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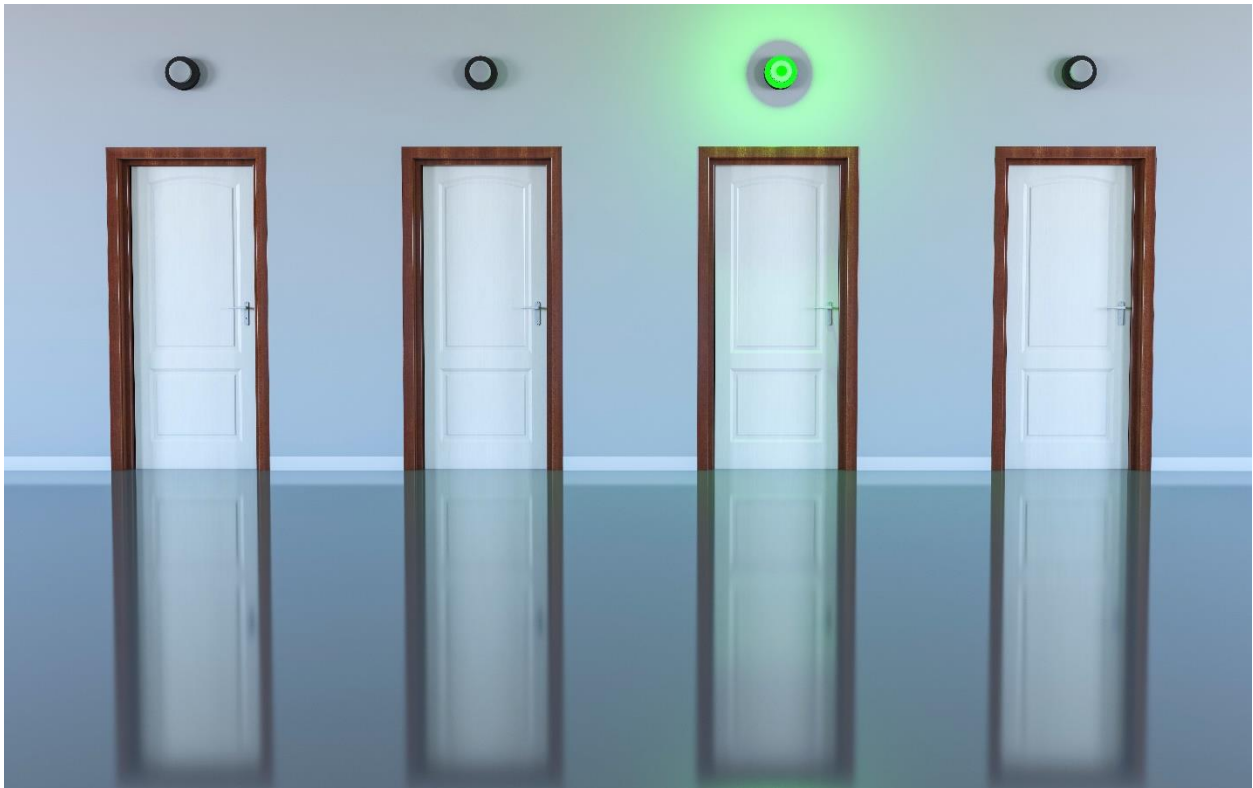
The Authority in Ethical, Responsible Clinical Research

June 2019 (Volume 33, Issue 6)

Insights and Imperatives

Clinical Researcher™

Clinical Researcher—June 2019 (Volume 33, Issue 6)

Table of Contents

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Clinical Researcher—June 2019 (Volume 33, Issue 6)

EXECUTIVE DIRECTOR'S MESSAGE

We're on An Adventure

Jim Kremidas

As the summer movie season hits theaters, I'm reminded of *Toy Story* hero Buzz Lightyear announcing some of his adventures by leaping high and saying, "To infinity! And beyond!"

Well, your Association is covering a lot of ground these days, too. From recent partnerships forged in Latin America and Singapore (and others on the horizon), to an exciting ACRP Southeast Regional Conference coming closer to home in the Research Triangle Park (RTP) area of North Carolina, we're working together the spread the word that it's time to truly professionalize the clinical trial workforce.

I'm especially excited about the fall regional event, which will mark the first time ACRP has done this sort of conference since the "Scientific Meetings" that supplemented our annual gatherings for a stretch of years in the early-to-mid 1980s. Scheduled for October 3–4, the ACRP Southeast Regional Conference is being organized in conjunction with the ACRP Research Triangle Park Chapter. Attendees will have a lot of fun, will learn a lot, and can garner 12 ACRP contact hours in the process. If the event is successful, we'll plan to do more in the future in different areas.

I'm also looking forward to the regional conference because that's where the winner of the PopUp Star competition will be announced. We're proud to be part of PopUp Star, an industry-sponsored contest to bring clinical trial awareness to the public by challenging stakeholders to lead teams that will create the ultimate clinical trial community awareness event. Diverse teams from across the world compete to raise awareness of the importance of clinical research as a care option within communities. PopUp Star has expanded to 12 entries this year from four in 2018.

It'll be an evening of celebration and festivity in RTP with the competing PopUp Star teams, judges, sponsors, and VIPs getting a chance to hang out, swap stories and ideas, and perhaps come up with new ways to further elevate the clinical trial workforce.

I hope to get the chance to see you in RTP!

Jim Kremidas (jkremidas@acrpnet.org) is Executive Director for ACRP.

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PEER REVIEWED

Why Your Clinical Research Site Needs a Quality Management System

Seema Garg, MS, MBA, CQA, CSSGB

Most of the time when someone in charge at a research site first brings up their desire for a quality management system (QMS), the first thought that comes to many staff members' minds is "Oh no! We have to buy another expensive software product!" But does a QMS really have to come in the form of software or a full-scale program? It can, but it does not have to. A QMS can simply be a set of procedures and processes that ensures the consistency and compliance of any task being performed.

I have been auditing clinical research sites for a while, and a few of the things that I find quite amazing for almost all sites include their dependency on monitoring and their lack of a site-level QMS.

Who's in Charge?

When presented with a concerning study audit finding, most clinical research coordinators (CRCs) that I have dealt with during this process will respond to the effect that "Our monitor didn't ask us about this." It's almost as if the site staff are on a robotic cycle of answering queries and findings from sponsors, monitors, and contract research organizations (CROs), so if no one asks about something, they assume that they don't have to do it.

There is a certain lack of understanding on part of the staff that it is the site's responsibility to operate according to the regulations and protocol, and that the monitoring is simply a verification of the site's operations. The regulations require the investigator and the study staff to conduct the study according to the protocol and regulatory requirements, and the sponsor to guide and oversee the clinical site through monitoring, auditing, and other processes.{1}

However, somewhere along the way, the dependence of site staff on monitoring has become an all-inclusive check for everything they do for the study, which is not always possible, especially with risk-based monitoring models.{2} One of the reasons this may have happened is because there are no formal education or training requirements for the CRC position; most of the training comes in an on-the-job fashion and this on-the-job training has a great emphasis on being trained by the monitors during the site initiation visits.{3}

Where's the Quality?

The lack of a site-level QMS at many sites is the second thing that amazes me. Most of the clinical sites I have audited will have a standard operating procedure (SOP) for conducting informed consent, but not an overall QMS.

Most study staff think of a QMS to be the sponsor's responsibility. However, a clinical site should also have its own QMS through which the site would ensure continuity and consistency of site processes, training of study staff, maintenance of essential documents, and site readiness for an audit or an inspection.

Examples of activities that should be included in a clinical site QMS would be:

- Training SOP describing requirements for regulatory training and protocol-specific training before any staff can be assigned to a study.
- Continuity SOP describing the process of study handover from one staff member to another, and how will new staff be trained if the staff changes without a proper handover.
- Informed consent process SOP.{4}

- Good Documentation Practices (GDP) SOP describing documentation and correction process of regulated data.

- Source documents SOP describing the process of generation and maintenance of source documents.{5}

- Internal assessment SOP describing process of clinical site's own internal assessment of its studies.

- Inspection readiness SOP describing what the site would need to do to prepare and host a regulatory inspection.

Many sites don't have these SOPs, or if they do, the procedures have not been read or revised by anyone in years. It may not be possible for smaller sites to implement all these procedures at the same time; however, it is important to start somewhere and then keep going. If a clinical site implements two SOPs a year, in three to four years it would have most of the needed SOPs. If the SOPs are reviewed and revised every two to three years, they will become second nature for the site staff as a routine part of conducting all clinical research studies.

An inspection readiness SOP is the most common one that I find lacking at sites. Most site staff have not experienced a regulatory inspection and are unfamiliar with how they are handled in terms of logistics and staff conduct.

Most site staff don't consider a lack of inspection readiness as a risk because the low probability of being inspected by a regulatory agency if they are not conducting high-risk studies or are not a high-enrolling site. This attitude can be an issue in itself, as the site staff become complacent and things start to fall between the cracks.

Case Studies

1. About a year after a site has started a long-term study, the assigned CRC leaves the site without training other staff on the regulatory procedures and systems required to continue the proper conduct of the study. The new study staff starts to miss procedures like calling subjects for follow-up visits, answering data queries from data management, re-consenting subjects on revised consents, etc.

- If the site had an SOP for study continuity, it would have allowed the outgoing staff member to conduct a proper handover to a newly assigned staff member—bringing him or her up to speed on the ongoing study with minimal disruption to timelines and participants.

- Additionally, a site internal assessment procedure would have helped, as it would have required the site to audit itself at least annually to see where other procedures were lacking.

2. A site enrolls a subject and during a follow-up visit, a CRC notices a note in the subject's file from a case manager indicating that the subject cannot read. The principal investigator decides to discontinue the subject from the study upon his confirmation of being illiterate. If the site had an informed consent SOP, it would have required an assessment of the reading and comprehension capabilities of the subject during the consent process. This would have allowed the enrollment and retention of the subject with the help of a literate, legally acceptable representative serving as witness.

3. A site generates its own source documents and worksheets and the case report forms (CRFs) are provided by its sponsors. Neither the site nor the sponsor of a current study have provided space on their documents for study personnel to initial and date for the procedures being performed or entries being made on these documents. The study keeps going until a monitor makes an observation that the source documents and CRFs are not attributable. If the site had a source documentation and GDP SOP, the site staff would have been trained to make this observation themselves and correct the forms.

Conclusion

A QMS does not have to be a large system; indeed, it can be simple and flexible. Conducting research in compliance with regulations and the protocol is first and foremost the clinical research site's responsibility—sponsors, monitors, and auditors can verify compliance, but the site staff are the ones who must comply.

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PEER REVIEWED

BIMO Inspections: Recommendations for Sponsors

Mary Kay Kessinger Sobcinski, RN, BSN, MHA; Susan Wiskow, CCRP

The U.S. Food and Drug Administration's (FDA's) Bioresearch Monitoring (BIMO) program is designed to protect the rights, safety, and welfare of subjects, verify the accuracy and reliability of clinical study data, and assess study compliance with FDA regulations. BIMO inspections can be conducted by FDA at any time during a clinical study, "for cause," near the time of study closure, or during agency review of a marketing application.

At the conclusion of an inspection, FDA may issue a Form 483, which outlines specific findings that need correction. If the findings are not addressed to the agency's satisfaction, or if the findings are egregious enough, FDA may issue a Warning Letter. These actions by the agency can delay or even obviate product approval. It is therefore imperative that study sponsors and sites are always prepared for a BIMO inspection. This article presents several recommendations to help ensure successful inspections.

Background

During FDA's fiscal year 2017 (FY17), the agency's Center for Devices and Radiological Health (CDRH) division conducted 287 domestic inspections. Of these, 198 were inspections of clinical investigators or study sites, and 48 were inspections of sponsors, clinical research organizations (CROs), or monitors.{1} The most common investigator/site deficiencies were:

- Failure to follow the investigational plan/agreement or regulations, or both.
- Protocol deviations.
- Inadequate recordkeeping.
- Inadequate subject protection (informed consent issues and failure to report adverse events [AEs]).
- Inadequate accountability of the investigational product.
- Inadequate communication with the institutional review board (IRB).
- Investigational product represented as safe/effective.

The most common sponsor/CRO/monitor deficiencies were:

- Inadequate monitoring.
- Failure to bring investigators into compliance.
- Inadequate accountability for the investigational product.
- Failure to obtain FDA and/or IRB approval prior to study initiation.

It is important to note that FDA also inspects entities outside the United States (OUS). In FY17, CDRH inspected 13 investigators/sites and four sponsors/CROs/monitors and found deficiencies similar to those identified domestically.

Many sponsors erroneously assume that FDA will not inspect OUS sites, but this is a dangerous assumption. FDA expects all study sites, regardless of location, to adhere to federal study regulations, and the agency will inspect OUS sites using the same rigor as it inspects domestic sites. Sponsors need to ensure their OUS sites are as carefully monitored and prepared as their U.S. sites, and it is especially important to ensure OUS

sites that contribute a substantial portion of study data to the marketing application are well prepared.

Ultimately, study integrity and compliance are the responsibility of the sponsor, who is charged by federal regulation to ensure the compliance of the investigators and their study site staff, CROs, monitors, and all other contractors to regulations and the study protocol. Delegating responsibility to another entity does not absolve the sponsor of its oversight responsibility.

Ensuring compliance is an ongoing activity, spearheaded by robust monitoring efforts to ensure sites and sponsors are always "inspection ready." To support inspection readiness, FDA has posted the *Compliance Program Guidance Manuals* online to direct its field inspectors on inspection conduct. These publicly available manuals are valuable resources for sites and sponsors/CROs/monitors as they indicate the information that will be reviewed by inspectors and serve as a great tool for inspection preparation.

Readiness requires top-level sponsor commitment and departmental prioritization to ensure all internal and external team members are confident and well-trained, processes are adequate and adhered to, and documentation is in place in order to demonstrate compliance. Sponsors need to ensure that their own files and those of their site contractors are ready at all times for a BIMO inspection.

Sponsor Readiness

The most effective and efficient way a sponsor can help sites and contractors to be ready is by setting standards for inspection readiness. Key measures include:

- *Ongoing and robust clinical trial document generation, collection, review, and filing.*

   Everyone who has worked on a clinical study, whether at the sponsor, CRO, or site level, knows that there is an extensive and never-ending stream of study documentation required by law and good clinical practices. Managing this mountain of paperwork is daunting and, frankly, not very interesting; however, it is *critically* important.

Failure to properly manage study documentation throughout a study will result in extensive, time-consuming, and very expensive remediation measures at the time of BIMO inspection. It is cheaper, easier, and far less stressful to develop a file management system before the trial starts and to maintain it for the entire course of the study, whether on paper or electronically in a 21 CFR Part 11–compliant system (as detailed in the *Code of Federal Regulations*).

It can be difficult to convince management of the criticality of robust study file management; it's often seen as an unnecessary administrative task. However, at the end of the study, FDA cares about two things: the integrity of the study data and how well the study was conducted, including subject protection. Every aspect of the study must be carefully, thoroughly, and accurately documented to assure the agency that the trial data are accurate, that subject safety was protected, and that the study was conducted in compliance with regulations and the protocol. If it's not documented, it wasn't done.

Recommendations to help ensure robust study file management include designating and training file management personnel on using a 21 CFR Part 11–compliant electronic trial master file system (eTMF). If an eTMF is not used, develop automated trackers to manage trial documents.

- *Development and ongoing review of standard operating procedures (SOPs) that encompass all clinical trial activities, are compliant to applicable regulations for all relevant geographies, reflect best clinical practices, and outline the actual processes used by the sponsor.*

It is challenging to develop SOPs that provide enough procedural structure to ensure regulatory and clinical practice compliance and consistency across studies, while remaining flexible to avoid boxing yourself into a corner with too much detail. Sponsors must be able to produce adequate documentation during an inspection that confirms SOPs are being followed, or that the sponsor recognized an SOP needed to be modified.

If modifications were needed, the sponsor must demonstrate that appropriate revisions were made, training was conducted, SOP modifications have been evaluated for

effectiveness, and that all of these elements are documented. FDA does not necessarily judge the quality of an SOP *per se;* the agency judges if an SOP is in regulatory compliance and if documentation adequately demonstrates it is being followed. The agency also looks for evidence that shows the sponsor recognizes when an SOP is not robust enough or is ineffective, and that it makes improvements to ensure compliance.

- *Systematic review of study operations and compliance at the site level through onsite and remote monitoring; this may be done by the CRO or monitor.*

  To ensure study integrity; to oversee protection of human subject health, safety, and welfare; to assess for fraud; and to ensure site compliance to regulations and the protocol, FDA mandates that a sponsor monitor its studies. Monitoring assures these key study elements are compliant and facilitates achievement of enrollment goals. Monitoring also builds important relationships with site personnel, including the investigators who are your customers, and allows you to correct mistakes that may affect the study's ultimate success and product approval. Monitoring is an excellent opportunity to ensure or correct site compliance and train sites for inspection readiness, including document organization, file review for completeness, proper inspection conduct, and how to interact collaboratively and effectively with FDA.

- *Conduct BIMO inspection training and mock inspections to ensure sponsor and site personnel are knowledgeable about the study and its current status and conduct a protocol review.*

  Site training should include a review of the site's specific contributions to the study as reported to FDA, including the site-specific start/stop dates; number of subjects screened, enrolled, and treated with investigational product and/or withdrawn, including reason for withdrawal; as well as the number and type of protocol deviations and the number and type of AEs. Provide each site with a copy of its protocol deviation and AE listings from the regulatory submission for product approval to ensure the site records match what was reported to FDA, and to be able to address discrepancies during the inspection.

Train the sponsor and site teams on what to expect during the inspection, including examples of the types of questions that may be asked, how to interact with the inspector(s), and how answer questions accurately and confidently without overexplaining or providing information that is not requested, speculating, or talking just to fill periods of silence.

If the sponsor does not have prior experience with FDA inspections, it is recommended to seek assistance from a clinical research consulting firm or CRO with proven inspection success helping sponsor and sites prepare for a BIMO inspection.

Clinical Investigator Inspections

Sponsor and CRO assistance to sites during a BIMO inspection helps ensure that site personnel feel well-supported and that they are able to act with confidence, ultimately contributing to a successful inspection. While some sites do not allow sponsors to be present during an inspection, in-person sponsor or CRO support before and/or during an inspection can be very helpful, especially for studies that had a long duration, were complicated, or closed more than a few months before FDA's visit.

Several days before the inspection, if the site allows, the sponsor should go to the site and assist the study coordinators with reviewing the study files to ensure they are in good order and to re-familiarize them with the study history and file structure. During the inspection, it can be helpful to have sponsor representatives ready to assist the investigators and study coordinators with locating documents requested by the inspector, logging the requested documents on the audit log, taking notes, supporting their responses to FDA questions, and providing guidance as appropriate to the site team. Onsite support of OUS sites is especially important and helpful, as site staff in these locations may be less familiar with FDA regulations, inspection practices, and how to work with the agency during an inspection.

Key Points for Sponsors and Sites to Remember During an Inspection

- Be polite and collegial. Alert your receptionist that an FDA inspector may be coming and what to do when the inspector arrives, such as who to notify and in what order.

- Do not leave an inspector alone or allow her/him to wander around unaccompanied. Inform all staff that an inspector is on site and to keep all documents off desks, counters, printers, etc., and to be mindful of hallway, elevator, and bathroom conversations.
- During the inspection, record the inspector's questions, requests, and comments, and log the documents provided to the inspector. Only provide the requested documents and be sure they are complete and in good order before you deliver them. Make two copies of each document: one for FDA and one for you.
- Be sure you understand a question before answering it and ask for clarification if you are uncertain. Never guess, speculate, or lie. If you do not know an answer, it's acceptable to tell the inspector you'll provide the answer later.
- At the end of each day, ask for a summary of the day's activities, clarify any issues that were raised, and try to resolve them immediately. Ascertain if there are any findings that may lead to a Form 483 issuance and ask for the next day's agenda.

What if You Receive a Form 483?

Don't panic! Form 483 is an official list of "Inspectional Observations" issued after an inspection, usually at a closing meeting. Sponsors should use the Form 483 as a guide for corrective action, as the FDA inspector does not usually make specific recommendations. Your firm can and should respond to the Form 483 during the discussion with the investigator before the investigation concludes. In fact, corrective actions or procedural changes that were accomplished immediately in the presence of the investigator are regarded as positive indications of your concern and desire to voluntarily correct discrepancies.

Consider seeking outside expertise for assistance in determining appropriate corrective actions and/or for help with your response. It is critical that you respond in writing with a thorough plan of corrective actions within 15 calendar days to satisfy the requirements of the FDA. The agency will issue an acknowledgment letter to confirm receipt of your response and may ask for additional information or notify you the corrective actions are not adequate. Failure to respond or failure to respond adequately may result in escalation to a Warning Letter. If you receive a Warning Letter, you must respond in writing within 30 days.

Be aware that FDA may conduct a future (and unannounced) inspection to verify corrective actions were implemented and adequately addressed the findings; this may occur as a result of a Form 483 or Warning Letter. Within six months of an inspection, FDA issues an Establishment Inspection Report (EIR), which is a factual narration of the inspection. Form 483s and EIRs are available through the Freedom of Information Act. However, Warning Letters are published on the FDA's website on a monthly basis and are therefore easily accessible to competitors and other interested parties.

Positive Results of Sponsor/CRO BIMO Inspection Support

Presented here are several case studies of successful BIMO inspection readiness activities. The readiness activities addressed potential or identified areas of risk, and ultimately resulted in a successful FDA inspection with no findings.

Case Study 1: BIMO Inspection of a Recently Closed Study

An application for an implantable Class III device was submitted to FDA for Premarket Approval (PMA), which triggered an expected FDA BIMO inspection. The sponsor proactively identified areas of risk for the study and sites, implemented appropriate readiness activities, and had successful inspections.

Areas of Risk

- Investigator noncompliance (repeated protocol deviations, inadequate device accountability).
- Inadequate efforts to secure investigator compliance or discontinue shipment.
- Inconsistent safety event review (lack of documentation to support that all AEs were reviewed by the Clinical Events Committee [CEC] as required).

Sponsor Readiness Activities

- The CRO conducted mock BIMO preparation audits at targeted sites and at the sponsor.

- A corrective and preventive action (CAPA) program was initiated by the sponsor to address noncompliance.
- The CRO provided BIMO inspection readiness training to sponsor and site personnel.
- The CEC adjudicated all AEs as required per the protocol prior to FDA inspections.

Results

- No Form 483 or Warning Letter was issued.
- The PMA application was approved.

Case Study 2: BIMO Inspection of an Archived Study

In a more unusual case, a clinical study for an implantable Class III device was successfully conducted and closed with statistically satisfactory results. However, the sponsor decided to not proceed with a PMA application for business reasons, so all study documents were archived. Several years later, the device was acquired by another firm, which proceeded with a PMA application submission.

Areas of Risk

- The study had been closed and archived for several years. There was extensive sponsor and site staff turnover.
- Some sites had missing files.
- Some sites had closed.
- FDA expressed concern that it would not be able to view source documents and verify that case report form data were true and accurate.

Sponsor Readiness Activities

- All sites were contacted by the CRO well in advance of the PMA submission to determine which study staff were still available, the status of the study documents, and the logistics involved with retrieving them from archive.

- The CRO retrieved the files from storage and carefully categorized and reviewed each document to ensure its completeness. Spreadsheets were developed to catalogue the documents at both the sponsor and individual site levels and missing/incomplete documents were noted.
- All available site files were retrieved from storage and carefully cataloged and filed by the sites.
- FDA was notified which sites had missing or inadequate files.
- Sites were given customized webinar training to refresh them on the study and their site's study details and results.
- The CRO supported the site inspections onsite and remotely by providing requested but missing documents in real time during the inspections.

Results

- FDA acknowledged the challenges for the sites to undergo inspections years after study closure and commended the sponsor for its inspection support.
- The CRO also underwent a successful inspection.
- No Form 483s or Warning Letters were issued for the sponsor, CRO, or sites.
- The PMA application is pending.

Conclusion

FDA inspections are an important component to ensuring product and subject safety and study integrity. Undergoing an inspection is often stressful, but being well organized throughout the study, keeping sponsor and site files in pristine order, training staff on inspection conduct, conducting inspection readiness activities prior to the inspection, and maintaining your composure during an inspection will help ensure a successful outcome.

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DATA-TECH CONNECT

Speeding Key Data Management Processes in an Era of Growing Data Volumes and Trial Complexity

Richard Young

According to Tufts Center for the Study of Drug Development (CSDD), the average time to build and release a clinical study database is more than 73 days and the average time to lock data at the end of a trial is nearly 39 days[1]; combined, this is more than five days longer than it was 15 years ago.[2] With increasingly complex clinical studies, the industry can't afford to go backwards. Study delays slow treatments to patients and can cost $1 million to $13 million dollars a day.[3]

In 2017, one pharmaceutical company* began addressing this issue head-on by setting aggressive internal targets despite already outperforming industry averages for most data management cycle times. This company implemented innovative processes and technology to tackle tough data challenges, such as reducing sites' data entry turnaround times, integrating external data sources, gaining buy-in from internal departments for timely data reviews, and reducing the lengthy rounds of user acceptance testing (UAT). The company has since reduced database build and release times from 12 to 14 weeks to six to eight, and data lock times from 22 days to just 15.

More Data, More Sources, More Stakeholders

The growing complexity of clinical trials has complicated data management processes in various ways. First, there is a greater volume of data in clinical trials. Overall, the number of datapoints has nearly doubled, from 494,236 in trials between 2001 and 2005 to 929,203 in trials between 2011 and 2015.{4} Sponsors and contract research organizations (CROs) report that handling today's high volume of data is one of the biggest challenges with data management.{1}

In addition to increased data volume, the number of data sources—including digital sources and wearable devices—is growing. According to Tufts CSDD, the average number of data sources used in clinical trials will increase from four to six in just three years.{4}

For many organizations, a third complication impacting data management is the number of stakeholders involved. In 2019, about half of all clinical trials are outsourced to CROs—often more than one CRO per trial—and each has its own data management methods and technologies. Most sponsor and CRO systems are disconnected from each other; therefore, sponsors lack direct access to their data and are dependent on periodic data transfers from their CROs. With each additional source, data cleaning and access become more complicated. Internal stakeholders including safety, medical, and statistics, also need to review the data, further raising the stakes on securing timely access to the data.

Smarter Ways to Speed Database Build

The pharmaceutical firm mentioned earlier began its journey by reviewing existing processes and technologies, and uncovered a number of opportunities to improve database build and release timelines. Here are three opportunities related to UAT:

1. Improve the efficiency of edit check UAT

On average, their teams have 300 to 500 edit checks per study. The firm was double- and triple-testing each edit check across functional areas—essentially creating multiple, redundant layers of edit check verification. Time can be shaved from this process by re-defining which teams test what edit checks and when. For many low-value datapoints, the vendor and data management

teams can test those edit checks with high quality results without involving other teams. In addition, the edit checks for other low-value datapoints never fire, which raised the question of whether it is worth the time and effort to create and UAT those edit checks within their legacy electronic data capture (EDC) system. They are now evaluating which edit checks should be tested by whom and where, as part of a risk-based approach to UAT.

Eliminating the review of low-value datapoints upfront has helped the company employ a timesaving, risk-based process to significantly increase process efficiency.

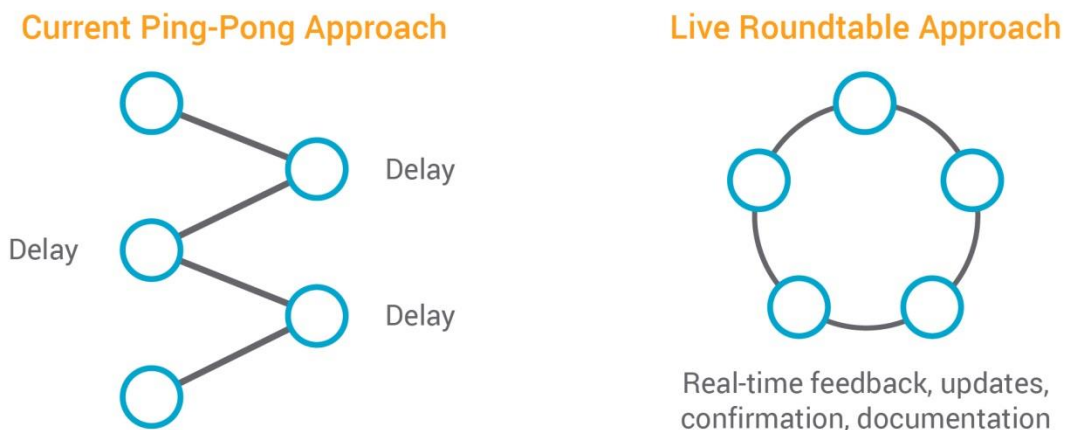*2. Eliminate UAT of data elements from previous studies*

UAT is a necessary but time-consuming process. The company maintained an extensive standards library but would still need to perform UAT on 100% of the edit checks in each study because it couldn't verify that nothing changed from the previously tested elements. However, after adopting a new EDC solution, the company receives reports that show precisely what is different between two studies. Standards within one study can now be validated ~~once~~ and re-used in another study without additional UAT.

The company is working closely with its quality team to vet this new process. Once it has been validated and incorporated into the standard operating procedures, the company will only conduct UAT on things that changed from the comparison study, further improving speed and efficiency. This process change will have a particularly high impact, as 90% of the company's trials are in one therapeutic area, so re-use from its standards library is high.

3. Move from ping-pong UAT to live UAT roundtables

Traditionally, UAT is a multiple-exchange, back-and-forth process between the sponsor and CRO. Internally, it can take many days to gather comments from all the stakeholders, and the CRO doesn't start making updates until the slowest reviewer has finished. In total, these ping-pong exchanges can take four to six weeks.

The company replaced this cumbersome process with a live, roundtable-style approach to UAT that brings the vendor and sponsor teams together—either physically or virtually—for collaborative review. Both groups review and provide feedback in real time, and the system is updated concurrently. The equivalent of three rounds of UAT are now completed in two to three days.

Current Ping-Pong Approach

Delay
Delay
Delay

Live Roundtable Approach

Real-time feedback, updates, confirmation, documentation

Lock All Trial Data 30% Faster

The process of locking the EDC database confirms that all quality checks, cleaning, and query resolution are complete and prevents further changes to the data. It is also an opportunity for the data management team to directly impact clinical trial timelines and help speed medicines to patients. In order to reduce data lock times, the company emphasizes the importance of reviewing clinical trial data immediately—from the first patient screened—and continuously by all relevant stakeholders throughout the trial.

Since 2017, the company has also worked to eliminate any lag time or delay in receiving data, for example by building integrations into its primary labs and automating the data transfers. Combined, their efforts resulted in reduced data lock time on all its data by 31% from 22 days in 2017 to just 15 days today—less than half the industry average.

A video detailing the company's journey to improve clinical data management is available by clicking here.

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RECRUITMENT & RETENTION

Accelerating Oncology Trial Recruitment by Identifying Patients at Diagnosis

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Oncology researchers face a sizable patient recruitment challenge. The numbers alone paint a revealing picture: roughly 14,000 oncology trials are actively recruiting,{1} garnering participation rates estimated at a mere 3% to 8% of possible candidates, with even more limited numbers in minority and geriatric populations.{2}

Low enrollment rates pose risks to more than just the success of individual clinical trials; they may hinder treatment advances and corresponding benefits to outcomes.{3} Despite the promise that trials hold to improve cancer care, most oncology researchers find themselves in fierce competition for patients who have little awareness of the opportunities that exist, or due to real or perceived barriers from a site perspective, which make the perception and reality that recruitment is a labor- and time-intensive process.

However, it should be noted, cancer treatments are fast approaching an inflection point, and fortunately, technology innovations are starting to offer new ways to overcome historic oncology recruitment barriers and disrupt the status quo. One example of technology rising to meet this need combines advanced clinical trial design with a digital pathology platform to help accelerate recruitment by identifying trial-eligible patients at the time of diagnosis.

Current Recruitment Obstacles

Current and traditional recruitment workflows rely heavily on oncologists' knowledge of their patient base, as well as their awareness of active clinical trials. Patients are rarely tracked as potential trial candidates until after they've failed a first-line therapy, and it as at this point that oncologists may propose study options, particularly those available in nearby academic institutions offering a wider variety of clinical trial options than a typical community-based site.

Given the growing movement toward precision medicine, however, more detailed clinical diagnostics are required to qualify patients for some trials. Based on the eligibility criteria for specific protocols, patients may need to obtain additional tumor samples or biomarkers. Consequently, oncologists are increasingly reliant on the diagnostic team—often pathology—for new assays or secondary review, or must rely on historic samples from outside institutions to verify for review. This somewhat retroactive approach is not only cumbersome for oncologists' and pathologists' case flows, it can also delay entry into active treatment protocols.

In addition to the emotional impact of treatment delays on patients, timing is of the essence in cancer trial recruitment. Clinical research coordinators have narrow windows of time to work within due to the complexity of diagnosing patients with specific inclusion/exclusion criteria. Currently, it is often challenging to obtain even baseline information in a consolidated fashion.

As noted previously, sites need to find patients who have appropriate tumor types *and* who are at the right juncture within various lines of therapy. Additional protocol eligibility considerations may require patients who are refractory to a certain class of drug, for example, or in relapse. That forces coordinators and physicians to identify candidates "in the gap"—after they've failed one therapy, but before they've started on another course of treatment—versus proactive identification and tracking of patients earlier on in lines of therapy.

The pressing need for information at precisely the right time is why it's beneficial for researchers to move upstream from the oncologist to the pathologist. Rather than wait for data to be entered into an electronic health record (EHR) or lab information system, they can leverage cloud-based pathology technology to identify and track trial-eligible patients at the time of diagnosis.

New Opportunities and Benefits

The sooner we can identify eligible oncology trial candidates after a diagnosis, the faster we can achieve value for researchers, providers, and—most importantly—patients.

To explain the efficacy of such a process, let's consider a scenario in which a patient is diagnosed with a cancer and goes on a standard line of therapy. A cloud-based, pathology-focused platform that allows tracking to begin at the time of diagnosis helps ensure the patient is not overlooked by study coordinators just because multiple inclusion/exclusion criteria have not yet been met.

From a site management perspective, contract research organizations (CROs) typically see 15% to 20% of sites underrecruit or not recruit at all. The situation is multifactorial, however, a large portion of this percentage comes from the inability to identify appropriate patients at the right time, or at all, to approach about participating in trials. Easing cumbersome workflows increases the likelihood patients will be identified for appropriate trials, alleviating the frustration of enrolling few recruits after completing months of upfront preparation.

Researchers and sponsors also can benefit from the compressed timelines possible through technology-supported trial designs. Fast-track enrollment can help alleviate delays that cost as much as $8 million per day.{4} In addition, the sooner patients are enrolled in a study, the longer the efficacy and safety data will have to mature. That, in turn, can help shorten the trial duration.

For pathologists, accelerating digitization and streamlining complex data management through algorithms and artificial intelligence (AI) presents two-fold benefits. First, it can strengthen trial recruitment and care coordination. Second, it can optimize workflows and free more time to work on a top-of-license basis.

For example, AI tools can enable more accurate mitotic index calculations almost instantly, thereby simplifying and improving secondary review. Technology platforms can quickly track down historical samples, as well as auto-generate forms and ease quality assurance, quality control, and tumor board requirements.

Furthermore, by leveraging the full value of the diagnosis, pathologists can assume a more integral role in the care team. Enhancing pathologists' ability to make oncologists more aware of trial potential at the time of diagnosis may deepen their collaborative relationships.

For oncologists and patients, timelier awareness of clinical research as a care option allows earlier, clearer, and more informed decision-making. Every percentage increase in cancer study participation represents new prospects to save lives.

Conclusion

The historic challenges associated with oncology trial recruitment—low enrollment rates amidst stiff competition—can be overcome. Identifying and tracking trial-eligible patients at the time of diagnosis is a new mechanism to get the best care for patients.

There is immense satisfaction, especially for study coordinators and clinicians, when cancer patients are appropriately enrolled in beneficial trials. By removing the friction points that can impede achievement of enrollment goals all along the continuum of care, we can help researchers, sponsors, and clinicians work together to improve the participant experience.

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CRO CLOSEUP

The Necessity of Open Technology Standards to Create a Connected Clinical Network

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The life sciences industry is experiencing tremendous innovation, bringing drugs to market at an accelerated pace. In 2018, the industry achieved a record-setting number of 59 drug approvals.{1} These new drugs offer tremendous hope, but the costs to develop new and complex therapies are significantly escalating. The average cost of Phase II clinical trials ranges from $7 to $19.6 million, while costs for a Phase III clinical trial can escalate as high as $52.9 million.{2}

Long timelines associated with clinical trials contribute to study delays and expense. Even as sponsors outsource clinical trial activities to contract research organizations (CROs) to gain efficiencies, disparate technology and a lack of data uniformity can increase the time and costs required to bring new medicines to market. Information sharing becomes especially difficult, because of the many different systems and data definitions used by stakeholders in disparate locations.

A connected clinical network supported by open technology standards can help increase sponsor and CRO productivity, reduce operational costs, eliminate duplicate work, and run trials faster. A clinical network can also address many of the collaboration and technology challenges that exist in today's clinical environment.

Common Challenges with Information Sharing and Clinical Collaboration

Clinical outsourcing is not only increasing in volume, but also in breadth as sponsors are now using CROs to manage nearly all phases of drug development, including preclinical research, clinical testing, and post-approval functions such as safety assessment, monitoring, commercialization, and consulting.{3} By 2020, sponsors are expected to outsource 72% of clinical trials to CROs,{4} and many will contract the specialized services of multiple CROs for one clinical trial to manage different functions, further complicating collaboration.

Different disconnected technologies used by CROs to support the essential components of their part of clinical trials often create barriers in communication and data exchange—especially when involving multiple CROs. ISR recently surveyed decision-makers across all phases of clinical development and found more than half (56%) of sponsors would switch providers for a CRO offering improved clinical technology integration.{5}

"The relationship between a CRO and a sponsor is contractual at its base level. However, it's really about people communicating with each other and information flow between those key clinical stakeholders," explained Henry Levy, general manager of Veeva Vault CDMS and president of Align Clinical CRO. "Today, no standard mechanism exists for data and document sharing."

For example, a life science company may contract one CRO for patient recruitment and monitoring, and another for data management. Each CRO is using different systems to manage the information that is valuable to all stakeholders. Often CROs must also interact with each other as well as the sponsor. In this type of environment, collaborative and fluent data exchange are key among different stakeholders, but can be stymied by the use of different technologies and processes. Information is exchanged via e-mail, which often requires manual reentry into different systems—a process prone to introducing errors. Lack of visibility into operations, too,

requires that sponsors conduct repetitive audits to ensure information is correct, as pharmaceutical companies are ultimately responsible for the clinical trial.

Standards Can Break Down System and Process Silos

In many cases, sponsors and their CRO partners use their own environments to automate the management of site contract information, clinical data management, and clinical trial records maintenance. Replacing disconnected and outdated systems with an interoperable system breaks down data silos while driving more efficient processes for all stakeholders through the different stages of the clinical trial processes. Common standards that define data formats and definitions can dramatically improve data exchange between systems.

For example, documents in the CRO's electronic trial master file (eTMF) system must also exist in the sponsor's eTMF system identically, but there are often version control challenges and redundancy leading to lost productivity. The CRO must load documents into its eTMF and then send duplicate documents to the sponsor who loads them into its eTMF.

The DIA TMF Reference Model has created standards for more effective mapping of documents across stakeholders in this area. Additionally, there are opportunities to introduce common standards to address challenges in other clinical data management areas. In a connected clinical network with standards for information exchange, document uploading can happen in real time and eliminate much of the duplicate effort that occurs today.

Standard Definitions and Vocabulary Have Big Benefits

"Every time any combination of the approximately 5,000 sponsors and 200 CROs that exist today shares data on a clinical trial, they have to agree what data will flow and the exact definition of that data. It's complicated, and doesn't always work well," noted Levy.

Definitions are critical. For instance, a CRO and sponsor may define "first patient in (FPI)" differently. Is FPI defined by the first patient randomized into the study, or is it based on when the first patient was dosed? To achieve clarity, both parties must go back and forth negotiating

definitions for all of the data fields and customize a file. "This takes time and is not always a perfect science," added Levy.

Next, the sponsor takes that file to its information technology department to manipulate it so data can flow into the clinical trial management system. Often, the upload doesn't work, or is too time-consuming or burdensome, so the CRO and sponsor resort to using spreadsheets and dashboards. The process is further complicated as most sponsors use multiple CROs rather than just one for a single study. For one large study, a sponsor might use 10 CROs and have hundreds of exchanges.

A standard vocabulary will allow stakeholders to speak the same language to create a universal source of truth. Labeled, formatted, and defined the same way in every study, datasets can have the same semantic meaning across different trials. One key to ensuring semantic interoperability is for stakeholders to use the same standards—the more parties who agree on them, the better.

With data structured identically in every study, sponsors and CROs could analyze aggregated data with powerful artificial intelligence tools to uncover rich insights and trends. By analyzing the results of multiple studies, sponsors can better predict a particular outcome to get closer to results faster. Companies also save time by re-using resources instead of reinventing the wheel with each trial. Data reuse also can help CROs when bidding on prospective new studies by basing costs and activities on past experiences. In turn, CROs can offer more attractive options to sponsors for saving time and resources.

New Group Focused on Creating Industry Standards

Understanding the value of a common language when using technology during clinical trials, leading CROs formed Align Clinical CRO last year to create open technology standards to improve trial execution and collaboration with sponsors. Align Clinical CRO now includes Advanced Clinical, ICON plc, PPD, Medpace, Inc, PRA Health Sciences, Syneos Health, and UBC.

Working with the life sciences technology provider Veeva Systems, and with input from the industry at large, Align Clinical CRO is developing open technology standards to help streamline

information sharing during trials and give sponsors greater visibility into study execution when working with CROs. With standards, both parties can learn to improve efficiencies study-over-study in the same class of drugs by identifying and mitigating risks more quickly and learning from published data. Further, with established standards, more sponsors and CROs will leverage new technologies to drive greater efficiencies.

The first standard proposed by Align Clinical CRO addresses common challenges with sharing operational metrics about trials data during study executive. This Operational Data Exchange standard will define the data and structure for a consistent and easy exchange of metrics and milestone information for areas such as general trial details, study start-up, patient enrollment, and data management. The standard will improve the exchange of information between sponsors and CROs during Phases II and III of clinical trials, and will provide technical considerations when developing application programming interfaces for clinical trial systems. The group will make the final standard available this year.

"Open technology standards can transform clinical trials to be more productive, reduce operational costs, and speed execution across the industry," said Levy. "Align Clinical CRO is committed to improving CRO collaboration with life sciences companies and reducing the time and effort needed to bring innovative therapies to patients."

Standards Will be the Foundation for a Connected Clinical Network

A connected clinical network is key to automate data and document flow among sponsors, CROs, sites, and even regulators for better and faster collaboration. Open technology standards are imperative to enable content and data exchange among different stakeholder systems without manual methods.

Through the creation of standards proposed by Align Clinical CRO and those already enacted by other groups, including CDISC (Clinical Data Interchange Standards Consortium) and the DIA, the concept of a connected clinical network can become a reality by guiding stakeholders to work by a common set of rules to collect and structure data that serve everyone.

"Open technology standards will transform clinical trials to be more productive, reduce operational costs, and speed execution across the industry," concluded Levy. "Standards can help create a new world in which research data can be shared and aggregated seamlessly to accelerate collaborative learning and streamline the path to new therapies."

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