THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Clinical Trial Imaging Standardization and Implementation:

The Perspective of a Clinical Site

Nicholas P. Gruszauskas, Ph.D., Technical Director, HIRO

Samuel G. Armato III, Ph.D., Associate Professor, Radiology

Last Revision: 18-Oct-2019
PINTAD Meeting

Introduction

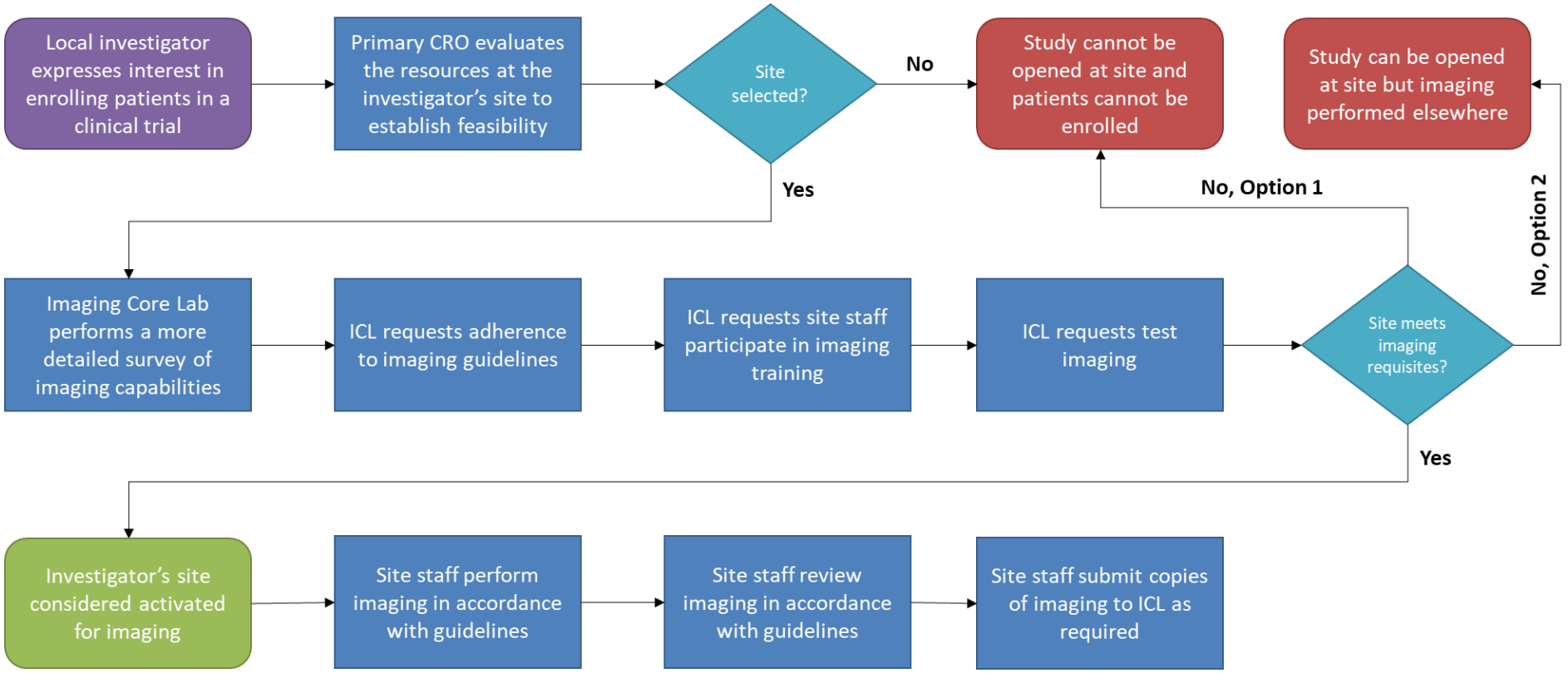
- Participation in clinical research can be both highly rewarding and logistically demanding.
- As highlighted by recent FDA guidance†, imaging has become a larger and more integral part of this research.
- The unique technical and administrative aspects of clinical trial imaging may differ substantially from those of standard-of-care imaging and thus challenge the established clinical infrastructure at investigational sites.
- Failure to comply with trial requirements can lead to unusable data, repeat imaging, or the removal of patients from the trial.
- It is therefore imperative that all stakeholders address these challenges to engage in clinical research successfully.

† US Food and Drug Administration. Clinical trial imaging endpoint process standards: guidance for industry. Draft Guidance, Revision 1. Federal Register Number 2015-05016. Docket Number FDA-2001-D-0586. Silver Spring, MD: FDA, 2015. Electronic.

Identifying the Challenges

- Contract Research Organizations (CROs) and Imaging Core Laboratories (ICLs) work to standardize imaging parameters and logistics.
- Standardization is key to minimizing variability and ensuring endpoints are accurately measured.
- This is often accomplished via questionnaires, guidelines documents, training sessions and manuals issued to investigational sites.
- Unfortunately, little attention is given to how sites are expected to implement imaging protocols. While CROs acknowledge both the importance and difficulty in addressing issues regarding site logistics, they have taken few steps to resolve them.
- **We have identified several challenges that impact the quality and viability of imaging within the context of clinical research.**

Identifying the Challenges



Identifying the Challenges

1. Site review of imaging requirements and logistics
2. Site management of imaging questionnaires and materials
3. Site imaging personnel training
4. Utilizing specific imaging equipment
5. Submitting de-identified images
6. Resolving imaging queries

Identifying the Challenges

1. **Site review of imaging requirements and logistics**
2. Site management of imaging questionnaires and materials
3. Site imaging personnel training
4. Utilizing specific imaging equipment
5. Submitting de-identified images
6. Resolving imaging queries

Challenge: Site Review of Imaging Logistics

- The early and prompt review of the imaging requirements of a new clinical trial by imaging personnel at an investigational site is integral to successful execution.
- Many sites do not have dedicated infrastructure or resources for an imaging-centric review. Engaging imaging personnel is left to the discretion of the local investigational site team.
- Without an imaging review by knowledgeable personnel, inconsistencies between local standard clinical and trial-specific imaging protocols might not be discovered until after patient imaging has been performed and evaluated as “non-compliant.”

Challenge: Site Review of Imaging Logistics

- **Example 1**: Brain MRI for evaluation of metastasis
  - Trial protocols will often simply note that "brain MRI scans" should be used to monitor for metastases.
  - Local investigators may reasonably assume their radiology department is capable of these scans ("I order brain MRI scans all the time").
  - Increasingly, ICLs issue imaging manuals that require the use of specific brain MRI parameters†.
  - The local radiology department's standard brain MRI protocol may not meet these requirements.
  - The investigator may not be aware of the differences and may not consult the radiology department for review.
- **Scans will not meet trial requirements. Deviations are likely.**

† Ellingson BM, Bendszus M, Boxerman J. Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials. Neuro Oncol 2015; 17(9): 1188-98. https://doi.org/10.1093/neuonc/nov095

Challenge: Site Review of Imaging Logistics

- Even with a full imaging review, it may still be difficult for an investigational site to assess the imaging requirements of a new trial.
- While it is common for a trial protocol to denote the use of a central laboratory, or to refer to forthcoming ancillary materials such as a laboratory manual, similar references to a central *imaging* reviewer or a forthcoming *imaging* manual are rare.
- ICLs often will not forward imaging materials to sites for review until *after* local IRB and regulatory approval, making it nearly impossible for imaging personnel to raise questions or concerns prior to patient enrollment.
- Local investigators may incorrectly denote the imaging capabilities of their site to the CRO.

Challenge: Site Review of Imaging Logistics

- **Example 2**: MRI requirements for gastroenterology clinical trial
  - One of the GI physicians at our facility expressed interest in participating in a clinical trial with an MRI component.
  - The trial protocol indicated that MRI scans with "PDFF and elastography" sequences would be required for all patients.
  - The GI physician "orders these scans for patients routinely" with no issues from the radiology department. He reached out to the sponsor and excitedly agreed to be a site for the trial.
  - The ICL eventually forwarded an imaging manual which specified *vendor-specific* pulse sequences. Radiology did not have a scanner that included all the necessary sequences.
    - The ICL suggested (amongst other ideas) that we might contact our sales rep to purchase the necessary sequences.
- **GI physician must now back out of the trial.**

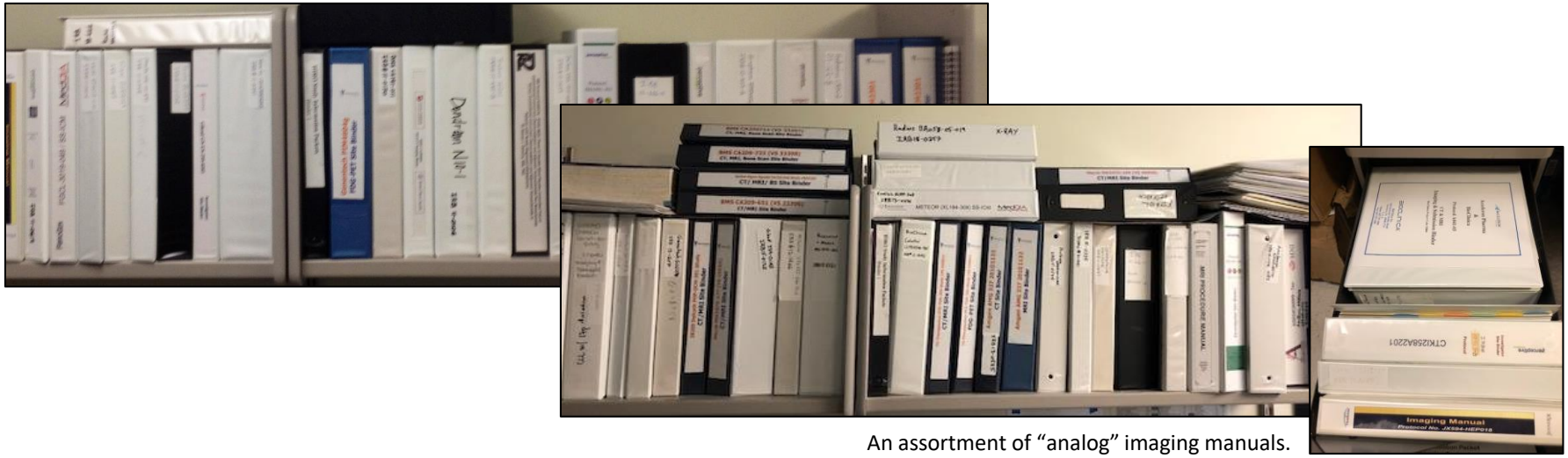
Challenge: Site Review of Imaging Logistics

- Some CROs attempt to resolve logistical issues by requiring the identification of a site radiologist.
  - The expectation is the radiologist will formally acknowledge the trial's imaging requirements and assume responsibility for all imaging aspects of the trial at the local level.
- This is generally both inefficient and impractical.
- Unless the trial's imaging is sufficiently complex as to warrant co-investigator status, requiring a radiologist to fulfill this role is expensive and unnecessary.
- Managing the administrative aspects of a clinical trial is beyond the scope of a radiologist's institutional responsibility.

Identifying the Challenges

1. Site review of imaging requirements and logistics
2. **Site management of imaging questionnaires and materials**
3. Site imaging personnel training
4. Utilizing specific imaging equipment
5. Submitting de-identified images
6. Resolving imaging queries

Challenge: Site Management of Materials



An assortment of “analog” imaging manuals.

- ICLs will provide investigators with materials such as imaging manuals and data forms for imaging personnel to review, complete, and update.
- Maintaining, organizing, and distributing these materials is not trivial.
- The materials must be accessible to imaging personnel and the investigator’s team, and they must be updated as new materials are issued.

Challenge: Site Management of Materials

- The site qualification process often requires the completion of questionnaires that identify an institution's imaging capabilities.
- Increasingly these questionnaires require detailed information regarding personnel and equipment, including maintenance and accreditation records.
- Compiling this information can be time-consuming, and consultation with imaging personnel is essential.
  - Local coordinators may rush to complete these questionnaires ahead of other initiation activities, leading to guesswork based on responses to previous questionnaires which may now be out of date.
  - If the coordinators *do* engage imaging technologists, the more complex questionnaires are burdensome and generally beyond the scope of their clinical duties.

Identifying the Challenges

1. Site review of imaging requirements and logistics
2. Site management of imaging questionnaires and materials
3. **Site imaging personnel training**
4. Utilizing specific imaging equipment
5. Submitting de-identified images
6. Resolving imaging queries

Challenge: Site Imaging Personnel Training

- Many clinical trials require that imaging technologists participate in a formal training session with the expectation that only these specific techs perform exams on trial patients and maintain associated records.
- Assigning responsibility for the integrity of a trial's imaging to specific clinical technologists is unnecessarily burdensome and generally beyond the scope of their institutional responsibilities.
- Requiring performance of all trial-related imaging by specifically approved technologists is often infeasible in all but the smallest of imaging centers; attempting to train all techs within an institution is similarly impractical.
- Clinical shift schedules, vacation schedules, and technologist turnover rates can make it extremely difficult to accommodate such a requirement while still allowing trial patients flexibility in scheduling appointments.

Challenge: Site Imaging Personnel Training

- While some trials allow “self-study” training, other trials require in-person training, including tele-trainings, automated presentations, or site visits.
- These training sessions can be lengthy and of limited relevance to the technologist, with content focusing on exam scheduling and operation of the data submission system; tasks generally handled by non-imaging personnel.
- These training sessions are often performed by CRO or ICL staff who are not themselves imaging experts and are thus unable to answer any technical questions posed by the site technologists.

Challenge: Site Imaging Personnel Training

- **Example 3**: Lengthy midday training sessions
  - One of the radiologists at our facility expressed interest in participating in a clinical trial with a breast MRI component.
  - The MRI parameters outlined in the imaging manual were relatively generic and in line with our standard clinical breast MRI protocol. Radiology identified a primary tech and backup tech for the trial.
  - The CRO required all technologists who may perform trial-related scans attend a *2 hour* in-person training session during the middle of a clinical shift. This requirement was incompatible with our clinical shift schedule.
  - After negotiations between the MRI manager, lead tech, study team, and CRO, it was ultimately agreed that one tech could attend for 30-45 minutes. This tech could train an additional tech at a later time.
- **Time and effort spent negotiating a training schedule when CRO should have recognized the impracticality of their request.**

Challenge: Site Imaging Personnel Training

THE UNIVERSITY OF CHICAGO | Human Imaging Research Office

- **Example 4**: Training led by non-experts
  - During a tele-training session for a new trial with SPECT/CT and PET/CT scans involving experimental radiopharmaceuticals, our nuclear medicine manager and physicist asked questions related to technical parameters and patient positioning.
  - The trainer was merely reading the imaging manual to those in attendance, and indicated she would need to follow up with the "imaging team" and get back to us at a later date.
  - Additionally, our team expressed concern over the high dose of tracer required and how this might impact other patients and staff.
  - The trainer simply stated "that will be difficult for you" and continued the training.
- **The trainer was not able to answer technical questions during the training.**

Challenge: Site Imaging Personnel Training

- Some ICLs have adopted a “train the trainer” approach. Even this paradigm is not without issues, however.
- The designated technologist must still assume responsibility as the primary imaging contact for the trial.
- ICLs may require the designated “trainer” at the site to be a clinical technologist and may refuse to allow a non-technologist to assume the role of trainer regardless of their position or qualifications.
- Some ICLs also expect any technologist who will perform trial-related imaging exams to have completed IRB training, human subjects research training, and/or ICH Good Clinical Practices training, which is an unrealistic expectation.

Identifying the Challenges

1. Site review of imaging requirements and logistics
2. Site management of imaging questionnaires and materials
3. Site imaging personnel training
4. **Utilizing specific imaging equipment**
5. Submitting de-identified images
6. Resolving imaging queries

Challenge: Site Equipment Utilization

- Some trials require the certification of specific imaging equipment at the investigational site through a qualification process.
- Only appropriately qualified imaging systems can be used to perform trial-related imaging and all upgrades, repairs, or changes to qualified systems must be reported to the ICL, with some changes requiring re-qualification.
- The qualification process can vary in complexity from simple documentation to test scans and on-site evaluations by experts from the ICL. All of these activities incur an expense of effort and resources.
- Communication between sponsors/CROs and ICLs often seems poor. **For example**, sponsors often don't appear aware of the activities requested by ICLs (like test scans), leading to protracted budget discussions and issues meeting qualification timeline expectations.

Challenge: Site Equipment Utilization

- Performing all of an enrolled patient's follow-up imaging with the same imaging system used to perform baseline imaging is extremely desirable.
- While these restrictions are reasonable in their goals to reduce variability, they are nonetheless difficult to implement, particularly in large centers.
- As with the technologist requirements noted previously, these equipment restrictions artificially limit the availability of patient appointments and increase the complexity of scheduling and patient management.
- Local study teams are often faced with deciding what is more important when scheduling patient imaging appointments: using the desired imaging equipment *or* following the appropriate imaging schedule.

Identifying the Challenges

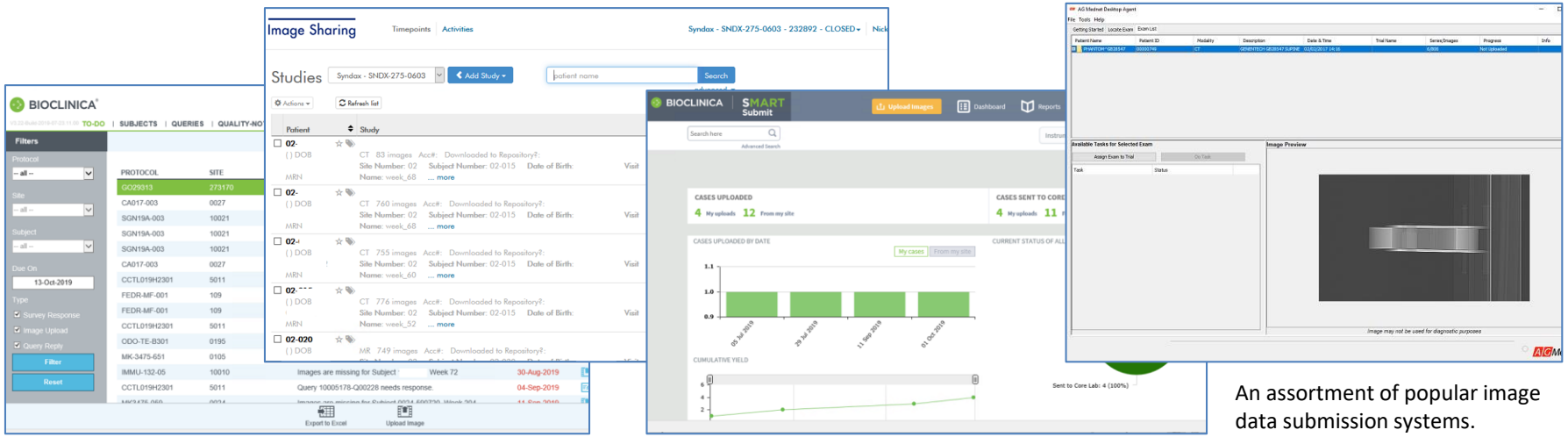
1. Site review of imaging requirements and logistics
2. Site management of imaging questionnaires and materials
3. Site imaging personnel training
4. Utilizing specific imaging equipment
5. **Submitting de-identified images**
6. Resolving imaging queries

Challenge: Submitting Image Data

- Local investigators must often submit copies of relevant images to the ICL.
- Retrieving and manipulating DICOM data is generally beyond the ability of most research coordinators, and some imaging departments do not have the resources to process large volumes of exams for research purposes.
- Some ICLs expect a technologist (or a radiologist) to retrieve and submit image data, which is expensive, impractical, and beyond the scope of their responsibilities.
- A data transmittal form generally must accompany images submitted to the ICL. Completion of these forms may require a technologist, and some forms require completion during the actual imaging exam.
- Ensuring the completed form is available at the time of image data submission can be challenging.

Challenge: Submitting Image Data

- Web-based systems for direct image submission to ICLs have become more advanced and user-friendly, but they can still present a burden to the local team.
- Some require software installation or present compatibility issues, necessitating local IT Department involvement.
- Nearly all systems require some form of training or have potentially lengthy manuals
  - **For example**, the manual for one popular image submission system is 40 pages in length.



An assortment of popular image data submission systems.

Challenge: Submitting Image Data

- These systems are generally separate from the primary EDC system used to manage all non-imaging aspects of the trial, creating an additional burden on the local team through separate training requirements, multiple electronic accounts, and disparate workflows.
- When issues arise, troubleshooting these systems can be time intensive and burdensome. The expectations of technical support personnel can be unrealistic.
  - **For example**, a research nurse at our institution was once asked by tech support to export the Java logs of her workstation for analysis.
- The unique complexities inherent in retrieving and submitting image data lead local teams to wait and submit multiple exams together in batches rather than submitting each exam directly after acquisition, thus reducing the timeliness of submissions and data analysis.

Identifying the Challenges

1. Site review of imaging requirements and logistics
2. Site management of imaging questionnaires and materials
3. Site imaging personnel training
4. Utilizing specific imaging equipment
5. Submitting de-identified images
6. **Resolving imaging queries**

Challenge: Resolving Imaging Queries

- When issues or discrepancies arise during an ICL's review of an imaging exam, they will generate a query.
- While queries regarding issues such as demographics or time points are best resolved by the local coordinator, other queries are more technical in nature.
- ICLs expect queries regarding technical issues to be resolved by an experienced imaging technologist, a process that can be time consuming and burdensome for both the technologist and coordinator.
- In addition, poor communication between ICLs and sponsors/CROs often generates queries and makes queries difficult to resolve.
    - **For example**, we often receive recurring queries regarding off-study patients. This information is communicated to the CRO via the primary EDC system but often *not* forwarded to the ICL. Additional time and duplicative effort is spent informing the ICL of details that have already been communicated to the CRO or sponsor.

Addressing the Challenges

- These challenges are both critical and nontrivial.
- Failure to address them can lead to delayed site qualification and patient enrollment, improperly executed imaging exams, improperly de-identified data, and delayed data submission.
- Consequences may include queries and protocol deviations, patient removal, FDA action, or citable HIPAA violations.
- This may impact the integrity of the trial, jeopardize the investigational site's participation in future trials, and adversely impact patient care and satisfaction.

Addressing the Challenges

THE UNIVERSITY OF CHICAGO | Human Imaging Research Office

- The University of Chicago created its Human Imaging Research Office (HIRO) to address these challenges directly.
- The HIRO operates similar to an investigational drug service or clinical research support office, and provides services to local investigators at our institution.
- These services include review of a trial's imaging requirements, management of site qualification activities, maintenance of a central repository for imaging materials, and submission of de-identified images to ICLs.

UChicago HIRO during Clinical Trials Day 2019!

- The HIRO charges fees for its services and delivers them via dedicated *nonclinical* staff: research imaging coordinators and image distribution specialists.

Addressing the Challenges

- HIRO staff participate in trial imaging training sessions, assist with query resolution, act as the "primary imaging contact" for CROs and ICLs, and guarantee the integrity of trial imaging.
- Importantly, the HIRO does *not* assist in the design of clinical trial protocols, and it does not provide disease response assessment measurements.
- The HIRO's efforts have increased the local efficiency and accuracy of research-related imaging at our institution.
- **Based on our experience, we believe the adoption of the following recommendations is vital to support the continued growth and management of clinical trial imaging at investigational sites.**

Addressing the Challenges:
Recommendations

1. Investigational sites should create a consortium with the mission of **(1)** developing standards for research imaging infrastructure, and **(2)** advocating for the implementation of these standards at all levels.

2. CROs, imaging core labs, industry consortia, and professional organizations should recognize imaging-related responsibilities in clinical trials as separate and distinct. These responsibilities should not fall to imaging technologists, radiologists, or research coordinators by default but should define separate roles for dedicated personnel where appropriate. These stakeholders should advocate for the development of dedicated research imaging infrastructure at investigational sites.

Addressing the Challenges:
Recommendations

3. CROs and imaging core labs must understand that the primary responsibility of imaging technologists is their clinical duties, not the execution of clinical trials. They must allow non-radiologist and non-technologist imaging personnel to assume responsibility for the integrity of imaging at investigational sites.

   CROs and imaging core labs must recognize the viability and importance of these individuals, they must acknowledge these individuals as domain experts who can fulfill training requirements, and they should modify their infrastructure to accommodate these individuals appropriately.

Addressing the Challenges:
Recommendations

4. Investigational sites must recognize the time, effort, and expertise that is required to successfully execute clinical trial imaging. Sites must invest in appropriate infrastructure and charge trial sponsors for the utilization of this infrastructure in the same manner they charge for other research-related services.

   Similarly, trial sponsors must recognize the increasing complexities associated with clinical trial imaging and must be willing to accept the accompanying costs for the benefit of themselves, CROs, imaging core labs, investigational sites, and the patients who willingly consent to becoming research subjects.

Addressing the Challenges:
Recommendations

5. CROs and imaging core labs should forward imaging manuals and related materials to investigational sites as early as possible to avoid delays in site qualification or patient enrollment. CROs should not expect sites to achieve regulatory and budgetary approval without these materials, nor should CROs insist that sites assert their adherence to imaging guidelines they have not had an opportunity to review.

- **For example**, the ASCO recently issued a statement critical of this practice with regard to research biopsy procedures ("Although [sites]…are authorized to review risks and benefits, they are often unable to review the scientific justification when these procedures are included in laboratory manuals rather than study protocols…sponsors should include laboratory manuals as part of the trial protocol…"†).

† Levit LA, Peppercorn JM, Tam AL, et al. Ethical Framework for Including Research Biopsies in Oncology Clinical Trials: American Society of Clinical Oncology Research Statement. J Clin Oncol 2019; 37(26): 2368-2377. https://doi.org/10.1200/JCO.19.01479

Practical Impact

- **Site Qualification**: Opening a new trial at an investigational site can be delayed while staff work to complete imaging-related qualification activities. A dedicated imaging team will manage and execute these activities more efficiently, leading to faster site qualification and patient enrollment.
- **Repeat imaging**: The cost of repeat imaging necessitated by poor quality or non-compliance with trial guidelines is generally borne by the investigational site. A dedicated team will reduce the number of repeat exams due to non-compliance.
- **Queries**: Responding to imaging-related queries can be time-consuming for local researchers. A dedicated team can effectively investigate queries quickly and reduce the overall number through enhanced compliance.
- **Deadlines**: Submission deadlines are generally imposed for trial-related data and institutions can easily become delinquent with image submissions. A dedicated team will provide the logistical support for the timely submission of imaging exams.
- **Liability**: Investigators and institutions can be held legally and ethically liable for the improper conduct of imaging within the context of research. A dedicated team responsible for research imaging compliance can reduce the institutional liability associated with improperly performed imaging exams and improperly de-identified image data.

Case Study 1 – Clinical Trial Queries

THE UNIVERSITY OF CHICAGO | Human Imaging Research Office

- The imaging query rate of a typical industry-sponsored, multi-site trial investigating the efficacy of an experimental drug therapy in patients with solid tumors was examined. UCM began participating in this trial in Jul 2013.
- Trial patients were required to undergo CT scans at routine intervals. Scan guidelines differed from UCM's standard imaging protocols. Dozens of UCM patients were enrolled in the trial.
- The HIRO developed a communication procedure in which the trial's research coordinators were required to inform the HIRO whenever a trial-related CT scan was scheduled. This procedure was implemented at the start of the trial.
- Shortly after enrollment began, a significant number of "non-compliant imaging" queries were issued. The HIRO performed an analysis of the queries to help identify the underlying causes.
- The HIRO's investigation identified "lack of communication" as the issue primarily responsible for the trial's imaging non-compliance. New communication procedures were developed. The HIRO actively monitored the number of new queries received.

* Gruszauskas NP, Marino JS, Armato SG III. Improving Medical Imaging in Clinical Trials: A Case Study. 11th Annual Quality & Safety Symposium, University of Chicago Medicine - Office of Clinical Effectiveness, Chicago, Illinois, 12 May 2016.

Case Study 1 – Clinical Trial Queries

THE UNIVERSITY OF CHICAGO | Human Imaging Research Office

- The HIRO tallied all CT scans that were performed for the trial between **Oct 2013 and Feb 2014** and categorized them based on whether or not the communication procedure was followed properly. When the HIRO's communication procedure was followed, the query rate **decreased from 30% to 13%**.
- The HIRO reached out to the trial team to stress the importance of communicating upcoming scans and provided additional avenues of communication.
- From **Mar 2014 to Apr 2015**, the rate of "non-compliant imaging" queries **dropped to 9%**.
- Between **May 2015 and Feb 2016**, the rate of "non-compliant imaging" queries **increased to 28%**.
- The HIRO investigated and discovered that a new coordinator had been assigned to the trial team in **May 2015**, and the coordinator had not been informed of the communication procedures.

* Gruszauskas NP, Marino JS, Armato SG III. Improving Medical Imaging in Clinical Trials: A Case Study. 11th Annual Quality & Safety Symposium, University of Chicago Medicine - Office of Clinical Effectiveness, Chicago, Illinois, 12 May 2016.

Case Study 2 – Site Coordinators

THE UNIVERSITY OF CHICAGO | Human Imaging Research Office

- The HIRO provides a variety of research imaging services to UCM investigators to support research projects and clinical trials.
- In 2014 the HIRO surveyed research nurses and clinical research coordinators to assess its effectiveness. The survey was forwarded to 61 staff members.
- The survey asked which HIRO services the recipient used, which services the recipient would be responsible for completing themselves in the absence of the HIRO, and for an estimate of the time saved by delegating tasks to the HIRO.
- 34 responses were received (56% return rate). 97% routinely used some or all of the HIRO's services.

* Gruszauskas NP, Torno MD, Marino JS, Santiago FD, Armato SG III. Improving the Quality and Efficiency of Research Imaging for Clinical Trials. 62nd Annual Meeting of the Association of University Radiologists, Baltimore, Maryland, 2014.

Case Study 2 – Site Coordinators

THE UNIVERSITY OF CHICAGO | Human Imaging Research Office

- **82%** indicated the HIRO saved time and increased imaging accuracy. **50%** indicated they could not comply with their trials' imaging requirements without the HIRO.
- Based on the average amount of time spent by coordinators doing imaging-related activities, the HIRO produced an estimated average time savings of **256 hours per person per year**. Based on staffing levels and the amount of work shifted, it was estimated the HIRO saved our institution 1 FTE per year (likely more now).
- We concluded the HIRO increased the level of satisfaction among clinical investigators at our institution, and research staff who use the HIRO benefit from a more efficient imaging experience.
- Other critical value-added elements which are more difficult to quantify include liability reduction, increased cost recovery, and increased competitiveness.

* Gruszauskas NP, Torno MD, Marino JS, Santiago FD, Armato SG III. Improving the Quality and Efficiency of Research Imaging for Clinical Trials. 62nd Annual Meeting of the Association of University Radiologists, Baltimore, Maryland, 2014.

Conclusions

- Managing the imaging associated with a clinical trial is a growing challenge for investigational sites as imaging becomes an increasingly integral part of trial design.
- With this increasing focus on clinical trial imaging standards, investigational sites can expect to play a more critical role in their implementation.
- The challenges associated with clinical trial imaging require an investment of resources from all stakeholders.
- Institutions that wish to participate must confront these challenges to **(1)** satisfy requirements with the highest level of efficiency and accuracy, **(2)** maintain a superior level of patient care, and **(3)** guarantee the integrity of the research.
- Similarly, sponsors and CROs must acknowledge the burden of clinical trial imaging and support the development of the necessary infrastructure at investigational sites.
- **Implementation of the recommendations described here will improve the execution of clinical trial imaging. Only through focused resources and deliberate attention to the conduct of imaging at investigational sites will all stakeholders truly utilize the full potential of medical imaging in clinical trials.**

Questions?

THE UNIVERSITY OF CHICAGO | Human Imaging Research Office

- **Thanks for your attention!**
  - **Website**: https://hiro.bsd.uchicago.edu
  - **Email**: hirohelp@bsd.uchicago.edu
  - **Twitter**: @HIRO_UofC
  - **For more info**: Gruszauskas NP, Armato SG. Critical Challenges to the Management of Clinical Trial Imaging: Recommendations for the Conduct of Imaging at Investigational Sites. Acad Radiol 2019; *in press*. https://doi.org/10.1016/j.acra.2019.04.003

Photo credit Sara Serritella/UChicago ITM