workflow, performance, user preference, IQ, device features, and open-ended feedback.

3.1.2 Safety Objective

The safety objective of this study is to collect safety information, including type and number of AEs, SAEs, and device issues. No clinical efficacy endpoints will be assessed.

4. STUDY DESIGN

4.1 Summary of Study Design

This is a pre-market, open label, prospective, non-randomized clinical research study conducted at one site in the United States. The study will be considered complete when subject enrollment requirements are met per the Sponsor's determination. The duration of subject participation is the time it takes to complete the ultrasound exam(s) (less than one day).

This study is not intended to support a comparative claim or test any hypotheses, such as superiority or non-inferiority, so no control group is necessary. All reasonable attempts will be made to control and minimize bias during the study. The study will not impact the clinically indicated scan used for clinical care. Subjects will be consecutively enrolled in this study as they present at the site for standard of care procedures. This type of sampling reduces, but does not eliminate, some risks of sampling bias. Additionally, site and Sponsor responsibilities are clearly defined to reduce additional biases during the conduct of study procedures.

4.2 Study Population

Subjects will be enrolled who meet all of the inclusion criteria and none of the exclusion criteria and are prescribed a standard of care procedure using an ultrasound device for a TEE exam, including either diagnostic or perioperative TEE, and/or a Transthoracic Echocardiography (TTE) exam. This population is representative of the general population that is expected for the device in clinical practice.

4.3 Number of Subjects

Up to 100 subjects may be enrolled in this study. This study will enroll the minimum number of subjects necessary to complete Sponsor engineering requirements for this stage of development and optimization of the device, which may be less than the maximum enrollment set forth in this protocol.

4.3.1 Enrollment Schedule

After the first 5 subjects are enrolled and complete study procedures, subject enrollment will pause. A progress update will be submitted to the EC, which will include safety-related information such as any adverse events, device deficiencies, or any other relevant issues that have occurred during the initial enrollment period. Subject enrollment will resume upon receipt of favorable opinion from EC.

4.4 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.

Neonates, children, or minor subjects: Neonates, children, and minor subjects under the age of 18 years old will be subjects in this study. These subjects are considered members of a vulnerable research population who are not legally competent to provide valid informed consent. This research will be approved by an EC, and two parents or legally authorized representatives (LARs), such as health care surrogate, attorney in fact, judicially appointed guardian, or proxy, must provide written informed consent for the child's participation. Assent will be obtained from minor subjects aged 7-17 years old.

The study activities cannot otherwise be performed without the use of vulnerable populations. Children have anatomical and physiological differences compared to adults, such as smaller and less developed anatomy, faster heart rate, and faster breathing rate, which affect ultrasound image acquisition. Children may also behave and move differently than adults during scans, which introduces additional challenges and variables. It is important to evaluate the device's performance in the intended population so it can be optimized for actual clinical use.

4.5 Eligibility Criteria

4.5.1 Inclusion Criteria

Subjects who meet all the following inclusion criteria may be enrolled:

1) Has a clinical indication for a TEE and/or TTE procedure with an ultrasound device;
2) Has a weight of at least 5kg;
3) Is able and willing to comply with study procedures;
4) If less than 7 years old, has two parents or legally authorized representatives able and willing to provide written consent to participate.
5) If 7-17 years old, is able and willing to provide written assent to participate AND has two parents or legally authorized representatives able and willing to provide written consent to participate;
6) If 18 years old or older, is able and willing to provide written consent to participate.

4.5.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will be excluded:

1) Pregnant or suspected to be pregnant based on the opinion of a clinician investigator;
2) Expected to be at increased risk due to study participation (e.g. due to sensitivities, relative or absolute contraindication to TEE), in the opinion of a clinician investigator;
3) Previously participated in this study or are enrolled in another research study that could be expected to interfere with participation in study procedures;
4) History of esophageal surgery or known vascular ring; OR

5) Experiences any complications or difficulty with the initial TEE procedure performed using the standard device.

   Note: It is not possible to assess exclusion criterion #5 prior to the point of enrollment; this exclusion criterion will be assessed during the initial standard care TEE procedure.

4.6 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.

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 the subject or the subject's parents or LARs sign and date the informed consent form (ICF), including the informed assent form as applicable. 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.

4.7 Criteria for Withdrawal/Discontinuation

A subject may withdraw from study participation at any time, for any reason. The Investigator may withdraw a subject at any time, for any reason. The reasons for withdrawal and discontinuation for any subject shall be recorded on a CRF. These will be reported to the Sponsor. The EC should be notified per their notification of subject withdrawal policy.

5. STUDY PROCEDURES

5.1 Subject Preparation

Study staff will confirm that the subject is eligible and complies with applicable site requirements prior to starting study procedures. No preparation beyond that required by the investigational site is required before procedures.

5.2 Description of Study Procedures

Eligible subjects will be enrolled into the study and positioned for their ultrasound exam. Standard clinical practice procedures will be followed using the standard of care device at the site to complete the clinically indicated exams.

After the clinically indicated exam, portions of the TTE and/or TEE exam will be repeated with the investigational Vivid E95 ultrasound device. Ultrasound scans in this study will take a similar amount of time and be performed in a similar manner as standard of care ultrasound exams at the site. The additional investigational TTE and TEE scans will add no more than about 15 minutes to the procedure time. For subjects having TEE in conjunction with surgery or an interventional catheterization procedure, the additional investigational scans will occur simultaneously while the hospital staff are preparing for or performing the procedure to avoid any delay in care. Images collected with the investigational device will not be used for patient management.

The device operator will store images from both ultrasound exams conducted with the standard of care device and the investigational device.

After completion of the investigational ultrasound exam, the ultrasound system and associated probes will be cleaned and disinfected as applicable, according to site standard of care and specifications in Sponsor instructions provided to the site.

The subject will be followed for adverse events (AEs) from the time the ultrasound exam begins with the investigational device to the time the subject leaves the scan room. Subjects may also contact the PI if they experience any additional symptoms after the study. Subjects will, if necessary, be provided with emergency care. In the event of any device issues, the event will be recorded.

Any AEs or device deficiencies/complaints observed by the operator will be reported to GEHC.

5.3 Follow-up

Study enrollment will end after the subject has completed his/her investigational ultrasound exam. AEs reported to the site will be followed until resolution. No other follow-up procedures will be conducted.

Any data, including de-identified images, collected for the subject, up until the time of withdrawal or discontinuation, may still be provided to GEHC, 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

Only data relevant to the conduct of the study shall be collected by the Sponsor.

6.1 Primary Assessment

The device user will save the images (raw DICOM) during the conduct of the procedures. Device users performing the scans will periodically be asked to provide feedback on User Survey forms prepared by the Sponsor.

Minimal data will also be collected per subject on a CRF, including:

- Date of consent/assent;
- Confirmation of eligibility, including age and weight;
- Investigational exam information [device user, procedure(s) completed (TTE and/or TEE), start/stop times, and probes used].

6.2 Safety Assessments

The description, severity, and device relatedness of any AE or SAE during the study will be recorded. 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

7.1 Staff Qualifications

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, per ISO 14155. If study staff or PI qualification lapses, the Sponsor will work with the site to requalify the respective role or ensure the duties are reassigned appropriately by the site. The Sponsor reserves the right to disqualify a PI with appropriate justification, such as repeated issues that impact participant safety and data integrity.

7.2 Training Plan for the Protocol and Research Device/Product

Before starting the study, the study staff will be trained on the clinical investigation requirements set forth in this study protocol.

The following training information will be collected in the training log prior to study enrollment:

- Title of Training
- Target audience (who will be trained)
- Training content (including device operation, protocol review and understanding)

Study staff directly operating or maintaining the research device or product will be trained based on the current available operator manual and Device Training provided by the Sponsor.

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

8. SAFETY

8.1 Anticipated Adverse Events

8.1.1 Non-invasive, or transcutaneous, ultrasound exams

Non-invasive diagnostic ultrasound involves minimal risk because it does not utilize X-rays or other types of ionizing radiation. Even though manifestation of risks during diagnostic ultrasound is rare, diagnostic ultrasound can produce effects on the body, such as:

Risk	Description	Likelihood
Tissue warming	In transcutaneous ultrasound, the probe may heat up slightly, causing sensation of warmness or heat of the skin at the site of the contact with probe.	Rare.
Cavitation	Formation of small pockets of gas in body fluids or tissues.	Rare.
Skin/tissue irritation or injury	Reddening, scraping, stretching, pulling, or other sensations of the skin/tissue that may cause minor discomfort. Contact with gel or disinfectants may cause allergic reactions or skin irritations.	Uncommon.
Bruising or Abrasion (tears) in skin or tissue	Skin bruising or abrasion/tearing caused by probe placement and movement across the tissue.	Uncommon.
Infection	There is a very low risk of infection from cross contamination of probe surface or gel, which is mostly theoretical in case of intact skin.	Rare.

The risk of these adverse effects is not expected to be greater for subjects in this study than those encountered during routine diagnostic ultrasound procedures conducted outside of the study.

The formation of an ultrasound image necessarily requires the exposure of regions of interest to ultrasonic energy, part of which is absorbed in the tissue through which it propagates, and part is reflected back to the transducer (probe) and forms the image. Biological effects of diagnostic ultrasound include heating of the tissues by absorbed ultrasound energy and the risk of cavitation from pressure gradient passing through the tissue (such as lung tissue and bowels with gas that may enter the ultrasound field of view during cardiac exams). The cavitation effects of acoustic energy are most pronounced at lower than diagnostic ultrasound

frequencies (in kHz range, not MHz range) and the human tissues have less nucleation sites and higher viscosity than water and the negative pressures from diagnostic ultrasound are lower than most testing done to evaluate cavitation.

8.1.2 TEE Ultrasound Imaging

TEE probes are optimized to ensure acceptable safety in terms of external atraumatic smoothness, probe size, trackability, steerability and maneuverability-stiffness while allowing adequate diagnostic imaging performance. The probes are also designed for robustness to foreseeable mishaps and reprocessing throughout their service life. User attentiveness is still essential for safe operation of the TEE probes.

Invasive ultrasound scans carry inherent risks associated with invasive nature of the procedure, such as:

Risk	Description	Likelihood
Perforation	Injury to the esophagus, throat and mouth could occur if the users are not appropriately trained in endoscopic procedures and familiar with the probe at hand. There are varied mechanisms for an esophageal perforation during a TEE exam. Direct mechanical trauma can cause an esophageal perforation; from a blind insertion and advancement of the probe; size discrepancy of the probe tip relative to the esophagus, and from a wide range of probe tip flexion and manipulation required to obtain certain images. Mechanical injury to esophageal tract is therefore an inherent risk due to the nature of the TEE procedure. The incidence, nature and severity of esophageal tears/perforations associated with endoscopic procedures are well characterized. [10]Injuries vary from self-resolving (local minor bleeding), to life-threatening (perforation, major bleeding, infection or death) requiring surgery or medical treatment. Significant injuries are uncommon when patient is low-risk, underlying the importance of careful assessment of suitability of the TEE procedure for a particular patient. Indirect trauma of the GI tract may be related to excessive or prolonged, continuous pressure at the TEE probe-mucosal interface, resulting in tissue ischemia and necrosis. The risk can be minimized by relaxing the pressure and moving the probe tip to a less sensitive area. This may occur particularly during cardiac surgical procedures, when the TEE probe is stationed in the thoracic esophagus, for long durations.	Rare.
Bleeding	Overstimulation of mucosa by manipulations of the TEE probe necessary to perform the examination may lead to tears ranging from minor to serious. The external surface of the probe could be damaged through impact, which could expose sharp edges and lead to bleeding. Pre-procedure inspection of the probe for defects is essential to minimize this risk, as these conditions are easily noticeable by user.	Rare.
Infection	Cross contamination could occur if the probe is not properly reprocessed or is damaged or worn in such a way that micro-organisms or disinfection chemicals could collect inside the probe to be released when intubated. Requirements for high-level disinfection must be met for patient contact areas. Note, there is no adequate means to disinfect a probe that has been contaminated by prions, such as Creutzfeldt Jacob's disease. In such case,	Rare.

	the contaminated device/probe MUST BE discarded in accordance with local biologic waste hazard procedures.	
Bruising	Irritation and discomfort of the throat due to placement and movement of the probe.	Uncommon.
Tissue warming	In case of invasive ultrasound, the probe may heat internal tissue (e.g. esophageal wall), but this would not be detectable to the subject. The system continuously monitors probe temperature and shuts the probe down automatically if unsafe temperature is detected well before a burn is expected.	Rare.
Chemical burns	Chemical burns can occur if the probe is not completely rinsed from residue of harsh disinfectants.	Rare.
Electric shock	There are electric currents present inside the TEE probe. In extremely rare cases of loss of integrity of the probe the patient may get exposed to the risk of electric shock. Structural integrity check using leakage current are incorporated as part of reprocessing, thus this risk is minimized.	Rare.
Damage to dental fixtures	Damage to teeth and dental prosthetics is also a concern when removing the probe or using bite guards.	Uncommon.

The investigational device is being used in addition to the standard of care device, so there is an increased risk of AEs associated with this extended procedure. The additional scan does not have risks beyond the standard of care procedure, but the secondary intubation may increase the overall likelihood of events occurring.

The Vivid E95 [redacted] ultrasound system is investigational and has not been cleared by the FDA. However, it has been developed based on technologies that are well understood and used in commercial ultrasound systems developed and marketed by GEHC.

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

8.2 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 and whether anticipated or unanticipated. 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 use of investigational medical devices or comparators.

Serious Adverse Event (SAE): an AEs that led to death; led to a serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following: a life-threatening illness or injury, a permanent impairment of a body structure or a body function including chronic disease, 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 including physical or mental impairment. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol without serious deterioration in health, is not considered a SAE.

Adverse Device Effect (ADE): an AEs related to the use of an investigational or comparator medical device. This includes any AEs 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.

Serious Adverse Device Effect (SADE): an adverse device effect that has resulted in any of the consequences characteristic of a SAE.

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 risk assessment. (Note, the ISO14155 term *USADE* encompasses the FDA term *Unanticipated Adverse Device Effect* or *UADE*, and shall be reported in accordance with FDA requirements.)

Serious health threat: signal from any AE or device deficiency that indicates an imminent risk of death or a serious deterioration in the health of subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons.

8.3 Documentation of Adverse Events

All AEs, including all SAEs, are required to be collected, investigated, and documented. AEs will be collected from the time the ultrasound exam begins with the investigational device to the time the subject leaves the scan room. All AEs will be followed through to their resolution. Documentation will include:

- Description of Event
- Date of onset
- Outcome, including date of resolution, unless resolution does not occur during study reporting period. In the instance that resolution does not occur, the status of the AE will be documented
- 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 or comparator medical device? (not related, possibly related, or related)
    - *Not related*: The AEs 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 AEs 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.
- Causal relationship to investigational procedure? (not related, possibly related, or related)
- Treatment given and/or action taken
- Anticipated (yes/no)
- Signals from AE that might indicate a serious health threat.

8.4 Reporting of Safety Events

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
- Any signal from an AE that might indicate a serious health threat
- Unanticipated AE and unanticipated ADEs

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.

The Sponsor contact for reporting safety events:

Research Program Integrator (see Appendix B)

E-mail: [redacted]

8.5 Reporting of Device Deficiencies/Complaints

Device deficiency: an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance, such as malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

The primary objective of this study is to collect user feedback about the investigational device. User feedback about the device that is provided to meet the objective of this study will not be considered device deficiencies. 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 during the study reporting period. The Principal Investigator is responsible for notifying the Sponsor if there is any device issue that could potentially lead to a SAE.

9. ETHICAL CONDUCT OF THE STUDY

The study will be carried out per the protocol and with principles enunciated in the current version of the Declaration of Helsinki; the guidelines of GCP for medical devices, as set forth by ISO 14155 and ISO 14971; applicable sections of US FDA 21 Code of Federal Regulations (CFR); and applicable regulatory authority's requirements of the United States.

The study will be conducted and reported per applicable policies of the EC and governing regulatory authorities.

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

9.1 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 notify the Sponsor and provide written explanation.

9.2 Regulatory Agencies and Competent Authority(ies)

The Sponsor will obtain approval from the local regulatory agency or competent authority before the start of the clinical trial, if necessary, per applicable local laws and regulations. Any additional requirements imposed by the EC or regulatory authority shall be followed, if applicable.

9.3 Management of Protocol Modifications and Amendments

Substantial amendments will only be implemented after approval of the EC. 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 competent authority (CA) as soon as possible, if applicable, and to the EC per their policy.

9.4 Management of Protocol Deviations

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/CA. Such deviations shall be documented and reported to the Sponsor and the EC/CA 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.

The Sponsor will assess and implement any corrective or preventative actions necessary, such as retraining the study staff and PI.

9.5 Subject Information and Informed Consent

The investigator or designee will explain to each subject based on their consenting/assenting age group 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. If the subject is too young to undergo the assent process, their parents or LARs will provide consent for the subject. Each subject will be informed that participation in the study is voluntary, that he/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 subject and/or parents or LARs must be informed that his/her medical records may be examined by authorized individuals other than their treating physician.

All potential subjects 18 years or older, and parents/LARs for minor subjects, will be provided an ICF describing the study and providing sufficient information to allow the subject (i) to make an informed decision about participation in the study, and (ii) to be fully aware of subjects' rights under the applicable. Informed consent documents will be subject to approval by the EC prior to enrolling subjects in the study. Minor subjects will be provided an assent based on their ability to comprehend information.

The subject, or parents/LARs, 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.

For minor subjects, written assent will be documented in addition to written informed consent from the parents or LARs, such as health care surrogate, attorney in fact, judicially appointed guardian, or proxy. An assent form will

be provided in language appropriate for eligible subjects, and the study staff will read or explain the assent form to the subject, per EC policy.

9.6 Suspension/Early Termination of the Study

The Sponsor, PI, EC, or regulatory authority may suspend or terminate the study prematurely for various significant and documented reasons. Reasons for suspension or termination may include but are not limited to insufficient participant recruitment, updated risk profile impacting subject safety, alterations in accepted clinical practice impacting study procedures, updates to software or improvement of product technology, early evidence of benefit or harm of the research product, or serious or repeated deviations by the investigator.

The decision to suspend or terminate the study should be shared in writing with all parties described above.

If the reason for study suspension is resolved, the deciding party shall inform all appropriate parties of the decision and actions to resume study procedures.

10. STATISTICAL METHODS

10.1 Statistical Hypothesis

No statistical hypothesis is being tested in this study.

10.2 Sample Size Determination

Sample size is based on the Sponsor's previous clinical experience and the number of user surveys required by engineering. This number is based on prior engineering development and testing experience of the Sponsor. Each ultrasound exam may utilize different combinations of features and probes, so multiple exams are necessary to assess all features. In addition, enrolling multiple subjects will allow the device to be evaluated across various characteristics (such as age, body habitus, and pathology), which is important to optimize the device for its intended use in a diverse patient population.

10.3 Statistical Analysis

No statistical analysis is prospectively planned.

10.3.1 General Statistical Methods

The study data will be presented in tables, listings, and figures, as applicable. Categorical variables will be described with counts, percentages, and sample size. User Surveys consist of Likert scales and qualitative feedback and this data will not follow a statistical analysis plan.

10.3.2 Safety Analysis

The number of AEs, SAEs, and device issues will be reported.

10.3.3 Interim Analysis

No interim analyses are intended to be conducted as part of this study.

10.4 Handling of Missing Data

Only collected data will be included, and no imputation will be done for missing data.

10.5 Deviation(s) from the Original Statistical Plan

No statistical analysis is planned for this study.

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 CRFs

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. 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.

11.1.2 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.
- **Subject records** containing the completed ICFs, assent, and CRFs.

The study staff will maintain a regulatory binder containing the protocol and any subsequent amendments, EC submissions and approvals, blank ICF(s) and assent forms, and site logs.

Operator's manuals or written training materials may be provided by Sponsor throughout study. 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.

11.1.4 Archiving

All study data must be archived for a minimum of 3 years after study completion or premature termination of the clinical trial.

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 per the protocol, written procedures, GCP ISO 14155, 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. Especially, data privacy will be ensured 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 CA, or an EC may require direct access to parts of the medical records relevant to the study, including subject medical history.

12.1.1 Storage of Images and Associated Health Data

Ultrasound images and associated data will be collected and disclosed to the Sponsor as part of this study.

[redacted]

13. RESEARCH AGREEMENTS

GE Healthcare will fund this clinical investigation, which will be conducted under contractual agreements between the investigational sites and the Sponsor, GE Healthcare.

13.1 Clinical Study Report and Publication Policy

Prior to recruitment, a description of this clinical investigation will be registered in a publicly accessible database. This database will be updated per regional or national requirements throughout the conduct of the clinical investigation.

A clinical study report will be generated upon completion of the study.

The results of this study may be used in future publications, per conditions described in any contractual agreement(s) between the investigational sites and the Sponsor.

APPENDIX A – STUDY SITE AND INVESTIGATOR LIST

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

[redacted]	[redacted]	[redacted]

[1] The 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 wellbeing of humans involved in the study. ***Co-Investigators*** or ***Sub-Investigators*** share only those responsibilities designated by the ***Principal Investigator***.

APPENDIX B – ADMINISTRATIVE STRUCTURE OF INVESTIGATION

Research Program Integrator **(Sponsor Contact)**:	[redacted]	[redacted]
Medical Monitor:	[redacted]	[redacted]

APPENDIX C – AMENDMENT (PROTOCOL VERSION 1.0 TO 2.0)

A detailed amendment is provided for version 1.0 to version 2.0. Version 1.0 was the first version to receive EC approval but was not implemented at the site.

Purpose of Amendment: To incorporate changes to eligibility criteria that were requested by FDA during review of the Investigational Device Exemption (IDE) application for this study.

The changes are not expected to increase subject or operator risk, affect study endpoints, or to adversely impact the scientific integrity or conduct of the study.

Item	Section	Revision or Clarification	Justification
1	Synopsis; 4.5: Eligibility Criteria	Updated inclusion criteria #4 and #5: “has a parent or legally authorized representative able and willing to provide written consent to participate” changed to “has two parents or legally authorized representatives able and willing to provide written consent to participate.”	To clarify requirement for two parental/LAR signatures.
2	Synopsis; 4.5: Eligibility Criteria	Added exclusion criteria #5 with clarifying note.	To add exclusion criterion required by FDA during IDE review.
3	4.4 Protection of Vulnerable Subjects; 4.6 Recruiting and Screening; 9.5 Subject Informed Consent	Multiple instances where parent or LAR is described in the singular were changed to two parents/LARs.	To clarify requirement for two parental/LAR signatures.

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