

# Clinical Researcher

## April 2018

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PEER REVIEWED

## **Study Start-Up Obstacles at an Academic Medical Center and How to Overcome Them**

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Few clinical trials are lucky enough to experience no start-up obstacles at an academic medical center (AMC). More often than not, these sites have a multitude of issues to overcome getting a study off the ground; however, sponsors are paying more attention to how long it takes sites to navigate the process from site feasibility and qualification to budget/contract execution and first patient enrolled.

Site staff must take note of what kinds of obstacles they face. Knowing how these obstacles can be addressed and their associated processes improved will put sites in a position of being more appealing to sponsors when they are recruiting potential sites for new studies. For this reason, it is advantageous for site leaders to be proactive on what may be an issue at start-up, in an effort to streamline the process for future studies.

### **Feasibility**

It is common for sponsors to send out feasibility questionnaires to determine if various sites might be qualified to conduct one of their studies. These assessments may elicit data from a site,

such as metrics of their patient population or whether or not sites have the designated staffing or equipment.

When it comes to site data, it may be challenging to get patient metrics in the time allotted to return the feasibility form. In an effort to be proactive, site staff should get updates on patient population metrics on a quarterly basis, so that the information is easily accessible when feasibility questionnaires arrive. Sites may also develop a website or brochure with this information to be easily accessible to sponsors.

The bottom line is to make your site look ready and marketable for the next study.

### **Checklists for Quality**

Once a feasibility questionnaire has been received, a study start-up checklist may be created in the eventuality the site is accepted for the study (see Table 1); this can help to keep the start-up process on track. A checklist would need to be adapted to the events in site start-up and serve as a guide to ensure all documents have been appropriately processed, equipment and supplies received, contract negotiated, and training completed.

Checklists may also need some adaptation based on site workflows, and can be used as a quality instrument in clinical research. In fact, healthcare safety activists have looked to checklists to solve a plethora of problems with their well-known utilization in the aviation industry.<sup>{1}</sup> Checklist compliance is increasingly utilized in healthcare organizations to improve quality, which can be translated to clinical research study start-up.

Site staff can construct their checklist to decide which start-up activities may be done in sequence and which items can be done simultaneously. Utilizing checklists at the beginning of the study is a means to keep staff on target with what remains outstanding and delaying study start.

### **Recruitment Plan**

A common problem in clinical research trials is difficulty enrolling patients. In fact, in an average clinical trial, 20% percent of principal investigators (PIs) fail to enroll any patients and

30% enroll more slowly than expected.<sup>{2}</sup> This is a very real obstacle that needs to be considered when starting a new trial.

A careful review of the eligibility criteria is necessary to determine if the site has access to the size and/or kind of patient population necessary to support the study. Eligibility criteria should be realistic for the disease under study, and broad enough to allow enrollment of a sufficient number of subjects.<sup>{3}</sup> If the criteria are stringent, site staff may be challenged to recruit and retain the contracted number of subjects.

As the old saying goes, “Those who fail to plan, plan to fail.” The recruitment plan should be finalized prior to the initial institutional review board (IRB) submission. This is why it is essential to have a well thought-out recruitment plan at study start-up, because implementation of any outreach method added after approval will be delayed until IRB review.

If achieving success cannot be accomplished from recruitment exclusively through the site’s existing patient population, community outreach may be a necessary form of recruitment. This is especially true if the intervention is a novel therapy. For sites that are parts of large organizations or research networks, utilizing electronic medical records and data mining may be useful in finding the select population.

If there are concerns with study eligibility and recruitment prior to study start, be sure to engage the monitor or study sponsor. Concerns and foreseen issues may not be unique to your site, but the reality across many sites.

If enough sites bring up potential difficulties, the sponsor may consider amending the criteria to make it easier for recruitment goals. For this reason, it is not just beneficial to your site to raise concerns, it may also be advantageous for the overall success of the study. The recruitment plan will need to be completed before IRB submission, so attention to this step should begin when considering feasibility and completed as soon as the site has been notified of acceptance.

## **Regulatory Affairs**

Regulatory affairs is another area that can be fraught with long wait times. Once the site has the IRB submission ready, it may sit in a long queue of studies waiting to be reviewed.

In the earliest stages of site feasibility, sponsors want to know how long it will take for IRB approval, and benchmarking may be used to compare the time frame to other sites. IRB approval times may vary based on whether the site uses a local or central IRB, or a combination of both.

Unpredictable timelines for institutional IRB and ethics committee deliberations may create significant delays for study start-up, and some organizations reported more efficiency and speed with the use of central IRBs.<sup>{4}</sup> This reality becomes clear when the time frames of local IRBs and the size of the institution are factored into the equation. For example, the large number of clinical trials being reviewed at AMCs may delay timely protocol review and explain why approval takes longer at these institutions.

Overcoming the long wait times from submission to approval can be difficult goal to achieve. The solutions for site staff include ensuring documents are complete in the initial IRB application and proactively address any key issues the IRB may identify. Having a contact at the IRB may help speed along the submission and provide updates on its progress, which can be relayed to the sponsor. For more active sites, it may be cost effective to have a full- or part-time regulatory specialist to handle this aspect of study management.

## **Budgets and Contracts**

The budget and contract are usually the first must-handle start-up items the site will encounter after being chosen, but the amount of time it takes for them to be fully executed can be onerous. Many reasons account for this, but one of the biggest comes from complex budget negotiation strategies and practices that are understood by few—and mastered by even fewer—research professionals.<sup>{5}</sup>

Before a site can begin to negotiate, an internal cost calculation needs to be completed.

Depending on the complexity of the study, requesting rates for different services may be a time-

consuming venture. Add to it, the back-and-forth nature of the process, and several weeks can go by.

Further, in some instances, the financial staff may have limited experience with budgets and negotiation. To overcome this obstacle, it is crucial to be prepared; study success or failure can rest on this.<sup>{5}</sup> Preparing means knowing the protocol and required procedures, understanding the cost of running the study, and identifying problem areas. This can help make sure the process runs in a smooth and timely manner.

### **Data Management—What's the Plan?**

Out of the many obstacles that can delay study start-up, data management can often be overlooked since the IRB, budget, and contract usually take precedence. That could be a mistake, because the site could end up having multiple issues in relation to the electronic data capture (EDC) system that could prolong study initiation.

Site staff should check the sponsor's EDC system requirements against capabilities at the site as soon as the information is available. Potential problems can include not having the right system requirements for the EDC system, not being able to submit data through tight firewalls, and not having fast enough Internet speed. Resolution of these issues may require support from the information technology department to upgrade web browsers or operating systems.

In addition, using EDC requires study personnel to have access to the system. Before that access can be granted, the study staff need to undergo training. Sites can inquire about training and access requirements for the EDC system, in order to alert personnel to the amount of time it will take to complete training; this may take several hours per individual, and any delays in having all of the necessary staff trained may impact access for everyone. Weekly reminders may be helpful to keep staff on task and avoid training procrastination.

### **Research Billing**

It is important to consider billable items for research and establishing the appropriate research billing accounts before the study begins. The logistics will take time to establish; first up, a

coverage analysis should be done to identify charges that may be covered by third-party payors, including Medicare. This may help to inform the study budget and may be considered with that process, too, in order to ensure compliant processing.

The goal is to correctly bill study items to the study and items covered by insurance to the patient. The necessity of this lies in the avoidance of fraud. Timeliness in the reconciliation of study and patient accounts when the study is ongoing will further support billing compliance.

Unfortunately, there are documented cases of sites that have not been successful at this process. Emory University agreed to a \$1.5 million settlement for falsely billing Medicare and Medicaid for clinical trial services that were not permitted by the Medicare and Medicaid rules in a whistleblower case, while what is now known as USC Norris Comprehensive Cancer Center settled for \$1.9 million after admitting to overbilling with oncology trials. {6}

Knowing your contract well at the start of the study can be a proactive measure that avoids downstream effects of study billing errors. It is typical for billing accounts to be established once the study is IRB approved, making this one of the final steps in the study start-up process.

## **Conclusion**

Conducting clinical trials is a test of one's skills in project management and the associated logistics that come with it. To get a study off the ground, many tasks need to be performed in order to maintain regulatory compliance and contractual obligations.

Knowing what the obstacles may be is the first step to devising a plan to overcome them. The second step is organization through the creation of a checklist to improve site quality by tracking completion of start-up tasks. Furthermore, centralized versus decentralized organizations may have additional variables that may further impact the flow of study start-up.

The ultimate goal is to eliminate the tendency to be reactive when things go wrong, and instead capitalize on proactive measures that lead to beautiful beginnings.

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**Table 1: Study Start-Up Checklist**

| TASK   | COMPLETED | DATE      |  | COMMENTS |
|--|-----------|-----------|--|----------|
|  |           | PERFORMED |  |          |
| Confidential Disclosure Agreement signed by PI and submitted   |           |           |  |          |
| Feasibility confirmed by team and submitted  |           |           |  |          |
| Notice of sponsor selection received   |           |           |  |          |
| Notify organization of new study, if applicable: Request contract and budget   |           |           |  |          |
| Receipt of regulatory packet or access to investigator portal online   |           |           |  |          |
| Recruitment plan developed   |           |           |  |          |
| Informed consent form versions approved by sponsor   |           |           |  |          |
| <u>Prepare IRB submission packet:</u><br><br><input type="checkbox"/> Site patient recruitment letter<br><br><input type="checkbox"/> Site Web advertisement<br><br><input type="checkbox"/> Questionnaires<br><br><input type="checkbox"/> Radio ad script<br><br><input type="checkbox"/> Sponsor's attachments<br><br><input type="checkbox"/> Phone script |           |           |  |          |

|   |  |  |  |
|---|--|--|--|
| <input type="checkbox"/> All print ads<br><br><input type="checkbox"/> Public service announcements<br><br>Protocol<br><br>Investigator brochures and package inserts   |  |  |  |
| Protocol submitted to IRB   |  |  |  |
| Regulatory packet to sponsor:<br><br><input type="checkbox"/> 1572-2 signed originals<br><br><input type="checkbox"/> CVs and medical licenses<br><br><input type="checkbox"/> Financial disclosures<br><br><input type="checkbox"/> Protocol signature page<br><br><input type="checkbox"/> Site responsibilities logs<br><br><input type="checkbox"/> Lab certifications and ranges |  |  |  |
| Establish accounts with Research Billing Office   |  |  |  |
| Internal budget finalized for sponsor   |  |  |  |
| IRB approval received and sent to sponsor   |  |  |  |
| Sponsor site initiation visit set up  |  |  |  |
| Medicare analysis form submitted and lab accounts established   |  |  |  |
| Sponsor's training completed  |  |  |  |
| Regulatory binders received   |  |  |  |

|  |  |  |  |
|--|--|--|--|
| Study drug received  |  |  |  |
| Study supplies received  |  |  |  |
| If laptops, ECG machines, or other pieces of equipment are provided by the sponsor, these need to be checked by clinical engineering |  |  |  |
| Dry ice agreements   |  |  |  |
| Site initiation complete   |  |  |  |
| Recruitment plan enacted   |  |  |  |



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## **Central IRB vs. Institutional IRB—Advantages and Disadvantages for Multicenter Trials**

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U.S. Food and Drug Administration (FDA) guidance documents, particularly the cooperative research guidance given in 21 CFR 56.114 of the *Code of Federal Regulations*, only provide suggestions and recommendations. These recommendations do not have legal force. Still, the FDA urges sponsors, institutions, institutional review boards (IRBs), and clinical investigators involved in multicenter clinical research to adhere to these guidelines and requirements as outlined in 21 CFR part 56.

These guidelines recommend the use of a centralized IRB review process in situations where doing so could improve the efficiency the review. In multicenter trials, however, review by both central and institutional IRBs can duplicate efforts, increase expenditures, delay clinical trials, and cause confusion and miscommunication. Meanwhile, undergoing only a centralized IRB review and foregoing the institutional IRB review can save time, reduce expenditures, reduce delays in subject enrollment, and decrease the workload and financial burden on an institution.

This article stresses that protecting the rights, safety, and welfare of study subjects is the most important element of clinical research, and that researchers can meet all of these goals by using either a central IRB or an institutional IRB, instead of using both.

## **Observations from the Field**

Taking part in the challenging development of a clinical research department in a brand new institution where the staff were unfamiliar with the fundamentals of clinical trials, the author found that administrators at the new facility wanted their studies to be reviewed by a local IRB, but at the time, they only had an incomplete IRB standard application. We found critical pieces of information regarding the operation of institutional IRBs were missing, such as the requirements for establishing an IRB infrastructure, IRB functions, initiation of the IRB review process, etc. Nor were the administrators aware of the option for using a centralized IRB review process.

Looking at the hospital infrastructure and the resources our site had, we thought the centralized IRB review process would be the most suitable option for clinical trial oversight at our facility. After all, quality conduct of clinical trials is of utmost importance, and trials should not proceed without thorough IRB review.

We e-mailed the FDA questions regarding IRB determination for our new research site, and we were pleased to receive a prompt response to our questions. After conversations with the FDA, we were able to answer the new facility's most puzzling questions. This experience prompted the development of this article to share the "lessons learned" from this experience.

## **Background**

The FDA's guidance regarding the use of centralized IRB review processes in multicenter clinical trials assists sponsors, institutions, IRBs, and clinical investigators in meeting the requirements of 21 CFR part 56. While these requirements have no legal force, the recommendations do provide standards to which facilities should try to adhere. {1}

The guidelines allow facilities to use only the centralized IRB review process, especially when this centralized review could improve the efficiency of the IRB review. Multiple offices within the FDA established these guidelines, including the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the clinical practice program in the Office of the Commissioner, and the Office of Regulatory Affairs. {2}

21 CFR part 56 addresses the IRB review and approval process. These guidelines apply to clinical investigations that are subject to Investigational New Drug (IND) regulations, unless they are exempt from IRB requirements under part 56.104.

Responding to a history of significant abuses human study subjects have endured in various notable experiments, regulators developed procedures intended to ensure the safety of participants. These abuses led to the creation of the National Research Act of 1974 and the Belmont Report, which required researchers who use human subjects to adhere to critical ethical principles. The ethical principles include respect for persons, beneficence, and justice. An IRB may approve human research only in situations in which a) the potential benefits to society outweigh the risks to subjects, b) there is unbiased selection of study subjects, and c) equal distribution of risks and benefits to eligible participants is present. {3}

### **Principle Investigator and IRB Review Responsibility**

The principal investigator (PI) bears ultimate responsibility for the complete oversight of the study, and for assuring compliance with IRB policies and procedures along with the locally applicable regulations and guidelines from competent authorities.

For studies conducted under the aforementioned IND application with the FDA, the sponsor of the IND must obtain assurance that the PI will meet the requirements outlined in 21 CFR part 56 pertaining to the IRB review and approval processes. In fact, sponsors initiate the process by submitting site information to the IRB, or by instructing the site to submit study and site information to a central IRB (the IRB suggested by sponsor) for review and approval.

In a multicenter trial, if the PI is conducting clinical research in an institution with its own local IRB, then he or she must follow the policies of that institution. However, the institutional policies can also state that the PI pursue review through a centralized IRB or through the institution's IRB, or through joint review responsibilities of both. {2}

### **The Requirements for IRB Membership**

As per 21 CFR 56.107(a), an IRB member must have sufficient experience, expertise, and diversity to ensure adherence to the IRB's advice and counsel in safeguarding the rights and welfare of human subjects.

Usually, sponsors utilize a central IRB to oversee a study. If an institution has its own IRB, then depending on the institutional policies, the institution may need to submit the study to its own IRB for study approval and oversight, it may opt to partially depend on a central IRB, or it may make the central IRB fully responsible for study oversight. {2}

### **Centralized IRB Review of Research Protocol**

In multicenter trial cases of institutions that have their own institutional IRB nevertheless wishing to rely on a central IRB for partial or complete review of the study, the institutional IRB should sign an agreement with the central IRB. Copies of that agreement should be held by the institution, the investigator, and the central IRB. {4} There should be written procedures for both IRBs that address these questions: {2}

- How does the institution's IRB determine that the central IRB is qualified to review research conducted at the institution?
- How does the central IRB intend to communicate with investigators, relevant institutions, and with the institution's IRB regarding its review?
- How does the central IRB ensure that it provides meaningful consideration of relevant local factors for communities from which research subjects will be enlisted for the study?
- How does each IRB share responsibilities under the agreement?
- How does the central IRB measure the ability of a remote site to participate in a study (e.g., to make sure the site has medical services appropriate to the complexity of the study)?
- How does the central IRB perform initial and continuing review responsibilities at remote sites? {2}

In the case of the study being launched by the research-naïve institution mentioned earlier, the author and others at the institution found the experience of using only a central IRB was extremely positive. Staff were able to start the study within two months of the day the sponsor

approached the institution with the new study proposal. While the contract department reviewed the contract and budget, a research coordinator submitted the study to the central IRB. By the time the contract and budget negotiations were finalized, the IRB had approved the research protocol.

In short, using the central IRB saved a remarkable amount of time, resources, and expenditures from the study start-up phase until its closure—time that was capitalized on by staff to focus on quality study conduct and oversight.

### **Benefits of Using a Central IRB**

In a multicenter clinical trial, it can become a very costly and time-consuming scenario if each institution involved submits the research protocol to its own IRB as per the institutional IRB guidelines, possibly leading to major delays in the initiation of the study activities at all of the study sites. Generally, institutions have multiple studies going on at the same time, and using both an institutional IRB and a central IRB in every case unnecessarily duplicates efforts, increases expenditures, and delays clinical trial conduct. {5-7}

Utilizing the centralized IRB review process for multicenter trials can save time and expenditures, reduce further delays in enrollment, and reduce the workload of the institutional IRB. Thus, many institutions use their own local IRB specifically for internally funded, investigator-initiated clinical trials, but opt for central IRB services for externally funded clinical trials.

The FDA's "Guidance for Industry Using a Centralized IRB Review Process in Multicenter Clinical Trials" mentions that the use of a centralized IRB review process is consistent with the requirements of existing IRB regulations. CFR 56.114 on Cooperative Research states that "institutions involved in multi-institutional studies may use joint review, or rely upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort." {8}

In fact, a central IRB can be created for reviews of multicenter trials in specific therapeutic categories by members who are highly qualified in their medical specialties. For example, the

National Cancer Institute (NCI) has a central IRB that reviews all NCI-sponsored adult oncology Phase III multicenter trials. Study sites conducting NCI trials can use the NCI's central IRB, or they can use their own IRB for study oversight. { 1 }

Some multicenter trials involve multiple academic medical centers. In such cases, each single medical center can use its own IRB, or can accept study oversight from another participating medical center's IRB. These two medical centers can sign the cooperative agreement accordingly.

One of the biggest advantages of using a uniform central IRB in a global multicenter trial is that the central IRB collects the clinical trial information from all of the active sites across the globe. If the central IRB review and oversight is efficient, then it will be able to detect safety problems quickly and easily, which will not only be helpful in further continuing the trial, but for all future pipeline studies for the same investigational product.

### **Issues with Utilizing a Central IRB**

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research suggested that IRB members should include “men and women of diverse backgrounds with sufficient maturity, experience, and competence, so that the IRB will be able to do its responsibilities, and its determinations will be accorded respect by investigators and the community served by the institution or in which it is located.”{9} It is also suggested that the IRB members be able to determine whether the proposed research is acceptable in terms of standards of professional conduct and practice, institutional commitments, regulations, and applicable laws.

A central IRB can be located within an institution that is conducting a multi-institutional research study, and can provide oversight for different sponsors and across study sites not located in the same territory in which the IRB and its host institution are based. In such cases, the central IRB may not be fully knowledgeable about the details “on the ground” at the various sites. For example, site management organizations or hospitals may use a central IRB that is not located in the community in which an actual study is being conducted.

However, the central IRB still needs to review a variety of factors with an unbiased approach, including the attitudes of the communities where the research is being conducted, the ethical standards found locally,{10} and any pertinent local cultural influences on the population from which research subjects will be enrolled. Even members of a very experienced central IRB may not be aware of these nuances in all of a study's settings.

Therefore, a centralized IRB review process should include the following provisions to ensure that these relevant local factors receive substantial consideration:

- 1) Individuals or organizations familiar with the local community of a study site should submit relevant local information to the central IRB.
- 2) The centralized IRB's limited review of the study should be followed by the relevant institutional IRB's limited review of the same study, focused on the issues of concern to the local community.{2}

According to 21 CFR 56.114, for the centralized IRB review process, "Institutions involved in multi-institutional studies may use joint review, or [may] rely upon review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort."

In the case of a joint review, confusion and miscommunication can occur, as not all of the study staff will be aware of the details of a local IRB's agreement with a central IRB. In such cases, knowledge must be thoroughly disseminated to the study staff so that both IRBs can efficiently oversee the clinical trial.

### **Local IRB Review of Research Protocol**

IRB regulations require that the IRB should be able to ascertain the acceptability of proposed research in terms of institutional commitments, regulations, applicable laws, standards, or professional conduct and practice. These requirements are applicable to both local and central IRBs.

IRB review through members who have been carefully selected (based on their subject matter expertise and/or familiarity with the local community) is intended to provide meaningful

consideration of a variety of factors in assessing research activities. These factors include unique local/state laws, local and institutional considerations, and cultural backgrounds of the population from which research subjects will be drawn (e.g., ethnicity, educational level, religious affiliations, vulnerable populations, inter-community differences, etc.). Additional matters that require assessments include whether mechanisms of subject selection will be equitable, whether adequate provisions are made to minimize risks to vulnerable populations, and whether the informed consent process is adequate.{2}

Local IRB records should contain the agreements and procedures that the IRB and its host institution are required to follow to conduct clinical trials (according to 21 CFR 56.115(a)), including guidelines regarding initial and continuing review of clinical trials, reporting of protocol events, reporting of clinical trial findings, and other actions expected on the parts of the investigator and the institution.

### **Benefits of Using Local IRB**

- Local IRBs can review multiple types of studies onsite, such as internally and externally funded trials.
- They can provide IRB services to other facilities and collaborating institutions as well.
- They can lead to a better understanding of local customs, sensitivity of community attitudes and ethical concerns, and standards of care in the community where the research study will be conducted and from which research participants will be drawn.
- The speed of the research protocol review is locally controlled.
- The IRB members and the investigators become familiar with each other and with the utilization of common research techniques, which is helpful in quick review of future upcoming studies.{11}

### **Issues with Using Local IRB**

- In the U.S., local IRBs must be registered with the Office for Human Research Protections within the U.S. Department of Health and Human Services, which requires Federalwide Assurance.

- Start-up costs and annual expenditures of a local IRB can be considerable. The host institution pays the salaries of the IRB members and the staff associated with it.
- Additional financial burdens can or will emerge, tied to such matters as a) the requirement of having expert IRB members representing the therapeutic/research areas of focus at the institution, b) increases over time in study workloads leading to a need for more staff to accomplish the IRB requirements, c) development and maintenance of written IRB policies and procedures, and d) obtaining substantial institutional/facility support.
- The activities demanded of local IRBs can be time-consuming concerns, especially at institutions which are highly active research sites for both internally funded/investigator-initiated trials and externally funded trials.

### **Risks of Using Both Central and Local IRBs**

Differences in what are considered approved research practices between multiple IRBs could affect the IRB review process and cause confusion for site staff. IRBs could interpret the same regulations differently as a whole, or interpretations among their individual members could differ. Therefore, in cases of complex protocols being reviewed, an IRB may want to apply higher (uniform) standards than those explained at a basic level in the federal regulations. {6}

For example, the expectations and criteria regarding staff reports of serious adverse events and protocol deviations could differ between local and central IRBs. As a result, some important events may not be reported. Research study staff are also burdened with multiple studies at one time; this could be an additional concern since the reporting criteria may differ between protocols as well as between IRBs.

The question arises, what are we going to achieve by using two IRBs for research study oversight? If the members of different IRBs are all qualified experts, it may be hoped that there is little to no variation in their opinions, assuming uniform regulatory standards are applied during the review process.

Monitoring is the most important and extensive part of clinical trials, as a study's results rely on the accuracy of study data and the authenticity of clinical trial conduct. We do not duplicate the

monitoring work, so why should we duplicate the IRB review process? Can we not achieve perfection without the redundancy? If not, then it would appear we need to duplicate every part of work in clinical trials, including coordinating, monitoring, PI review, FDA submission, etc. {6}

### **Benefits of Using Both Local and Central IRBs**

Research study–related findings or violations that may go unnoticed in a review by one IRB may get caught by another IRB’s review, so having both a local and central IRB for study oversight can act as a double layer of protection for the study subjects and for ethical, quality conduct of clinical trials.

### **Conclusion**

This article addressed various advantages and disadvantages of having central and institutional IRBs involved in the clinical trial process. The key responsibility of an IRB is to protect the rights, safety, and welfare of study subjects, which are essential matters in the clinical research process itself. We can achieve this goal by using either central or local IRBs, as long as the ethical practice of clinical trials are guaranteed and the autonomy and beneficence of study subjects are fully protected.

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## APRIL 2018 CLINICAL RESEARCHER

### HOME STUDY

## The ABCs of IRBs and AMCs

### Study Start-Up Obstacles at an Academic Medical Center and How to Overcome Them

#### LEARNING OBJECTIVE

After reading this article, participants will be able to identify the obstacles in study start-up and have an understanding of how to deal with them.

#### DISCLOSURE

Julie Agriesti, CCRC; Paula Smalles, RN, MSN, CCRC, CCRP: *Nothing to disclose*

#### 1. Why do sponsors send out feasibility questionnaires?

- a) To obtain patient and therapeutic area metrics.
- b) To build a database of sites conducting trials.
- c) To determine if sites might be open to merger or acquisition.
- d) To determine if sites are qualified to conduct one of their studies.

#### 2. What is the purpose of a checklist?

- a) To help keep the start-up process on track.
- b) To ensure that remote staff are aware of documents being tracked.
- c) To assist site staff with handling protocol amendments.
- d) To give investors an overview of the trial progress.

#### 3. What other uses can be achieved by adapting a checklist?

- a) It replaces expensive study tracking software.
- b) It ensures site staff are compliant with regulations.
- c) It may be used as a quality instrument.
- d) It solves disputes over budgets and contracts.

#### 4. In an average clinical trial, what percentage of investigators fail to enroll patients?

- a) 15%
- b) 20%
- c) 30%
- d) 25%

#### 5. What should be done by site staff to determine if they have access to the required patient population?

- a) Review of the financial portion of the feasibility questionnaire alone is necessary.
- b) Allow a pre-study visit to be conducted by the sponsor only if they demand one.
- c) Conduct a careful review of all eligibility criteria for the study.
- d) Assessment of investigator expertise and experience in the therapeutic area alone is necessary.

**6. When should the recruitment plan be finalized?**

- a) Prior to initial IRB submission.
- b) After initial IRB review incorporating comments from IRB.
- c) After IRB approval and prior to site initiation visit by sponsor.
- d) After IRB review and agreement with sponsor on number of subjects required.

**7. According to the article, IRB approval times may vary. What would be the reason for this?**

- a) The number and qualifications of IRB members.
- b) It should not vary, since IRBs have set meeting dates for the year.
- c) The type of IRB being used (local, central, or a combination of both).
- d) The time to when queries are raised by IRB and need to be addressed by the study team.

**8. Regarding the study budget, what does the site need to complete prior to negotiation?**

- a) An internal cost calculation.
- b) A checklist of resources required for the project.
- c) A list of vendors and services required for the study.
- d) An agreement stating that there will be clinical trial insurance at the site.

**9. IRB approval and contract and budget negotiations usually take precedence during study start-up, and some vital aspects may be overlooked. Name one such aspect mentioned in the article.**

- a) Site staff training.
- b) Data management.
- c) Logistics around patient billing and accounts.
- d) Site capacity for storage of patient files, study files, and investigational product.

**10. What is the ultimate goal mentioned in the article when trying to overcome obstacles at study start-up?**

- a) To provide good quality data within the timeframes specified at the beginning.
- b) To use checklists for all tasks and tracking tools to ensure that deliverables are met.
- c) To eliminate the tendency to be reactive and capitalize on proactive measures.
- d) To engage with IRB members early in the process to ensure detailed and complete applications for submissions.

**Central IRB vs. Institutional IRB—Advantages and Disadvantages for Multicenter Trials**

LEARNING OBJECTIVE

After reading this article, participants will understand the functions of both central and institutional IRBs with the primary objective of maintaining subject safety.

DISCLOSURE

Pranali M. Wandile, MS, CCRP: *Nothing to disclose*

**11. Which guideline tied to IRBs does the FDA encourage sponsors, IRBs, investigators, and institutions to adhere to?**

- a) 21 CFR part 11.
- b) 21 CFR part 56.
- c) 21 CFR part 50.
- d) 21 CFR part 52.

**12. What could happen if both central and institutional IRBs are used?**

- a) Increased expenditures, confusion, and miscommunication.
- b) Site staff may refuse to acknowledge one IRB's decisions.
- c) Maximum health benefits for subjects enrolled in a clinical trial.
- d) An increase in patients volunteering for studies at the site.

**13. What did regulators develop in response to a history of human subject abuses?**

- a) Central and local IRBs.
- b) FDA 21 CFR part 56.107(a).
- c) National Research Act of 1974.
- d) The Declaration of Helsinki and Nuremberg Code.

**14. Who bears the ultimate responsibility for complete oversight of the study?**

- a) IRB members
- b) Sponsor executives
- c) Study monitors
- d) The principal investigator (PI)

**15. What must the sponsor of an IND application obtain?**

- a) Loyalty oaths from all site staff who will be involved in the study.
- b) Both IRB and regulatory approval to conduct a study.
- c) Assurance that the PI will meet the requirements outlined in 21 CFR part 56.
- d) Permission to import un-marketed medications for clinical trial use.

**16. As per 21 CFR 56.107(a), what should an IRB member have?**

- a) Sufficient experience and expertise.
- b) Experience in review of study budgets and contracts.
- c) Experience from conducting at least four studies as a principal investigator.
- d) The necessary rights to sign agreement with sponsor on advertising for the study.

**17. Some sites choose the IRB based on:**

- a) Institutional affiliation.
- b) The timelines for the review process.
- c) Whether the trial is internally or externally funded.
- d) The workload and cost of review process for studies of all phases.

**18. Which organization would have a better understanding of the customs, attitudes, and sensitivities found in a study site's community setting?**

- a) A local IRB.
- b) A central IRB.
- c) The Center for Drug Evaluation and Research.
- d) The National Cancer Institute.

**19. What are the risks of using both a central and local IRB?**

- a) Increase in screen failures at the site.
- b) Likelihood of increased site staff turnover.
- c) IRBs may interpret the same regulations differently.
- d) Different IRBs may litigate against one another.

**20. What are the benefits of having both local and central IRB for study oversight?**

- a) More reviewers mean a better chance of study approval without comment.
- b) Varying review times will enable some sites to start the study earlier.
- c) May act as a double layer of protection for study subjects.
- d) IRB members will recommend sponsors send more business to sites they have reviewed.