# Study Protocol

**TITLE:** BEFAST (Bubble-Enhanced FAST) for the Evaluation of Solid Organ Injury in Hemodynamically Stable Blunt Abdominal Trauma

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Title Page

Full Study Title: BEFAST (Bubble-Enhanced FAST) for the Evaluation of Solid Organ Injury in Hemodynamically Stable Blunt Abdominal Trauma

Short Study Title: BEFAST

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2. External Collaborators: n/a

3. Precis/Abstract

Title: BEFAST: Bubble-Enhanced FAST for the Evaluation of Solid Organ Injury in Patients with Hemodynamically Stable Blunt Abdominal Trauma

Rationale: The Focused Assessment with Sonography for Trauma (FAST) exam is widely used and accepted as part of ATLS protocol, but its low sensitivity for identifying solid organ injury in the absence of hemoperitoneum is a significant limitation. Contrast-enhanced ultrasound (CEUS) has the potential to significantly enhance the evaluation of the trauma patient with acute intra-abdominal injury through the use of intravascular microbubbles that allow direct visualization of lacerations to solid organs. European studies have demonstrated that ultrasound contrast markedly improves the sensitivity of ultrasound in detecting solid organ injury, when the exam is performed in the radiology suite. CEUS, however, has never been validated in the US in the hands of emergency medicine providers.

Research Hypothesis: We hypothesize that the bubble-enhanced or BEFAST exam will be more sensitive than traditional FAST for identification of solid organ injury in hemodynamically stable blunt abdominal trauma patients when performed by emergency providers.

Specific Aims:
Objective 1: To determine if contrast-enhanced, i.e. bubble-enhanced FAST (BEFAST) outperforms non-enhanced FAST in the evaluation of solid organ injury in hemodynamically stable blunt abdominal trauma patients when performed by frontline providers using CT as gold-standard.

Objective 2: To determine whether emergency physicians can incorporate BEFAST evaluation at the point-of-care in a trauma evaluation of a hemodynamically stable adult blunt abdominal trauma patient.

Objective 3: To determine the inter-rater reliability between bedside emergency physicians and radiologists for identifying solid organ injury with BEFAST.

Significance: A specific concern that the BEFAST exam addresses is the low sensitivity of FAST for identification of solid organ injury in the absence of hemoperitoneum. If the proposed work is successful we will demonstrate that the BEFAST exam adds critical information at the point-of-care by identifying intra-abdominal injury that would be missed by the traditional FAST exam. The BEFAST exam may be able to replace the FAST exam as a more sensitive screening tool of intra-abdominal injury. In addition, while CT remains the gold standard for blunt abdominal trauma, BEFAST has the potential to impact the field by providing an alternative imaging strategy to CT in cases of medical necessity (renal failure, allergy to contrast dye), patient preference (pediatric or pregnant patient), or limited resource (surge/MCI, austere environment, international EM).

4. Introduction and Background

Our primary hypothesis is that the bubble-enhanced or BEFAST exam will be more sensitive than traditional FAST for identification of solid organ injury in hemodynamically stable blunt abdominal trauma patients when performed by emergency providers. The purpose of this study is to ascertain whether the BEFAST exam is a more sensitive screening tool than traditional FAST exam. BEFAST addresses a major limitation of conventional FAST in that it can identify lacerations to solid organs even in the absence of hemoperitoneum. Acceptance of the BEFAST exam as an appropriate alternative to CT in select situations may positively impact patient care by leading to decreased CT utilization and a change to current trauma algorithms.

Blunt abdominal trauma - whether from motor vehicle crash, assault, fall, or recreational injury - is a leading cause of morbidity and mortality [1]. According to the 2016 National Trauma Database, 12 % of all patients with trauma admissions had abdominal trauma, the majority of which is blunt [2]. The diagnosis of intra-abdominal injury due to blunt abdominal trauma can be challenging. The physical exam is unreliable in patients with altered mental status or with impairment due to drugs or alcohol. Utilization of the FAST exam has dramatically improved clinical care by enabling frontline providers to screen for injury non-invasively.

While the FAST exam is considered a first line tool in the triage of hemodynamically unstable patients with abdominal trauma to CT scanner versus the OR, its inability to identify lacerations to the solid organs in the absence of hemoperitoneum limits its utility in the hemodynamically stable patient. A 2018 Cochran review noted substantial heterogeneity of reported sensitivity of the FAST exam; pooling results from 34 studies it estimated FAST sensitivity for abdominal trauma to be 68% and specificity to be 95% [3]. Most studies use free fluid as the only criteria for a positive FAST exam. When FAST is used to detect solid organ injury it is less sensitive; both McGahan et al and Rothlin et al. showed a sensitivity of 41% for the ability of FAST to detect solid organ injury [4-6]. In comparison, gold standard CT has a sensitivity of 97-98% and specificity of 97-99% for intra-abdominal injury [7]. The use of the BEFAST exam may bridge this diagnostic gap between FAST and CT if it can demonstrate improved sensitivity in detecting lacerations to liver, kidney, spleen, and pancreas.

While CT can rapidly and accurately diagnose injury, emergency physicians have raised concerns that the use of CT has become overly liberal [8]. Over the last few decades there has been a paradigm shift in the management of solid organ trauma with increasingly nonoperative management of both low and high-grade injuries in hemodynamically stable patients [9-10]. 25% of all CTs are ordered through the ED, but less than 20% of abdominal CTs obtained in patients with blunt trauma have intra-abdominal injury, and less than 3% require a surgical intervention [7].

The risks of overutilization of CT in hemodynamically stable blunt abdominal trauma include increased health care costs, lengthy stays in the emergency department, risks of contrast-induced nephropathy and radiation-induced malignancy, and patient anxiety when “incidentalomas” are discovered that need extensive and often unnecessary workup

[11]. And yet, CT usage in trauma patients has increased dramatically by 3.5-fold between 1995-2007 [12]. With the yearly rise in ED census and CT utilization, it is becoming an increasingly impractical and expensive strategy to “pan-scan” trauma patients without further risk stratification. This is especially true when the patient is hemodynamically stable and unlikely to need an operative intervention. Strategies for minimizing radiation burden of CT include use of clinical decision tools, guidelines for appropriate use such as the Image Wisely and Image Gently campaigns, reduced CT dosage, and technological innovations such as contrast-enhanced ultrasound [12-14].

Contrast-enhanced ultrasound uses microbubble contrast agents consisting of an inert gas surrounded by a stabilizing shell. The microbubbles reflect sound waves and enhance the ultrasound image. These gas-filled microspheres are about the size of a red blood cell and remain in the intravascular space; unlike CT contrast, microbubble contrast agents do not leak or diffuse into the tissue [15-6]. Microbubbles metabolize when they break via exhalation of the gas, and the shell is metabolized by the liver. The contrast is completely eliminated from the body within 10-15 min [17-8].

In 2016, the Food and Drug Administration (FDA) approved Lumason (sulfur hexafluoride lipidtype A microsphere) for characterization of focal liver lesions with CEUS in both adult and pediatric patients, opening new areas of research in the United States [19]. Lumason is a second generation contrast agent that is more stable than previous ultrasound contrast agents and does not require refrigeration. Other currently approved indications include use in echocardiography and in evaluation of urinary reflux in children. Although approved for intravascular and intravesical use, Lumason’s use in trauma is off-label and an emerging application in the United States [12].

Previous European literature supports the superiority of CEUS to conventional ultrasound for the identification of solid organ injury. In a 2009 multi-center study by Catalano et al. of 156 patients, the use of contrast by radiologists improved the sensitivity and specificity of renal trauma seen on conventional US from 36% to 69% and from 98% to 99% [12]. For liver trauma, ultrasound contrast agents improved the sensitivity and specificity from 68% to 84% and from 97% to 99% [12]. For splenic trauma, contrast improved the sensitivity and specificity from 77% to 93% and from 96% to 99% [12]. CEUS performs even better when used only for lowenergy isolated trauma where it has a sensitivity of up to 95% [20]. An example of a liver laceration seen on contrast-enhanced ultrasound vs conventional FAST is depicted in Figure 1.

Figure 1. Comparison of liver laceration seen with CEUS on left and no contrast on right

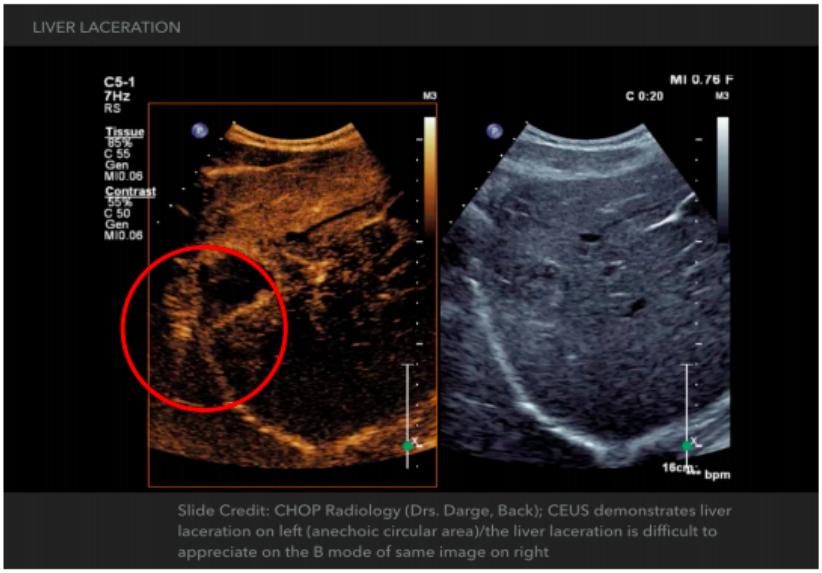


Figure 1. Comparison of liver laceration seen with CEUS on left and no contrast on right

CEUS may also be used to grade injury to solid organs using AAST criteria. In a 2014 study by Lv et al., two radiologists were able to classify contrast-enhanced images into mild, moderate, and severe injury with high inter-rater reliability ($\kappa = 0.973$) [21]. CEUS can also identify active extravasation as a pool of contrast or a jet outside of blood vessels [22]. In a 2011 study by Lv, et al., 392 patients with hepatic injury were examined by both CEUS and CT; CEUS detected extravasation in 16% of cases and had a similar performance to CT with sensitivity of 72% vs 81%. [23]. The presence of active bleeding is critical information in the management algorithm of blunt abdominal trauma and suggests the need for emergent surgical or interventional radiology consultation and/or treatment.

Contrast-enhanced ultrasound (CEUS) has the potential to enhance the diagnostic capabilities of point-of-care ultrasound while still offering the traditional advantages of ultrasound over other imaging modalities. These advantages include its portability, repeatability, lack of ionizing radiation, lack of necessity for labs prior to study, and lack of necessity for transport of the patient to the radiology suite. If the BEFAST outperforms the FAST exam in identification of intra-abdominal injury, our study would lay the groundwork for the argument that just as the FAST exam largely replaced DPL, the use of microbubble contrast agents in contrast-enhanced ultrasound is the next evolution in trauma triage. We wish to show that the BEFAST is a more advanced trauma screening tool. As providers become more comfortable with the BEFAST exam and the use of contrast in the trauma bay, CEUS may find an increasing role in decreasing the utilization of CT in select scenarios. CEUS may also play a role as a risk-stratification tool for disposition decisions to ICU vs floor via grading of injury by AAST criteria. Although CT with IV contrast provides the most information in the evaluation of intra-abdominal injury, CEUS may play a substantial role in the future in a multi-modal approach to

trauma. Further investigation is needed to discover the capabilities and limitations of CEUS in the hands of emergency providers.

Our study is distinct from previous European literature because the CEUS exam would be performed and interpreted by emergency physicians rather than by radiologists. We wish to demonstrate the feasibility of this exam outside of the radiology suite because of the potential for BEFAST to impact patient care by enabling frontline providers to make real-time clinical decisions at the bedside.

5. Objectives:

Objective 1: To determine if contrast-enhanced, i.e. bubble-enhanced FAST (BEFAST) outperforms non-enhanced FAST in the evaluation of solid organ injury in hemodynamically stable blunt abdominal trauma patients when performed by frontline providers using CT as gold-standard.

Objective 2: To determine whether emergency physicians can incorporate BEFAST evaluation at the point-of-care in a trauma evaluation of a hemodynamically stable adult blunt abdominal trauma patient.

Objective 3: To determine the inter-rater reliability between bedside emergency physicians and radiologists for identifying solid organ injury with BEFAST.

6. Study Design and Methods:

This single center prospective study will enroll 267 adult patients with hemodynamically stable blunt abdominal trauma who present to a Level 1 ACS verified Trauma Center.

Inclusion Criteria:
Age 18 and older
Clinical suspicion of intra-abdominal injury
Presentation within 24 hours of injury
Planned CT of the abdomen/pelvis within 24 hours
Ability of patient to provide informed consent

Exclusion Criteria:
Co-existing penetrating abdominal injury
Known hypersensitivity reaction to contrast agent
Pregnant patients
Prisoners
No appropriate IV Line able to be inserted
Hemodynamic instability at time of enrollment (sustained systolic blood pressure < 90 mm Hg or sustained HR >120 despite initial resuscitation)

Study Interventions/Procedures:
1) Baseline Grayscale US Exam
2) Contrast Enhanced US exam with IV administration of LUMASON
3) Chart Review for abstraction of clinical and demographic data

Risks/discomforts:

Risks from ultrasound use are minimal – this modality does not use ionizing radiation. Most commonly the patient may complain of coldness of gel or minor discomfort from pressure of the ultrasound probe.

The less common risks and discomforts expected in this study are (in 0.02% of patients):

Headache, nausea, dizziness, flushing, back pain, kidney pain, chest pain, shortness of breath, hypertension, mild allergic reactions

Rare but possible risks include: hypersensitivity to contrast resulting in low blood pressure (0.007% of patients).

Potential benefits include: identification of injuries with BEFAST not seen with conventional FAST

Ultrasound studies will be performed by a team of ultrasound faculty who have attended a didactic session on the BEFAST exam and grading of solid organ injury by AAST criteria. They will be evaluated with a post-test to check for comprehension.

After consent, a baseline FAST exam will be performed and documented. This FAST will be distinct from the initial ATLS resuscitation FAST in order to avoid any interference in the trauma evaluation. A 20g or larger intravenous line if not already placed, will be established according to standard practice for trauma patients. The investigator will use a phased array or curvilinear transducer to record video of their baseline FAST exam. The investigator will also note start/stop time of the FAST exam.

Using the same machine, a BEFAST exam will be performed using a low mechanical index setting in contrast-specific imaging mode. Lumason will be injected into the patient's IV for the CEUS exam by either a nurse research coordinator or one of the clinical staff. The contrast will be injected using the straight port of a 3-way stopcock and flushed through the side port. To eliminate shear of microbubbles, contrast will not be injected through a clave connector. The contrast will be injected once for the right side of the body, and once for the left side of the body looking for disruptions in the normal enhancement pattern and evidence of active bleeding. If an antecubital line is placed, 2.4 mL contrast will be given over slow IV push (2-3 seconds) and flushed with 5 ml saline; if only a peripheral hand IV is established, the investigator may use a 10 ml saline flush.

To examine the right side of the body: the right kidney and liver will be imaged. The investigator will examine the RUQ for evidence of solid organ injury, free fluid, or active extravasation by examining the kidney in short and long views and the liver in coronal, anterior, and subcostal views.

The examiner will screen the liver during approximately the first 10-20 seconds after IV contrast administration to see hypoperfusion in the arterial phase or extravasation before scanning through all organs in the venous phase (kidney, then back to liver). The exam will be timed from start of saline flush after contrast and video clips will be saved (stored using patient study number).

To examine the left side of the body: the pancreas will be imaged first, followed by the kidney and the spleen. The investigator will note evidence of solid organ injury, free fluid, or active extravasation in the LUQ. The pancreas, kidney, and spleen will be visualized in short and long. The exam will be timed from start of saline flush after contrast and video clips will be saved. If adrenal glands are visualized on either side these may be recorded as well.

In general, the investigator will scan one side of body at time but may cross to the other side if imaging on one side is complete. Investigators will be allowed to re-dose contrast on either or both sides if the first examination is not clear or if there is inadequate time to complete the exam. Either right side or left side may be examined first.

The investigator will note the presence or absence of injury to the liver, kidney, spleen, or pancreas, as well as the presence or absence of free fluid or active extravasation. If an injury to a solid organ is detected, the investigator will grade injury per American Association for the Surgery of Trauma (AAST) criteria. There will be an attestation noting whether there was unintended disclosure of either the primary team's FAST exam or CT imaging read prior to bedside interpretation of the BEFAST study. The investigator will note whether there were physical exam signs suggestive of injury that may have biased their interpretation. The investigator will note start/stop time of BEFAST exam. Exams will be saved to QPATH and to the US machine; the data will also be archived on an encrypted USB. QPATH will be password protected, and the USB will be kept in a locked file in a locked office. The US machine will be kept in a locked area.

A study is complete if the patient tolerates the study (no severe adverse event to contrast, patient allows the provider to complete the scan) and if it results in images of adequate quality to answer the focused clinical question.

A serious adverse event (SAE) is defined by the FDA as any adverse drug event (experience) occurring at any dose that in the opinion of either the investigator or sponsor results in any of the following outcomes: 1) death 2) life-threatening adverse drug experience 3) inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours) 4) persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5) congenital anomaly/birth defect 6) important medical event (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

For the FAST exam, the focused clinical question is whether there is free fluid in the abdomen or fluid in the pericardium. The following views should be obtained to meet minimum requirements: RUQ, LUQ, suprapubic, and subxiphoid views with adequate visualization of Morison's pouch, inferior pole of right kidney/liver tip, area under the diaphragm on the LUQ side, pelvic views in transverse and sagittal. If an adequate

subxiphoid view is not possible, a parasternal long view may be substituted. For the BEFAST exam the focused clinical question is if there is solid organ injury to the liver, kidney, spleen, or pancreas. For the BEFAST exam the liver, kidney, spleen, and pancreas should be examined using a low mechanical index setting in contrast-specific imaging mode.

In order to determine interrater reliability of the ultrasound exams, the interpretation of the point-of-care EM physician (who will attest they are blind to the CT read and the ATLS FAST read) will be compared to the interpretations of two board-certified radiologists (blinded to the FAST reads and the CT read) for the presence or absence of solid organ injury, free fluid, or active extravasation. Injured organs will be graded per AAST criteria.

7. Video clips collected for this study will be saved for future education and training purposes, and also used in research presentations at national conferences.

8. N/a: The study does not target a particular community.

9. Participant Selection:

Requested sample size: 267; expected refusal or withdrawal rate – conservatively we set at 90%.

Inclusion Criteria:
Age 18 and older
Clinical suspicion of intra-abdominal injury (IAI)
Presentation within 24 hours of injury
Planned CT of the abdomen/pelvis within 24 hours
Ability of patient to provide informed consent

Exclusion Criteria:
Co-existing penetrating abdominal injury
Known hypersensitivity reaction to contrast agent
Pregnant patients
Prisoners
No appropriate IV Line able to be inserted
Hemodynamic instability at time of enrollment (sustained systolic blood pressure < 90 mm Hg or sustained HR >120 despite initial resuscitation)

Justification:
We did not include pediatric population because FAST sensitivities are different in adult and pediatric populations.
HD stable because unstable patients might go immediately to OR
Clinical suspicion of IAI and presentation within 24 hours because this would be the most clinically relevant presentation for an emergency physician using the BEFAST exam which is a point-of-care study in the acute presentation of possible IAI.
Planned CT because of the need for confirmatory gold standard study.

Exclusion Criteria:
We excluded penetrating abdominal injury to focus on blunt abdominal injury in isolation.
We excluded patients with known hypersensitivity reaction so that we could avoid SAE.
We excluded pregnant patients and prisoners as vulnerable populations.
We excluded patients without sufficient access because we would not be able to insert contrast.

Subject recruitment plan:
Initial contact will be made by the study staff (clinical research coordinator, ASSET team, PI, co-investigator) upon presentation of potential subjects (i.e. subjects meeting the inclusion criteria) in the emergency room/hospital. Study staff will obtain written informed consent.

Screening for eligibility:
In order to effectively screen potential patients for the study, the study personnel will ID subjects in the ED as appropriate through conferring with medical records, trauma logs, triage notes, radio reports of trauma alerts, and on-duty doctor and nurses to identify potential subjects. Many of the inclusion/exclusion criteria can be evaluated by a review of the potential subject's medical records such as: mechanism of injury, time of injury, presence or absence of concurrent penetrating trauma. All female patients of childbearing age will be offered a serum or urine pregnancy test (standard of care for evaluation of female trauma patient with suspected intra-abdominal injury). A patient may exercise their autonomy and waive pregnancy testing (due to reasons such as prior hysterectomy, tubal ligation) but are still eligible for the study as long as they are informed that Lumason is a Category B medication which means that animal studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. The patient's refusal of pregnancy test will be documented in the medical record. No identifiable data will be collected from subjects during screening.

Procedures when a subject withdraws from a study:
In the case of withdrawal from study, videos saved up to the point of withdrawal may be kept as outlined in the study consent form. Once linkages are destroyed it will not be possible to identify an individual's video clips for destruction.

10. Informed Consent Process
A research team member will consent the patient at Grady Memorial Hospital.

We are requesting a partial HIPAA waiver to look at identifiable patient information prior to consent as part of the screening process in order to see if a patient meets inclusion/exclusion criteria. Elements of interest include: name, medical record number, age, mechanism of injury, timing of injury, pregnancy status, institutionalization, vital signs, allergies.

We are not studying children, prisoners, pregnant women/fetuses, or patients with cognitive impairment. Students and employees are not targeted groups for enrollment.

We will ensure comprehension of the informed consent information by allowing the patient ample time to ask questions and have the patient express understanding of the study. The study team will explain the purpose, risks, and potential benefits of the study and patient will be given the option of continuing participation or stopping.

Study consent discussion will take place in Grady Memorial Hospital. Study staff (research coordinator, ASSET team, PI, or co-I) will conduct the discussion and obtain consent. We are not requesting a waiver of signed documentation of informed consent.

In the event that the patient is cognitively capable of consent for the study but has a physical impairment (such as a broken arm) that prevents them from signing the consent document, the research team will obtain a signature from a witness to the consent process who is not a member of the research team. The witness will sign the consent paperwork (their signature, time, and date), leaving the patient fields blank. An informed consent process note will also be filed to document the circumstances, who served as a witness, and the relationship of the witness to the patient (e.g. related or unrelated to subject).

11. Incidental Findings

The research team will relay any findings related to injury to solid organs and hemoperitoneum to the primary treatment team for further management. The FAST and BEFAST exams are screening exams only and not comprehensive abdominal exams; additional findings are not anticipated. If additional incidental findings are noted they will be relayed to primary treatment team for appropriate triage, referral to clinical specialists, and patient education as needed if the finding is clinically significant. All study patients will also obtain confirmatory imaging with CT study.

12. Compensation for time and effort: $25 single payment as reimbursement for parking expenses, time, effort.

13. Statistical Analysis:

**Objective 1**: To determine if contrast-enhanced, i.e. bubble-enhanced FAST (BEFAST) outperforms non-enhanced FAST in the evaluation of solid organ injury in hemodynamically stable blunt abdominal trauma patients when performed by frontline providers using CT as gold-standard.

Descriptive Statistics. The primary results will be described using sensitivities and specificities with 95% confidence intervals. Categorical variables will be described using frequencies and percentages. Continuous variables will be described using means and/or medians as appropriate.

Primary Analyses. Agreement with the CT results will be examined using a mixed-effects/multi-level logistic regression in order to account for clustered measurements. Results from this regression will also be adjusted for the following covariates:

demographics (e.g. age, sex, race), BMI, sonographer experience, contrast redosing, the presence of outward signs of injury. In the event that the logistic regression fails to estimate properly or provides poor fit to the data and/or to show consistent results across methods, alternative methods will be explored: (1) P-values and confidence intervals will be computed using a bias-corrected and accelerated bootstrapping procedure (≥5,000 resamples); (2) Sensitivities and specificities for BEFAST and FAST will be compared using McNemar's test.

Sample Size Calculations. Two primary issues were taken into consideration when calculating the required sample size: 1) statistical power, and 2) the expected rate of positive outcomes.

1) Power calculations were based on previous studies examining the sensitivity and specificity on standard and contrast-enhanced ultrasound. The results from these studies were meta-analyzed (fixed-effects, inverse-variance method) and indicated that (1) the sensitivity for CEUS (lower limit = 0.87) is greater than the sensitivity for standard ultrasound (upper limit = 0.68); and (2) the specificity for CEUS (0.98) is similar to the specificity for standard ultrasound (0.95). This analysis aimed to ensure that the present study has sufficient power to show improved sensitivity when using CEUS. Note that, because this sample size calculation uses the lower limit of the CEUS estimate and the upper limit of the standard ultrasound estimate, actual power will likely be greater. Given the small meta-analytic difference in specificities between methods, it is unlikely that differences in specificity will be detected. These values were used to estimate the sample size required to achieve 80% power using Monte Carlo simulations (10,000 samples) implemented in R v3.4.1. This analysis determined that the sample size would need to be at least 187.

2) Using the rule of thumb 10 positive results for each predictor, we aimed to ensure that there will be a sufficient number of positive results for a model with two predictors (i.e. at least 20 positives. Thus, the current study will aim for a sample size of at least 187; however, data collection will not end until at least 20 CT+ patients are enrolled. Importantly, this stopping rule is entirely a priori and ceasing data collection will not be dependent on any statistical analyses, significance tests, or interim analyses. No analyses will be conducted until after this stopping rule is reached.

Missing Data. In the event of substantial missing data, data will be imputed using a multiple imputation procedure. The type of procedure and the number of imputed data sets will be determined by the amount of missing data and the pattern of missingness. As a sensitivity analysis, we will 1) assume the worst and assign a "does not agree" outcome for that patient and 2) assume the best and assign an "agrees" outcome for that patient. These analyses will describe the boundary conditions for the models described above.

**Objective 2**: To determine whether emergency physicians can incorporate BEFAST evaluation at the point-of-care in a trauma evaluation of a hemodynamically stable adult blunt abdominal trauma patient.

An exam is complete if the patient tolerates the exam (no severe adverse reaction to contrast, patient allows the provider to complete the scan) and if it results in images of adequate quality to answer the focused clinical question.

Completion rates will be described as percentages with 95% confidence intervals. Assuming maximal variance for a binomial variable ($\pi = 0.5$), a sample size of 187-267 (approximate) will result in 95% CIs that are no wider than ± 7.2% to 6.0%. FAST and BEFAST completion rates will be compared using either the multilevel/mixed effects logistic regression described above or McNemar's test.

**Objective 3**: To determine the interrater reliability between bedside emergency physicians and radiologists for identifying solid organ injury with BEFAST.

Inter-rater Reliability for the presence/absence of an injury will be evaluated using Cohen's or Fleiss' kappa as appropriate. The reliability of AAST scores will be evaluated using a weighted kappa statistic.
Assuming a minimal sample size of 187, the current study will have sufficient power ($\geq$ 80%) to detect reliability coefficients exceeding 0.23. For clinically relevant ratings, such as this, reliability is generally required to be high. Guidelines vary and are generally arbitrary; however, 0.8 and 0.9 are often used as cutoffs for "high" agreement, whereas a value such as 0.23 would be considered unacceptable. Thus, the current study is sufficiently powered to detect clinically acceptable levels of agreement.

14. Data and Safety Monitoring and Reporting:

<u>Monitoring the Progress and Safety of the Trial</u>
During the screening process, patients will be excluded if they belong to vulnerable populations such as pediatric, pregnant, or imprisoned patients or if they have a known hypersensitivity to ultrasound contrast agent.

Measures to protect participants against risk include use of a physician or certified health care professional (nurse practitioner, physician assistant or registered nurse) to administer contrast. Confidentiality of participants will be protected by keeping data and US images password protected. The study will utilize a code number as the only identifier for each subject and the master list will be kept under lock and key with access limited to the PI and study coordinator.

<u>Site Monitoring Plan</u>

This study will not be followed by a separate Data and Safety Monitoring Board. A medical monitor will be responsible for monitoring the data and for conducting safety reviews on a quarterly basis. Scope of monitoring includes informed consent process, eligibility, adverse event reporting.

During the review process, the monitor will evaluate whether the study should continue unchanged, require modification or amendment, continue or close to enrollment. A monitoring report will be provided to the PI within 5 days of review. PI will document

receipt & review of the monitoring report, resolutions, and/or corrective actions to findings on the Site Monitoring Log; PI will notify IRB according to policies and procedures.

Oversight of the progress and safety of the trial will be provided by the PI. Adverse events are not anticipated, but any occurring will be documented and reported according to Emory IRB policies and procedures. Cumulative adverse events and study progress summary will be communicated to the IRB at the time of continuing review.

A serious adverse event (SAE) is defined by the FDA as any adverse drug event (experience) occurring at any dose that in the opinion of either the investigator or sponsor results in any of the following outcomes: 1) death 2) life-threatening adverse drug experience 3) inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours) 4) persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5) congenital anomaly/birth defect 6) important medical event (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The PI will be responsible for reviewing protocol compliance, data collection and verification. The PI will immediately notify IRB in the event of a serious adverse event according to the Emory IRB reporting requirements. Once an unanticipated event is recognized and reported, the event will be investigated to determine if the event represents an unreasonable risk to the subject so as to terminate all or part of the study.

15. Confidentiality:

We plan to protect subjects' privacy during the course of their participation in the study by de-identifying data and assigning each patient a code. The linkage between code and patient will be kept in secure location – locked file cabinet, locked office, accessible only to PI and study team members and only during the duration of active study. Whenever possible, a study number, rather than the patient's name will be used on study records. The patient's name and other identifying information will not appear when the study is published or results presented.

Electronic data will be secured via a secure network that is password protected. Studies will be backed up to encrypted USB. Hard copy will be secured in a locked office in a locked filing cabinet.

All links to identifiable data will be destroyed after publication and presentation of research data. De-identified video clips will be archived indefinitely (as outlined in consent) for education and future research.

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