Safety Guidelines for Imaging Human Subjects with Verasonics Ultrasound Systems

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Verasonics has helped several groups obtain IRB (Investigational Review Board) approval for human subjects research using the Verasonics ultrasound system. Verasonics has had reports of successful IRB applications in the US, Canada, Australia, and Korea. An IDE (Investigative Device Exemption) application was approved by the FDA in 2013 at the University of Washington, in Seattle. These guidelines summarize Verasonics' understanding of what some research groups have done in the US to obtain such approval. The guidelines provide a set of recommendations to the researcher, but may be either insufficient, or, overly conservative, depending on the local institution's policies. This document has not been submitted to any regulatory body for approval.

The basic approach to applying for human studies approval is to provide a letter to the institution's local IRB panel arguing that the Verasonics ultrasound system (when used in non-extended transmit imaging modes) is very much like a conventional ultrasound imaging system in terms of patient exposure, and should be assessed for safety in that context. In initial attempts, too much emphasis was placed on explaining the flexibility of the system as a research tool, which raised more concern than it alleviated, particularly when new imaging modes were discussed. For example, the use of unfocussed beams which ensonify wide areas are unconventional, and can be described in ways that are either alarming or reassuring. Ultimately, the researcher and the IRB are responsible for the safety of patients. Quantitative acoustic field measurements are the rational basis for safety assessment and are strongly recommended as part of an application.

In addition to the usual non-instrumentation components of an IRB application for human studies, such as descriptions of the clinical exam, the patient consent form, etc., successful applications have included:

- The general statement that the Verasonics ultrasound data acquisition system, combined with a researcher-provided commercial transducer and the researcher's software (acquisition sequence control program), produces ultrasound signals and exposures that are similar to those produced by approved clinical systems (i.e., it produces ultrasound exposures that are like those from an "ordinary" ultrasound system, and under FDA limits).

- A description of the ultrasound exposure regime and imaging sequence as programmed in the script(s).

- Selected field beam patterns (simulations), calibrated hydrophone field measurements, and associated TI (Thermal Index) and MI (Mechanical Index) calculations indicating that the exposures generated by the system are within the

FDA limits. Users can obviously perform their own simulations, but the '`showTXPD.m`' transmit beam intensity function provided with the system should be sufficient to identify the most intense field regions of interest. [Though not supported by Verasonics' Risk Analysis document (see below), if you are doing elastographic radiation force "push" sequences that include extended transmits in profile 5, you'll need to spend some time making the water tank AP&I (acoustic power and intensity) measurements.]

- A display of the TI and MI on screen via custom graphical print statements, unless the exposure levels are sufficiently far below the FDA limits, as is often the case for any broad beam transmit fields.

- A description of the steps you will take to ensure that the clinical user will only be able to use the software you have evaluated and tested, and that no settings clinical users have access to would permit them to exceed the limits you have established. (This is primarily a software version control exercise, but also indicates that the FDA limits have been assessed and that the user is unable to exceed them by adjusting settings on the GUI, for example).

- An electrical inspection/ certification that must be done at your institution with your system. This is a test of electrical leakage current and ground quality/integrity for the entire system, once you have chosen a PC and transducer to use. Because the construction of the system uses medical power supplies and medical grade EMI shielding, these tests have always passed without the use of an isolation transformer, even with the computer connected to the VDAS via the PCIe cable and plugged into typical grounded wall power receptacles. Researchers need to inquire with their local instrumentation safety certification testing facility to arrange for testing at their site.

- The Verasonics VDAS Risk Analysis, a document that follows the FDA's guidelines for IDE applications, listing various hazards and their severity, and any mitigations Verasonics has undertaken. The document supports the idea that where electrical safety concerns arise, Verasonics has taken steps to mitigate all significant risks. *This document only covers imaging applications*, and does not address extended transmit regimes that are possible to achieve with the Extended Transmit System Option, and most definitely not with the external power supply HIFU Option which is capable of ablative energies. The Risk Analysis clearly identifies issues that are the user's responsibility, since the system can be programmed by the user to do a wide range of applications beyond Verasonics' control.

In addition, to protect Verasonics hardware in higher power modes, we have developed a rather sophisticated piece of software that evaluates many hardware operating state parameters, as programmed by the user's sequence, and then tests those operating parameters against predefined limits. This infrastructure is normally invoked only in high energy modes (specifically, NOT during imaging sequences which are intrinsically safe

for the system), but the software is available to the user for enforcement of AP&I limits (of their choosing) as well. This approach can supplement normal programmable limits on the HV supply (transducer transmit voltage), and can make use of the operational safeguards built into the system for any protocol you choose. See the `Matlab Simulator/HIFU/ TXEventCheck.m` function. (Verasonics will probably need to provide some help if this approach is used, though there is relevant documentation in the manual regarding the HIFU mode and the limit checking function.)

These guidelines have evolved over time; they were originally much more ambitious than needed, and may still be too conservative for many applications. Verasonics does not have any copies of the IRB applications submitted by various groups. In our experience and from user reports, each IRB application is different. Meeting in advance with the human subjects committee representative was very helpful to the University of Washington groups with whom we have had the most experience. When the IRB panel has no ultrasound expertise, either having an independent expert sit in or write a letter of support is recommended.

NOTE 1: References from successful applicants may be provided by request, from support@verasonics.com.

NOTE 2: The Risk Analysis document for the Vantage system is included in the documentation package provided in the customer's software download folder: Documentation/Safety. The Risk Analysis document for V-1 is available in the software release folder: Matlab Simulator/Documentation/Safety.

BIBLIOGRAPHY

1. IEC 60601-2-37 Medical electrical Equipment, Part 2-37: Particular requirements for the safety of electronic medical diagnostic and monitoring equipment. (2001)
2. IEEE Guide for Medical ultrasound Field Parameter measurements, IEEE Std. 790-1989. (ANSI recognized)
3. NEMA Standards Publication UD 2-2004, Rev 3. Acoustic Output Measurement Standard for Diagnostic Ultrasound Equipment.
4. NEMA Standards Publication UD 3-2004, Rev 2. Standard for real-time display of thermal and mechanical acoustic output indices on diagnostic ultrasound equipment.
5. Duck, F.A., 2007. Medical and non-medical protection standards for ultrasound and infrasound. Progress in biophysics and molecular biology, 93(1-3), pp.176–191.
6. Haar, G.T. & Wells, P.N.T., 2009. Ultrasound bioeffects and safety. Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 224(2), pp.363–373.
7. Harris, G.R., 2009. FDA regulation of clinical high intensity focused ultrasound (HIFU) devices. Conference proceedings, Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference, 2009, pp.145–148.
8. Shaw, A. & Haar, ter, G., 2006. Requirements for measurement standards in high intensity focused ultrasound (HIFU) fields. NPL Report DQL AC, 15.
9. Zeqiri, B., Hodnett, M. & Wells, P.N.T., 2009. Measurements, phantoms, and standardization. Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 224(2), pp.375–391.