

Institutional Not-for-Cause Compliance Review Programs

Over the last few years, many academic institutions have begun to routinely audit ongoing research with human subjects to identify and mitigate risks to research participants, to ensure compliance with approved protocols, and to educate investigators about various matters related to protocol compliance and human research protections. These “not-for-cause” compliance reviews are an institutional oversight mechanism for the conduct of research that complements the oversight activities of institutional review boards (IRBs) required by federal research regulations. While a few institutions developed not-for-cause reviews in the 1990s, the growth of this type of compliance review program is fairly recent. Yet to our knowledge there are no published regulations, guidelines, texts, or manuals to assist institutional officials in determining the frequency, scope, or operational methods for conducting not-for-cause compliance reviews. Consequently, institutions that are establishing these programs may be uncertain about the extent of personnel resources to assign to such programs, the number of compliance reviews that should be performed over time, the process for completing the reviews, and the effectiveness of a review program to ensure that investigators comply with research protocols.

At the University of Michigan, the Office of Human Research Compliance Review (OHRCR) recently started conducting not-for-cause compliance reviews of IRB-approved research studies. The OHRCR, which reports to the Office of the Vice President for Research, is independent of any of the IRBs at the university. In developing the compliance review program, the vice president for research requested that the OHRCR contact peer institutions to get a sense about how they

approach this type of review activity. To help inform other institutions currently conducting or planning to conduct not-for-cause compliance reviews, we report here what we discovered about how other institutions carry out this type of review activity.

What Not-for-Cause Reviews Look Like

We used a structured interview format in talking by telephone between May and June of 2008 with administrators or senior staff persons in the compliance review programs at 11 institutions. We asked the administrators/senior staff persons to describe 1) the number of IRB-approved studies being conducted at their institution; 2) the nature of the not-for-cause reviews and the methods used; 3) the estimated number of full-time equivalent (FTE) positions—excluding administrative positions and secretarial support—dedicated to the compliance reviews in the previous 12 months; and 4) the number of reviews completed per FTE. Other compliance activities—such as for-cause reviews, educational programs, IRB attendance, and policy development—were not included in FTE estimates.

Nine of the institutions had a medical school, and two were large academic health centers affiliated with a medical school. Four of the institutions reviewed only biomedical studies, and seven reviewed both biomedical and behavioral studies. Nine of the institutions had a Clinical Translational Science Award (CTSA) from the National Institutes of Health (NIH), and nine of the institutions were accredited through the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP). At the time we contacted the institutions, the combined number of studies across all institutions ranged from 1,800 to 5,000; the median number of studies was 3,200.

All respondents acknowledged that the numbers

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Table 1.
Summary Descriptive Statistics

	# Protocols	NFC/year	% Protocols	FTEs	NFC/FTE
Range	1,800–5,000	11–206	0.34%–8.20%	1.2–5.5	3.7–82.0
Median	3,200	85	2.78%	2.5	34.0

they provided represented an estimate of a “moving target.” Median values and value ranges were calculated for the number of total active IRB protocols at an institution, not-for-cause reviews done per year at an institution, the percent of total IRB protocols that were reviewed per year, the FTEs assigned for not-for-cause review activities, and the number of reviews per FTE.

■ **Nature of Reviews.** Although the nature of a not-for-cause compliance review varied markedly across institutions, we identified three general types of review activities. The most complex and time-consuming review was a thorough review similar to the review that would be conducted pursuant to regulations of the Food and Drug Administration (FDA) for industry-sponsored drug or device trials. These FDA-type reviews took 40 hours or more per study to complete. However, some activities conducted in the FDA-type of audit were not included—for example, regular examination of clinical chart source documentation, adverse event reporting, or checking essential documents in the study binder.

We categorized another type of review as a “focused” review. For this approach, the review focused only on protocol activities that directly involved research participants, e.g., matters related to informed consent, eligibility criteria, and treatment outcomes. It appears that the focused review approach was a routine one—in other words, no specific concern or issue prompted the review. Moreover, the focused approach gave experienced reviewers the opportunity to “dip” into study data and if problems were found, to take a “deeper dive” into the conduct of the study.

Another type of review we categorized as a “preventive” review. This type of review—which could take as little as three to four hours—is conducted after the IRB approves a protocol when only a few or no subjects are enrolled in the study. It includes the use of educational materials to promote safe, efficient, and compliant conduct of the research study.

None of the administrators/staff persons we talked

to said that their not-for-cause review program had developed a standard approach to review all of the data pertaining to enrolled research participants. However, they all reported that the review included looking at the research records and interviewing or following

up with the principal investigator. Despite the variation in the nature and complexity of review methods, all administrators/staff persons said their not-for-cause reviews were designed to be educational for and collaborative with principal investigators, not to establish a policing mechanism or to pursue punitive measures.

■ **Evaluating Effectiveness.** Only one institution had an established parameter—frequency of identified noncompliance—for evaluating the performance and effectiveness of their reviews. Over time, this institution noted a decrease in the frequency of investigator noncompliance. Three organizations obtained information from investigators regarding their satisfaction or concerns with the review process. These organizations routinely had investigators provide feedback after their protocol was reviewed.

■ **Number of Reviews.** The percentage of IRB-approved studies reviewed annually varied widely, ranging from 0.3% to 6.6% of the total IRB portfolio (See Table 1). Size of IRB-approved portfolio does not appear to be associated with the number of reviews completed. When asked what guided the number of not-for-cause reviews that were completed, most institutions stated it was a function of available resources and provided no other rationale. Administrators/staff persons at two institutions said that the ideal would be to review all investigators within a defined time period, perhaps every two to three years. On the other hand, one institution reported that they attempted to review all investigators with studies receiving a full-board IRB review in that fiscal year. All institutions reviewing biomedical studies were concerned when faculty had regular investigator responsibilities as well as sponsor-investigator responsibilities required by the FDA. Moreover, regardless of the number of reviews completed, institutions considered the studies in which faculty had both sponsor and investigator responsibilities to be high risk and a review priority. Overall, institutions appeared to be less concerned with the number of reviews completed than with

mitigating risk of harm to research participants.

■ *Characteristics of Review Staff and Number of FTEs.* At five of the institutions, staff members with graduate degrees conducted the not-for-cause reviews. At two of the institutions, some of the staff members had graduate level degrees. For the rest of the institutions, staff with a bachelor's degree conducted the reviews; some of these reviewers had nursing training. There was a relatively narrow range of number of FTEs assigned to not-for-cause review activities, but wide variation in number of protocols reviewed per FTE (see Table 1). Looking across institutions it appears that wide variation in the number of protocols reviewed per year depends on the type of review methods. Those institutions using more thorough, complex methods generally completed fewer reviews.

Discussion

The information we gathered about not-for-cause review programs at 11 institutions reveals wide variation in review methods, the number of reviews completed, and the number of reviews conducted per FTE. Of special note is that all of the institutions said that their review program is designed to be a mechanism for education and collaboration, rather than a punitive program. There was relatively small variation in the number of FTEs assigned to conduct the reviews. All institutions agreed that with regard to noncompliance, they were most concerned about FDA-regulated investigational new drug and investigational device exemption studies where faculty had both sponsor and investigator responsibilities. Of note, it is concerning

that only one institution used any kind of evaluative criteria to determine the effectiveness of the reviews on decreasing the level of investigator noncompliance.

Undertaking not-for-cause compliance reviews is a relatively new activity at academic institutions that conduct human subjects research. Thus, it is not surprising that there is little information about the nature of these programs or about standards that have been accepted or even proposed to determine the effectiveness and/or the quality of such a program. As more institutions develop not-for-cause compliance review programs, it will be necessary to thoroughly and accurately define the spectrum of compliance review activities, and to obtain evidence-based data about the effects of review outcomes in mitigating research-related risks. Furthermore, creating national affiliations for not-for-cause reviewers in academic settings would provide reviewers with an opportunity to share strategies, develop expertise, and work collaboratively on a larger national agenda regarding not-for-cause compliance review programs.

Disclaimer

The authors determined that their inquiries did not constitute human subjects research; thus, a protocol was not submitted to a University of Michigan IRB. All administrators/staff members we talked to reviewed a draft of the manuscript to verify that no identifying information was present; all were in favor of it being submitted for publication.

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