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PEER REVIEWED

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

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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**

| *Operational Element* | *Description of Complexity* | *Proposed Mitigation/ Management Strategies and Recommendations* |
|---|---|---|
| **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

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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** (**Pri**ority **Me**dicines). 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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## CLINICAL RESEARCHER—MARCH 2020 (Volume 34, Issue 3)

## HOME STUDY

## *Starting Off on the Right Foot*

### Article 1: Assessing the Operational Complexity of a Clinical Trial: The Experience of the National Institute of Mental Health

LEARNING OBJECTIVE

After reading this article, the participant should be able to describe how the NIMH assesses operational complexity as a component of clinical trial risk, and to relate the concept to aspects of study design, regulatory oversight, and data collection, coordination, and/or management.

DISCLOSURE

Sharon L. Smith, DNP; Galia Siegel, PhD; Ashley Kennedy, PhD: *Nothing to disclose*

**1. As part of a recent initiative, each NIH institutes and centers enhanced procedures for:**
a. Decreasing the number of subjects required for clinical trials.
b. Mitigating the complexity of approvals involved in clinical trials.
c. Assessing and managing risk in funded clinical trials research.
d. Decreasing the costs associated with clinical trials supplies.

**2. The Clinical Trials Operations Branch in the Office of Clinical Research at the NIMH developed a framework for:**
a. Decreasing the need for hiring regulatory review experts to speed approvals for clinical trials from competent authorities.
b. Increasing the involvement of new principal investigators in attracting funding to NIMH for clinical trials.
c. Promoting participation in clinical trials to underrepresented populations through various outreach efforts.
d. Assessing the operational complexity of clinical trials based on potential operational challenges presented in the planned research.

**3. The term "clinical trial operations" refers to:**

a. Implementation activities involved in the execution of a trial from start up to close out.
b. A specific set of tactical activities occurring only during the start-up phase of a clinical trial.
c. Patient follow-up procedures that occur during the data analysis phase of a clinical trial.
d. Budget considerations that of importance only during the close-out phase of a clinical trial.

**4. The operational assessment is conducted:**

a. Pre-award for all clinical trials.
b. After IRB approval.
c. After Phase I clinical trials are complete.
d. After the first DSMB review.

**5. Study design includes:**

a. Whether the study is conducted under the U.S. FDA.
b. How data will be collected/stored and eventually disposed of.
c. How study monitoring and compliance will be tracked.
d. Randomization and masking of treatment conditions.

**6. The aspect of operationally relevant issues in clinical trials that includes the number of sites and vulnerable population oversight is:**

a. Study design
b. Regulatory oversight
c. Data collection, coordination, and/or management
d. Budget development

**7. The aspect of operationally relevant issues in clinical trials that includes eligibility criteria/participant characterization is:**

a. Study design
b. Regulatory oversight
c. Data collection, coordination, and/or management
d. Budget development

**8. Regulatory oversight includes:**

a. How challenging the intervention and follow-up will be to deliver per the protocol.
b. How data will be interpreted ahead of publication of the results.
c. How study-related documentation and approval will be tracked.
d. Ensuring all study coordinators and monitors are certified.

**9. Data collection, coordination, and/or management includes:**

a. The number and schedule of retrieval of assessments.
b. Identification of underserved and vulnerable populations.
c. Whether the study results are reproducible.
d. How non-compliant patients will be penalized.

**10. The primary goal of operational assessment of clinical trials is:**

a. To provide an accurate view of the resources required to conduct a clinical trial for budget negotiations purposes with sponsors.

b. To minimize the size of the clinical trial and reach the futile/non-futile decision-making point for the DSMB as rapidly as possible.

c. To conduct as many trials at an individual study site as possible, given the availability of local patient populations.

d. To think through challenges in study design, regulatory requirements, and data collection/management in relation to the protocol.

**Article 2: Expediting Drug Development Regulatory Pathways Globally**

LEARNING OBJECTIVE

After reading this article, the participant should be able to explain current challenges to maintaining efficient drug development timelines and describe various expedited pathways for improving the situation in the U.S., EU, Japan, and China.

DISCLOSURE

Aman Khera: *Nothing to disclose*

**11. The new guidance released by the FDA in November 2019 shows support for:**

a. Classic clinical trial designs

b. Much larger clinical trials

c. Much longer clinical trials

d. Adaptive clinical trials

**12. Global regulatory agencies have a historical reputation for:**

a. Being the “no” people

b. Being flexible

c. Being collaborative

d. Being empathetic

**13. Currently, part of the common theme among most of the expedited pathways involves the potential for a drug:**

a. That is cheaper to produce

b. That requires smaller clinical trials

c. That meets unmet clinical needs

d. That doesn’t require DSMB review

**14. When applying for an expedited pathway designation in the U.S., engagement with the FDA is encouraged:**

a. Early in the development process
b. When the product enters Phase II
c. When the product enters Phase III
d. When the clinical trials are complete

**15. Which of the expedited pathways in the U.S. has a requirement that "preliminary clinical evidence demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy"?**

a. Breakthrough therapy designation
b. Fast track designation
c. Accelerated approval
d. Priority review

**16. Which of the expedited pathways in the U.S. is used a little later in the drug development journey and allows the use of a surrogate endpoint to speed FDA approval?**

a. Breakthrough therapy designation
b. Fast track designation
c. Accelerated approval
d. Priority review

**17. The expedited pathways in the EU tend to:**

a. Occur toward the end of the drug development journey
b. Involve larger clinical trials
c. Involve more expensive drugs
d. Occur earlier in the drug development journey

**18. Which of the expedited pathways in the EU is used when more data are needed to widen a drug's indications?**

a. Accelerated assessment
b. Authorization under exceptional circumstances
c. Adaptive pathways/licensing
d. PRIME (Priority Medicines)

**19. Which of the expedited pathways in the EU 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?**

a. Accelerated assessment
b. Authorization under exceptional circumstances
c. Adaptive pathways/licensing
d. PRIME (Priority Medicines)

**20. Which of the expedited pathways in Japan 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?**

a. MHLW preliminary analysis
b. Priority review
c. Conditional early approval system
d. Sakigake designation system