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Considerations for AMCs When Debating the Use of a Central IRB

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Introduction

In 1981, when the U.S. Department of Health and Human Services (HHS) regulations for the Protection of Human Subjects at 45 CFR 46 in the *Code of Federal Regulations* and the equivalent U.S. Food and Drug Administration (FDA) regulations at 21 CFR 50, 56 were promulgated, institutional review boards (IRBs) were found mainly at institutions with National Institutes of Health (NIH) funding, such as academic medical centers (AMCs). However, over the ensuing years, the clinical trial enterprise underwent a remarkable evolution in terms of growth and complexity.

Clinical trial sites have migrated away from AMCs into the private sector, and clinical research has gone global. Further, contract research organizations (CROs) have proliferated, as have commercial IRBs and various types of not-for-profit central IRBs (e.g., NCI CIRB, NeuroNext, Wisconsin IRB Consortium, Fred Hutchinson Cancer Consortium IRB, and the Big 10 Cancer Consortium IRB). Clearly, investigators and IRBs currently function in a distinctly different and more complex environment.

Many AMCs are now, or soon will be, considering whether it is advantageous to use a central IRB, particularly a commercial IRB for review of multicenter trials (MCTs). The primary intent of this white paper is to succinctly present the main points of maintaining local IRB review and oversight of MCTs versus outsourcing to a commercial IRB as the IRB of record. However, given the 2014 NIH Draft Policy on the Use of Single Institutional Review Boards for Multisite Research, comment will also be offered on the difficulties local IRBs will face when serving as the IRB of record for multiple sites. Certainly, institutions must decide on the IRB paradigm that best fits their needs.

Using the Local IRB for Review and Oversight of MCTs

The premise upon which the IRB concept was originally founded espouses the need for an institution to maintain local control and oversight of its own research. This, of course, is not surprising since most research was conducted at single sites in earlier times. While the current environment is dramatically different, as indicated above, many AMCs are still unwilling to outsource IRB review.

It is, therefore, imperative for reluctant AMCs to recognize the necessity of providing their IRBs with the expertise and resources necessary to efficiently accommodate the workload associated with serving as the IRB of record for all of an institution's research. Indeed, as will be mentioned later, the IRB should obviously be provided sufficient resources, regardless of any decision to outsource or not.

The following are major reasons commonly expressed for continuing to use the institution's IRB as the IRB of record for review of MCTs.

1. Frequent IRB meetings

In order to accommodate the workload, many AMCs hold IRB meetings as often as multiple times per week. Indeed, it is not uncommon for institutions to add more IRBs as the number of clinical trials and other research increases.

2. Turnaround time

The turnaround time from the date of protocol submission to the IRB and final approval to activate the research is more or less equivalent at local IRBs to the services provided by commercial IRBs. While a commercial IRB may perform the review more quickly, permission to activate the protocol at the institution is often delayed due to local requirements that must be satisfied (e.g., investigator training, conflict of interest management, coverage analysis, and other institutional review committee requirements).

3. Supportive and collegial relationship with investigators and other research staff

It is important for an IRB to have a supportive and collegial relationship with study personnel. This, in turn, helps maintain compliance. When investigators and study coordinators know the local IRB staff and can visit the IRB office in order to obtain help, this obviously promotes a collegial relationship and

avoids confusion, misunderstandings, and other difficulties that may affect the research.

4. Extended area of expertise

AMCs usually have many faculty members who are nationally and even internationally known in their fields. This allows the institution to recruit experienced investigators as IRB members, and to quickly access consultants who can provide advice regarding scientific, medical, and ethical issues that may arise during protocol review.

5. IRB members become better investigators

Serving on an IRB is one of the best ways for an investigator to become a responsible researcher who understands the regulations and the importance of ethical guidelines, such as the Nuremberg Code, the Belmont Report, and the Declaration of Helsinki. It is common for AMCs to rotate IRB members, thus providing broad-based training for the institution's investigators. In addition, IRB members can serve as resources and can advocate for the ethical conduct of research within their departments.

6. Faculty rewards

Service on the IRB is generally recognized as being very labor intensive. Academic faculty are expected to perform research, publish, teach, serve on committees, and treat patients if they are healthcare professionals. Many AMCs now recognize the importance of IRB service in promotion and tenure decisions. Thus, it is not unusual to have faculty volunteers serving on IRBs.

7. Responsibility and accountability

In keeping with the premise upon which IRBs were founded, AMCs should be responsible and accountable for the review of research conducted by their investigators—within and beyond the institution.

8. Proactive compliance

Local IRB review goes hand-in-hand with local compliance oversight and quality improvement. It is important to identify a compliance problem early on, fix the problem, and implement a corrective action plan to minimize noncompliance in the future. This is best accomplished through partnerships of investigators and IRBs working together to promote the ethical conduct of research. In addition, review by multiple local IRBs is more likely to identify problems in MCTs than review by a single commercial IRB.

9. Knowledge of community values

The local IRB is in the best position to understand and appreciate the values of the community served by the AMC, and any cultural factors to be considered during the course of IRB review. In fact, many local IRBs have two or more community representatives as members.

10. Legal liability

The institution has legal liability for its research whether the IRB review is performed in-house or outsourced. If malpractice occurs in a clinical trial, plaintiffs will likely sue the investigator and the institution; they may also name the commercial IRB as a defendant. Therefore, contracting with a commercial IRB does not necessarily reduce or increase liability.

Local IRBs Serving as the IRB of Record for MCTs

It is common knowledge that many local IRBs struggle to maintain an efficient and high-quality operation in the face of an increasing number of studies and an escalation of new guidance documents issued by FDA and the Office for Human Research Protections (OHRP). The situation is further complicated by pharmaceutical firms and the NIH demanding more efficiency in the IRB review process. In addition, the evolving healthcare enterprise is exerting more pressure on AMCs to increase research productivity and generate more patient revenues.

Consequently, AMC faculty who serve on the typical labor-intensive IRB and IRB support staff are approaching, or have exceeded, their workload threshold. Therefore, any new initiatives

adding to IRB workloads must be implemented in consideration of resource needs. Clearly, the IRB community is concerned about any initiatives that would increase the workload and negatively impact human subject protection.

As mentioned previously, the NIH issued a draft policy in 2014 regarding the use of a single IRB for review of MCTs. According to the NIH Office of Science Policy, more than 70% of the 167 comments received were supportive of the single IRB concept. While the analysis of the comments is not yet available to the public, it is clear that implementation of any final policy will require allocation of sufficient resources to support the IRB operation.

In general, local IRBs are currently not structured or resourced to serve as the IRB of record for MCTs. As a matter of fact, even if an AMC provided its IRB with more staff, the problem of identifying volunteers from the faculty who were willing to assume the additional workload would likely remain.

Simply put, local IRBs are not the equivalent of commercial IRBs that are structured and resourced to handle MCTs. Indeed, that is what drives the commercial IRB business model. Therefore, while the premise of the NIH draft policy makes sound economic sense, any future implementation will require considerable planning.

Outsourcing to a Commercial IRB for Review of MCTs

The IRB workload at most AMCs has increased significantly over time, particularly during the last decade. In order to cope with this increase and remain competitive in attracting industry-sponsored clinical trials, most, if not all, AMCs have at least discussed whether to use a commercial IRB. In fact, there is a growing number of AMCs that have decided to use one or more commercial IRBs for the review of MCTs. This is evidence that the relationship between AMCs and commercial IRBs is working effectively.

The following are the major reasons commonly expressed for AMCs to outsource IRB review to commercial IRBs:

1. Frequent IRB meetings

In general, commercial IRBs meet far more frequently than local IRBs. Some commercial IRBs meet on a daily basis and can quickly increase the number of meetings in order to meet demand.

2. Turnaround time

Commercial IRBs are businesses and, therefore, do not generally suffer from the inadequate resources, staffing problems, or bureaucratic impediments that are characteristic of many AMC environments. Indeed, typical larger IRBs have more than 100 people on staff, which allows for very efficient processing systems. The IRB turnaround time is usually very efficient and better than the average local IRB.

3. Decreases the workload of the local investigators and IRB members

AMC investigators are no longer required to complete an often lengthy local IRB application and develop informed consent forms (ICFs) to conform to institutional templates, because the sponsor submits all required documents directly to the commercial IRB. In addition, ICF translations and other services are readily provided by the commercial IRB. Thus, investigators have more time to engage in research, patient care, and other activities important to their academic success. IRB members, in turn, also experience a reduction in their workload and gain the same advantages as the investigators.

4. Extended area of expertise

Commercial IRBs provide review and oversight for thousands of research sites extending across the U.S., and often internationally. Therefore, such IRBs have huge pools of potential consultants. This allows them to quickly access subject matter experts who can provide advice regarding scientific, medical, and ethical issues that may arise during protocol review.

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5. More cost-effective for the AMC

Outsourcing IRB review of an MCT to a commercial IRB allows the AMC to decrease the number of IRBs (and IRB members) involved, commensurate with the workload reduction. This is clearly an economic benefit to the institution. However, outsourcing IRB review does not mean there can be a corresponding decrease in IRB staff, since the staff is still responsible for other components of the local Human Research Protection Program (HRPP), such as investigator training, quality improvement, and research.

6. Greater financial resources

Since a commercial IRB is a business, revenue is generated. This, in turn, allows the business to quickly develop and implement advanced technology and processing systems that enhance the submission and review process.

7. Sponsor/CRO support

The trend is moving toward sponsors/CROs requiring AMCs to use one or more designated commercial IRBs for the review of MCTs. Indeed, in some cases, placement of the clinical trial at the site requires use of a commercial IRB, and this is likely to increase in the future.

8. FDA, OHRP, ANPRM, NIH Draft Policy Support

The FDA, the OHRP a recent advanced notice for proposed rulemaking (ANPRM) by HHS, and the NIH draft policy all support the use of a single IRB for the review of MCTs. In fact, few local IRBs have the bandwidth to effectively manage a large volume of multisite projects.

9. Package of HRPP services

The larger commercial IRBs provide an array of ancillary services, such as consultation, standard operating procedure development, training, and technology assistance. The regulatory environment has become extremely complex, and many AMCs need assistance in order to ensure compliance and avoid regulatory and/or legal penalties.

10. More cost effective for the pharmaceutical industry

The current system of having multiple local IRB reviews of the same protocol is simply not cost effective. In addition, there is no evidence of value gained in the quality of human subject protection by having the IRB at the local site review the MCT. Indeed, multiple IRB review and oversight of the same MCT inevitably leads to inconsistent human subject protection across sites. Thus, having fewer IRBs of record for an MCT reduces inconsistency and may, in fact, result in a higher standard of protection across all sites.

Summary

It is clear that AMCs face difficult decisions when contemplating whether to require Local IRB resources or outsource those to a central IRB. Decisions in an area this important and complex must be fueled by quality information. Given the complexity and pressures inherent in the current clinical trial enterprise, as well as an ever-evolving regulatory environment, it sound be understood that all AMCs involved in human subject research must assess the adequacy of their HRPP in terms of human subject protection and the facilitation of important research. Some AMCs may decide it is in their best interest to outsource IRB review to a commercial IRB, whereas others may choose to maintain local control. Some AMCs may elect to serve as the IRB of record for multiple performance sites, and others may decline to accept this responsibility. Regardless of the decision, it is imperative that protection of the rights and welfare of participants in research comes first and is never compromised.