The Role of a Research Administration Program in Adverse Event Reporting

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Authors' Note

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Abstract

The reporting, analysis, and management of adverse events (AEs) provide an ongoing assessment of risk in the context of a clinical trial and enhance the protection of human research participants and the informed consent process. Effective and efficient review of AEs has been a long-standing challenge for Institutional Review Boards (IRBs) and Research Administration programs, especially as protocols and ethical/legal issues become more complex. Furthermore, AE reporting is governed by many different regulations and sources, with inconsistencies in standards and requirements. Reporting standards for AEs

were adopted when single-center clinical trials were the norm. With the increased prevalence of multi-center trials, IRBs are now inundated with AE reports. This paper will review the current issues in AE reporting and the challenges encountered by research administration programs when reassessing current policies and procedures and implementing a significantly revised reporting policy. The implementation plan and educational strategies used with the investigators and research staff will be described. Preliminary outcome data will be presented to evaluate policy revisions and to take into consideration the concepts of "quality of review" versus "quantity of reporting."

Introduction

Clinical research has endured remarkable and beneficial expansion in the past 25 years, although this growth has resulted in an unprecedented increase in workload for the human research protection system. Most of the expansion in clinical research has been in the form of multicenter trials, which present significant challenges for a local institutional review board (IRB). The dramatic increase in the number of multicenter clinical trials over the past two decades coincides with a tremendous influx of clinical trial funding from industry, which has resulted in the exposure of inadequacies in human subject protection programs developed to manage clinical trials on a smaller scale, usually at single sites (Morse, Califf, & Sugarman, 2001).

One of the leading challenges facing Human Research Protection Programs (HRPPs) is the volume of AE reports that sponsors and clinical investigators file with IRBs. The current process is burdensome, inefficient, and fails to provide IRBs with meaningful information needed to fully ensure the safety of human research participants. The federal Office for Human Research Protections (OHRP) has estimated that approximately 5% of all AEs reported to IRBs actually warrant some level of review; 70% have little or no impact or concern resulting in meaningful action(s) taken by an IRB, and only 25% require resources for assessment or further consideration by an IRB (Weschler, 2004). The current challenge is how to triage the 70% efficiently and address the remaining 30%, while dedicating resources toward action on the small percent of that latter group where an impact can be made. IRBs have a greater responsibility and ability to evaluate AEs at the sites over which they have purview.

As noted by Burman, Reves, Cohn, & Schooley (2001), additional trends include a recent major change in federal oversight that resulted in a three-fold increase in regulatory actions against local IRBs, with a marked increase in regulatory actions against the IRBs of academic medical centers (1 in 1997 compared with 14 in 1999). Inadequate review of safety reports was among the list of reasons for regulatory actions by both OHRP and the U.S. Food and Drug Administration (FDA). Recent reviews by the Office of the Inspector General (OIG) of the Department of Health and Human Services (DHHS) and the National Institutes of Health (NIH) concluded that the continuing review process should be reevaluated and that local IRBs should not be required to review off-site (external) safety reports (OIG, 1998; NIH, 1999). On the basis of a series of reports, the OIG concluded that IRBs are now forced to "review too much, too quickly, with too little expertise," and with inadequate resources (OIG, 1998). A major contributing factor to this dismal outlook for HRPPs is the volume of AEs submitted to IRBs for review.

Background

A key factor in the current crisis in the function of local IRBs is the escalation of multicenter clinical trials as the consistent method for the performance of clinical research. Though Data and Safety Monitoring Boards (DSMBs) have become commonplace in multicenter trials, federal rules and regulations concerning human subject protections require that local IRBs bear the fundamental responsibility of research oversight (Morse et al., 2001). Current rules encourage researchers and sponsors to report all unexpected, serious, or related AEs to a number of parties, including IRBs, FDA, and other regulatory and research agencies in the United States.

One AE alone can result in a multitude of reports to various organizations, which in turn must be assessed by the IRB (Weschler, 2005). For multicenter clinical trials, an IRB receives individual external AE reports. The receipt of reports that are not aggregated and that come from disparate sources contributes to confusion and an added workload for the IRB. More importantly, the format of the reports jeopardizes the IRB's ability to make an informed judgment on the appropriate action, if any, to be taken. According to Burman, et al. (2001):

> Local IRBs were not designed to handle the initial evaluation and ongoing **review** required by the rapidly increasing number of multicenter clinical trials. Furthermore, local IRB **review** of the thousands of safety reports from multicenter clinical trials monopolizes resources without promoting patient safety. (p. 152)

These policies were effective when the majority of clinical studies were conducted at a single site; however, they are producing chaos with the increase in multi-center trials involving multiple researchers and numerous participants. There is certainly a need for IRB **review** of multicenter trials, but it is not clear that patient safety is enhanced by duplicating this process at the IRB of every study site. AE reporting ideally should provide useful information regarding safety in a clinical trial. The DSMB is chartered to review such duplicate reports of a single AE, while the local IRB's responsibilities should focus only on those AEs involving human subjects of its own institution's studies and continued review of the DSMB's findings (Levine, 2001).

Morse et al. (2001) stated:

> Some of the excessive burden that adverse event reports (AERs) create for IRBs may be attributed to following: confusing terminology in the regulations that govern trials, differing requirements of the governmental regulatory bodies involved in ensuring patient-subject safety, and inconsistencies in the regulations themselves. The FDA requires the investigator to "promptly report to the IRB all unanticipated problems involving risk to human subjects or others". HHS regulations require prompt reporting to the IRB of "any unanticipated problems involving risks to subjects or others". In contrast to myriad requirements for reporting AEs, US regulations lack provisions about how IRBs should handle these reports once they have been received. Flooded by AERs and poorly positioned to interpret the emerging trial data, IRBs have tended to focus on optimizing regulatory compliance instead of using AERs to determine whether the risk-benefit assessment for locally enrolled patients is affected. When the prospect of many individual IRBs in large studies all attempting to replicate an assessment of the safety and efficacy of the therapy of interest is considered, the implications are magnified. At the same time, the enormous amount of work

> performed by IRB administrators and members to complete these functions is likely to be costly. (p. 1203)
>
> Morse et al. (2001) further observes that
>
> IRBs do not have sufficient statistical or clinical expertise or access to appropriate information to allow them to evaluate properly the issues of safety and benefit that arise in the course of a trial. As a result of these factors, IRBs frequently are unable to translate observations regarding individual AEs into a coherent assessment of the overall risks and benefits for a trial. (p. 1203)
>
> To conduct a valid assessment of an AER, it is necessary to have information beyond that contained in the report itself, such as the number of patients in the study as a whole, the expected frequency of the AE reported, and, in a blinded study, information about whether the patient-subject in questions is receiving the test agent. Information on efficacy is also necessary to weigh risks and benefits. (p. 1202)

When AEs are reported accurately, their potential importance may not be fully recognized if they are not reviewed and classified in a comprehensive and systematic fashion. Such activity would most likely fall under the charter of a DSMB and be arm's length from the IRB.

Given the lack of harmonization of guidance on AE reporting policies and the trend towards increased IRB workload and burden, the research administration staff of the Center for Clinical Research at University Hospitals of Cleveland (UHC), developed a systematic process to address the issue of AE reporting and created a strategy for educating the research community.

Purpose

Evaluation and revision of event reporting policies and procedures by a research administration program are completed with the intent to improve the effectiveness and efficiency of the IRB in the protection of human research participants. The goals of the research administration program aim to interpret policy guidelines in compliance with current regulations, assess the impact of a revised event reporting policy on the quality and quantity of review, and develop a pilot collaborative educational strategy between the research administration office and the research community with regards to event reporting.

Design and Methods

An AE reporting subcommittee was established which included the IRB Chair and Vice-Chair, Clinical Research Manager, Research Compliance Specialist, and the Director of the IRB Office. An extensive review of the AE reporting literature was performed, including a search of IRB websites for related policies and procedures and an in-depth review of the federal regulations and guidances. Recommendations from the American Academy of Medical Colleges (AAMC) (Dickler, 2005) and Applied Research Ethics National Association (ARENA) and Public Responsibility in Medicine and Research (PRIM&R) (O'Rourke, Borasky, & Hansen, 2005) were reviewed as a final step in the policy reassessment process and to further focus the revised local policy (see Table 1). A revised Event Reporting policy was drafted, which included specific categorizations for AEs, unanticipated problems, and protocol deviations. The policy revision was distributed to the IRB for review and approval and to the IRB Executive Committee, IRB staff, investigators, and clinical research coordinators.

Table 1

Recommendations from AAMC, ARENA, and PRIM&R (O'Rourke, Borasky, & Hansen, 2005)

AAMC Statement Regarding Adverse Event Reporting Prepared for the FDA Hearing

Internal AEs: IRB should review individual reports of serious, unexpected, and related events; all AEs that do not meet these criteria should be aggregated for Continuing Review.

External AEs: IRB should review summary/aggregated reports of serious, unexpected, and related AEs.

Applied Research Ethics National Association (ARENA) and Public Responsibility in Medicine and Research (PRIM&R) Guidelines

Internal AEs: IRB should only review individual reports of AEs that meet one or more of the following criteria: event is serious and unanticipated, events that indicate an increase in the potential risk to subjects, event requires revision of the protocol, consent documents, and/or IDB.
External AEs: IRBs should not review individual reports of external AEs; IRBs should receive aggregate reports with an analysis and conclusion at intervals appropriate to the level of risk; should only receive reports that require revision of the protocol, ICF, IDB or reports of unanticipated problems that may affect subjects at local site.

Educational feedback sessions and focus groups were scheduled with individual departmental research staffs to review the policy and further develop effective tools to promote investigator compliance. Issues and concerns were discussed openly and changes were made based on input received. Additionally, communications were distributed via e-mail to the research community, including an overview of the policy and its development, a flowchart, a policy synopsis sheet (see Table 2), and AE reporting logs. Overall, recognition of the need to improve event reporting efficiencies and to ensure that potentially significant events were reviewed adequately was met with positive feedback.

Table 2

Interventional Studies (Greater than Minimal Risk): Adverse Event Reporting Requirements

	Internal		External
	Study Related or Possibly Study Related	Not Study Related	
Death Expected or Unexpected	Within 3 working days	Within 3 working days	Within 3 working days
Serious Expected or Unexpected	Within 10 working days	At Next Continuing Review or Study Termination	At Next Continuing Review or Study Termination
Non-serious Expected or Unexpected	At Next Continuing Review or Study Termination	At Next Continuing Review or Study Termination	Retain in Investigator's File

Note. For all study designs (observational, non-interventional, and interventional), any event that changes the risk/benefit ratio or causes a change in the protocol or consent form must be reported to the UHC IRB within 10 working days of learning of the event or of being notified of a required change.

A final round of educational feedback sessions was scheduled with departmental research staffs to review the policy revision and related reporting forms. Examples of AE reports were triaged in the session to provide practical experience with the new tools.

Following administrative policy review and feedback from the educational groups, the policy was officially enacted in August 2005. Full compliance (i.e., use of new forms and reporting strategies) was required by September 2005.

Retrospective collection of information back to January 1, 2005 began during the policy lead-in period from August through September 2005. This was done to enable descriptive statistical comparisons for the period immediately preceding the policy revision versus a post-policy time period. The IRB database was used to collect the raw number of AEs received and to differentiate between internal and external occurrences. The IRB database was also used to capture the total number of AEs reviewed by the full IRB for both the pre- and post-policy revision time periods.

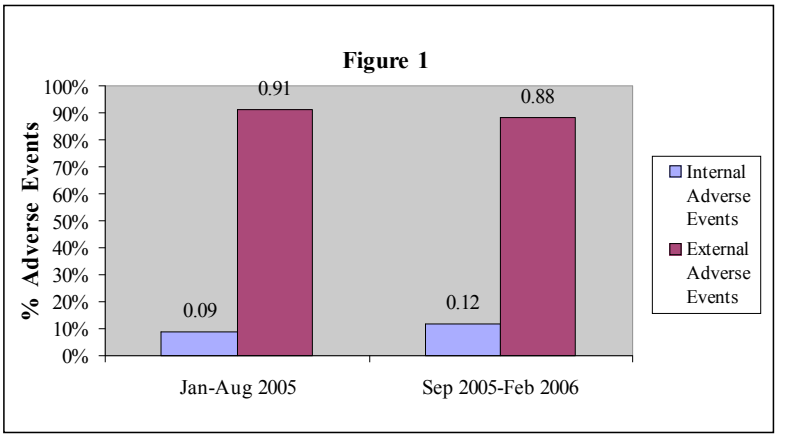
Calculations were made of the percent of internal versus external event reports received, monthly average of total AE reports received, and the percentage of the AE reports brought to full IRB for review. Each of these measures was compared by time periods before and after the change in policy.

Results

There was an immediate reduction in the total number of AE reports received by the IRB in September 2005. This was especially

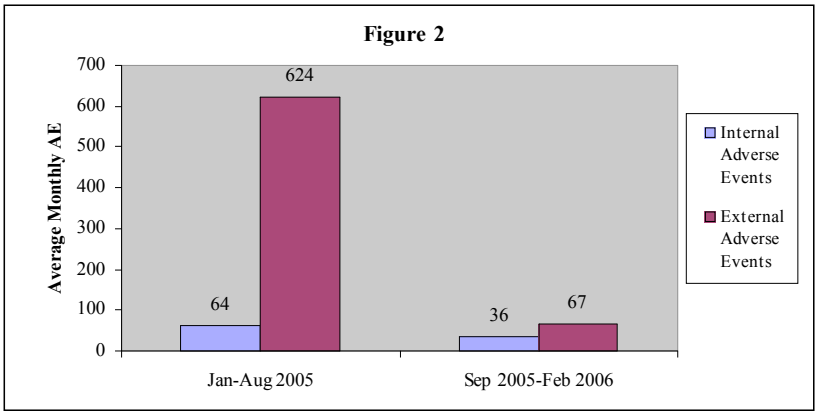
the case for the number of external AEs. This supported the argument that academic medical centers were not only inundated by the volume of event reports for review, but that the number of external reports was so great that it forced the inefficient use of resources and less-than-optimal reviews (see Figure 1). External AE reports yielded incomplete, duplicative, and minimally useful information while only increasing the IRB's workload.

Figure 1. Percentage of internal vs. external adverse events before and after policy implementation.



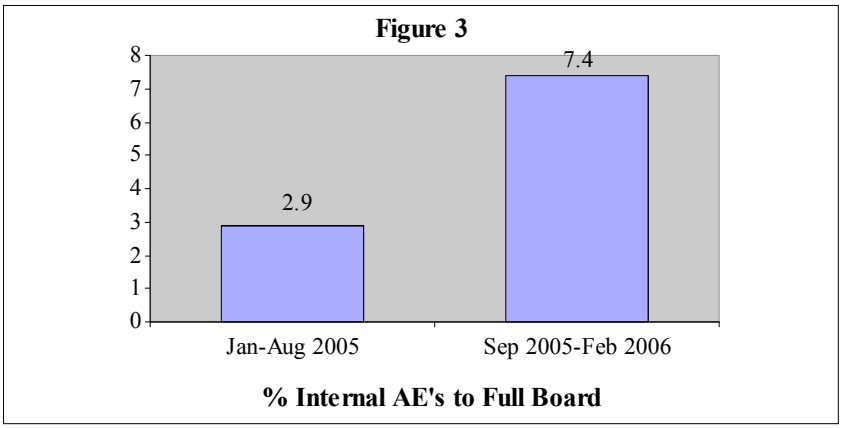
The new policy was instantly effective in shifting the focus away from reviewing large numbers of AEs toward attention on internal reports (see Figure 2). Furthermore, changes had to be implemented to address a projected 89% increase in total AE reports submitted to the UHC IRB in 2005 (i.e., total AEs in 2004 = 4,680 and the total AEs reported through August 2005 = 5,892, or a projected annual total of 8,838).

Figure 2. Average monthly internal vs. external AEs before and after policy implementation.



Less than 1% of all external AEs were deemed necessary for full IRB review from January 2004 through August 2005. During this same time, 3% of all internal AE reports were brought to the board. However, since the policy revision more than 7% of the internal AE reports have been brought to the full board (see Figure 3). Thus, it appears that more focus is being given to events on which research administrators and IRBs can have a positive human subject protection impact.

Figure 3. Percentage of internal AEs brought to full IRB before and after policy implementation.



Due to a reduced volume of external AEs accompanying the policy change, more attention and resources can be given by the IRB to relevant internal AEs. Thus, patterns and trends in AEs can be identified and proper adjustments can be made to improve human subject protection outcomes.

Conclusions

The reduction of external AEs received by the IRB and the increase in proportion of internal AEs reviewed by the full board may be the result of confounding variables and continued analysis will be necessary to ensure results can be generally attributed to the policy revision. However, the immediate results of September to December 2005, demonstrating the desired decrease of external AE influx and increased full Board review of internal AEs, were corroborated by a second review of additional results from the initial months of 2006 that showed similar trends.

Preliminary monitoring of AE reporting policy revision outcomes suggests the following: 1) a decrease in the volume of AE reports may allow improved quality review of AEs by the IRB; 2) decreased focus on external AE reports is in line with national recommendations and allows for better use of research administration resources in focusing on internal AE review; 3) a reduction in time and IRB resources resulted from the policy revision, which contributes to improved Human Research Protection Programs (HRPPs); and 4) policy revision outcomes regarding IRB review of internal AEs need continued monitoring to determine long-term effectiveness.

Positive outcomes of collaboration between research administrators, the IRB, and the research community in the process

of revising AE reporting policies and procedures include: 1) involvement of the research community in the development phase of a policy revision improves acceptance and enhances positive communications between research staff and research administrators; and 2) the use of focus groups and educational sessions increases the awareness of AE reporting requirements and predicts improved compliance.

Viewing the process of AE reporting in the broader context of human subject protection emphasizes the need for continued development of approaches aimed at maximizing IRB efficiency of AE report reviews.

On January 15, 2007, The Office for Human Research Protections (OHRP) issued revised "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events." This guidance provides instructive clarification of definitions for unanticipated problems and AEs, considerations for reviewing and reporting of unanticipated problems and AEs, and appropriate timeframes for reporting unanticipated problems to the IRB, appropriate institutional officials, the department or agency head, and OHRP. Based on the revised definitions, it is improbable that IRB procedures will change significantly; rather, the revisions will allow more obvious determination of the subset of AEs that are unanticipated problems that must be reported under 45 CFR part 46. Furthermore, the OHRP guidance supports the current UHC IRB practice for review of external AEs.

> Specifically,
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> OHRP advises that it is neither useful nor necessary under the HHS regulations at 45 CFR part 46 for reports of individual adverse events occurring in subjects enrolled in multicenter studies to be distributed routinely to investigators or IRBs at all institutions conducting the research. Individual adverse events should only be reported to investigators and IRBs at all institutions when a determination has been made that the events meet the criteria for an anticipated problem. (p. 11)

OHRP further notes that AEs for multicenter studies "should be submitted for review and analysis to a monitoring entity (e.g., the research sponsor, a coordinating center or statistical center, or a DSMB/DMC) in accordance with a monitoring plan described in the IRB-approved protocol." The OHRP guidelines for prompt reporting of unanticipated problems have established specific timeframes for reporting based on the specific nature of the unanticipated problem, the nature of the research associated with the problem, and the entity to which reports are to be submitted. As a result, the UHC IRB has developed a new policy, Reporting to Regulatory Agencies, Department Heads and Institutional Officials.

Finally, concerns remain that involvement of local IRBs in all aspects of multicenter clinical trials overloads the system, and as a result the local IRB cannot carry out its unique functions. Presently, HRPPs rely heavily on documentation of human research protection processes rather than more creative, quality improvement approaches to improve deficiencies. Improved efficiency in review of AEs by IRBs would allow for more emphasis on active monitoring of research conduct, including the informed consent process.

References

Burman, W. J., Reves R. R., Cohn, D., & Schooley R. (2001). Breaking the camel's back: Multicenter clinical trials and local institutional review boards. *Ann Intern Med*, 132(2), 152-157.

Dickler, H. (2005). Statement regarding adverse event reporting prepared for the FDA hearing March 21, 2005. Association of American Medical Colleges (AAMC). Washington, D.C.

Levine, R. J. (2001). Institutional review boards: A crisis in confidence. *Ann Intern Med*, 134(2), 161-163.

Mahoney, J. D. (1999). NIH initiative to reduce regulatory burden: Identification of issues and potential solutions. *NIH Office of Extramural Research*. Washington, D.C.

Morse, M. A., Califf, R. M., & Sugarman, J. (2001). Monitoring and ensuring safety during clinical research. *JAMA*, 285(9), 1201-1205.

National Institutes of Health. (1999). Guidance on reporting adverse events to institutional review boards for NIH-supported multicenter clinical trials. Washington, D.C.: DHHS.

Office for Human Research Protections (OHRP). (January 15, 2007). *Guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events*. Retrieved February 28, 2007, from http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm

Office of Inspector General (OIG). (1998). *Institutional review boards: A time for reform*. (DHHS Publication No. OEI-01-97-00197). Washington, DC: U.S. Government Printing Office.

O'Rourke, P., Borasky, D., & Hansen, K. Applied Research Ethics National Association (ARENA) and Public Responsibility in Medicine and Research (PRIM&R) Official public comment related to adverse events in the Federal Register, February 8, 2005, Volume 70, Number 25.

Weschler, J. (2004). Streamlining clinical research oversight. *Applied Clinical Trials, June 1, 2004*.

Weschler, J. (2005). Streamlining adverse event reporting in trials. *Applied Clinical Trials, June 1, 2005*.