QIBA Newsletter

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RSNA Science Advisor

IN MY OPINION

Experiences with Imaging in Clinical Research: Perspectives from an Academic Radiology Department

BY SAMUEL G. ARMATO III, PHD, AND NICHOLAS P. GRUSZAUSKAS, PHD

Editor's Note: This article is a response to the In My Opinion, "Imaging CRO Perspectives and Priorities in Quantitative Imaging," in the January 2014 QIBA Newsletter.

Participating in clinical research can be both highly rewarding and logistically demanding for investigators and their parent institutions. As medical imaging becomes more integral to this research, the value and the challenges become greater still. Of note is the impact that imaging has on multisite clinical trials: although it is not often the focus of a trial but is "merely" used to establish the efficacy of a new therapy, there is nonetheless a need to standardize the imaging performed across all participating sites so investigators can be reasonably assured that the results of the trial are due to the novel therapy and not variability in imaging parameters.

Although the sponsors of multisite clinical trials will often engage an imaging contract research organization (iCRO) to both manage the imaging of a trial and conduct independent assessments of the imaging studies themselves, it is nevertheless incumbent upon local investigators to ensure that all applicable imaging guidelines are met at their institutions. As the science of quantitative imaging moves forward and QIBA-recommended guidelines become more important, making compliance with a research protocol's requirements become equally significant and challenging.

Assuming an investigator enlists the help of appropriate imaging personnel, complying with the imaging requirements of a small number of concurrent clinical trials is likely to be relatively trivial for an institution's radiology department. However, institutions with large portfolios of clinical research are likely to see their local radiology department overburdened with juggling clinical trial subjects who require unique imaging. And since most institutions do not have dedicated imaging

equipment and imaging personnel for research—clinical trial imaging must generally be inserted into the standard clinical workflow.

While iCROs attempt to keep things running smoothly by providing sites with imaging manuals and conducting training sessions with key personnel, the local investigator's team and, more likely, the local radiology department, are still ultimately responsible for ensuring the integrity of a trial's imaging—a daunting task even for trials with relatively simple imaging requirements (for example, a slice thickness requirement that differs from the department's standard thickness). Maintaining strict adherence to quantitative imaging guidelines for a subset of patients enrolled in a clinical trial will be even more challenging. Our experience handling these issues at the University of Chicago led us to create an office dedicated to the management and administration of research-related imaging: the Human Imaging Research Office (HIRO).

"HIRO" Ensures Imaging Integrity, Compliance

HIRO is an independent, service-oriented office, with the purpose of ensuring that all research-related imaging at our institution is performed and distributed in compliance with the research protocol, IRB requirements and HIPAA regulations. Delegating these responsibilities to a dedicated office alleviates the burden on radiology department personnel (whose primary responsibility is the clinical workflow) and the local investigator's team (whose primary responsibility is managing their patients' clinical care and who may or may not know the intricacies of medical imaging). HIRO personnel are experts in their domain; they are knowledgeable in conducting of clinical trials, they are familiar with the details and logistics of clinical and research imaging and they are able to process, de-identify and distribute image data in a DICOM-compliant and HIPAA-compliant fashion. At our institution, HIRO's goal is to facilitate the imaging needs of both investigators and imaging personnel during the course of clinical research.

In the "In My Opinion" article in the January 2014 QIBA Newsletter, Gregory Goldmacher, M.D., Ph.D., a senior director at ICON Medical Imaging (one of the premier iCROs), noted that QIBA recommendations and quantitative imaging in general is of critical importance to both iCROs and their clients [1]; however, quantitative imaging guidelines, and indeed all research-specific imaging guidelines, may greatly impact sites that participate in clinical trials. An iCRO will typically develop scanning guidelines for a clinical trial in the form of an imaging manual, for example, and then distribute this manual to the local investigators at each site. It is then up to the local investigator to implement these guidelines, which may prove difficult if the investigator does not perceive any difference between the guidelines outlined in the manual and those already in place, or if the investigator's institution does not provide any infrastructure to assist with the review and implementation of the guidelines.

At the University of Chicago, the HIRO offers the expertise necessary to properly review the imaging manual and the personnel to provide the requisite logistical support to ensure proper execution of the guidelines. An iCRO may additionally require the local investigator to identify key personnel within the institution's radiology department who will assist with the implementation of the imaging guidelines and it may further require that all personnel participate in tele-training sessions to discuss the guidelines. But again, it is up to the local investigator's team to identify appropriate personnel and arrange participation in the training sessions. At our institution, the HIRO fills this void as well: HIRO personnel work directly with imaging personnel on a constant basis and are able to identify those individuals who would be best suited to assist with the trial. Additionally, HIRO personnel generally attend the tele-training sessions in lieu of imaging personnel when possible; they can then train imaging technologists and radiologists as appropriate and become the institutional imaging resource for the trial. Furthermore, tele-training sessions are often unfeasible for our technologists due to scheduling conflicts with their clinical responsibilities, and it is not reasonable to assume a select few "trained" technologists will be available whenever a trial imaging study is scheduled.

With the increased use of medical imaging in clinical research, the development of QIBA Profiles (imaging guidelines) and the continued growth of quantitative imaging, the relative rewards and complexity of research are only poised to grow. It is our opinion that investigators and institutions who wish to competently participate in this type of research will need to make appropriate investments in their research imaging infrastructure. We further believe that the creation of a Human Imaging Research Office in institutions with large numbers of concurrent clinical trials is not only prudent but also increasingly necessary to ensure the appropriate management of and adherence to research-related imaging guidelines.

An added institutional benefit of such an office is overall liability reduction. While adherence to imaging guidelines ensures the scientific integrity of the trial, FDA and HIPAA guidelines must be met. HIROs help ensure a local site's adherence to protocol guidelines and that all resulting image data is processed and delivered in a HIPAA-compliant fashion. It is our hope that this service-oriented model will spread to become the de facto standard among all institutions conducting clinical research, as it will improve the efficiency, accuracy and overall experience between investigators, imaging scientists and personnel, iCROs and clinical trial sponsors.

References:

1. Goldmacher, GV. In My Opinion: Imaging CRO Perspectives and Priorities in Quantitative Imaging. *QIBA Newsletter* 2014; 6(1).
2. Armato SG III, Gruszauskas NP, MacMahon H, Torno MD, Li F, Engelmann RM, Starkey A, Pudela CL, Marino JS, Chang PJ, Giger ML: Research imaging in an academic medical center. Academic Radiology, 19: 762–771, 2012.

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Nicholas P. Gruszauskas, PhD, is the technical director of the University of Chicago's Human Imaging Research Office. His research interests include DICOM and PACS standards and workflow issues with research imaging.

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ANALYSIS TOOLS & TECHNIQUES

QIBA Ultrasound SWS Phantom Project: Phases I & II

BY MARK L. PALMERI, MD, PHD

Ultrasonic shear wave elasticity imaging (SWEI) methods have been developed over the past decade that utilize acoustic radiation force excitations to generate shear waves in soft tissues and standard ultrasonic displacement estimation methods to

track micron-scale, transient displacements for several milliseconds; shear wave speed (SWS) is estimated from the resultant propagating shear waves using time-of-flight algorithms. [1,2] Noninvasive characterization of liver fibrosis using SWEI has been the most popular clinical target of first-generation commercial ultrasonic elasticity imaging systems, whereas SWS has been correlated with increasing fibrosis stage for a variety of liver disease etiologies. [3]

First-generation commercial imaging systems have related estimated SWS to underlying stiffness (μ, which increases with increased fibrosis) under elastic assumptions as SWS = sqrt(μ/ρ), where ρ is the tissue density. To characterize the variability of different acoustic radiation force excitation focal configurations and SWS reconstruction algorithms implemented across commercial imaging systems, a Phase I tissue-mimicking phantom study was performed using two different stiffness elastic phantoms fabricated by CIRS (Computerized Imaging Reference Systems, Inc.) that were distributed to 12 academic, commercial and clinical research sites. The phantoms were made using CIRS's Zerdine® hydrogel, with the stiffness modified by varying the concentration of water within the polymer matrix. Figure 1 shows the comparison of the reconstructed SWS in each phantom type at the 12 different sites along with average SWS speeds measured in different fibrosis stages from clinical studies. Results of the Phase I study have catalyzed industry efforts, in collaboration with academic research groups, to reduce SWS estimate variance and remove measurement bias, including biases with imaging focal depth.

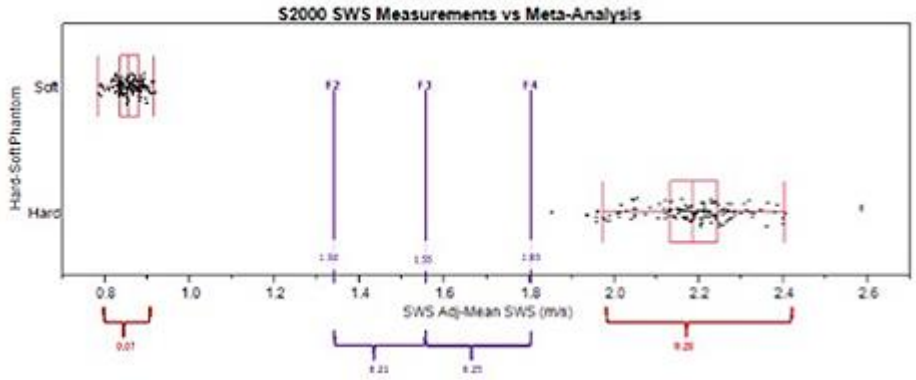

Figure 1. *A comparison of the SWS estimates in the two stiffness CIRS phantom samples in the Phase I study compared with mean SWS measured in different fibrosis stages in clinical studies utilizing the Siemens SCUSON S2000™. [3] The S2000 is one of several research and commercial imaging platforms used in this Phase I study. (Figure provided courtesy of A. Milkowski. [4])*

Soft tissues, including the liver, are known to have appreciable viscosity, which means that the apparent tissue stiffness (μ) and associated SWS are dependent on the spectral content of the propagating shear wave. Shear wave spectral content is modulated by the acoustic radiation force focal configuration, introducing another source of variability between commercial imaging systems. Phase II of this phantom study is underway, with CIRS and researchers at the University of Wisconsin, Madison, fabricating tissue-mimicking phantom materials that resemble viscous behavior that researchers at Duke University [5] and the Mayo Clinic [6] have measured in human liver studies. Figure 2 shows data comparing the reconstructed shear wave phase velocities as a function of frequency in human data (black circles) with test phantom material samples currently in development from CIRS. CIRS has mixed emulsified oil particles into the standard Zerdine® formulation to increase the phantom material viscosity.

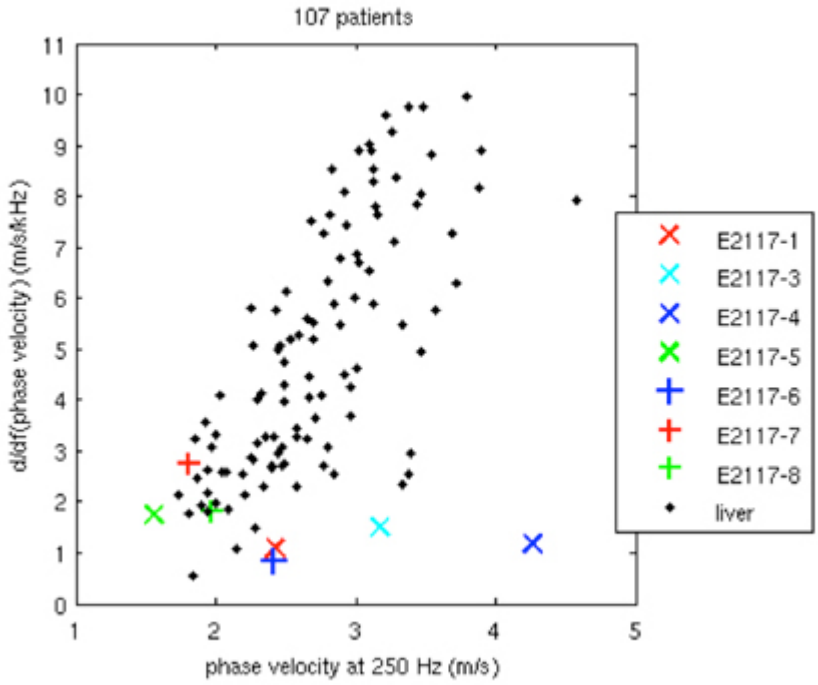

Figure 2. *Scatter plot comparing mechanical properties of liver (black dots) in 107 patients [5] and the CIRS Phase II phantom test samples. Points are plotted as a function of phase velocity at 250 Hz, and the change in phase velocity as a function frequency (dcT⁄df) using a linear dispersion model.*

In our future work, these Phase II studies will provide data about the variability between ultrasonic SWS imaging systems in the presence of viscosity, and data will be generated to determine the best algorithms and material models to characterize viscoelastic shear wave propagation for clinical application in soft tissues.

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[1] Sarvazyan et al. “Shear wave elasticity imaging: a new ultrasonic technology of medical diagnostics,” Ultrasound in Medicine and Biology, 24(9):19-35, 1998.
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QIBA ACTIVITIES

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3. *Articles that are generated by Quantitative Imaging Biomarkers Alliance (QIBA) research teams*
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