CenterWatch Weekly

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Sept. 13, 2021

Sites Face Tighter Imaging Needs for Certain Trials as Use of Imaging Keeps Climbing

By James Miessler

As the use of imaging in clinical research continues to grow, certain trials are requiring that sites meet increasingly complex and specific requirements for imaging technology and techniques. Those that can't fulfill them may be passed over.

The use of medical imaging in trials has increased dramatically over the past two decades, fueled by advances in science, technology, software and broadband speeds. A variety of imaging modalities are currently used in clinical trials to gather images of the anatomy for examination; chief among them are X-rays, ultrasounds, computed tomography (CT) scans, MRI scans, positron emission tomography (PET) scans and nuclear medicine scans.

But some sites may need specific, recent equipment to be considered an option for certain trials. For example, in the cardiovascular space, they may be expected to have very new, sophisticated CT scanners that are fast enough to capture the heart beating in between a patient's breath, Dan Braga, Medidata's vice president of product management for medical imaging, told *CenterWatch Weekly*.

"Hospitals realize that to play in the clinical trial space and to receive the referrals, or to perform the imaging for those particular timepoints, that they need to make sure that they have the proper equipment. And it's

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Ask the Experts: Questions about Advertising for Clinical Trials

The FDA's Office of Good Clinical Practice responds to inquiries on a variety of trial-related subjects, providing answers on the agency's official regulations as well as best practices. The following is a selection of questions and answers excerpted from the CenterWatch publication, *GCP Questions, FDA Answers*.

Question: In section A of the information sheet on recruiting study subjects, there are certain types of materials that are called out as being not included in media advertising (communications for healthcare professionals, news stories and publicity for other audiences). Is it intended that those materials that are "not included" are those that are not subject to IRB review, or that they shouldn't be included in any clinical study recruitment campaign?

We have had a news release and a radio interview with a study investigator pitched as an idea for helping with clinical trial recruitment, and we aren't sure if it would be an acceptable practice. We understand that media coverage of clinical trials can happen without our involvement, and those are outside our control, which is likely why they aren't included as something that would be subject to IRB review. But can a sponsor try to get coverage of the trial picked up by the media and help shape what that coverage looks like? We would, of course, obtain an IRB review of the pitch materials and any guidance that

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Upcoming Events

22 SEPT — WEBINAR
Spreadsheet Validation: *Best Practices to Maintain Compliance*

28 SEPT — VIRTUAL CONFERENCE
4th Annual WCG MCC Clinical Trial Risk & Performance Management Collaborative vSummit

12 OCT — VIRTUAL WORKSHOP
Effective Root Cause Analysis and CAPA Investigations for the Life Sciences

18 OCT — VIRTUAL CONFERENCE
MAGI's Clinical Research vConference — Fall 2021

[VIEW ALL EVENTS]

Industry Briefs

Clinical Investigator Warned for ClinicalTrials.gov Noncompliance

A Los Angeles doctor is the first individual investigator to receive an FDA warning letter for failing to report trial results to ClinicalTrials.gov, a violation that could result in thousands of dollars in fines, the letter said.

In an Aug. 31 letter, the agency warned Andrey Petrikovets that he had 30 days to submit to the ClinicalTrials.gov registry results of a phase 4 postoperative pain-relief trial he conducted at the University Hospitals Cleveland Medical Center. The trial concluded in June 2018 and the agency first notified Petrikovets of his noncompliance in a July 20, 2021, letter.

Petrikovets submitted the results to ClinicalTrials.gov one day after receiving the warning letter, sidestepping a potential fine of at least $10,000 for every day he was in noncompliance. According to the registry's website, the information is currently undergoing quality control review before being posted.

The Petrikovets letter is the third such warning the FDA has given for noncompliance with ClinicalTrials.gov requirements. Previously, the agency cited two trial sponsors — Acceleron Pharma and Accuitis — for the same violation (*CenterWatch Weekly*, Aug. 23).

Read the warning letter at https://bit.ly/3C3n8Uz.

CDER Finds Broad Variations Among PROs in Multiple Myeloma Trials

Despite the FDA's efforts to make patient reported outcome (PRO) collection and analysis more consistent in clinical research, a recent agency review has found wide variation in how PROs are approached in multiple myeloma trials.

Looking at 17 pivotal trials that contained submitted PRO data and were conducted to support multiple myeloma indications between 2007 and 2020, researchers with the agency's Center for Drug Evaluation and Research (CDER) and Oncology Center of Excellence saw variation in a number of PRO-related areas.

After reviewing trial protocols, statistical analysis plans and clinical study reports, the researchers found "substantial heterogeneity" in how PROs were collected, measured, defined and analyzed.

For example, the researchers found that these trials varied in the types of PRO questionnaires they used, according to the study, which was published in the *Blood Cancer Journal*.

The trials also varied in the number of PRO questionnaires they employed. Specifically, seven of the trials (41 percent) used two surveys, five trials (29 percent) used three, two trials (12 percent) used four, and three trials (18 percent) used just a single survey.

PRO measure compliance, similarly, saw variation across the trials in how it was described. While a majority of the 17 trials (14) defined compliance as "completing enough items to calculate the score in any domain [or some variant]," two trials defined it as completing half of the questions, while a single trial defined it as full questionnaire completion.

In addition, the researchers observed substantially different methods used across the trials to deal with missing data and to conduct statistical analyses.

"These differences in PRO analyses within the same disease and therapeutic setting may hinder the ability to effectively capture and interpret patient experience in multiple myeloma clinical trials, which are valuable information for patients and clinicians," the researchers advised.

To begin making PRO approaches more consistent, at least in multiple myeloma trials, sponsors should begin referring to the core PRO outcome guidance published by the FDA for oncology trials. The guidance is intended to help industry become more consistent in PRO collection and analysis and was published in June (*CenterWatch Weekly*, June 14).

The researchers also advised sponsors that synchronization of PRO research questions "with the [ICH E9 R1] estimand framework, clear description of statistical methods and justification for thresholds will lead to more meaningful PRO results that can be shared with patients and healthcare providers."

Read the full study here: https://go.nature.com/2X3pX9h.

Black Adults Are Still Underrepresented in Federally Funded Cardiovascular Trials

NIH-funded cardiovascular trials still have a lot of work to do when it comes to increasing their enrollment of Black adults, a group that is disproportionately affected by cardiovascular disease but isn't properly represented in clinical research, a new study has found.

Researchers at Duke, Harvard, Johns Hopkins, New York University and the University of Vermont conducted a systematic review of NIH-funded cardiovascular trials registered on ClinicalTrials.gov between 2000 and 2019, looking at their enrollment of Black adults and the recruitment strategies they employed. They found that Black patients were not proportionately enrolled in these trials despite the fact that they are at a greater risk of heart disease.

Of the 100 trials they assessed, nearly half (46 percent) of them had enrolled populations that were less than 25 percent Black, according to the study, which was published in the *Journal of the American Heart Association*. Additionally, almost a quarter of trials failed to specify what percentage of their trial population identified as Black.

And after analyzing the 62 trials with protocols that had been published, the researchers found that they seriously lacked diversity targets. Just 13 trials (21 percent) clearly mentioned recruitment goals for

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Industry Briefs (continued from page 2)

historically underrepresented populations and only a single trial reported that it had met its goal for recruiting Black participants.

On recruitment strategies, 56 trials (90 percent) said they had active recruitment strategies in place, including electronic medical record-based recruitment (47 percent), community-based recruitment (13 percent) and provider-based recruitment (58 percent). Just three of the 62 trial protocols explicitly mentioned bringing in community members to help design the trial, while only two trials had community members outside of academic medical institutions as co-authors.

"While there is a considerable need for research on effective strategies to improve enrollment of Black adults, the first step is for Black inclusion to be a priority at the trial design phase through defined recruitment targets and intentional recruitment strategies," the researchers advised. "Greater transparency, tracking of recruitment yields by demographic group, involvement of local stakeholders in trial design, and support of recruitment research may also represent long-term strategies to address this tremendous disparity in cardiovascular disease research."

Read the full study here: https://bit.ly/2YC8Eg1.

MHRA Sets Data Security Requirements for Remote Monitoring

Concerns about the security of remotely accessed data has led the UK's Medicines and Healthcare products Regulatory Agency (MHRA) to list five features electronic health records (EHR) systems should have if sponsors want to remotely monitor a trial.

Sites providing remote access to their EHR systems should have the same amount of control over their systems as they would in an onsite monitoring visit, the guidance says, use a read-only login to block monitors from making any changes to the data, require two-factor authentication to access the read-only account, restrict printing, copying and downloading, and include an automatic timeout setting. MHRA further says that sponsors should only conduct remote monitoring with a site's agreement.

In a second guidance update, MHRA has expanded its recommendations for conducting clinical trials during the pandemic to include short-term solutions for remote monitoring of systems that do not have all of the desired security functions, such as confirming monitors' identity and access permissions via video contact, creating password locks with short timeouts on monitors' devices and revoking monitors' access as soon as they complete their work.

Read the EHR guidance at https://bit.ly/3njL4PF.

Read the guidance on managing clinical trials at https://bit.ly/3nlwNSl.

Tighter Imaging Needs

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not just the proper modality," Braga said. "Do you have a CT scanner, yes or no, is no longer good enough. It's 'do you have a CT scanner that acquires 64 slices and all these different characteristics?' There's very specific imaging protocols and imaging charters that are being developed by the sponsors and the CROs that go out to the sites to qualify them to make sure they have the right equipment."

Some trials may also require specialized imaging techniques and measures from sites; for example, imaging equipment used in a pediatric trial may need to be calibrated differently with a mind to radiation exposure, and special training may be needed because staff are working with and imaging children.

"Let's say an imaging center can perform X-rays and MRI of the brain, but that clinical trial needs some specialized imaging with some specialized imaging expertise," Todd Joron, president and chief operating officer of WCG Intrinsic Imaging, said. "If they don't have that expertise, or that type of equipment, then they may not be a great candidate anymore to participate in that trial if that trial needs a certain type of imaging or scanner capabilities."

"Imaging equipment and expertise drives the industry. You can imagine that hospitals who want to participate in trials, if they come across ones that require advanced imaging expertise, it's going to be difficult for them to achieve their goals if they cannot participate," he said.

There's also specialized imaging in trials being done using very obscure modalities, such as optical coherence tomography, though these are reserved for specific therapeutic areas. But in general, companies still want to use modalities that hospitals are trained in, familiar with and already in possession of, Braga said. According to Braga, Medidata's medical imaging database is comprised primarily (approximately 80 percent) of CT images because the CT scan is a fast, inexpensive and common modality to use.

"In the industry, every year, every few years, there's advancements made both on the hardware side and on the software side for the imaging of the body. That will continue, and it gets more complex as technology always does."

—Todd Joron, president and chief operating officer of WCG Intrinsic Imaging

The imaging core lab market, valued at $1.1 billion today, is expected to rise to $1.8 billion in about five years, according to Joron. While its main catalyst is the increase of imaging as a therapeutic endpoint in trials, it's also fueled by increased R&D spending by pharma and biotech companies and increased amounts of outsourcing to imaging core labs like Intrinsic Imaging.

"In the industry, every year, every few years, there's advancements made both on the hardware side and on the software side for the imaging of the body. That will continue, and it gets more complex as technology always does," he said. "And so that complexity requires specialists. So from our perspective, the demand becomes higher, and on the sites, the impact is they're going to naturally see requests for them to participate in more trials but there will also be a need for more sophisticated imaging and more advanced type imaging as the industry evolves."

The use of imaging in trials has also expanded thanks to how much easier it's become to exchange images. Instead of shipping CDs with images burned on them (which posed myriad potential issues), now images are being shared electronically.

"If you rewind 15 years ago in clinical trials and medical imaging, people were scared for any clinical trial that used medical imaging, because it involved burning images to a CD, shipping them to an imaging core lab. Everything was done manually," Braga said. "The introduction of an electronic exchange of medical images in clinical trials has really allowed things to just operate at a much higher level."

A number of notable achievements in medical imaging have been strongly fueled by the incorporation of AI and machine learning technology into imaging systems and data platforms, according to a Medidata white paper.

"For the first 125 years of medical imaging, technological advances focused primarily on new modes of imaging as we progressed from the discovery of the X-ray in 1895 to ultrasounds, MRIs, PET and CT scans in the late 20th century. Now, arguably, the most notable advances are being made in how images from those technologies are securely shared, managed, stored and assessed," Medidata said.

For example, there's great potential in analyzing images through radiomics, which uses software to pull qualitative and quantitative data from images, finds associations between them and employs algorithms to identify clinical information that can't be seen by humans. This could be used, for instance, to automatically gather tumor feature information and use that data to make outcome assumptions and correlations. While this radiomic data can already be obtained from images, the challenge will be figuring out how to best incorporate it into clinical trials.

Medidata also predicted that medical image viewers will gradually shift from software tools that need to be installed on individual workstations to cloud-based systems that can be used at any time, on any device, by any reader.

In addition, the future will see computer programs that automatically assess medical images from trials against quality control parameters, rather than requiring a technician or imaging specialist to perform the check themselves. And algorithms can be created

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Tighter Imaging Needs

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that identify potential imaging criteria deviations sometimes made by radiologists when subjectively interpreting images. These algorithms can help to facilitate early action so that anomalies don't evolve into systemic issues, Medidata said.

An August 2018 paper written by researchers at the Dana-Farber Cancer Institute names a number of practical applications for AI tools in the field of oncology. For instance, AI software is being used to characterize liver lesions as benign or malevolent and prioritize those that require follow-up, the researchers said.

Similarly, AI tools can serve an essential purpose in finding colonic polyps and monitoring them early on, as ones that go undetected or misclassified can pose a potential risk of colorectal cancer. AI software is also being used to automate assessments of radiation treatment, improving the speed and accuracy of evaluating how well patients have responded to radiation therapy.

AI solutions are also being used to support screening mammography, which is difficult to interpret manually, by identifying and characterizing microcalcifications in the breast, the researchers said. And importantly, AI is being used to automatically identify and characterize lung cancer nodules to increase the chance of early detection, which is critical in treating lung cancer.

There are two types of AI methods that are widely used today, according to the researchers: machine learning algorithms, which use predefined, engineered features with specific parameters based on expert knowledge, and deep learning algorithms, which do not require explicitly defined features and have been empowered only in recent years thanks to the availability of sufficient data and computing power.

AI in medical imaging has been in development for decades, but in the past five or six years, it has it reached a gelling point where computer technology, software and internet speeds are fast enough to make it practical, Joron said. Companies are currently developing AI solutions across every organ of the body, and Joron predicted that this surge will continue for many years to come.

Braga, too, believes that industry will continue to implement AI solutions in their clinical trials for increasingly different things.

"I think a lot of people are just kind of scratching the surface now with using AI for doing edit checks or quality checks or different things like that, whereas, in the future, in the oncology world and a lot of therapeutic areas, [it could be used for double-blinded reviews]," he said. "We look at AI as not any time soon replacing radiologists but aiding them in performing their jobs better."

Ask the Experts

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is created for the media interviews, but there is still some element of it that we wouldn't be able to completely control.

Answer: IRB review may not be required for news stories. However, every particular situation is different. You as the sponsor will need to closely work with your reviewing IRBs and document any conversations or decisions.

FDA has not developed guidance on the use of social media for clinical trial subject recruitment. FDA's Center for Drug Evaluation and Research held a November 2009 public meeting on the use of social media tools to promote FDA-regulated medical products. As FDA considers policy and guidance in this regard, we will be looking broadly at how its use impacts products we regulate and clinical studies of such products.

Also, please be aware of patient/subject confidentiality under the HIPAA privacy rules. FDA does not administer HIPAA; that law is implemented by the Department of Health and Human Services, Office for Civil Rights (OCR). For more information about the applicability of relevant HIPAA regulations, you would need to contact OCR directly.

With regard to the advertisement of the availability of clinical trials, our present guidance was written before networking of this type (media coverage) was common. Our thoughts are summarized here:

"Generally, FDA believes that any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included in advertisements. It should be noted, however, that FDA does not require inclusion of all of the listed items.

- The name and address of the clinical investigator and/or research facility;
- The condition under study and/or the purpose of the research;
- In summary form, the criteria that will be used to determine eligibility for the study;
- A brief list of participation benefits, if any (e.g., a no-cost health examination);
- The time or other commitment required of the subjects; and
- The location of the research and the person or office to contact for further information."

Question: Should the IRB review and approve material used to advertise or documents provided to the public during community consultation efforts? If the FDA considers direct advertising the start of the informed consent process and therefore needs review and approval, is this also applicable when there is no informed consent? What type of review is required for materials created after approval (infographics, flyers, etc.)? Would the Recruiting Study Subjects — Information Sheet be applicable at this point?

Answer: Research involving the exception from informed consent requirements for emergency research is a unique type of research that requires the IRB find and document a number of additional protections for subjects, such as a determination that participating in the research holds out the prospect of direct benefit to the subject, that available treatments for the condition under study are unproven or unsatisfactory, and that subjects are unable to give their informed consent as a result of their medical condition.

Item #64 in the FDA guidance Exceptions from Informed Consent Requirements for Emergency Research recommends IRBs review the protocol and the plans for community consultation and public disclosure as a package (i.e., collectively) given that the adequacy of the community consultation plan and the public disclosure plan cannot be properly considered without understanding the protocol. As part of the review, IRBs should review and approve materials to be used as part of the community consultation and public disclosure; this would include materials used to advertise the study and documents provided to the public during community consultation efforts.

For additional materials created after approval of the study, FDA recommends they be reviewed by the IRB before they are used in any community consultation or public disclosure activity. The Recruiting Study Subjects — Information Sheet is a useful guidance to consider when reviewing information to be shared during public disclosure and community consultation.

However, it must be remembered that the intent of public disclosure and community consultation is not recruitment but rather should be considered as activities designed to disseminate information and provide an opportunity for discussion with, and soliciting opinions from, the community in which the study will take place and the community from which the study subjects will be drawn.

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Drug & Device Pipeline News

Company	Drug/Device	Medical Condition	Status
Trials Authorized			
GNT Pharma	nelonemdaz	Acute ischemic stroke	IND approved by South Korea's regulatory authority for a phase 3 trial
Gannex Pharma/ Ascletis Pharma	ASC42	Primary biliary cholangitis	Trial authorized by China's regulatory authority
PharmAbcine	olinvacimab plus Keytruda	Metastatic triple-negative breast cancer	Phase 2 trial authorized by the Australian regulatory authority
Trials Initiated			
Cortexyme	COR588	Periodontal disease and other P. gingivalis-related indications	Initiation of phase 1 trial
EdiGene	ET-01 (gene-editing hematopoietic stem cell therapy)	Transfusion-dependent β-thalassemia	Initiation of phase 1 trial
Inversago Pharma	INV-202	Metabolic conditions	Initiation of phase 1 trial
Denali Therapeutics	DNL343	Amyotrophic lateral sclerosis	Initiation of phase 1b trial
Jasper Therapeutics	JSP191	GATA2-related myelodysplastic syndromes	Initiation of phase 1/2 trial

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Drug & Device Pipeline News

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Company	Drug/Device	Medical Condition	Status
NovaVax	NVX-CoV2373 (COVID-19 vaccine) and NanoFlu (flu vaccine)	Combination vaccine for COVID-19 and seasonal influenza	Initiation of phase 1/2 trial
Hutchmed AstraZeneca	Orpathys (savolitinib) in combination with Tagrisso	Locally advanced or metastatic nonsmall-cell lung cancer with activating EGFR mutations and MET overexpression	Initiation of phase 3 trial
Inventiva	lanifibranor	Nonalcoholic steatohepatitis	Initiation of phase 3 trial
Approvals			
Impel NeuroPharma	Trudhesa (dihydroergotamine mesylate) nasal spray	Acute treatment of migraine with or without aura in adults	Approved by the FDA
Intelivation Technologies	Advantage-C PEEK cervical interbody fusion device	For use during spinal surgery	Approved by the FDA
RenovoRX	RenovoCath delivery system	Targeted treatment of solid tumors	Approved by the FDA
Pfizer	Cibinqo (abrocitinib)	Patients 12 years and older with moderate-to-severe atopic dermatitis	Approved in the UK
Merck	Keytruda	First-line treatment for locally advanced unresectable or metastatic carcinoma of the esophagus or gastroesophageal junction	Approved in China
JW Therapeutics	relmacabtagene autoleucel injection	Relapsed or refractory large B-cell lymphoma	Approved in China
Sinovac	CoronaVac	Coronavirus vaccine	Approved for emergency use in Chile
Sumitomo Dainippon Pharma Nabriva Therapeutics	Xenleta (lefamulin)	Community-acquired pneumonia	Approved in Taiwan

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