American Institute of Ultrasound in Medicine Recommendations for Contrast-Enhanced Liver Ultrasound Imaging Clinical Trials

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Abbreviations
AIUM, American Institute of Ultrasound in Medicine; ALARA, as low as reasonably achievable; CEUS, contrast-enhanced ultrasound; CT, computed tomographic; FDA, Food and Drug Administration; MI, mechanical index; MR, magnetic resonance; PVC, premature ventricular contraction

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Preamble

The American Institute of Ultrasound in Medicine (AIUM) is a recognized authority in the clinical utility, education, and safety of ultrasound imaging. The AIUM has many standing committees, including the Clinical Standards Committee, Continuing Medical Education Committee, and Ultrasound Practice Accreditation Council. The Bioeffects Committee monitors the safety of ultrasound and contrast agents on a continuing basis.[1,2]

As a multispecialty, clinically oriented organization of ultrasound specialists, the AIUM participates closely in developments that it identifies as essential for the medical community to improve patient care. The introduction of ultrasound contrast media in the mid-1990s has already revolutionized the practice of ultrasound imaging in those countries where they are available. In particular, it has been established that ultrasound imaging performed with contrast enhancement (contrast-enhanced ultrasound [CEUS]) allows for accurate characterization and detection of focal liver lesions, which often are not possible with conventional ultrasound imaging. Numerous single- and multi-center investigations of CEUS have shown that both detection and characterization of liver masses are comparable to those achieved with contrast-enhanced computed tomographic (CT) or magnetic resonance (MR) scans. Ultrasound imaging performed with contrast enhancement is clearly superior to ultrasound imaging performed alone. In fact, the lack of specificity for the confident diagnosis of liver masses with ultrasound imaging alone is so well recognized that,

in most cases, the identification of a liver mass on ultrasound imaging provokes confirmatory imaging with either a CT or an MR scan. In patients at risk for hepatocellular carcinoma or metastases, there is recognition that confirmation of all masses identified on ultrasound imaging with either CT or MR scans is essential.

In addition to the lack of specificity for ultrasound-based diagnosis of liver masses, ultrasound-based detection of focal liver masses can be poor, especially in patients at risk for metastatic liver disease. Although some metastases may be easily seen on ultrasound imaging because they are either echogenic or hypoechoic relative to the liver parenchyma, many others have backscatter similar to that of the background liver. These so-called "isoechoic" or "invisible masses" have backscatter that is identical to that of the adjacent normal parenchyma, and they are difficult if not impossible to detect without the aid of ultrasound contrast. Studies have shown that these masses can be identified with a sensitivity comparable to that of contrast-enhanced CT or MR imaging by the addition of ultrasound contrast agents. A review of the world literature on the efficacy of CEUS imaging compared with non-CEUS imaging for the detection and characterization of liver lesions is documented in "Appendix A."

A key element in the evolution of medical imaging technology has been the development from plain imaging to techniques enhanced by intravascular contrast agents. In many countries outside the United States, it is no longer considered sufficient to perform only non-CEUS imaging of the liver for detection and characterization of focal liver masses.

It is the AIUM's considered opinion that the lack of availability of CEUS for noncardiac imaging in the United States hinders the delivery of optimal diagnostic imaging services to our patients. As a result, we lag behind the rest of the world in the appropriate and proven uses of contrast agents for liver mass diagnosis and detection. The AIUM believes that this is having an adverse impact on clinical care in the United States.

Therefore, pursuant to the request by the US Food and Drug Administration (FDA), the AIUM proposes the following recommendations for consideration for future CEUS clinical trials.

I. Appropriate End Points for Assessment of Ultrasound Contrast Efficacy in the Liver

Ultrasound imaging of the liver in the United States is currently performed without contrast media. Contrast media are intended to improve lesion conspicuity for increased lesion detection sensitivity and/or to improve lesion characterization for increased diagnostic specificity. Improved detection sensitivity and/or diagnostic specificity when a contrast agent is used compared with conventional non-CEUS imaging should be sufficient to establish efficacy for approval. A recommended trial, therefore, should compare the non-CEUS imaging performance with the CEUS imaging performance against an accepted truth standard. The basis for FDA approval should be a significant improvement of CEUS over non-CEUS imaging.

The AIUM believes that there are situations in which it is clearly obvious that the improved diagnostic/prognostic information achieved with CEUS imaging is clinically useful. These should be considered an adequate basis for FDA approval. Possible beneficial outcomes from the use of CEUS may include, but are not limited to, the following:

- Improved characterization of focal liver masses with CEUS imaging, such as to determine whether a focal liver mass is benign or malignant, compared with non-CEUS imaging.
- Improved ability to detect focal liver masses with CEUS imaging.
- A reduction in referral for further workup using other imaging or diagnostic procedures.
- Assessment of therapeutic response.

II. Examination Procedures

A. The contrast agent should be prepared and administered according to the manufacturer's recommendations.
B. Equipment should be quality controlled and capable of performing CEUS imaging as described in section III, "Equipment Criteria and Variables."
C. Scans should be performed by qualified personnel as described in section V, "Training."

D. Baseline (noncontrast) ultrasound imaging should include representative images of the liver and any visible hepatic lesions.
E. Contrast-enhanced ultrasound image data should be acquired and stored as a real-time digital data set from before contrast agent injection until achievement of the diagnostic effect as determined for each agent/protocol.

III. Equipment Criteria and Variables

A. Contrast studies of the liver require contrast-specific imaging modes that operate at a low mechanical index (MI).
B. The trial protocol should specify the performance requirements of high-end systems for the study.
C. Manufacturers of ultrasound equipment have products with specifically designed presets for CEUS imaging of the liver, and these should be used.
D. Machine presets should include system parameters as well as settings that can be controlled by the user. Careful limits should be placed on the ability of the user to adjust controls once the preset has been selected. Considerations for specific settings should include the following:

    1. *Nonlinear Contrast Imaging Mode*. As real-time imaging is a key requirement for liver imaging, a low-MI mode is needed that does not disrupt the contrast microbubbles. The mode detects the echo returning from the bubbles and suppresses the echoes from the tissue containing them. Nonlinear modes that meet these requirements usually employ multiple pulses, which are modulated in phase and/or amplitude. These schemes go under various commercial names. A machine that does not offer such a mode is not suitable for contrast imaging. Examples of suitable modes in some systems currently on the market are listed in "Appendix B."
    2. *Available Transducers*. The appropriate transducer for contrast imaging of the liver must be specified in the protocol.
    3. *Mechanical Index*. The MI should be maintained at a level that minimizes microbubble loss in the anatomic region of interest. The actual exposure of the agent to the ultrasound beam varies with anatomic conditions, so the fixed setting of MI provided by the preset should be used as a starting point. The displayed MI is an estimate only; actual microbubble loss is determined by factors other than the MI alone. Therefore, the appropriate MI setting should be determined separately for each ultrasound scanner model and the body habitus of each specific patient. In general, the lowest MI consistent with a successful examination should be used.
    4. *Operating Frequency*. The operating frequency for a given machine should be specified in the protocol. In general, contrast-specific nonlinear imaging modes are more sensitive at lower operating frequencies, which also offer better penetration but lower spatial resolution. Thus, sensitivity to the agent is added to the trade-off between resolution and penetration.
    5. *Multiple Modes*. The user must be able to view both the noncontrast and contrast images because contrast-specific imaging modes suppress the echo from tissue. Machines that offer simultaneous noncontrast and contrast-specific images are preferred. The noncontrast image MI should be controlled so that no inadvertent microbubble loss occurs.
    6. *Line Density/Frame Rate*. In general, the lower the exposure of microbubbles to ultrasound, the lower the rate of microbubble loss. Reducing line density and frame rate to the minimum consistent with diagnostic interpretation is recommended. Zoom or magnification modes should not be used.
    7. *Focal Zones*. Focal zone settings should be set according to manufacturers' instructions and not changed during an examination.

8. *Initial Gain*. The initial gain setting, if not provided automatically by the machine, should show system noise in the far field of the contrast image.
9. *Data Storage*. The machine should be capable of capturing real-time image data, preferably continuously, for the duration of the contrast enhancement (at least 3 minutes is required). Storage to a local or network device is required.

E. Trial designers should work with system manufacturers to standardize machine presets for each trial.
F. Contrast-enhanced ultrasound modes should be well documented, with setup algorithms and work flow guides (see "Appendix B"). A step-by-step procedure for use of the system during the examination should be specified.
G. While the technology for CEUS modes may continue to evolve, it is recommended that the technology for an individual trial should not be changed once the trial begins.

IV. Safety

In medical procedures, considerations should always be given to comparing the risks with the benefits to the patient. Clinical utility from improved diagnostic image information has been demonstrated with ultrasound contrast agents. Approval for the use of such agents in the United States and internationally has resulted in numerous examinations using a variety of agents (millions of doses). The general safety record of ultrasound contrast agents has been quite good, as discussed below. It is the responsibility of the ultrasound community to help maintain the safety record of ultrasound imaging and determine any risks associated with the methods used. Several aspects need to be considered:

General Safety Record of Ultrasound Imaging

Medical ultrasound imaging has been used since the 1950s. Since its introduction, this modality has been considered one of the safest methods of medical imaging. As indicated by the general clinical safety statement from the AIUM (see "Clinical Safety" at http://www.aium.org/publications/statements/statements.asp), there are no confirmed harmful biological effects in patients from exposure to ultrasound energy at levels commonly used for diagnostic imaging. The possibility exists that biological effects may be identified in the future, but the benefits of the prudent use of ultrasound outweigh the risk, if any, that may be present. Although this statement has largely been considered in terms of conventional non-CEUS imaging, it is important to remember that the same assessment should be made when weighing benefits and risks in clinical CEUS imaging. In the absence of specific evidence of risk and with demonstrated patient benefit, the prudent use of contrast agents should be appropriate. Additionally, when the use of a contrast agent provides significant diagnostic information, not performing such a procedure may also increase medical risk to the patient.

Potential for Bioeffects

The currently approved ultrasound contrast agents use microbubbles to produce the added contrast provided by the agent. Contrast agents are a relatively new addition to ultrasound imaging, and identifying potential risks is an ongoing process. There is a wealth of theoretical and experimental knowledge about the interactions of microbubbles and ultrasound energy. This knowledge results from a considerable number of investigations on bubble-ultrasound interactions, including cavitation activity that can have enough energy to induce bioeffects.

There have been several studies in vitro and in animal models that have shown potential bioeffects. Many of these animal studies have been related to ultrasound exposure of cardiac tissue in the presence of microbubble contrast agents.[3–10] One early study in humans reported induction of premature ventricular contractions (PVCs) using a high MI and end-systolic triggering.[11] However, other studies using different exposure conditions did not find an increased frequency of PVCs.[12–15] The induction of PVCs in humans appears to require a relatively high MI, imaging at a specific point in the cardiac cycle, and substantial contrast agent filling of the cardiac tissue.

In terms of noncardiac studies, some animal studies have been positive for effects,[7,16–19] but the relationship to the clinical situation has not been clearly established. Of particular relevance to cancer imaging, 1 study[20] did not find an enhancement of metastatic spread in mouse melanoma tumors using diagnostic levels of ultrasound in the presence of contrast agents. The identification of any potential biological effect must be placed in context. The likelihood of the effect in the clinical situation and the clinical significance of such effects should be assessed.

To the credit of the ultrasound community, there have been very active researchers who have carefully considered mechanisms for biological effects of ultrasound. These individual researchers and collective activities such as those of the Bioeffects Committee of the AIUM have helped identify potential effects that have been explored further. These efforts should continue as part of maintaining the established reputation of diagnostic ultrasound as safely practiced in medicine. The prudent use of ultrasound and CEUS imaging, including the application of the ALARA (as low as reasonably achievable) principle, should continue to the benefit of patients.

Safety of CEUS Imaging

It has been recognized for years that there are finite risks associated with the use of contrast media in medical imaging. For example, the adverse reaction rates of intravenous CT contrast agents are 4% to 12% for ionic contrast and 1% to 3% for nonionic.[21] For ultrasound contrast agents, the most common effects are headache, a warm sensation, and flushing, all of which resolve in a short time. More unusual events such as nausea, dizziness, chills, altered taste, and chest pain occur in 0% to 5% of patients at a rate similar to that seen in placebo groups.[22] Note that in postmarketing surveillance, the serious adverse event rate for gadolinium diethylenetriaminepentaacetic acid in MR imaging was found to be 1 to 2 per 100,000.[23] Considering the most extreme effects, the death rate from intravenous CT contrast agents is 1 to 3 per 100,000 (0.002%).[21] Only 3 deaths in approximately 160,000 doses were reported in conjunction with current ultrasound contrast agent use, all associated with 1 agent. However, continued use of this agent with changes in contraindications has yielded no additional fatalities, and debate remains as to the role of the agent in the previous deaths. No deaths have been attributed to the other agents in clinical use in the United States and elsewhere. The total number of doses for all ultrasound contrast agents combined is now almost 2 million. Therefore, the death rate associated with ultrasound contrast agents is likely significantly less than that from CT contrast agents.

Obviously these are investigations of commonly found adverse effects, and further study would be needed to follow any potential adverse effects unique to ultrasound contrast agents. However, the general safety profile is as good as or better than that of other imaging agents that are routinely used and currently deemed as acceptable risks given the benefits to the patient.

Guidance for Clinical Trials

As with any ultrasound procedure, the ALARA principle should be followed; that is, one should use only the ultrasound output power level and contrast agent dose needed for diagnostic efficacy. In terms of ultrasound exposure, the advent of low-MI imaging has significantly reduced the requisite pulse amplitude for optimal contrast imaging. Information from bioeffects studies in animals has generally found a threshold for effects at an MI of approximately 0.4, generally higher than those typically used for low-MI imaging. This might serve as some guidance in CEUS imaging studies; however, again the specific need for higher output levels to achieve diagnostic information may be justified. For example, higher levels of acoustic power may be required on the basis of patient factors such as obesity or a deeply located lesion or if the contrast is to be eliminated from the imaging field to measure contrast flow dynamics into a lesion. In any case, the lowest level of acoustic output necessary has always been a guiding principle in medical ultrasound, and this is unchanged when considering the use of CEUS imaging.

The lack of availability of CEUS imaging for noncardiac applications in the United States denies patients a beneficial procedure, resulting in other forms of risk.

V. Training

The AIUM recognizes the importance of proper qualifications of investigators and blinded readers who participate in clinical trials of CEUS. Proper experience and training are important for ultrasound imaging professionals to participate in clinical trials using ultrasound contrast agents. Although the use of contrast media requires unique skills that may not be possessed by many professionals in the United States, these skills are not difficult to learn provided the professionals have a minimum level of knowledge and experience in clinical ultrasound applications. Participation in such a program is intended to ensure a standard skill set for the purposes of the clinical trial and is not necessary after contrast agent approval, although appropriate training should be obtained by those performing clinical CEUS.

Training cases are recommended before enrolling subjects. In addition, qualified study personnel familiar with both imaging technology and contrast agent procedures should serve as onsite monitors to ensure the quality of patient examinations. Two training program models are shown in "Appendix C."

VI. Conclusion

The AIUM believes that implementation of these recommendations will decrease variance among sites and increase the likelihood of successful clinical trials.

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Appendix A: Bibliography of the World Literature on CEUS

Overview

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Appendix B: Work Flow Examples

The following manufacturers have provided current examples of work flow sequences for the use of CEUS: GE Healthcare (Milwaukee, WI), Philips Medical Systems (Bothell, WA), and Siemens Medical Solutions (Mountain View, CA). Work flow sequences from other manufacturers will be added as they become available. Draft summaries are below.

1. Contrast Work Flow for Coded Contrast Imaging, GE LOGIQ 9, 7, and 5 (Draft)

Select New Patient control on console	Enter patient information; select Abdominal preset; exit
Select transducer	System will automatically default to factory- or user-programmed image parameter settings for a routine exam
Select Contrast control on console	Contrast menu appears on touch panel
Select TruAgent Detection on touch panel	System will automatically default to factory- or user-programmed low-MI contrast-specific image parameter settings, including: • Operating Frequency • Acoustic Output • Gain • Dynamic Range • Line Density • Edge Enhance • Pulse Repetition Integral • Focal Zone number and position • Gray Map • Dual View Imaging mode
Adjust gain and focal zone position as necessary	
Select Contrast Clock on touch panel on agent injection	Contrast timer displays on monitor
Select Print 1 on console to store loops or still images	System will store raw DICOM image or loop to system hard drive
Select End Exam on exam completion	System displays all recorded images and loops, ends exam, and resets for next patient entry

(continued)

Appendix B (continued): Work Flow Examples

2. Contrast Work Flow for Philips iU22 (Draft)

Enter patient demographics	Press Patient Data key	System provides screen menu for patient data entry
Cine loop capture length	Setups Print/Network tab	Set prospective capture length to 3 minutes (only needs to be set once)
Select transducer (or select exam first)	Select Contrast Gen preset	System sets parameters for low-MI B-mode for preinjection imaging
Invoke contrast mode	Press Contrast Touch Panel (TP) button	• System activates low-MI contrast agent imaging • System sets transmit frequency/ line density across sector • System sets transmit focus to encompass depth of field • System sets acoustic power to MI 0.07 • System sets initial gain value • System sets persistence value • System sets gray map value • System sets Xres values • System sets compression • System sets 2-dimensional pulse repetition frequency
Administer agent	Press Contrast Timer TP button	System time stamps each frame in system with time since injection for viewing in review
Record clip	Press Capture	System simultaneously records DICOM and native data clips of up to 3 minutes
Stop recording clip	Press Capture key	System stops clip store
Terminate time stamp	Press Contrast Timer	System stops rolling timer
To change transmit frequency	Toggle 2D Opt (Pen, Gen, Res)	System sets new transmit frequency and recalculates MI and MI at the focus (MIF) values
To display live dual imaging	Press Contrast Side/Side	System displays agent image on one side and tissue image on the other side
To do region of interest (ROI) analysis or microvascular imaging (MVI) processing (to view bubble outline of vasculature)	Press QLab, in review; then press ROI or MVI	Select ROI or MVI

(continued)

Appendix B (continued): Work Flow Examples

3. Contrast Work Flow for Contrast Pulse Sequencing (CPS), Siemens Sequoia System

Enter patient demographics	Press Begin Exam key	System provides screen menu for patient data entry
Select exam (or select transducer first)	Press Exam key; select CPS Abdomen from Exam list	
Select transducer (or select exam first)	Press Transducer key; select transducer from soft key	• System sets parameters for standard B-mode preinjection imaging • System sets standard B-mode imaging presets • Exception: system sets digital clip capture for 8 minutes
Invoke contrast mode	Press Cadence key	• System activates low-MI CPS agent imaging • System sets to lowest transmit frequency • System sets transmit focus to encompass depth of field • System sets acoustic power to –21 dB and calculates corresponding MI and MIF • System sets initial gain value • System sets persistence value • System sets post processing map value • System sets enhancement value • System sets Delta value • System sets agent-only display
Equalize image brightness	Press TEQ key	• System sets lateral and axial gain • System detects and subtracts background noise
Administer agent	Press Stopwatch key	System time stamps current time of day and initiates rolling stopwatch
Record clip	Press Clip Store key	System simultaneously records DICOM and QuickTime clips of up to 8 minutes
Stop recording clip	Press Clip Store key	System stops clip store
Terminate time stamp	Press Stopwatch Stop/Reset soft key	System stops rolling stopwatch and zeros stopwatch
To change transmit frequency	Toggle MultiHz key	System sets new transmit frequency and recalculates MI and MIF values
To display live dual imaging	Press Dual key	System displays agent image on one side and tissue image on the other side
To switch from agent-only to mix or tissue-only display	Toggle Balance key	System displays mixed agent and tissue image or tissue-only image or agent-only image

Appendix C: A CEUS Imaging Training Program

Two concepts for training programs have been developed as described in the outline below. The training programs are generic (ie, they are not designed to be used for a specific contrast product), but they could be easily modified to incorporate any unique or product-specific requirements related to a given ultrasound contrast agent (eg, preparation, doses, etc). Once the trainees complete the training program(s), they would be required to take an examination that would indicate their level of competency in CEUS imaging studies.

Participants

Proof of adequate experience and/or participation in these training programs is required for all ultrasound imaging professionals that intend to perform CEUS examinations as part of clinical trials and those that will function as "blinded readers" of CEUS studies performed in other laboratories.

It is suggested that proof of adequate experience and/or participation in a training program also be required for clinical representatives (eg, application specialists, etc) of pharmaceutical and ultrasound system vendors that will be involved in the clinical trials.

Similar training programs could be used for professionals that desire CEUS training after CEUS is approved for clinical trials.

Training Programs

I. Two training programs could be developed.
   A. One program would be designed for physicians who intend to be "blinded readers" for CEUS clinical trials.
   B. One program would be designed for physicians and sonographers who intend to participate in CEUS clinical trials.

II. Applicants would be required to possess prerequisite qualifications to participate.
   A. For physicians, board certification and a minimum of 5 years' experience in ultrasound would be required.
   B. For sonographers, American Registry for Diagnostic Medical Sonography certification in abdominal ultrasound would be required.
   C. Laboratory accreditation as a requirement may be considered.
   D. Qualified individuals could participate in either or both training programs.

III. Training programs would be generic in terms of the contrast media (ie, they would not be designed for a specific contrast product).

IV. Applicants would be required to take a pretest before beginning the training programs and a posttest after completion of the programs.
   A. Use of pretests and posttests permits analyses of the level of knowledge that trainees obtain by completing the training programs as well as the adequacy of the educational programs.

V. Relevant reference materials would be made available to applicants.
   A. Materials may include published reports, book chapters, European contrast agent guidelines, white papers, etc.

VI. Training would include the following:
   A. Didactic training for all applicants.
   B. Hands-on training for applicants who intend to perform CEUS clinical trials.
   C. Didactic lectures would include the following:
      1. Physical principles of CEUS, including instrumentation and scanning techniques.

(continued)

Appendix C (continued): A CEUS Imaging Training Program

2. A review of the relevant anatomy, physiology, and pathology as it pertains to CEUS for liver applications.
3. Pitfalls, limitations, safety, and other relevant issues.
4. Patient/subject selection.

D. Hands-on training would use a wet lab with an animal model and all ultrasound systems that are deemed appropriate for CEUS trials.
1. Trainees would perform CEUS studies using equipment that they would use in their own lab with supervision by CEUS-experienced nurses, sonographers, and physicians.
2. Contrast media manufacturers' representatives would also be involved in the wet lab training (for a given agent).

VII. Case reviews would be performed.

A. Before the trainees could perform or interpret CEUS protocol studies, a specified number of CEUS teaching cases would be reviewed.
1. The training cases would be in real time on DVD (or other video format).
2. Trainees would review the cases and complete a questionnaire that would include a description of the features of the CEUS studies, diagnostic impressions/differentials, limitations, level of suspicion, final assessment, etc.
3. The trainees' responses on the forms would be compared with those of a panel of experts.

VIII. Trainees who successfully complete the formal training programs, case reviews, and posttests would be "signed off" as being competent to perform and/or interpret CEUS protocol examinations.

A. Trainees who do not successfully complete either the formal training and/or the required number of case reviews would be required to continue the training process with emphasis on their areas of weakness as determined by the posttest and/or case review questionnaires. They would then be required to retake the posttest until successful.