

Clinical ResearcherTM

The Authority in Ethical, Responsible Clinical Research

March 2020 (Volume 34, Issue 3)



Starting Off on the Right Foot

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Clinical Researcher™

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Table of Contents

4 Executive Director’s Message—Let’s Get This Thing Started

Jim Kremidas

6 Chair’s Message—Growing Together by Chapter and Verse

Paul Evans, PhD

PEER REVIEWED

8 Assessing the Operational Complexity of a Clinical Trial: The Experience of the National Institute of Mental Health

Sharon L. Smith, DNP; Galia Siegel, PhD; Ashley Kennedy, PhD

18 Expediting Drug Development Regulatory Pathways Globally

Aman Khera

COLUMNS

29 Site Strategies—Tool or Bludgeon: Technology Can Support Clinical Trial Sites or Undermine Them. How Are *You* Using It?

Diane Carozza

34 Data-Tech Connect: Eliminating Standalone Technical Specs Helps Accelerate Study Start-Up

Drew Garty

SPECIAL ADVERTISING SUPPLEMENT

39 RealTime-CTMS—Advanced Clinical Research System: The Top-Down Approach



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Clinical Researcher—March 2020 (Volume 34, Issue 3)

EXECUTIVE DIRECTOR'S MESSAGE

Let's Get This Thing Started

Jim Kremidas



We all know how difficult it can be to get a clinical trial launched successfully. Whether it's patient recruitment and retention, supply chain challenges, contracting complexities, or myriad other obstacles and challenges, it's no wonder some of the [study start-up statistics remain discouraging](#).

However, we are missing an opportunity if we don't examine how sites with certified personnel consistently post faster rates of study start-up and patient enrollment, and with fewer deviations along the way. It's clear that further professionalizing the clinical trial workforce with performance-driven certifications, aligned job titles, and clear roles and responsibilities will help improve those tough study start-up stats.

Several contributors to this issue of *Clinical Researcher* address various technological and process-oriented approaches to study start-up challenges directly, while others touch on the topic at least partially by way of considering the overall environment of study complexity and regulatory approaches for expediting drug development globally.

I hope you find the information and insights in this issue to be helpful to you in your career as we work together to elevate the entire clinical trial industry.

I'd also like to take this opportunity to celebrate two new members of the [Partners in Workforce Advancement](#) (PWA), a multi-stakeholder collaborative initiative to grow the clinical research workforce and to set and support standards for workforce competence. In February, [we welcomed Dartmouth-Hitchcock Health](#) as the Elite Partner of the PWA, and this month, [we welcomed TRIO \(Translational Research in Oncology\)](#) as a Workforce Champion PWA member.

The PWA members—who now include more than 25 sponsors, contract research organizations, investigator sites, academic institutions, regulatory agencies, and more—provide strategic direction and support for initiatives to grow the workforce and to define, align, and validate competence standards.

Organizations aligned with ACRP's mission are working together to improve clinical trial quality and outcomes for patients by focusing where others have not—on workforce planning, development, and assessment. Why? Because in clinical research, people are everything. We are thankful for the support of Dartmouth-Hitchcock Health and TRIO, and look forward to working together to overcome these critical challenges.

Jim Kremidas (jkremidas@acrpnnet.org) is Executive Director of ACRP.

CHAIR'S MESSAGE

Growing Together by Chapter and Verse

Paul Evans, PhD



Many of you are familiar with ACRP's annual meeting and regional conferences, but did you know your Association also has a vibrant community of more than 50 [ACRP Chapters](#) dotted across North America and elsewhere on the globe?

These exciting forums can enhance your personal and professional development; provide opportunities to develop your leadership, managerial, public speaking, and group decision-making skills; and offer continuing education credits, not to mention invaluable face-to-face networking opportunities with people like yourselves on the front lines of clinical trials. The leadership structure of these chapters varies widely and allows you numerous options for involvement.

We encourage you to become a member of your local chapter. In fact, now's a perfect time because ACRP is working with many chapters to help them reorganize in order to devote more time to networking and outreach events. We'll have more to share on these initiatives in the coming weeks, but we've already made great progress with chapters in Atlanta, Las Vegas, New Orleans, and the Research Triangle Park region in North Carolina.

ACRP is here to advance the profession of clinical research and to help you individually thrive. Your Association's increased commitment to cultivating its chapters is another example of how we're working to bring us all together in common cause.

However, members like you are the key to every initiative. Without your active input, our relative success has a far lower ceiling. I've seen firsthand how important chapter meetings have been, both for connecting like-minded professionals and for sharing best practices. I know my own career is all the richer for the existence of ACRP Chapters.

I invite you to explore the many opportunities offered by ACRP's vigorous chapter program. You can find more information at <https://acrpnet.org/networking/chapters/>.

Paul Evans, PhD, is President and CEO of Velocity Clinical Research, and Chair of the Association Board of Trustees for ACRP in 2020.

Clinical Researcher—March 2020 (Volume 34, Issue 3)

PEER REVIEWED

Assessing the Operational Complexity of a Clinical Trial: The Experience of the National Institute of Mental Health

Sharon L. Smith, DNP; Galia Siegel, PhD; Ashley Kennedy, PhD



In recent years, the National Institutes of Health (NIH) has prioritized strengthening the stewardship of clinical trials.^{1,2} The intent of these reforms is to improve the management and oversight of clinical trials research, increase transparency in the research endeavor, improve the efficiency and quality of scientific research, strengthen scientific rigor and reproducibility, and provide study outcomes to the scientific community and the public in a timely manner.

As one of the initiatives, each NIH institute and center enhanced procedures for assessing and managing the risks presented by funded clinical trials research. The National Institute of Mental Health (NIMH) identified operational complexity as a key component of clinical trial risk assessment.

The Clinical Trials Operations Branch in the Office of Clinical Research at the NIMH developed a framework for assessing the operational complexity of clinical trials based on potential operational challenges presented in the planned research. The purpose of this paper is to disseminate the initial framework for an operational assessment that emerged as the outcome of this effort. Note that this assessment occurs independent of scientific review and is only applicable to clinical trials that receive funding.

Operational Assessment Working Definitions

Clinical trial operations refer to the broad range of trial implementation activities involved in the execution of a clinical trial from study start up to close out. Prioritizing ethical conduct, participant safety, and data integrity, operations focus on the conduct of a clinical trial in accordance with a study protocol approved by an institutional review board (IRB), the tenets of Good Clinical Practice (GCP), and International Council for Harmonization guidelines.

Clinical trial operations include procedures that support participant safety, protocol compliance, data quality, efficient study completion, data sharing, and timely publication and dissemination of results.

Assessment of operational complexity refers to a process of identifying aspects of a clinical trial that may be difficult to implement according to the timeline or procedures outlined in the grant application, thereby increasing the possibility that the trial encounters challenges to successful completion. The goal of the assessment is to evaluate these operational aspects of the trial in conjunction with the study team's resources, capacity, and plans for managing them.

The operational assessment is conducted pre-award for all clinical trials, and then for a select subset of studies continues over the life cycle of the project, in order to make recommendations that support the timely and successful completion of clinical trials.

Operational Assessment Elements

The data utilized for the NIMH operational assessment include a detailed description of the study design, participant recruitment, enrollment and retention, study procedures/interventions,

regulatory oversight, and data collection, coordination, and management. The operational assessment elements discussed below highlight potential operational challenges and examples of resources and procedures that may be helpful to mitigate these are offered.

This brief discussion does not represent a comprehensive list of operationally relevant issues in clinical trials, but is meant to illustrate the approach developed by NIMH to identify issues of interest to operational functioning. A graphic tool, such as that in Table 1, may be useful when performing an operational assessment.

Table 1: Operational Assessment

<i>Operational Element</i>	<i>Description of Complexity</i>	<i>Proposed Mitigation/ Management Strategies and Recommendations</i>
Study Design		
Size of trial/enrollment and retention plans		
Eligibility criteria/participant characteristics		
Randomization and/or blinding		
Demands of trial participation (i.e., intervention delivery, follow-up completion)		
Regulatory Oversight		
Number and type of regulatory bodies involved (i.e., FDA, single or multiple IRBs, DSMB)		
Number of sites		
Types of sites (i.e., foreign, tribal nations)		
Vulnerable population oversight		
Data Collection, Coordination, and/or Management		
Data management plan, collection, tracking, storage, and quality assurance		
Quantity, quality, and type of data collected		
Fidelity and consistency of data collection		
Data coordinating center factors		
Other		

Study Design

Study designs vary greatly and can present challenges related to numerous aspects of the trial design. The operational assessment requires a review of the key questions the study was developed to answer, the trial design, and the study procedures and interventions. The assessment considers the size of the trial, participant characteristics, the demands of trial participation and/or the demands of executing the trial intervention(s), and planned follow-up assessments, among other components of the trial procedures.

Challenges with enrollment and retention of study participants are a common occurrence in clinical research. The operational assessment considers how difficult it will be for a study team to enroll participants into the study. Are eligibility criteria broad and participants expected to be easily found in the setting where the study is taking place? Alternatively, are there extensive and specific inclusion/exclusion criteria that few potential participants will meet? Another point to consider is the target sample size. Will it be feasible to fulfill the planned enrollment targets in the proposed timeframe given the participant population?

In addition to successfully enrolling eligible individuals in a study, a trial relies on having enough retention of subjects through study completion to have the statistical power to answer the proposed research questions. There are numerous factors that contribute to study dropout and follow-up completion rates, some controlled by the study team and others not (e.g., a population that is less clinically stable than expected). Consideration of what is being asked of the participants in terms of frequency and burdensomeness of procedures is necessary to assess if individuals will be willing to enroll and remain engaged for the duration of a study.

Another aspect of study design included in the operational assessment is randomization and masking of treatment conditions, specifically the potential threats to the randomization scheme and to maintaining the blind. Numerous factors can impact randomization, such as unbalanced stratification across treatment arms and inconsistent enrollment patterns across time and sites. An operational assessment asks whether a study has planned an ongoing schedule to review randomization balance to identify potential problems over the course of the study.

Some studies have straightforward blinding schemes in which only one staff member (i.e., the statistician), is unblinded to treatment condition and outcome data. Others may have more complicated masking in which some study staff are blinded to both the study condition and outcome data, while other study staff are not. The operational assessment notes whether procedures are in place to protect the blind, including training for study staff and validation to assure that procedures are in place and working. Procedures should also include documentation identifying under what circumstances the blind should be broken, and who on the team will be unblinded if that event occurs.

The specifics of intervention delivery and follow-up completion represent another area of the operational review. Consideration needs to be given to how challenging the intervention and follow-up will be to deliver as per protocol, and what might interfere with successful implementation. This includes factors described above, such as frequency and burdensomeness of procedures, as well as who on the study team can conduct certain procedures and the impact on scientific integrity and safety when those procedures can't be delivered as described in the protocol.

For studies involving a pharmacological product, additional operational challenges can arise. In early-phase research, there may be constraints on where or how much of the product can be obtained. The regulatory process can also impact drug supply and expiration, which can directly affect study viability.

Studies that require higher levels of precision and specificity in their intervention design may present more operational challenges, especially in multisite studies requiring cross-site harmonization. Study teams need a plan to ensure adequate operational oversight across all study sites, such as dedicated staff or a coordinating center, for tracking protocol fidelity and data quality and harmonization over the course of the study.

Regulatory Oversight

The operational assessment also focuses on regulatory aspects of a trial, specifically whether a study is under U.S. Food and Drug Administration (FDA) oversight, involves single or multiple

IRBs, or includes prisoners, the last of which carries additional regulatory requirements. This component considers the level of regulatory oversight a trial requires, as this will impact staffing needs, as well as the overall timeline, cost, and efficiency of conducting a clinical trial.

Regulatory demands on a study depend on such factors as the number of sites involved, study locale (e.g., domestic or foreign sites), and whether it is an investigational product or a device that is under study. What follows are some key elements to consider when assessing the operational impact of the regulatory oversight required for a trial.

The number of sites involved in the conduct of a study can significantly impact the regulatory demands. Consideration needs to be given to whether the study will operate under a single IRB review or whether multiple IRBs are permissible or required. Both the U.S. Department of Health and Human Services' [Revised Common Rule](#) (45 CFR 46 in the *Code of Federal Regulations*){3} and the NIH's [Single IRB Policy for Multisite Research](#){4} include requirements for streamlining the IRB review process for multisite research.

The number of regulatory bodies (e.g., IRBs, ethics committees, Ministries of Health, data safety monitoring boards) that have oversight over the safety and conduct of the study needs to be considered and tracked. An operational assessment reviews how a study team plans to track these activities and the associated timelines to stay abreast of the regulatory review process.

Exempt from these policies, foreign sites and tribal nations may have local laws and regulations that influence the regulatory context of running a study. Foreign sites may require a study to be reviewed by a Ministry of Health and/or multiple ethical bodies at a local level.

Based on the number of regulatory bodies and anticipated timing of their reviews, study teams can develop a timeline to plan the most efficient and orderly way to seek and maintain needed approvals. Factors to consider include: 1) frequency of regulatory body meetings, 2) prerequisites to initiating the IRB review process, and 3) varying documentation requirements of different oversight and governmental bodies.

For studies required to submit to the FDA or a comparable entity outside the United States, has the study team considered the time needed for back and forth communication and/or wait time

and built this into the study timeline? Additional regulatory protections are required for some populations (e.g., pregnant women, human fetuses, neonates, prisoners). Study staff need training and experience to address the regulatory, logistical, and clinical challenges of working with those specific populations.

An operational assessment also reviews how study teams are planning to track all the documentation and regulatory approvals for the trial. A study team might utilize a regulatory matrix to document and track the dates of reviews and approvals from relevant regulatory bodies for each version of a document.

Ensuring all regulatory approvals are in place at the onset of the study and at continuing review is crucial. Are procedures established to ensure all staff across the various sites are using the most updated version of study documents, and that all regulatory bodies have the same version of each study document at any given point in time? Is version control implemented to ensure synchrony in documents across all sites and regulatory bodies?

Data Collection, Coordination, and/or Management

A final aspect of the operational evaluation relates to data collection, coordination, and management. The relevant information includes how study data will be collected and stored, the quantity, quality, and type of data being collected, and in cases of multisite trials, the fidelity and consistency of data collection and the capacities of the data coordinating center. An assessment of challenges and ongoing review is advantageous so that study teams might implement strategies to improve the quality, reproducibility, reliability, and validity of study outcome data. Operational issues may arise at any point in the process from data collection, entry, validation, and reporting, as well as database design.

The complexity of the data collection, coordination, and management effort is influenced by the sources, type, volume, storage, transfer, and communication of data. Related factors include the processes for protecting confidentiality of participants and study data, the training of study staff, the reliability of assessments, and the quality assurance/quality improvement processes related to the entry, monitoring, and auditing of the study data.

Most clinical research is based on a combination of data sources and/or measurements. Each source of data presents challenges to the operational complexity of the overall study. An assessment of the sources of data in a study includes careful attention to what, how, and from whom data are collected.

There are unique concerns when relying on self-reported data or data from electronic medical records housed in one or more systems, external sources like state or vital records, paper-and-pencil sources versus electronic data capture (EDC) sources, social media, mobile devices, and other digital or imaging formats. What systems does a study team have in place to assess the completeness, verifiability, reliability, and validity of each data source?

Additional operational issues to consider include the number and schedule of assessments, the challenges to collecting the assessment and outcome data, how narrow the time frame for data collection, and the likelihood that participants will be hard to reach or become lost to follow-up.

The processes and schedule of retrieval of assessment data from electronic sources, as well as peculiarities of the data storage and management systems, must also be considered, as they contribute to the integrity of the data. Many software tools and programs are available for data management. There are standards for EDC in the *Code of Federal Regulations* for the pharmaceutical industry that are also recommended as GCPs in other settings. These standards include controls for security provisions such as individual log-in, timestamp, attribution, audit trails, and system validations.

There is a significant difference in data security when using a 21 CFR 11–compliant database (e.g., RedCap) versus a noncompliant spread sheet (e.g., Excel). Studies with datasets in formats that are not readily verifiable, reliable, and attributable may prove challenging to creating a complete dataset at the end of a study.

Additionally, studies may rely on previously obtained data, data obtained from external systems, or data entered into multiple data systems. These layers add operational complexity, as the integration of these data is needed to finalize the study dataset.

If the study is conducted at multiple sites, study teams need to assess how data management and reporting are harmonized. Is there one integrated database for all study data or multiple databases? Is there a coordinating site or an identified data coordinating center (DCC)? In cases where a DCC is used, has the study team considered the budget, infrastructure, staffing, and experience needed to handle the regulatory oversight for the study?

Studies that have many sites benefit from a clear plan for data harmonization. These issues are best identified before the study starts, so that they can be addressed and minimized to assure fidelity, consistency, and compliance.

Finally, the operational assessment considers whether there is a data management plan in place prior to the start of the study. Such a plan provides guidelines for database design, data entry and tracking, quality assurance/improvement, serious adverse event identification, discrepancy management, data transfer/extraction, and database locking. This may mitigate data collection, coordination, and management issues that can arise during the conduct of the study and afterward.

Conclusion

The primary goal of conducting operational assessments of clinical trials is to think through—pre-award and throughout the duration of the study—how challenging a study’s design, regulatory requirements, and data collection and management will be to implement and maintain as per protocol. A comprehensive operational review allows NIMH staff and study teams to make more informed decisions about whether a team has the staffing, resources, and procedures in place to run a trial successfully from the outset. Thus, by reviewing factors that contribute to operational complexity during the study planning process and lifecycle of the trial, NIMH is better positioned to enhance its stewardship of the clinical trials it supports.

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PEER REVIEWED

Expediting Drug Development Regulatory Pathways Globally

Aman Khera



Medicine and healthcare are evolving at an impressive rate. Artificial intelligence models, for example, are beginning to aid the detection of cancer and other serious diseases. The onset of digital therapeutics is creating innovative avenues for improved interventions. To keep pace with such transformation, drug development must follow suit.

Data and technology advances are fueling the current speed of innovation and are expanding the breadth of the drug discovery pipeline to an extent where we can no longer navigate the drug development process fast enough. Already, the industry is struggling with too many trials and too few patients. If we continue with these existing drug development models, we will experience even slower patient recruitment and longer trials—a stark contrast to recent efforts aimed at shortening development pathways.

For example, new guidance released in November 2019 by the U.S. Food and Drug Administration (FDA) shows support for the use of adaptive clinical trial designs.^{1} At the same time, the final concept paper for the third revision of the ICH E6(R3) Guideline for Good Clinical Practice from the International Council for Harmonization (ICH) was endorsed by the organization’s Management Committee.^{2}

The evolution of such guidance and endorsements demonstrates increasing industry flexibility for accommodating technology and data sources in clinical trials. We must continue to embrace the power of digital technologies and their potential to transform how clinical trials are conceived and realized.

Likewise, expedited pathways for drug development have significantly increased in the past several years. Global regulatory agencies are making more accommodations for studies involving pediatric populations, rare diseases, and other indications challenged by limited patient populations and other data-gathering obstacles. Rather than their historical reputation as “the ‘no’ people,” regulatory agencies today are taking a more empathetic and collaborative approach to get beneficial therapies to market—and to patients—sooner. When properly allied, these agencies can become supportive resources for sponsors and researchers.

Efficiency and Time Savings

Adhering to the adage “time is money,” anything sponsor companies can do to shorten an effective drug’s time to market is valuable. Expedited pathways can provide an opportunity for shorter clinical development, meaning that drugs can potentially reach markets and patients faster. Therefore, sponsor companies should seriously consider not only the drug development journey, but also how to optimize it through the use of one or more expedited pathways.

Not every drug will qualify for an expedited pathway, of course. Currently, the common theme among most of these regulatory pathways involves the potential for a drug to meet unmet clinical needs and/or work better than existing therapies. Still, there are many avenues for using expedited pathways available in the United States (U.S.), European Union (EU), Japan, and China.

Expedited Pathways in the U.S.

In the U.S., early engagement with the FDA is strongly encouraged when applying for any expedited pathway designation. Sponsors that do so typically benefit from the fact that regulatory scientists essentially become integral members of the development team, helping guide sponsors along the development path.

Expedited pathways in the U.S. include:

- **Breakthrough therapy designation.** This designation debuted in 2012 and occurs early in the drug development journey. The FDA notes, “*Breakthrough therapy designation is intended to expedite the development and review of drugs for serious or life-threatening conditions. The criteria for breakthrough therapy designation require preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy. A breakthrough therapy designation conveys all of the fast track program features ..., more intensive FDA guidance on an efficient drug development program, an organizational commitment involving senior managers, and eligibility for rolling review and priority review.*”{3}
- **Fast track designation.** Fast track designation typically transpires during the Investigational New Drug phase of drug development.{4} It “...*emphasizes the critical nature of close early communication between the FDA and sponsor to improve the efficiency of product development.*”{5} The FDA adds, “*Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need... If there are available therapies, a fast track drug must show some advantage over available therapy...*”{6}
- **Accelerated approval.** The Accelerated Approval Program typically is used a little later in the drug development journey. It allows the use of a surrogate endpoint to speed FDA approval, although Phase IV confirmatory trials still are necessary. “*The FDA instituted its Accelerated Approval Program to allow for earlier approval of drugs that treat serious conditions, and that fill an unmet medical need based on a surrogate endpoint. A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit.*”{7}
- **Priority review.** Among expedited pathways in the U.S., priority review arises latest in the drug development process. Although priority review does not affect the length of the clinical trial period, it shortens the application review period from the standard 10 months to six months.{8}

Expedited Pathways in the EU

Expedited pathways available in Europe tend to occur toward the end of the drug development journey. Nevertheless, just as with the FDA in the U.S., sponsors are encouraged to engage and collaborate with the European Medicines Agency (EMA) and other regulatory agencies early in the development process. This might take the form of receiving scientific advice from the EMA, for instance, or national scientific advice from individual agencies.

Meanwhile, in the post-Brexit case of the United Kingdom (UK), there still will be access to a National Scientific Advice procedure with the Medicines and Healthcare products Regulatory Agency (MHRA), but the precise mechanics of expedited pathways in the UK are currently unknown.

Expedited pathways in Europe include:

- **Accelerated assessment.** The review of a drug marketing authorization application by the EMA typically happens within 210 days. Accelerated assessment enables approval within 150 days for products “...*expected to be of major public health interest, particularly from the point of view of therapeutic innovation.*”{9}
- **Authorization under exceptional circumstances.** When a dearth of data exists and cannot be obtained—particularly in rare disease studies involving exceptionally small patient populations—this pathway allows for ongoing safety monitoring after a drug is on the market with annual risk/benefit reassessments.{10}
- **Adaptive pathways/licensing.** This designation often is used when more data are needed to widen a drug’s indications. It originally was termed “adaptive licensing,” but has since been renamed “adaptive pathways.”{11} The focus is on early dialogue between sponsors and regulatory agencies, as well as an iterative development approach that leverages real-world data.
- **Conditional marketing authorization.** The conditional marketing designation offers temporary, one-year approval in situations where the benefit of immediate drug availability outweighs the risk of less comprehensive data than normal.{12} Unlike “authorization under exceptional circumstances”—which grants approval when data are

not obtainable—conditional marketing authorization is allowed when it is likely that comprehensive data eventually will be gathered.

- **PRIME (Priority Medicines).** The PRIME scheme, which was launched in March 2016, is quite advantageous for sponsors in early clinical development stages. It provides early and enhanced scientific and regulatory support, allowing for multiple scientific advice meetings with EMA, in addition to the possibility of parallel advice with EMA and Health Technology Assessment bodies.^{ 13 } It is aimed at optimizing clinical trial design as well as engaging technology and payer perspectives.

Expedited Pathways in Japan and China

Even with the best clinical trial strategies in place, there are multiple challenges that may require sponsor companies to look outside the conventional U.S. and EU regions. Regardless of whether the sponsor needs to expand its patient recruitment area or wants to quickly bring a product to market in new areas, it is critical to understand the regulatory environments around the world. For instance, Japan and China could deliver worthwhile patient recruitment options.

Japan

Japan's regulatory landscape aligns somewhat with the EMA and the FDA. Many of the expedited pathways offered by Japan's Pharmaceuticals and Medical Devices Agency (PMDA) and its Ministry of Health, Labor, and Welfare (MHLW) apply toward the end of the drug development journey. They include:

- **Priority review.** This pathway allows a shortened review period—nine months vs. 12 months—for all orphan drugs, as well as for any drugs that may deliver better outcomes for serious indications.^{ 14 } This also applies to products for treating a serious disease when no standard therapy exists or if there is superior clinical usefulness compared to existing products in terms of quality of life of patients, efficacy, or safety. (Although orphan designations are not an expedited pathway in the EU or U.S., it is common for orphan drugs in those regions to also utilize expedited pathways.)

- **Conditional early approval system.** This designation speeds the approval process for drugs that may offer better outcomes for serious indications, but for which confirmatory clinical trials are difficult because of small patient populations. The post-market surveillance period is lengthened.{15} Instituted in October 2017 in Japan, the conditional approval system may be granted if a drug is intended to treat a serious condition or if there is no standard therapy that exists. This system may also be used if superior clinical usefulness can be demonstrated compared to existing products in terms of quality of life of the patient, efficacy, or safety, and it is problematic or would take too long to conduct a confirmation study.
- **Sakigake designation system.** Available since 2015, the Sakigake designation encourages early engagement with authorities and aims to shorten the review period for innovative medical products first developed in Japan that satisfy certain criteria. To obtain this designation, products must show early promise of prominent effectiveness. The target review period for the designated products can be reduced to as short as six months, which is half the typical 12-month review period for pharmaceuticals. Benefits of the designation include “...*prioritized consultation (reduced waiting time), substantial pre-application consultation, expedited review (a target total review time of six months only for drugs, devices, and IVDs), the assignment of a PMDA concierge, and an extended reexamination period...*”{14,16}

China

There is less alignment between China’s regulatory environment and the EMA and FDA. However, in 2017, China joined the ICH as a full regulatory member.{17}

China’s focus for joining the ICH centered on resetting its regulatory processes for the approval of innovative therapies. Whereas it used to take roughly two years to obtain approval to conduct a clinical trial in China, it now takes 60 working days to gain approval from the National Medical Products Administration (NMPA). Moreover, U.S. regulators now accept Chinese data. Additionally, a joint EU and China effort established in 2010 aims to promote information exchange and understanding of pharmaceuticals and other medical and regulatory science issues, and discussions are ongoing.{18}

A New Era of Collaboration

In the global effort to speed therapies to market, regulatory agencies are engaging with sponsors and with each other more than ever before. This collaborative spirit benefits not only the agencies, but also patients and sponsors.

For example, sponsors can now make parallel applications to the FDA and EMA for orphan drug designation via a single common form. Although the definition of rare disease and the requirements for orphan designation vary across regions, a sponsor company could submit for orphan designation to both agencies at the same time using the same data.

More recently, in September 2019, the regulatory agencies of Australia, Canada, and the U.S. announced that they jointly approved a combination immunotherapy for a form of endometrial cancer. This joint approval arose from an initiative called Project Orbis, which was set up by the FDA to enable agencies to collaborate on additional oncology treatment targets for previously approved therapies. Accelerated approval, priority review, and breakthrough therapy designations all were granted as the FDA conducted its review under the Oncology Center of Excellence's Real-Time Oncology Review pilot program. {19}

As far back as 15 years ago, the FDA Office of Hematology and Oncology Products began holding regular meetings with global regulatory agencies from Australia, Canada, Europe, Japan, Switzerland, and China. The FDA also has indicated that it is looking to collaborate further with global partners, reinforcing its commitment to serve the U.S. population and other global patient populations.

Likewise, agencies in some emerging markets now are open to other regions' approvals, acknowledging the detailed review process that products are subjected to in places such as the U.S. and Europe.

Strategic Teamwork for Better Outcomes

Pursuing expedited pathways in multiple geographic regions (e.g., U.S., EU, Japan, and China) may give sponsor companies several advantages. Tapping into global populations not only serves

to increase patient recruitment, but also may help ensure more accurate clinical knowledge of how a product works within diverse patient populations.

However, sponsors cannot afford to think of regions in a staggered manner if they wish to develop products that truly benefit patients globally. They must recognize the similarities and differences among regions from both the development perspective and the payer perspective. In addition, they must understand the vital role that regulatory expertise plays in adherence to an optimal path.

In the rapidly changing global regulatory landscape, strategic planning is essential. A sound starting point is to consider a regulatory strategy plan coupled with a clinical development plan, which will assist in awareness of the necessary timing and requirements for expedited pathways. Plans should be flexible and adaptable according to data, intelligence, and results.

A good regulatory partner will have the expertise to know when and where to employ various expedited pathways and to help sponsors decide an optimal strategy. They will also have experience effectively managing relationships with regulatory agencies—from presenting applications in a timely and effective manner, to preemptively answering regulators' questions and addressing their concerns. Well-thought-out, high-quality submission documents are crucial whether a sponsor is requesting a meeting or applying for a designation.

Today, global clinical trials and expedited pathways give sponsors practical opportunities to drive faster, more efficient drug development. A primary key to success, however, is the early engagement of regulatory agencies. Although these agencies stand ready to assist, full engagement is not a theoretical exercise.

There are many intricate pieces to the puzzle of product development. Sponsors need to have dedicated, hands-on internal resources as well as experienced partners capable of staying on top of the quick decisions and frequent interactions. However, sponsors with the right pathway strategies and resources in place can help ensure that promising drugs reach patients faster, providing hope for improved interventions and outcomes.

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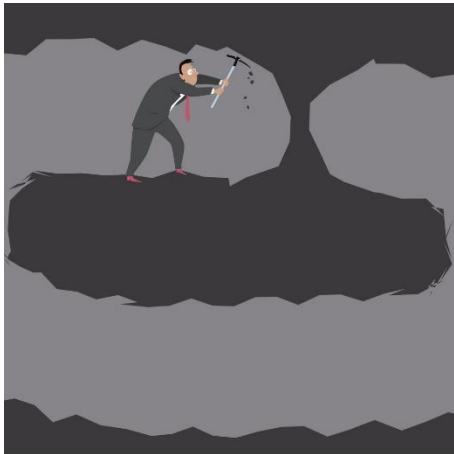


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SITE STRATEGIES

Tool or Bludgeon: Technology Can Support Clinical Trial Sites or Undermine Them. How Are *You* Using It?

Diane Carozza



The last thing an overburdened investigator site needs is for a sponsor to insist upon the use of yet another potentially pricey, isolated, and complicated technology solution to facilitate the conduct of (possibly) just one new study.

However, that's what's happening every day at sites around the world.

Consider the following:

- On average, the typical investigator site is working with *12* different systems to collect clinical research data;
- Fewer than 10% of sites believe that technology solutions provided by sponsors and clinical research organizations (CROs) do a good job of meeting their operational needs;
- Most sites feel strongly that there are too many usernames and passwords that they must manage. { 1 }

The problem isn't really the technology itself; it's the way sponsors and CROs expect sites to use it.

Deployed appropriately, technology allows sites, sponsors, and CROs to streamline processes, reduce costs, and deliver therapies to market sooner. It augments the site/sponsor relationship. It keeps the people-processes-technology triad in harmony.

Too often, technology becomes the primary focus; what *should* be a high-touch/high-tech relationship becomes a low-touch/high-tech one. This interferes with the important work of scientists, clinicians, and others involved in a clinical trial.

It is of little surprise that sites are exasperated. We hear the same complaints wherever we go. They fall into one of two categories:

- The hassle of too much technology and too much red tape.
- The lack of time to talk to the sponsor or CRO representative, in person, about scientific concerns.

Sponsors and CROs are also frustrated. In fact, 30-40% of sponsors and CROs report being somewhat or completely unsatisfied with their site initiation processes. {2}

The solution is to rebalance the people-processes-technology triad. That starts with minimizing the technology burden, especially as it relates to study implementation.

Technology: Getting it Right

So how *do* we reduce the site burden related to technology implementation? What would make it less cumbersome?

The answer is consistency. *Sponsors who use the same technologies across all programs and studies allow sites to become trained in and familiar with them.*

Sponsors who do this need to train sites only once, regardless of how many studies they work on. Instead of forcing sites to learn a whole new technology tool at each engagement, smart sponsors are moving to this streamlined approach, capturing data and using it for all studies moving forward, whenever possible.

This allows training certifications, data, contact information and site-attribute information to be used multiple times in future studies. This makes sense in an array of training areas, including:

- Good Clinical Practice
- Electronic data capture
- Safety systems
- Feasibility and study start-up systems

The same logic applies to data collection: The site needs to be able to provide contact information, attribute information, etc. only once. At the same time, sponsors can provide an easier way to manage multiple usernames and passwords. Minimize the points of entry and you maximize site efficiency.

All these efforts to streamline technology and training pay off in another area: more meaningful encounters.

People: Make Face Time Count

Sites frequently tell us they don't have meaningful face-to-face conversations with CROs and/or sponsors. Even when they do meet in person, the time is often squandered on logistical issues related to the technology or redundant training. That leaves little time to talk about what really matters—the science, the patients, and the trial.

Using consistent technologies allows sponsors and CROs to spend critical onsite time with investigators and coordinators discussing, among other things, the scientific details of the study, potential recruitment challenges, and strategies for patient support.

It's all about the relationship. When the technology serves the relationship, rather than undermining it, everyone benefits.

Processes: Consider the Big Picture

To reduce the technology burden and create the opportunity for meaningful interactions, sponsors need to invest time at the beginning. Start asking questions like, “How can I frame this

question so I need to ask it only once?” and “How can I offer this training one time and have it applied to future studies?”

When we talk about the site/sponsor relationship, we’re talking about something that should be a long-term relationship across studies, indications, and programs. Investigators are the critical business partners to sponsors. The goal in any site identification/site selection effort is to find highly motivated and highly qualified sites, engage them, and retain them as long-standing partners in the development of a sponsor’s research program.

For too long, sponsors and CROs have taken a piecemeal approach to site selection and startup. Sponsors pour resources into getting one particular investigator at one particular site up and running on one particular study. They train that site on the technology. And for the next study? They go to a different site and start all over again.

It’s simply not logical. We know that site startup takes 10 weeks longer at new sites than at repeat or familiar ones.{2} Study site selection is an important aspect of the clinical trial process, and study centers with a track record of successful performance are historically more likely to meet enrollment targets.

Overall, research suggests that if an investigator performs well on a trial, he or she will likely do so again on another study of similar indication and phase.{3,4}

Taking a Portfolio Approach

When you find highly qualified sites and get them engaged on that first study, that’s the beginning—*just* the beginning. You want to retain them for the long haul so you can build that relationship. They need to feel supported by the infrastructure of the sponsor organization, not just in the technical communication pathway that’s established through the technologies being used in the trial.

The smart approach is to engage with a site that’s interested in working with you on an entire program, not just a single trial. Sites and sponsors alike benefit from such consistency. Sponsors

develop relationships with sites they know and can rely on. Sites know these sponsors will treat them well, pay on time, and reduce the overall site burden.

Keep sites engaged by streamlining the technology and taking a high-touch, as well as a high-tech, approach. Give equal weight to people, processes, and technology.

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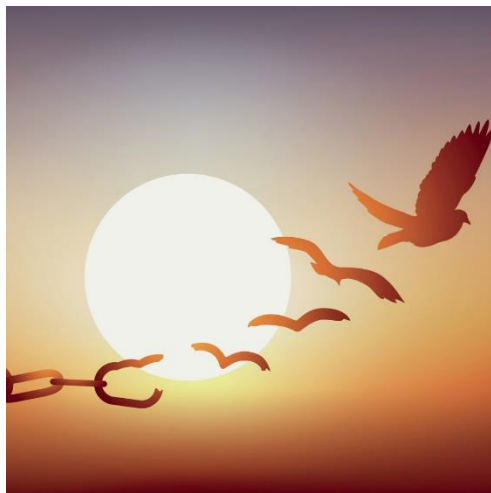


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DATA-TECH CONNECT

Eliminating Standalone Technical Specs Helps Accelerate Study Start-Up

Drew Garty



The average time from protocol completion to study start-up is four months.^{ 1 } For data managers, the primary deliverable is the technical specification document that provides detailed instructions for configuring the electronic data capture (EDC) and other eClinical systems. The more complex the trial, the harder it is to describe the data collection requirements and provide accurate instructions for capturing and checking data quality in an EDC system.

Since the software engineers programming and testing the EDC often lack deep clinical expertise, granular instructions are needed. A 10-page document on data collection requirements can expand to a 100-page technical specifications document that is challenging and time-consuming for the study team to review.

Data management can improve quality and shave months from study start-up by eliminating these standalone specification documents for data collection instruments such as EDC casebooks. However, eliminating standalone specs may be welcome news for some, and sound impossible to others.

Kent Thaelke, executive vice president and chief scientific officer at PRA Health Sciences, recently warned against getting too comfortable with established practices in his keynote at the Society for Clinical Data Management conference. “As an industry, we are holding ourselves back using the excuse of serving in a regulated environment,” Thaelke explained. “We are failing to embrace the opportunities and technologies that already exist today.”

Moving forward, there are two ways EDC systems can eliminate the need for technical specs:

1. The TransCelerate Common Protocol Template and Digital Data Flow initiatives conceptualize a machine-readable protocol and EDCs that automatically generate a casebook based on that protocol.
2. EDC systems that can consolidate the authoring of specifications and developing the casebook into a single process within the EDC itself.

Automating EDC Casebook Creation, Leveraging a Digital Data Flow

The TransCelerate initiative called Digital Data Flow (DDF) aims to improve the speed and quality of study start-ups by automating the setup and configuration of eClinical systems using a standardized and machine-readable protocol defined by the Common Protocol Template.

The protocol would be built within a separate, standalone study definition tool that generates an XML-based description of the study and data collection requirements. To create the protocol, a study designer would draw from a repository of stored definitions for standard design elements and configure those as needed for the individual study.

“The proposed system would capture digitized protocol elements and present them in standardized formats to enable automated configuration of downstream systems and efficient consumption of protocol information across the study ecosystem,” according to TransCelerate.^{2}

The DDF vision spans all systems used during study execution. Involving multiple systems improves downstream system interoperability and data quality, as well as increases the cumulative time savings.

The initial priority is to automate study configuration within the EDC.^{2} The EDC would receive an XML output file from the study definition tool, and automatically create and configure a new casebook according to the specifications provided. Automating these processes would immediately reduce the time and effort required for study start-up.

The standards and technologies needed to support this vision would not only help speed study start-ups, but also reduce barriers to making mid-study changes. Any changes made within the central study builder could be easily propagated to downstream systems. Given that implementing changes typically takes 10 working days at a minimum, this type of operational efficiency would help make trials more agile.^{3}

These TransCelerate initiatives are exciting and promising for the industry. However, the DDF effort is in early stages and a significant amount of work remains to be done. Therefore, companies should pursue interim steps that are possible today and aligned with the goals of adopting standards and automating system configurations during study start-up.

Fusing Specifications and Design Within the EDC

Combining the specification and design processes within the EDC can also eliminate standalone specification documents. With this approach, the study designer reads the protocol, defines the data collection requirements, and translates that vision into a functioning casebook within the EDC.

Modern technologies can increase the intelligence of an EDC system to understand study parameters and casebook design requirements. Now, data managers and study designers can work with a purpose-built interface for specifying data collection requirements. The result is a much simpler solution that no longer necessitates technical specifications to communicate requirements between people.

As an individual defines and configures the study using a visual design tool, the EDC generates metadata descriptions of each element. The schedule, forms, fields, rules, and data validation checks—are all stored as metadata that can drive the system. The EDC uses the metadata to

automatically generate casebook pages, data validation checks, and rules. Writing the specifications and building the database become one.

A second advance in EDC technologies allows EDCs to be self-documenting. The configuration metadata are also used to generate a spreadsheet that documents every aspect and attribute of the casebook, including the study schedule, form definitions, rules, and more. A standalone specifications document remains important for compliance and sponsor sign-offs. Generating these automatically improves the speed, quality, and completeness of the spec while removing a long and onerous review cycle.

Creating specifications with a purpose-built tool is easier than working in generic applications such as spreadsheets because the constructs for data collection are pre-built. Users work from standard design templates, drag-and-dropping pre-defined study elements like case report forms or individual data fields to compose the casebook. Configuration and simple edit checks are defined within the metadata.

More complicated rules and edit checks are scripted in a rules engine that provides pre-defined variables, functions, and actions to choose from. A technically savvy data manager or clinically savvy programmer can write all the rules and edit checks without traditional coding and without a spec, based on his or her understanding of the trial and data management requirements.

Conclusion

Speeding study start-up is a priority for all sponsors and contract research organizations (CROs). To help, data management teams can eliminate inefficient and manual aspects of their workflow, including the siloed technical specs created in spreadsheets and other documents.

The standardization and automation outlined in the TransCelerate initiatives would be transformational in terms of speed, quality, and simplification. If achieved, human errors and effort would be minimized while maximizing the opportunity for greater integration and data flows between clinical systems. Sponsors and CROs should be pushing their technology providers for metadata-driven systems and templates aligned with TransCelerate's vision.

A metadata-driven architecture enables dramatic productivity improvements, such as fusing EDC specifications and design into a single step. These are bold advances that will allow clinical researchers to spend more time focusing on science instead of their clinical systems.

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Advanced Clinical Research Systems: The Top-Down Approach

The clinical research process, especially as it relates to data, primarily functions off paper source documentation and manually transcribed data into electronic data capture (EDC) systems. Most clinical research sites are still utilizing paper regulatory processes. Due to these primarily paper-based systems, there are numerous inefficiencies and detriments to the speed and accuracy of the clinical research process. So why are many sites still using paper-based research systems?



The Problem

As it relates to advanced research systems, U.S. Food and Drug Administration (FDA) regulations have paved the way for electronic document storage, eSignatures, and EDC. However, there is still an evident uncertainty in the industry about the FDA's acceptance of a paperless process. The slow adoption of these advanced systems, unfortunately, is holding back the clinical research industry from a much more efficient and cost-effective future.

The Top-Down Approach

The top-down (or sponsor-driven) approach to adopting advanced research systems has proven to be a long-winded process. Adherence to site policies and procedures for data accuracy, Good Clinical Practices, regulatory compliance, and protocol compliance makes transitioning to paperless systems a significant hurdle. Current top-down systems do not have the users' (site staff and doctors) needs in mind regarding workflow and ease of use.

The Solution

The shift to advanced research systems such as eDOCS and eSOURCE is inevitable. Additionally, EDC vendors need to help pave the way by offering intuitive data sync capabilities that will bring value to all parties and keep EDC companies relevant in this inevitable shift. As sites adopt site-based eSOURCE and eDOCS systems, the need to efficiently transfer files and data into sponsor-managed electronic trial master file (eTMF) systems and EDC systems will become imperative. The pendulum has shifted! Advanced electronic systems are proving their value across all organizations!

So, what are you waiting for?

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