Mass General Brigham

Improving the performance of ultrasound shear wave elastography (SWE) in obese fatty liver disease patients by developing a Conditionally Increased Output (CIO) enhanced ultrasound system

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Institutional Review Board
Intervention/Interaction Detailed Protocol

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Project Title: Improving the performance of ultrasound shear wave elastography (SWE) in obese fatty liver disease patients by developing a Conditionally Increased Output (CIO) enhanced ultrasound system

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For Intervention/Interaction studies, submit a Detailed Protocol that includes the following sections. If information in a particular section is not applicable, omit and include the other relevant information.

1. Background and Significance

a) Historical background

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the United States, with an estimated prevalence of approximately 30%[1]. NAFLD is a disease with a spectrum that can be categorized as 1) simple steatosis/non-alcoholic fatty liver, defined as excess liver fat without inflammation, and 2) non-alcoholic steatohepatitis (NASH) in which excess liver fat is associated with inflammation, fibrosis, and healing, ultimately culminating in cirrhosis[2]. Nonalcoholic steatohepatitis (NASH) can progress to conditions associated with high morbidity and mortality such as portal hypertension, cirrhosis, liver failure and hepatocellular carcinoma[3]. NASH is currently the second most common indication for liver transplantation in the United States, and is expected to become the leading cause in the near future[4-6].

Liver biopsy is currently accepted as the gold-standard method to detect liver fibrosis, though it is an invasive procedure with high morbidity and mortality rates. Alternatively, imaging is useful for NAFLD diagnosis, disease management, and monitoring treatment response. Several imaging methods are used for these purposes, including ultrasound, MRI, and CT based techniques. Ultrasound (US) is preferred by many physicians because it is a low-cost technique that is widely available. Shear wave elastography (SWE) is an ultrasound-based technique that is commonly used for liver fibrosis staging[7]. When performing ultrasound imaging, it is known that several patient-related factors may influence the quality of the image.

In NAFLD patients, several factors including high skin-to-liver capsule distance (SCD) may change the attenuation and aberration of the acoustic waves, change the quality of the image, and make diagnosis harder for radiologists. SCD is the distance between skin and Glisson's capsule, when assessed with standard B-mode ultrasound imaging[8-13]. In patients with high SCD, and particularly in patients with abdominal obesity, the shear wave elasticity elastogram box may not fill properly, which may cause unreliable SWE measurements, as shown in Figure 1. Technical failure and unreliable SWE measurements have been previously reported[14, 15].

The current FDA guidelines recommend the use of a maximum derated spatial peak temporal average intensity (I_{SPTA}) of ≤ 720 mW/cm^2, and either the maximum MI should be ≤ 1.9 or the maximum derated spatial peak pulse average intensity (I_{SPPA}) should be ≤ 190 W/cm^2 [16]. In addition, clinical justification is required if the TI exceeds 6. Several diagnostic modes that are clinically used and FDA approved[7, 17, 18] use acoustic output values that approach these maximum guidelines. These diagnostic modes include acoustic radiation force impulse (ARFI) based techniques, harmonic imaging techniques, and Doppler based techniques. In the past decade, the AIUM has published reports on the benefits and limitations of both the TI and MI[19-21], including recommendations that transient increases may be warranted if there were associated clinical benefit[19, 21].

Using the acoustic and thermal limits in current FDA guidelines, it is not always possible to get reliable SWE measurements. Therefore, conditionally increasing the acoustic pressure of a SWE system may help clinicians to obtain reliable and accurate SWE results from patients with abdominal obesity, potentially minimizing the need for liver biopsy.

In this study, we aim to assess possible bioeffects that may be caused by the use of SWE with conditionally increased acoustic output pressure (CIO). Bioeffects will be monitored by of a series of liver function tests (LFTs) with results graded according to the NCI scale for drug hepatoxicity. LFTs will be collected prior to SWE imaging using CIO, as well up to 7 days post-imaging. Results will be compared to LFTs collected from the same patient after a washout period followed by standard SWE imaging. Secondarily, we aim to understand the degree to which SWE imaging results have improved with the use of COI.

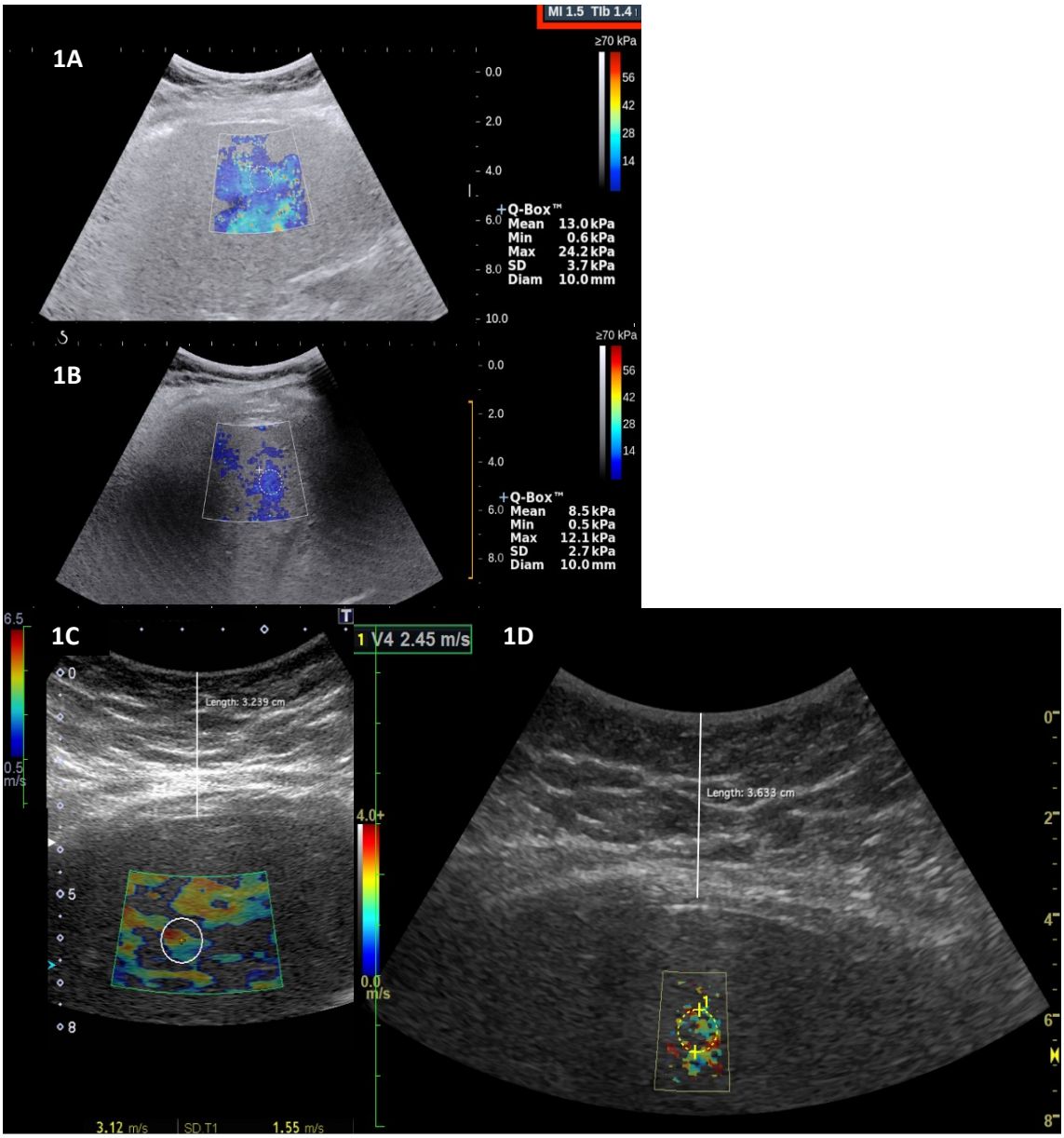


Figure1A. Standardized MI and TI display (red area) Ultrasound systems meeting the U.S. FDA 510(k) guidance for 'Track 3' systems will display TI and MI values on the ultrasound image. Figure1B. Unreliable SWE measurement with high SCD value. Figure1C, 1D: Poor region of interest (ROI) filling due to poor shear wave propagation. High skin to liver capsule distance may be an important factor for poor ROI filling.

b) *<u>Rationale behind the proposed research, and potential benefits to patients and/or society</u>*

As the use of the SWE, is a non-invasive, low-cost and widely available imaging diagnostic tool for liver fibrosis staging, and the acoustic and thermal limits in current FDA guidelines typically do not give reliable SWE measurements in obese patients with high skin-to-liver capsule distance

(SCD), our aim is to conditionally increase the acoustic pressure (CIO) of a SWE system to help clinicians obtain accurate SWE results in obese patients. We aim to reduce the need for monitoring hepatic fibrosis and steatosis using liver biopsy, as it is and costly, invasive with high morbidity and mortality rates, and is subject to sampling error.

2. Specific Aims and Objectives

Aim 1: Ascertain if hepatic bioeffects occur when increasing acoustic output above FDA limits for SWE imaging.

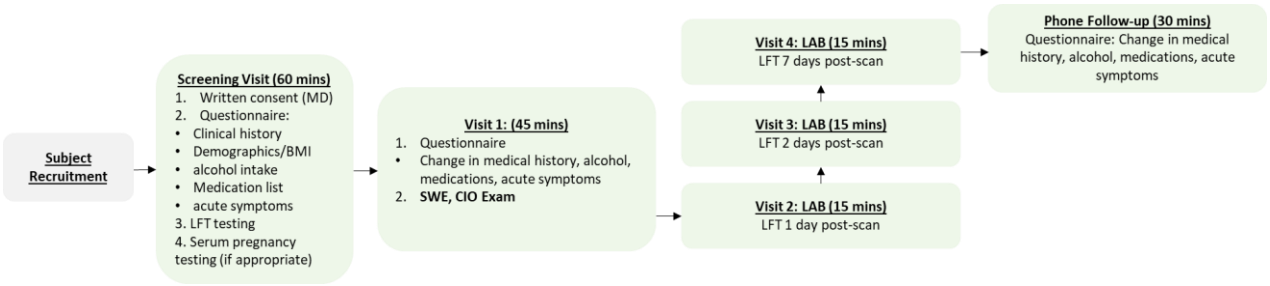
Aim 2: Determine if SWE image quality improves when using increased acoustic output.

Aim 3: Quantify the effect of phase aberration on SWE tracking.

Hypothesis: Increased acoustic output will improve SWE image quality without causing hepatic bioeffects.

3. General Description of Study Design

This is a prospective pre/post single arm non-inferiority study to show that the increase in liver function tests following increased acoustic output SWE is not more than two standard deviations.



4. Subject Selection

a) <u>Inclusion criteria</u>

- Age 18-65
- BMI 18.5-39.9
- Able to undergo abdominal ultrasound
- Able to undergo repeated blood sampling
- Stable medication and supplement list and dosing for 30 days preceding enrollment
- Willing to participate

b) <u>Exclusion criteria</u>

- Excess alcohol consumption: > 7 units/week (F) or > 14 units/week (M)
- Current diagnosis of drug induced liver injury
- Prior liver transplantation recipient
- Prior diagnosis of viral hepatitis
- Receiving drug/placebo in treatment trial now or within 30 days
- Received systemic chemotherapy within past 30 days.
- Confirmed or suspected pregnancy
- Pacemaker, nerve stimulator, or other implanted electronic device
- Plans to alter medication or supplement list or dosage during the study period
- Active or recent (within 30 days) acute illness
- Recent ultrasound contrast administration
- Recent alanine transaminase (ALT), aspartate transaminase (AST), or alkaline phosphatase (ALP) greater than the laboratory upper limit of normal.
- Other factors that the PI considers likely to compromise study endpoints or subject safety

c) Source of subjects and recruitment methods

A flyer will be posted on Rally and interested subjects will be contacted by phone by a member of the study team. Efforts will be taken to enroll an approximately equal distribution of study subject sex. We will attempt to enroll approximately equal numbers of subjects stratified by body-mass-index cohort [18.5-24.9, 25-29.9, 30-34.9, 35-39.9]. No particular demographic group will be focused on in this study. Individuals will not be excluded from the proposed research study on the basis of either minority status or sex.

5. Subject Enrollment

a) Pre-screening

Rally volunteers will be contacted by phone to assess interest in participation and eligibility. After obtaining verbal permission to ask eligibility questions, a brief history will be obtained to assess inclusion and exclusion criteria. Additional information, such as the consent form, will be provided by send secure email to allow sufficient time to choose to participate. Interested and eligible participants will be scheduled for screening visit. If not already performed, subjects will be guided to register as patients at MGH.

b) Consent Process

Written informed consent will be obtained from all subjects by a licensed physician at the screening visit. This discussion will be either in person or virtual via MGB Zoom or Microsoft Teams. When virtual, the licensed physician will screen share an electronic copy of the consent form with a study staff member physically present with the subject and review the form in standard fashion. The consent form will be signed electronically using RedCap by the subject

and physician prior to initiation of any study procedures. We will not target non-English speaking subjects.

6. STUDY PROCEDURES

a) Study visits and procedures

Each subject will be asked to participate for a period of approximately 2 weeks, during which they will have 1 screening visit, 4 study visits, and 1 phone follow up visit.

Prior to study visits:
Eligibility via telephone will be confirmed and informed consent documentation as well as study visit appointment details will be shared by send-secure email. Within 24 hours prior to the study visit, volunteers will be asked the MGH COVID-19 symptom survey (or applicable MGB COVID preventions procedures should they change) to confirm absence of symptoms.

Screening Visit:
The screening visit is expected to take approximately 60 minutes. The study team will obtain written informed consent to participate and will then obtain participant demographics, anthropomorphics, medications, alcohol intake, and brief medical history to assess liver-related diagnoses. The participant will undergo blood sampling, 10 mL or less (1-2 specimen container(s) – less than 90mL), to assess liver function tests [including alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP)] and serum bHCG level for postmenarchal and premenopausal women who have not undergone surgical sterilization (tubal ligation or bilateral oophorectomy) or hysterectomy. Subjects with liver function testing values greater than 3x the laboratory upper limit of normal or with a positive serum pregnancy test will not undergo increased acoustic output imaging or follow up liver function testing.

Study Visit 1:
The first study visit is expected to take approximately 45 minutes. This will occur within 48 hours of the screening visit blood sampling and may occur on the same day as the screening visit. Subjects will fast for 4 hours prior to the exam. Subjects will then undergo a conventional standard of care ultrasound SWE exam of the liver and a repeat exam with increased acoustic output. The standard SWE exam consists of 10 diagnostic elastography measurements in the right lobe of the liver via an intercostal window during suspended respiration. If non-diagnostic values are obtained, repeat acquisitions are attempted up to a total of 20 imaging attempts. For increased acoustic output, the operator will set the mechanical index (MI) value of 2.9, 10 SWE measurements will be repeated in a similar fashion, with 20 acquisition attempts allowed. Additional standard clinical B-mode ultrasound images (within FDA energy deposition limits) will be obtained while capturing raw RF data.

Study Visits 2, 3, 4:

Participants will undergo blood sampling of 10mL or less (1 specimen container – less than 90mL) for liver function testing 1 day after visit 1, 2 days after visit 1, and 7 days after visit 1.

Phone Follow Up Visit:
Within 1 week following study Visit 4, the study team will contact subjects by phone for the completion of a final questionnaire (to be completed by study staff) to obtain information regarding alcohol consumption, change in medical history, and adverse events.

b) Devices and imaging procedures

A commercial curved abdominal ultrasound probe GE C1-6 will be used. The software version of the device will be R2.5.2NeatG. An MI of 2.9 will be used for CIO.

Staff will assess the probe's individual channel sensitivity profile to ensure adequate functionality using the electronic probe assessment tool (E-PAT). E-PAT testing will be performed 1) after imaging each subject and 2) at least once within 14 days prior to each subject (if not already performed), including the initial subject. Additional testing may be performed if there are any concerns of probe malfunction (i.e. accidental probe drop).

c)Data to be collected and when the data is to be collected

	Prescreening	Screening	V1	V2	V3	V4	Phone F/U
Fits within Screening Age**	X						
Demographics#		X					
Social Security Number*		X					
Height/Weight	X						
Medication Stability@	X						
Medication List and Dose$		X					
Liver Disease History%	X						
Concurrent Clinical Trial Participation	X						
Chemotherapy Screening	X						
Pregnancy Screening	X						
Implantable Electronic Device Screening	X						
Alcohol Consumption	X						
Ultrasound Contrast Exposure Screening	X	X	X				
Acute Illness / Symptoms	X	X	X				X
Change in Medications			X				X
Change in Alcohol Consumption		X	X				X
Change in Medical history		X	X				X
Liver Function Testing		X		X	X	X	
Serum bHCG^		X					
Conventional SWE			X				
Increased acoustic output SWE			X				

**yes/no response to inclusion/exclusion age criteria
#age, date of birth, sex, race/ethnicity
*for Advarra compensation
@change in medication over last 30 days and expected change over next 30 days

[$]prescription, over-the-counter, herbal/dietary supplements
[%]transplantation, viral hepatitis, abnormal prior LFTs
[^]for women of child bearing potential

d) Result Reporting

Liver function testing results will be accessible to subjects through patient gateway. Subjects will be contacted by the study team for lab values higher than 3x the laboratory upper limit of normal. Positive pregnancy testing will be reported to subjects.

The results of the SWE exams are not planned to be shared as the interpretation of the SWE values requires clinical correlation. Furthermore, exams may be performed by research staff who are not credentialed at MGH to perform clinical ultrasound elastography scanning. As a result, image quality may not meet clinical standards which may reduce the reliability of SWE results. Results from increased acoustic output SWE will not be released as this technique is experimental and the results have not been correlated with histopathology.

e) Incidental Findings

Should incidental findings, imaging or otherwise, of perceived clinical significance be identified, the research team will contact the subject to inform them of the finding. Permission to contact the subject's primary care physician will be obtained prior to communicating results for continuity of care.

f) Study Termination Criteria

Subjects with baseline liver function testing values greater than 3x the laboratory upper limit of normal or with a positive serum pregnancy test will not undergo increased acoustic output imaging or follow up liver function testing. We will attempt to contact non-responding subjects for a period of 4 weeks after enrollment, at which point, they will be deemed 'lost to follow up'.

g) Remuneration

Following the completion of Study Visits 1, 2, 3, and 4, as well as the follow-up phone call, subjects will receive $150 total by card using the Advarra participant payment system, divided into the following increments, given after each visit:

- Screening Visit: $15 and parking voucher
- Study Visit 1: $40 and parking voucher
- Study Visit 2: $15 and parking voucher
- Study Visit 3: $15 and parking voucher
- Study Visit 4: $15 and parking voucher
- Completion of all study components: $50

A participant is considered to have completed this study if the scheduled scan has been performed, and all requested demographic, clinical history, LFT blood test results, and anthropometric information has been collected.

h) External Data Sharing

De-identified laboratory, clinical, and imaging data will be shared with the study sponsor via the MGH Secure File Transfer service.

7. Risks and Discomforts

a) Complications of surgical and non-surgical procedures.

Conventional ultrasound is painless, non-invasive, and does not require the administration of ionizing or X-ray radiation. Subjects may experience minor discomfort from needing to remain still, the pressure of the ultrasound probe, or the need for repeated breath holding.

The risks associated with elevated MI ultrasonic imaging include thermal and non-thermal bioeffects. Non-thermal risks associated with elevated MI imaging are related to the potential for inducing cavitation. ***A recent AIUM report concluded that exceeding the recommended maximum MI given in the FDA guidance (i.e., 1.9), up to an estimated in situ (effective MI, MIE) value of 4.0, could be justified without concern for increased risk of cavitation in tissues without gas bodies if there were a clinical benefit***[21]. ***Since there are no endogenous sources of air in the liver, and these studies will be performed on patients that have not had ultrasound contrast agent in the previous 24 hours, and because the measured MI values will be kept ≤ 3.0 - which, conservatively, should keep the in situ value, MIE, ≤ 4.0, the potential for cavitation is very small. If, however, it were to occur, the likely impact of the resulting tissue damage would be limited given the large mass of the liver relative to the small volume of the insonated tissue. Thus, it is unlikely that clinically significant liver damage would result, if any at all.***

Blood sampling requires needle placement into a peripheral vein which is likely to cause brief minor pain. A small bruise may result. The small volume of blood obtained during the study is unlikely to be of clinical consequence.

b) Drug side effects and toxicities

Not applicable

c) Device complications/malfunctions

The images acquired in this study will not be used for clinical decision making; thus, any acquired images with suboptimal image quality should not otherwise affect patient care. Malfunctioning channel elements may reduce image quality, however the malfunction would be expected to lead

to less energy deposition with a subject, and thus less risk of tissue injury, which is already considered low. Significant complications from peripheral venous blood sampling would be unusual.

d) Psychosocial (non-medical) risks

There is a small risk of loss of confidentiality, however strict measures are followed to maintain confidentiality. The data being acquired and analyzed is not considered sensitive.

e) Radiation Risks (statement provided by Radiation Safety Committee)

Ionizing radiation is not used for this study.

f) Risk Reduction

Energy levels selected for increased acoustic output SWE acquisition are based on prior human study and expert opinion and are likely to be safe. The target study population will be selected such that subjects are of generally good health and would be expected to tolerate small amounts of liver damage were it to occur without catastrophic consequences. Subjects will be carefully screened and excluded if active/ongoing significant liver injury is present to prevent the additive effects of the investigational technology. Pregnant women are excluded from this study as the risks to an embryo or fetus from increased acoustic output ultrasound are unknown. Subjects will be carefully monitored throughout the study with serial lab testing to assess early and late hepatic effects from increased acoustic output SWE. Subjects will be enrolled in EPIC in order to capture unanticipated hospital visits that could be related to the intervention. Frequent E-PAT testing will be performed to identify probe malfunctions at the channel level. Such hardware failures would result in a pause to enrollment while hardware repair or replacement occurred in order to maximize image quality and scientific benefit from each subject. Such a malfunction is not expected to increase risk as energy deposition is expected to be lower.

8. Benefits

There are no expected direct benefits to the subjects participating in the study. Liver biopsy, the current gold standard test to assess fibrosis is imperfect, costly, invasive, and subject to sampling error. The imaging strategy that will be evaluated, increased output SWE, has the potential to reduce the number of liver biopsies performed for the diagnosis and monitoring of hepatic fibrosis and steatosis. Patients, particularly those who are obese, may potentially benefit in the future by having a better non-invasive test to stage their liver fibrosis and thus, may be spared more invasive testing.

9. Statistical Analysis

Three biomarkers based on liver function test which are associated with liver injury are used in our study[22].

Alanine transaminase (ALT). ALT is an enzyme found in the liver that helps convert proteins into energy for the liver cells. When the liver is damaged, ALT is released into the bloodstream and levels increase. The normal limit for ALT at MGH is 7 to 55 U/L[23, 24]. The standard deviation for ALT is 12 U/L[23, 24].

Aspartate transaminase (AST). AST is an enzyme that helps metabolize amino acids. Like ALT, AST is normally present in blood at low levels. An increase in AST levels may indicate liver damage, disease or muscle damage. The normal limit for AST at MGH is 10 to 40 U/L. The standard deviation for AST is 7.5 U/L.
Alkaline phosphatase (ALP). ALP is an enzyme found in the liver and bone and is important for breaking down proteins. Higher-than-normal levels of ALP may indicate liver damage or disease, such as a blocked bile duct, or certain bone diseases. The normal limit for ALP at MGH is 45 to 115 U/L. The standard deviation for ALP is 17.5 U/L.

The power calculations shown below are based on paired non-inferiority testing assuming no mean difference between pre and post imaging liver function tests and a non-inferiority margin of 1σ (1/2 upper limit of normal) with alpha = 0.05, target power = 0.9, and an assumed dropout rate of 25%[25]. For comparison, many drug trial use 5x the upper limit of normal as the criteria for drug hepatotoxicity. Our non-inferiority margin has been selected to be much more stringent given that ultrasound is an otherwise noninvasive diagnostic test.

Non inferiority margin	Assumed difference in mean	Standard deviation of biomarker	Sample size	Sample size + Dropout rate (25%)
1σ = 12	0	1σ = 12	18	24

10. Monitoring and Quality Assurance

a) <u>Data integrity</u>

A unique source record will be available for each study subject including completed Informed Consent Forms, eligibility assessment, social security number, laboratory values, and all records related to ultrasound imaging of the subject. The PI will designate a physician study staff member to review data entries at least quarterly to assess for data completeness and regulatory compliance.

At the time of enrollment, subjects will be assigned a study number that will be the only identifier included on study documents, aside from the consent form, Rally volunteer list, and payment information form that includes subject social security numbers for subject compensation. Blood specimens will be obtained, labelled, and handled per standard clinical routine by MGH outpatient phlebotomy services. Subject name and study number will be saved

in a single file on an MGB server running antivirus software. Access will be restricted to MGB study staff and will not be shared beyond MGB. All remaining data will be stored separately using only subject number to identify data. Printed study documents will be stored in a secure cabinet in a locked office at the Center for Ultrasound Research and Translation (CURT). Only MGB study investigators and staff will have access to study files. Data shared with collaborators will not include identifiable information. Confidentiality of subjects will be strictly protected. The investigators will comply with the human subject investigation guidelines of Massachusetts General Hospital

b) Safety monitoring

Safety monitoring will be performed by study staff members and the PI; the PI will be responsible for overall monitoring. Subject safety will be monitored by research staff to detect any changes in health status from enrollment. Subject safety will be monitored from the time each subject signs the Informed Consent Form until completion of study participation. Subjects will have available the contact information of study personnel should an adverse event occur following the study visit. The PI will be notified within 24 hours of potential adverse events including any laboratory value outside of the normal range.

c) Outcomes monitoring

Any possible bioeffects that may be caused by SWE imaging with CIO will be monitored and determined by liver function test (LFT), with results graded according to the NCI scale for drug hepatoxicity (grade 1 = 1-3x upper limit of normal; grade 2 = 3-5x upper limit of normal; grade 3 = 5-20x upper limit of normal; grade 4 = >20x upper limit of normal). Participants will attend study visits to obtain blood samples collected 1 day post-scanning, 2 days post-scanning, and 7 days post-scanning to trend liver function tests and assess laboratory value normalization.

d) Adverse event reporting guidelines

The PI will be responsible for safety monitoring of enrolled subjects during the study period. Subjects will be evaluated for signs of pain and discomfort before, during, and immediately after the study visit. Any significant adverse event will be reported to the IRB and followed up by the study staff.

All Adverse Events, Serious adverse events, Adverse Device Effects, and Device Deficiencies will be collected at the time of reporting by the subject or when detected by the Investigator. They will be source documented and maintained as part of the study record.

An assessment of the following metrics will be made by the Investigator for each Adverse Event:

- severity,
- seriousness,

- anticipated or unanticipated,
- relation to study participation or investigational imaging technique,
- action taken,
- outcome (resolution, sequelae, etc.)

Definition of adverse events (AE) in this study will be ‘’any untoward or unfavorable medical occurrence in a human subject, including any abnormal physical exam or certain unexpected abnormal laboratory finding, symptom, or disease, temporally associated with a subject's participation in the research’’.

Definition of serious adverse events (SAE) in this study:

A SAE is any AE that:
Results in death, or
Is life-threatening, or
Results in hospitalization or prolongation of existing hospitalization, or
Results in a persistent or significant disability/incapacitation, or
May jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed above. No SAEs are anticipated in this study.

All AEs will have their relationship to study procedures assessed by the PI. The following criteria will be used to identify causality; (0) Not related, (1) Unlikely to be related, (2) Potentially related, (3) Probably related, (4) Definitely related. PI will be responsible for determining whether an adverse event (AE) is expected or unexpected in this study. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with known ultrasound risks and complications, which are very limited. The occurrence of an AE or SAE may come to the attention of study personnel during ultrasound scans. Any medical condition that is present at the time that the participant is included will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

The following will be reported in the case report forms for each Device Deficiency that occurs:

- device ID,
- device event description,
- date of deficiency,
- whether the deficiency caused or could have caused an Adverse Device Effect to occur.

The disposition of all safety events, assignment of relatedness, and determination of seriousness is the responsibility of the Investigator. All Adverse Events will be reported in the final Clinical Study Report for this study.

The Investigator is responsible for reporting the event to the approving IRB as dictated by the guidelines defined by the IRB and, if applicable, regulatory authorities. Additionally, the Investigator will report to the sponsor and regulatory authorities as required by national regulations.

The principal investigator will review adverse events on an individual basis, the subjects will have the phone numbers of the research team and a 24-hour phone number to call in the case of any adverse events.

11. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☐ Additional privacy and/or confidentiality protections

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