Current Challenges and Opportunities in Clinical Research Compliance

Wendy Portier, RN, MSN, CCRC, CCRP and Claire Dunne, PhD

BACKGROUND

Compliance with the rules and regulations related to clinical research is like working your way through a maze, and the federal agencies tasked with clinical research oversight can sound like alphabet soup to the uninitiated (e.g., FDA, OHRP, DHHS, JCAHO). Clinical research regulatory oversight is the responsibility of two main governmental agencies: the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP). Both FDA and OHRP are agencies under the Department of Health and Human Services (HHS). The FDA enforces the Food Drug and Cosmetic Act, which regulates foods, drugs, devices, and cosmetics, and OHRP regulates any research that is federally funded. The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) now also reviews aspects of clinical research activities during site assessment visits. Keeping abreast of all the rules, regulations and compliance issues related to clinical research can be a daunting task (see Figure 1).

Ochsner Clinic Foundation (OCF) has taken a unique approach to clinical research compliance by creating a Research Compliance Program (RCP). The RCP fits into a larger organizational Corporate Compliance Program, which includes the seven elements of a compliance program as outlined by the Office of the Inspector General (OIG). The RCP is also one component of OCF's overall Human Research Protection Program.

Human subject protection is the highest priority while conducting clinical research. In recent years, clinical research has come under increased public scrutiny due to media attention related to institutional research "shut downs" and subject deaths. Due to this level of heightened awareness, the compliance bar has risen for clinical research. The balance of this paper highlights challenges and opportunities related to clinical research compliance including areas possibly targeted by federal and state regulators.

HOT TOPICS

FDA

For the past several years, the FDA has stepped up its enforcement efforts related to clinical research. Figure 2 reviews the five most common FDA compliance citations.

Informed Consent

Obtaining informed consent is not merely the task of getting a subject to sign the Institutional Review Board (IRB) approved consent form. It is a process that involves a dialogue between the investigator and the subject where the subject is encouraged to discuss any concerns they may have about participating in the study. The investigator should address the risks and benefits of the study and answer any questions the subject may have. The subject must be given a copy of the consent form to take away with them.

Figure 1. Governmental Resources

Agency	Function	Contact Information
Department of Health & Human Services (DHHS)	Protects the health of all Americans and provides essential human services.	*www.hhs.gov*
Food & Drug Administration (FDA)	The FDA is responsible for protecting the public health related to drugs, medical devices, our nation's food supply, cosmetics, and products that emit radiation.	*www.fda.gov* Warning Letters – *www.fda.gov/foi/warning.htm* Code of Federal Regulations Search *http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm*
Office for Human Research Protections (OHRP)	Provides oversight to all federally funded research.	*ohrp.osophs.dhhs.gov* Compliance & Oversight Information– Determination Letters - *ohrp.osophs.dhhs.gov/compovr*
National Institutes of Health (NIH)	NIH is the steward of medical and behavioral research for the Nation.	*www.nih.gov*
Joint Commission on the Accreditation of Healthcare Organizations (JCAHO)	JCAHO sets the standards by which health care quality is measured and now includes clinical research in their assessments.	*www.jcaho.org*
Office of Civil Rights (OCR)-HIPAA	OCR enforces the HIPAA regulations.	*www.hhs.gov/ocr/hipaa*
Centers for Medicare & Medicaid Service (CMS)	Assures the health care security for beneficiaries.	*www.cms.gov* Medicare Coverage ~ Clinical Trials Final National Coverage Decision *www.cms.hhs.gov/coverage/8d2.asp*
Office of the Inspector General (OIG)	Charged with protecting the integrity of Department of Health and Human Services (HHS) programs.	*oig.hhs.gov*

Figure 2. Five Most Common FDA Compliance Issues

Issues	Actual FDA Warning Letter Citations	Other Problems
1. Informed Consent	"Failure to obtain informed consent from study subjects"	Improperly executed informed consent, Outdated informed consent form used
2. Protocol Deviations & Violations	"Failure to inform the IRB of changes to the protocol" "Failure to conduct your study in accordance with the approved protocol"	Changes made to the protocol without first notifying the sponsor & IRB
3. Drug & Device Accountability	"Failure to maintain device accountability records."	Inadequate record keeping related to investigational drugs & devices
4. Inadequate Medical Records	"Failure to maintain adequate and accurate records" "Failure to maintain accurate, complete, and current subject records."	Trial related source documentation is not properly recorded which can lead to problems especially if the subject suffers an adverse event.
5. IRB approval not obtained	"Failure to adhere to the general and specific responsibilities of a clinical investigator"	IRB approval not obtained or lapse in IRB approval (no continuing review)

(Clinical Trials Compliance, Sept, 2003 & Food and Drug Administration, 2003)

This discussion must then be documented in the subject's chart as an accurate and complete record of the initial consenting process. The date and time consent was obtained should also be recorded. Each time the subject returns to see the investigator for a study visit they should be asked if they wish to continue to participate and if they have any questions or concerns regarding the study. This information should be documented in the subject's medical record to demonstrate the ongoing process of informed consent.

As the study progresses the consent form may go through some changes and updates so several versions exist. It is important that the most current version is used to consent the subject and a signed and dated copy is kept by the investigator. The FDA regulations at 21CFR50 detail the requirements for a consent form: 21CFR312.62(b) requires the maintenance of adequate and accurate case histories for drug studies.

Protocol Deviations and Violations

A protocol deviation or violation occurs when the established procedures and/or inclusion/exclusion criteria set out in the protocol have not been adhered to. Whenever it is under the control of the PI, all protocol deviations must obtain PRIOR approval from the IRB, if it affects subject safety or scientific validity, etc., and the sponsor. Any deviations from the protocol need to be documented. When a deviation occurs to eliminate an immediate hazard to subjects, prior approval may be waived.

Drug and Device Accountability

Drug and device accountability records are maintained to provide evidence that all investigational material is accounted for. At the conclusion of a study the Sponsor (and in some instances, federal regulators) may use these records to ensure the test article was distributed and disposed of correctly.

Inadequate Medical Records

It is the responsibility of the Principal Investigator to ensure that adequate and accurate records are maintained for each study subject. These records should include information on, but not limited to, the following: medical history, inclusion/exclusion criteria, physical and other relevant findings, informed consent process, subject education, each study visit, adverse events, exposure to test/control article, test reports, and procedures.

IRB Approval

The IRB is tasked with protecting the rights, safety and welfare of participants in research studies. The IRB is guided by the Belmont Report and is subject to regulation by federal oversight agencies, including FDA (21CFR50 and 56) and, in many cases, OHRP (45CFR46). The Principal Investigator must ensure the IRB is provided with all necessary and relevant information to allow an effective review of the research prior to study commencement. After the initial approval, the IRB must be kept informed of the progress of the study through the continuing review process and be informed of any changes to the research.

IND/IDE Applications

The FDA is focusing more attention on the need for Investigational New Drug (IND) / Investigational Device Exemption (IDE) applications prior to beginning certain clinical research studies, specifically studies that are sponsor-investigator initiated. IND and IDE applications allow the FDA to review studies for scientific validity and safety prior to study commencement thereby fulfilling their commitment to protect the public. The need for IND/IDE applications came to light out of a tragedy. Ellen Roche, a healthy 24-year old volunteer at Johns Hopkins, died after inhaling hexamethonium (a shelf chemical), which damaged her lungs. The FDA cited the researcher for failing to apply for an IND (1), which may be needed even in clinical studies with approved drugs and devices. See "Frequently Asked Questions on Drug Development and Investigational New Drug Applications" at *http://www.fda.gov/cder/about/smallbiz/faq.htm* for further guidance.

Office of the Inspector General (OIG)

The OIG's mission is to improve HHS programs and operations and to protect them against fraud, waste, and abuse by conducting audits and investigations. Annually, the OIG issues a Work Plan that describes the various project areas perceived as mission critical to the OIG and HHS. In recent years, clinical research has received more and more attention by the OIG. The 2003 and 2004 Work Plan addressed the following areas related to clinical research: human subject protections for children, commitment of Principal Investigator's effort in grant applications, grantee administration of funds, clinical trial oversight, and adverse event monitoring and reporting (2). At OCF, we use the OIG Work Plan to assist in planning our corporate and research compliance program initiatives.

Compliance Program Guidance

In August 2003, the OIG began soliciting public comment related to developing and implementing effective "Compliance Program Guidance (CPG) for Recipients of NIH Research Grants." The OIG's request has

Figure 3. Professional Organizations

Organization	Details	Contact Information	Certification Offered
Association for Clinical Research Professional (ACRP)	Provides global leadership for the clinical research profession by promoting and advancing the highest ethical standards and practices.	*www.acrpnet.org*	Research Coordinators and Investigators
Applied Research Ethics National Association (ARENA)	Supports professionals concerned with issues relating to the protection of human subjects and other ethical issues pertaining to biomedical and behavioral research.	*www.primr.org/arena.html*	Institutional Review Board Professionals
Public Responsibility in Medicine & Research (PRIM&R)	Committed to the advancement of strong research programs and to the consistent application of ethical precepts in both medicine and research.	*www.primr.org*	
Health Care Compliance Association (HCCA)	Champion ethical practice and compliance standards in the health care community	*www.hcca-info.org*	Healthcare Compliance Professionals
American Academy of Pharmaceutical Physicians (AAPP)	Dedicated to enhancing the proficiency of pharmaceutical physicians	*www.aapp.org*	Investigators
Drug Information Association (DIA)	Offers educational programs, training courses and areas to support career development within highly regulated health care and related industries.	*www.diahome.org*	Investigators
Other • International Conference on Harmonisation (ICH)	The purpose of ICH is to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines in different countries.	*www.ich.org*	
• Organizational Policies	See local policies		
• Institutional Review Board (IRB)	Protects human subjects	See IRB of record policies	

highlighted the need for research compliance programs that must include an audit function in order to adequately assess the internal control structure of an organization. Risk areas tentatively identified include: the proper allocation of charges to grant projects, "time and effort" reporting, including an accurate reporting of the commitment of effort by researchers, and use of program income (3).

Segregation of Sales & Marketing from Research

In April 2003, the OIG published a compliance guidance aimed at assisting pharmaceutical manufacturers in developing and implementing internal controls and procedures that promote adherence to applicable regulations and requirements of the federal health care programs. One area of interest to clinical research sites is the need for sponsor companies to separate sales from research activities, which is especially applicable to Phase 4 post-marketing studies. The OIG's Guidance states, "Post-marketing research activities should be especially scrutinized to ensure that they are legitimate and not simply a pretext to generate prescriptions of a drug. Prudent manufacturers will develop contracting procedures that clearly separate the awarding of research contracts from marketing. Research contracts that originate through the sales or marketing functions – or that are offered to purchasers in connection with sales contacts – are particularly suspect" (4). The concepts outlined in this CPG can also be applied to the device industry.

Clinical Trial Billing & Residual Funds

A solid billing program is necessary in order to ensure proper billing to third party payors and study sponsors. Billing errors in clinical trials can lead to issues such as "double-dipping" and/or Medicare billing fraud, e.g., billing a third party payor for procedures paid for by the sponsor. Substantial penalties are associated with violations of federal and state billing requirements (5).

In 1995 and 2000, the Centers for Medicare and Medicaid Services (formerly known as Health Care Financing Administration - HCFA) issued National Coverage Decisions (NCD) related to clinical trials. In certain instances, Medicare may be billed for "routine costs" associated with a "qualifying" clinical trial. Implicit in these NCD's is the requirement to clearly document the segregation of individual procedures between those that are considered "standard therapy" and/or "medically necessary" and those that are trial induced. See Figure 1 – CMS for further guidance.

Another risk area is associated with residual funds. According to Clinical Trials Compliance September, 2003 issue, "a lack of policies and procedures regarding leftover money at the end of a trial can also raise issues"(5).

HIPAA
HIPAA is the acronym for the Health Insurance Portability and Accountability Act, which became law in August 1996. The Secretary of HHS was mandated to produce a regulation to protect the privacy of certain health information. This mandate resulted in the publication of the regulation (45CFR160 and 164) "Standards for Privacy of Individually Identifiable Health Information", more commonly referred to as the "Privacy Rule." By the compliance date of April 14th, 2003 (April 14th, 2004 for small health plans) covered entities were required to have standards implemented to protect individually identifiable health information (usually referred to as "protected health information" or "PHI") from misuse.

The Privacy Rule defines research as a "systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge". While this definition is similar to the definition of research under the federal Common Rule, the Privacy Rule is broader in its coverage. For example, the Common Rule exempts research where information cannot be readily identifiable but under the Privacy Rule this information may still qualify as PHI and require an authorization or waiver of authorization.

The implementation of HIPAA has had a significant impact on clinical research because of these new requirements for authorization and protection of health information.

Conflict of Interest
The Enron and WorldCom scandals shook the accounting world. Both of these financial debacles were fraught with conflicts of interest from the Chief Executive Officer to the Board of Directors to the External Auditors. These accounting scandals have resulted in new laws, e.g., Sarbanes Oxley Act, which specifically addresses conflicts of interest.

Conflict of Interest is also a hot topic in clinical research encompassing institutional officials, members of the Board, investigators, and IRB members. Currently, the FDA requires financial disclosure from every investigator involved in a FDA clinical study. If an investigator has a financial conflict of interest, as defined by institutional policies, in a clinical study, the conflict can represent risk to the subject, the organization, and the sponsor. Therefore, disclosing and managing conflicts of interest upfront is of utmost importance. The Code of Federal Regulations currently forbids IRB members to participate in the review of a project in which they have a conflict of interest (45CFR46.107e).

One example of a possible institutional conflict of interest occurred at one of the nation's largest cancer centers when 195 people were enrolled in a study without being informed that the institution's president held a financial interest in the product that could potentially earn him millions (6).

Conflict of interest is an important issue for institutions, IRBs, and single investigators to address. Guidance regarding conflict of interest can be obtained from the following governmental agencies and professional organizations: FDA, OHRP, NIH, Association of American Medical Colleges (AAMC), and the Association of American Universities (AAU) to name a few.

CONCLUSION

Complying with all of the rules and regulations related to clinical research can be overwhelming. The root causes of non-compliance can be found in poor record keeping and lack of training (5). To address these causes, several clinical research professional organizations offer educational opportunities including certification for clinical research coordinators, investigators, and IRB professionals (see Figure 3).

According to the American Academy of Pharmaceutical Physicians (AAPP), 2003, certification signifies the presence of a basic knowledge sufficient for the safe and ethical conduct of a clinical trial in accordance with the appropriate ethical, scientific, legal, and regulatory standards. Recently, the AAPP President, Dr. Hans de Haan, specifically discussed investigator certification at the Mayo Clinic conference, and the title of his talk sums up one approach to address the current challenges and opportunities in clinical research compliance: "Current Issues in Clinical Research: How Education, Certification, and Validation Will Improve the Quality of Research" (7).

Wendy Portier, RN, MSN, CCRC, CCRP
Compliance Officer - Director of Compliance & Audit

Claire Dunne, PhD
Managing Auditor

REFERENCES

1. Clinical Trials Compliance (June 2003). FDA warning letter signals move to tighten oversight. Strategies for Medicare Billing, FDA, and Research Compliance, 2, 1-12.
2. Office of the Inspector General (2003). Work Plan. Retrieved October 14, 2003 from the World Wide Web: *http://oig.hhs.gov/publications/workplan.html*
3. Federal Register (September 2003). Solicitation of Information and Recommendations for Developing Compliance Program Guidance for Recipients of NIH Research Grants. Retrieved October 14, 2003 from the World Wide Web: *http://oig.hhs.gov/authorities/docs/FRcpgNIHsolicitation.pdf4.* Office of the Inspector General, CPG (2003). Compliance Program Guidance for Pharmaceutical Manufacturers. Retrieved October 14, 2003 from the World Wide Web: *http://oig.hhs.gov/fraud/docs/complianceguidance/042803pharmacymfgnonfr.pdf*
5. Clinical Trials Compliance (September 2003). Sidestepping the five most common FDA compliance pitfalls. Strategies for Medicare Billing, FDA, and Research Compliance, 2(9), 1-3.
6. Gillis, J. (June, 2002). A hospital's conflict of interest - Patients weren't told of stake in cancer drug. Retrieved October 14, 2003 from the World Wide Web: *http://www.commondreams.org/headlines02/0630-03.htm*
7. Haan H. (September, 2003). American Academy of Pharmaceutical Physicians. Retrieved October 14, 2003 from the World Wide Web: *http://aapp.org/pdf/HansMayoPresentation.pdf*