

## Development and Progression of a Model: Prospective Research Compliance Monitoring

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### Authors' Note

The opinions in this paper are those of the authors and do not reflect the official policy of the Center for Clinical Research and Technology, University Hospitals Case Medical Center. Dr. Carol Fedor is the corresponding author. The evolution of the program described in this paper has been an ongoing process, including paper and poster presentations at previous SRA International Symposia. Finally, the authors acknowledge our Research Interns, Stephanie Polites and Lauren Seeds, for their contributions in data entry and assistance with compilation of information.

### Abstract

Recent trends in Human Research Protection Programs (HRPPs) have contributed to the rising emphasis on prospective monitoring of clinical research and education programs. Therefore, internal efforts and resources to monitor investigator compliance and site performance have become an important focus in the conduct of clinical research. Once the science and ethics of the research is approved by the Institutional Review Board (IRB), the investigator has the overall responsibility for conducting the research, protecting human subjects, and providing periodic reports and updates related to the research to the IRB. Any potential non-compliance issues that arise during the conduct of the study will be reported to the IRB and potentially prompt decisions about the continuation of the study. Nevertheless, institutions should recognize that

IRB review processes, investigations of noncompliance and prospective monitoring are distinct components within an HRPP. The Center for Clinical Research and Technology (CCRT) at University Hospitals Case Medical Center (UHCMC) recently implemented a prospective monitoring and education program and collected data to evaluate the program's development. Trends associated with resource utilization, monitoring procedures and educational activities of the program will be presented, as well as an analysis of the impact of the program.

*Keywords:* prospective monitoring, research compliance, responsible conduct of research, research administration

### Introduction

More than a decade ago, Weijer (Weijer et al., 1995) called for institutional research compliance monitoring programs for several purposes: education of researchers; prevention of problems; and avoidance of financial loss due to fraudulent research. In 2001, the FDA monitoring program revealed that 70% of human subject protection deficiencies are the result of investigator noncompliance (Wolfe & O'Rourke, 2002). Following the 1999 death of a healthy volunteer, the University of Pennsylvania developed the Office for Human Research (OHR) to assume internal compliance monitoring responsibilities. The focus of OHR was on investigator-initiated studies and moderate- to high-risk research whose mission was "not only to discover possible noncompliance but also to provide the education, tools, and resources to correct noncompliance" (Sherwin & Fromell, 2002). The UHCMC CCRT implemented a comparable approach, emphasizing post-IRB approval monitoring in unison with research education to promote research integrity.

Prior to the development of a prospective compliance monitoring program, investigation of allegations of noncompliance was a burdensome task requiring extensive resources by the UHCMC IRB office. Rather than compromising the effectiveness of the IRB and compliance program by exhausting shared personnel, the CCRT recognized that separate staff with compliance expertise would ensure efficiency of the monitoring program. The CCRT's prior experience also demonstrated that directed monitoring, or monitoring required by the IRB in response to a noncompliance issue, was not an effective or proactive means by which to manage noncompliance. As a result, the Office of Research Compliance (ORC) was created under the quality improvement initiatives for the Human Research Protection Program (HRPP), and was introduced to the research community as research-support services. The ORC applied the Association for the Accreditation of Human Research Protection Programs (AAHRPP) requirements as the foundation for the ORC's Standard Operating Procedures (SOPs). The initial SOP manual summarized the monitoring process, including the categories listed in Table 1.

Table 1  
*Components of Monitoring Process*

<b>Pre-Monitoring</b>	<b>Monitoring</b>	<b>Post-Monitoring</b>
Protocol selection	Monitoring Visit	Grant and Contract Review and Research Billing
Notification letter to Investigator	Informed Consent Observation	Investigational Pharmacy Evaluation
Scheduling visit, review of monitoring visit requirements		Certification Verification
IRB File Review		Conflict of Interest Assessment
Preparation for Monitoring		Post-Monitoring Letter
Informed Consent Document Review		Follow-up assistance
Pre-Monitoring Interview		

The following factors are considered when identifying priorities for monitoring of clinical research protocols: risk level; study population; whether the study involves treatment or intervention; and whether the study is investigator-initiated, industry or foundation originated, or federally funded. These categories represent factors to classify research conduct that poses greater than minimal risk to participants and may have a lesser amount of oversight by external regulatory monitors.

Congruently, with the development of the prospective compliance monitoring program, research education resources were being dedicated to establish a consistent offering of individualized and interactive education sessions. Beginning in September 2000, institutional programs were developed in preparation for the NIH mandate for investigator certification requirements in Human Subject Protections. Along with the initial core training utilizing the text “Protecting Human Subjects in Research” (Dunn & Chadwick, 1999) and subsequent adoption of the Collaborative Institutional Training Initiative (CITI) core curriculum, institutional seminar series, panel discussions, and workshops were developed, marketed and conducted monthly. The following categories of individuals from the research community were targeted for the research education and training (Table 2).

Table 2  
*Populations Targeted for Research Education*

Principal/Responsible Investigators	Co-investigators
Residents/fellows/graduate students	Research Coordinators/staff
Research Administrators	IRB members

These extensive efforts have successfully culminated in improving the conduct and oversight of research and establishing a program that transformed compliance monitoring into research integrity through principles of research conduct.

## Background

The diverse roles of research administrators have become progressively more comprehensive as this discipline moves toward continued professionalization and the conceptualization of research expands to an all-encompassing Human Research Protection Program (HRPP) (Cola, Fedor, & Haffke, 2005). Research administrators are responsible for the legal, fiscal, ethical, and scientific and compliance reviews of protocols from their initiation through completion. In the past, research administrators were regarded primarily as grant or IRB administrators (Cola, Fedor, & Haffke, 2005). In response to recent trends in clinical research and growth of regulatory oversight requirements, the profession has become more encompassing, and research administrators have assumed the roles of grant writers, clinical research coordinators, human subject protection and compliance specialists, and research billing professionals. This professional evolution has led to increased awareness and understanding of the vital roles that research administrators serve in the conduct of both basic science and clinical research.

A distinct area that has recently gained considerable momentum has been the role of the clinical research compliance monitor. Similar to other academic or business specialties, the process of conducting clinical research is closely monitored. Historically, this monitoring has been performed by external sources (i.e., the sponsor, contract research organization(s), or federal agencies). During the past decade, given the remarkable growth in clinical research, it has become evident that relying solely on external monitoring is inadequate to preserve the responsible conduct of research. Slater (2002) noted that, not only has federal funding for research doubled in the past decade, but from 1997 to 2000, the estimated number of participants in federally funded research increased from 7 million to 12 million. Non-federally sponsored research has grown at a similar pace (Slater).

These trends have driven the desire and need to create internal research compliance monitoring functions in an effort to improve research programs and to provide supportive services to investigators that allow them to conduct clinical research effectively. Some institutions have developed these programs in response to specific compliance findings discovered by external monitoring activities (Steinbrook, 2002). Such shortcomings in human subject protection programs at major institutions should serve as a catalyst for all institutions, researchers and IRBs that are charged not only with promoting clinical advances, but first and foremost, protecting the human subjects involved in the process (Shalala, 2000).

Additionally, the continuing education of research administrators and institutional officials makes it apparent that internal compliance monitoring programs that proactively review the conduct of clinical research at the institution are essential. Research institutions must commit to regular and routine internal monitoring of all research activities. Critical self-examination can bring to light weaknesses and other issues before significant errors occur (Icenogle, 2003).

It is believed that, to be effectively connected to the other critical components areas of an HRPP (i.e., the administrative functions of an IRB and grant accounting), compliance monitoring programs should be established within Offices of Sponsored Projects at Universities and Research

Administration of hospitals based in Academic Medical Centers (AMCs) (Speers & Cooper, 2003, Institute of Medicine, 2001). Research compliance monitoring and education programs are not only a routine function of these types of institutions, but rather specialized functions that enhance the overall research administration effort.

In June 1998, the Office of Inspector General of the Department of Health and Human Services issued four investigative reports, which indicated that IRBs have excessive workloads and inadequate resources (Shalala, 2000). The inadequate resources included insufficient staff, expertise, space, and equipment such as databases.

It is difficult to absolutely ascertain the accuracy and impact of these reports on the behavior of AMCs, however, the information provided has prompted research institutions to define the role of the IRB in greater detail and to expand the scope of programs better designed to ensure the protection of human subjects in research. These programs have been developed by institutions through research administrative offices to provide assurances of their compliance with regulations (Sherwin & Fromell, 2002). Out of these developments, the focus has shifted from traditional research administration toward a prospective compliance and education focused approach.

The fusion of internal monitoring programs and research administration activities into central research offices has also led to the creation of external accrediting bodies for Human Research Protection Programs (HRPPs) (Cola, Fedor, & Haffke, 2005). This may be attributed to the concept that preparation for voluntary accreditation includes a self-assessment of the overall research protection programs, including compliance and safety (Burke, 2005). These programs are often construed as being synonymous with IRB accreditation, however the scope and purpose of such programs goes beyond the operational matters of an IRB and its corresponding administrative office and assesses many more components (i.e., institutional support and understanding; congruence with grant administration; research educational programs for investigators, clinical research coordinators, research administrators, research participants; and research compliance programs). Accreditation must approach the HRPPs broadly from an organizational perspective that is beyond a focus of IRB operations to examine whether policies and procedures of the organization as a whole result in a coherent, effective scheme for the protection of human research participants (Speers & Cooper, 2003).

Efforts aimed at improving HRPPs would be remiss if comprehensive education was not an integral component of the approach. As Shalala (2000) notes, "The never-ending challenge for academic institutions and other organizations participating in research is to make sure that researchers and other personnel have up-to-date training and a thorough knowledge of their responsibilities. Those responsibilities include communicating with IRBs, ensuring that procedures for informed consent are followed, monitoring compliance with protocols, and reporting on safety issues." Comprehensive education efforts for the entire research program at AMCs should be focused not only on facilitating the understanding of federal regulations and institutional policies and procedures, but also on the results of their own compliance activities.

Through compliance activities, AMCs are able to scrutinize the clinical research conducted at their institution, monitor for common non-compliance trends, and identify areas of needed continuing research education. Furthermore, improved educational efforts and compliance activities in conjunction with all components of research administration serve to improve the overall quality of the research, increase the quality of human subject protections, and enhance the efficiency of the IRB (Sugarman, 2000).

This paper aims to describe the development and implementation of a research compliance monitoring program along with the specific research educational support at an AMC. This combination allows for a focus on the role of research administration functions in the responsible conduct of clinical research. The combination of compliance monitoring and education advances research integrity and as a consequence research administrators are better able to account for and incorporate these activities into their institutional responsibilities.

### Methodology

An essential strategy for the ORC was to identify each of the activities involved in research compliance monitoring that would be captured for future benchmarking. Therefore, a database was created to accurately document the time and resource requirements for the entire monitoring process. A monitoring activity worksheet documented the date of the activity, the IRB protocol number, the principal investigator, the times the activity began and ended, and the specific activity that occurred. A Research Compliance Specialist (RCS) recorded and maintained the monitoring activity worksheet and database.

A summary of UHCMC ORC monitoring activities (n=14) is summarized in Table 3. In general, the activities are completed in the order that they are listed, although informed consent observations can occur at any time due to the random nature of participant enrollment. From February 2006 to August 2007, 55 protocols were monitored. For the purpose of this presentation, 49 monitored protocols are included in the summary; 6 were excluded because not all of the intended activities were completed at the time of analysis (August 2007). The sample of monitored protocols included 26 investigator-initiated protocols (23 prospective, 3 directed) and 23 sponsored (federal and industry) protocols (12 prospective, 11 directed). Prospective monitoring refers to a routine, random selection of protocols that have been approved by the IRB. Directed monitoring refers to a review requested by the IRB in response to a protocol deviation/unanticipated problem or compliance issue that is identified.

Table 3  
*Summary of ORC Monitoring Activities*

<b>Monitoring Activity</b>	<b>Examples of the Activity</b>
Administrative	Composing and mailing of initial contact letter to principal investigator; creating compliance monitoring files
Scheduling	Explanation of the monitoring program; scheduling monitoring visit (s)
IRB File Review	Review all protocol submissions (New, Continuing Review, Amendments, Adverse Events, etc.)
Preparation for Monitoring	Review of protocol; copy of informed consent; creating inclusion and exclusion criteria checklist
Informed Consent Document Review	Thorough review of consent document for required and suggested elements
Pre-Monitoring Interview	Interview to discuss the study roles and responsibilities, location where protocol and consent process is conducted, and how and by whom the consent process is implemented
Monitoring Visit	Review of the subject source documents; subject recruitment; informed consent and Health Insurance Portability & Accountability Act documents; confirmation of eligibility; adherence to protocol; Adverse Event reporting; data collection; lab tests; research and medical records; all related study correspondence
Informed Consent Observation	In-person observation of the informed consent process
Grant and Contract Review	Review budget; contract status; patient billing; and other study expenditures
Investigational Pharmacy Evaluation	Test article accountability; site of storage; inventory and transaction records
Certification Verification	Review protection of Human Subjects Certification
Conflict of Interest Assessment	Verification of appropriate Conflict of Interest disclosure (if applicable)
Post-Monitoring Letter	Composition of summary of findings for principal investigator
Follow-up	Assist investigators with response, and addressing any findings

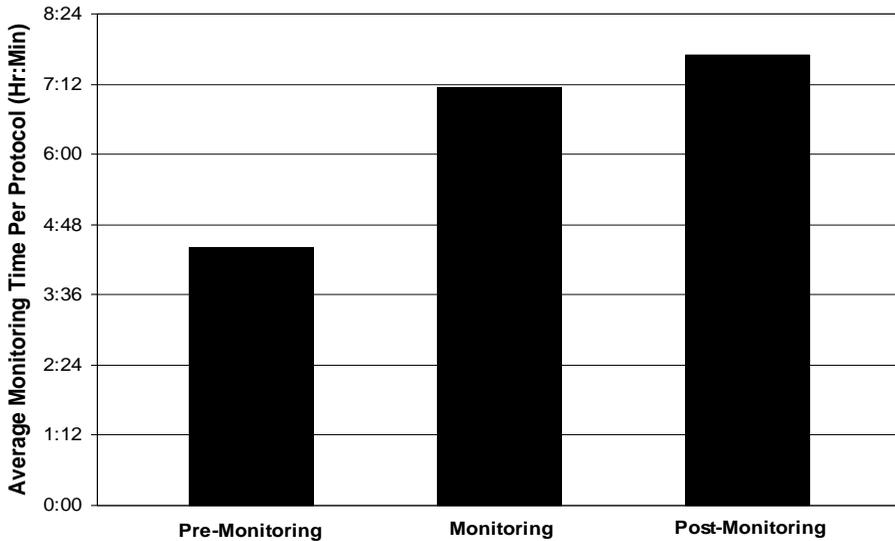
## Results

To estimate the required resources for the monitoring program, a projected monitoring time was calculated, including each of the monitoring activities listed above. It is important to note that while a protocol may not utilize investigational pharmacy, monitoring would still encompass review of proper drug or device accountability. The resulting projected monitoring time was a total of 19 hours and 17 minutes. Actual monitoring time was analyzed by determining the average time required to monitor a protocol, which was found to be 17 hours and 15 minutes per protocol (Range: 5 hours 19 minutes to 40 hours 57 minutes). An average of 9 monitoring activities was completed per study.

The monitoring activities were pooled based on the following categories as listed in Table 1: pre-monitoring, monitoring, and post-monitoring. On average, the pre-monitoring phase required 4 hours and 25 minutes, the monitoring visit required 7 hours 9 minutes, and the post-monitoring phase required 7 hours and 42 minutes (Figure 1). The pre-monitoring phase required less than one-fourth of the total monitoring time, while both the monitoring and post-monitoring phases required approximately 40% of the total monitoring time. Of note, the post monitoring letter

that is completed during the post-monitoring phase requires 3 hours and 42 minutes (46.1%) of the total 7 hours and 42 minutes needed to complete this entire phase.

Figure 1  
*Average time per monitoring phase.*



In addition, the time requirements for monitoring were categorized by how the study was chosen: directed versus prospectively selected protocols. On average, prospective protocols required approximately 15 hours and 25 minutes, and directed protocols required 18 hours and 54 minutes to monitor. Further analysis was done using the Fishers exact test to calculate the differences in types of studies and how the studies were selected (i.e., investigator-initiated / sponsored and prospective/directed). The result of this analysis ( $p = 0.01$  two-tail) indicated that there was a significant difference in the types of protocols and method of selection.

As a result of the trends and common findings observed during the monitoring program, the ORC developed a series of education seminars for the research community that encompassed regulatory requirements, institution specific policies, and incorporated existing research coordinator training. The seminars addressed topics such as adverse event reporting, informed consent, IRB submissions (including chart reviews and research with discarded tissue), and exempt research. Continuing research education credits were offered for each of the sessions. A total of 437 individuals attended 23 one-hour sessions that were held from February 2006 through August 2007.

In addition, education sessions were developed in response to specific non-compliance matters reviewed by the IRB. These were mandatory education sessions that included topics such as adverse event reporting, informed consent, investigator responsibilities and an overview of responsible conduct of research. A total of 139 individuals attended 19 two-hour sessions that were held from February 2006 though August 2007.

While the total number of attendees was greater for the continuing research education sessions, the time investment per person for the mandatory education sessions was more intensive. The continuing research education sessions required 3 minutes per person compared to 16 minutes per person for the mandatory education sessions; a five-fold increase in the time and resources invested.

## Conclusions

The CCRT prospective monitoring and education program has increased awareness in the research community amongst Principal Investigators, Clinical Research Coordinators and IRBs of the need for continual re-assessment of how research should be conducted. While the initial impression of a monitoring visit may be met with anxiety and a multitude of questions, the outcome has resulted in the perception of support and education. Deficiencies are noted, corrective actions are implemented and, most importantly, a relationship is established for improving ongoing communication. The ORC staff are the key individuals, in this setting, providing infrastructure for educational training sessions for principal investigators and research staff. The response to these training sessions and attendance has been very positive, bestowing credence to the ORC's role in education.

Furthermore, prospective compliance monitoring and education may ultimately reduce research staff workload and administrative burdens on the IRB office, as ongoing prospective monitoring and education will allow for earlier identification and correction of discrepancies. In other words, prospective monitoring in combination with continuing research education requires significantly less time and resources than directed monitoring and mandatory education. This allows for more efficient research administration, encourages the responsible conduct of research, and promotes the protection of human subjects.

For a research compliance and education program to be effective, continual assessment and quality improvement of the program are essential. The data collection and results of the monitoring program enabled the UHCMC CCRT to target the essential areas in the educational sessions. Research Monitoring and Education programs should be designed to support the needs of all members of the research community and emphasis placed on the responsible conduct of research. Effective approaches to research administration of an HRPP should include prospective compliance monitoring and continuing research education in order to more efficiently utilize resources and successfully educate a greater number of research community members.

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