Compliance Requirements for Clinical Research

What You Need to Know for an Affective Compliance Program

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Clinical trials research is subject to a number of federal and state laws and regulations. In addition, sponsors set down their own requirements through contracts and protocol designs that require investigators to comply with or adhere to certain expectations in conducting clinical trials. The failure to achieve compliance can have many consequences, including federal exclusions or debarment of individual investigators, civil monetary penalties, and, in some instances, the application of criminal law. The failure to achieve compliance may also be evidence of a breach of a standard of care. Thus, if a subject is injured as a result of the failure to meet such a "standard," resulting in foreseeable harm, noncompliance may be used to prove negligence. Noncompliance may also signal a breach of contract between a clinical investigator or research organization and the sponsor. The failure to abide by compliance standards in such instances could lead to withdrawal of funding for the research and termination of the clinical trials agreement. The subsequent adverse publicity from regulatory action or litigation may have additional consequences, such as adverse publicity in the community and a reticence on the part of researchers or sponsors to conduct trials at the health care organization.

One way to avoid such problems is through corporate compliance programs. As a voluntary set of guidelines embraced by health care organizations and clinical research organizations (CROs), compliance programs can lead to conformity and good research practices, reduce the risk of subject injury, and help to maintain the reputation of the institution and researchers. Adopting such programs involves more than paying "lip service" to a set of ethical principles. It means adhering to well-defined parameters of conduct. Regulators and sponsors expect that the compliance plan, once adopted, will be followed by health care entities and CROs. Treating the plan as "window dressing" is unacceptable. Indeed, there can be severe consequences for those who profess to have a culture of corporate compliance when in fact it is nothing more than a pretext for securing funding. This paper examines the operational aspects of a research compliance program and the steps that can be taken when there is evidence of regulatory or contractual noncompliance.

**Relationship between Corporate Compliance and Clinical Research**

Many aspects of clinical trials come within the scope of the laws used to combat fraud and abuse in Medicare, Medicaid, and other federal reimbursement programs, including the False Claims Act, the Stark self-referral provisions, and the fraud and abuse "antikickback" laws. Some examples help to explain how these laws pertain to clinical trials research.

*Making False Statements.* When a researcher, a health care entity, or another body signs an assurance that it is compliant with all federal requirements, knowing that such statements are false, it implicates the False Claims Act. A researcher who knows, for example, that his study does not comport with Part A of the HHS regulations governing clinical trials could be in legal jeopardy by executing a "false" statement that the ongoing study is in compliance with the regulations.
• **Making a False Claim.** When a health care organization bills a federal health program for a "procedure" that is actually a cost item covered under a federal grant, such a submission is a false claim.

• **Falsified Research.** When a researcher or organization submits a final report on a study to complete remuneration of study costs, knowing that the data are false, it constitutes an infraction under the "false statement" component of the False Claims Act.

• **Antikickback Provisions.** When a researcher gives substantial sums of money for steering patients into clinical studies as part of a recruitment scheme or gives a physician money to participate in questionable research, it may violate the antikickback law, which prohibits transactions that lead a caregiver to make referrals or to compensate them for doing so. It should be noted that there are so-called "safe harbor" provisions under this law permitting activities that would otherwise be unlawful. Whether the clinical trial comes within the scope of safe harbor requires a thorough analysis of the study and transactions.

• **Self-Referral Provisions.** Under the Stark provisions, a clinician is precluded from making a referral of a Medicare or Medicaid recipient to a facility that provides certain designated health care services if the caregiver has a financial relationship with that entity. There are some exceptions under the Stark provisions. However, it is possible that a physician-researcher can have the type of "financial relationship" that triggers the application of the Stark law with respect to a patient-subject. Much depends upon careful evaluation of the legal relationship between the clinician and the facility.

There are other ways in which noncompliance can generate application of federal law, for example, failure to report adverse events when it is required under regulations, violation of laws protecting the disabled or handicapped in terms of subject recruitment or consent, and failure to meet confidentiality provisions. Infractions in these instances provide evidence of a breach of assurance and contract statements promising to meet federal protections and standards, especially if a researcher or sponsor claims to subscribe to nationally accepted standards for avoiding conflict of interest. A breach of these undertakings may constitute loss of federal contracts or assurance or private sponsorship contracts and become evidence of noncompliance under institutional programs.

Other laws may be pertinent, too. For example, using the U.S. Postal Service or electronic transmission of data across state lines may trigger the application of a different class of laws. Sending false reports in the postal system may amount to mail fraud, just as an e-mail of false data in a multicenter study may trigger wire fraud when the intent is to use the information to secure grant funds or unlawful remuneration of costs.

The federal government has a cadre of civil and criminal tools to use to make researchers, sponsors, and health care facilities become compliant. If a good plan is in place to avoid improper conduct, they should not need to do so.
Beside federal civil and criminal enforcement action, administrative authority is vested in federal agencies with oversight responsibilities for clinical trials. Some of this activity is undertaken by the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the Public Health Service (PHS), and other regulatory bodies that support or have responsibility for human research trials. It is useful to see how some of these bodies handle compliance oversight.

**Office of Management Administration**

Within the NIH, the Office of Management Administration (OMA) reviews allegations of fraud, waste, and abuse involving internal matters as well as those involving extramural grantees and contractors. In essence, the major focus of the OMA is on financial mismanagement in clinical trials. When serious misconduct or fraud becomes apparent to the OMA, the information may be shared with the Office of Inspector General of HHS. It is also possible that the matter could go beyond administrative intervention. Thus, instances of fraud and abuse in NIH funded research could become the subject of a criminal prosecution by the U.S. Attorney's office.

**Office of Extramural Research**

The Office of Extramural Research of NIH handles an issue of growing importance in clinical trials-conflict of interest. As this topic impacts consent to participate in clinical trials research, subject recruitment, study design, data management and reporting, and a number of other concerns, it is bound to capture more attention in the future. Not only is there the potential for findings of misconduct for failure to disclose a conflict of interest, but there is a very real issue of possible criminal liability under the False Claims Act. This is especially the case when a researcher signs documentation assuring the PHS that he or she does not have a conflict of interest. Securing federal funding for clinical trials on the basis of a false statement (that is, where the researcher does have) a conflict of interest, could form the basis for criminal proceedings.

**Office of Research Affairs**

In the FDA, the Office of Research Affairs (ORA) has a broad mandate covering research misconduct involving the testing and evaluation of human and animal drugs, food and feed additives, human biological products, and medical devices. The ORA processes this misconduct work through its Division of Compliance Policy. Additionally, under compliance authority vested in ORA, the FDA can take steps to ensure the quality of data submitted to the Agency with respect to safety and efficacy of regulated products and to determine that human research subjects are adequately protected. This mandate is important. If an Establishment Inspection Report documents violations of a serious nature that necessitate administrative or regulation action, the consequences can be quite burdensome. The FDA may start proceedings to disqualify the investigator or recommend
criminal prosecution. Another option is a consent decree with the clinical investigator. The FDA may seize nonexempted test articles or seek injunctive relief.

**Office of Research Integrity**

The Office of Research Integrity (ORI) is the successor authority to the Office of Scientific Integrity in the Office of the Director of NIH and the Office of Scientific Integrity Review that was in the Office of the Assistant Secretary for Health. The ORI includes the Division of Research Investigations (DRI) and the Division of Policy and Education. Legal services are furnished by the Office of the General Counsel of the Research Integrity Branch of HHS.

ORI handles research misconduct for biomedical and behavioral studies supported by the PHS. It is noteworthy that the PHS is comprised of NIH, the Centers for Disease Control and Prevention, the FDA, the Substance Abuse and Mental Health Services Administration, the Health Resources and Services Administration, the Agency for Health Research and Quality, the Agency for Toxic Substances and Disease Registry, and the Indian Health Service. With the exception of the FDA, ORI's responsibility encompasses all the entities under the PHS.

In dealing with research-related scientific misconduct, ORI relies upon the definition found in the federal regulations. For this purpose, "scientific misconduct" means "fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research."

The ORI assesses allegations of scientific misconduct, reviews inquiries and investigations from institutions, and carries out inquiries and investigations at extramural entities and intramural investigations in PHS. Following a preliminary assessment of the situation, the institution that has received PHS funding may conduct an inquiry. This process is designed to evaluate available information to determine whether there is sufficient evidence to proceed with an investigation. The investigation is a formal mechanism that culminates in a report and a determination by the institution. The final report, in turn, is submitted to ORI. After reviewing a report of scientific misconduct, ORI may perform its own investigation. ORI may impose sanctions on the investigator as well as on the institution. As a result, the research institution may impose its own sanctions on the researcher involved in scientific misconduct.

The regulations prompt notification of ORI at any stage of the inquiry or investigatory process when it becomes apparent that there is an immediate health hazard, that there is an immediate need to protect federal funds or equipment, that there is an immediate need to protect the person who is making the allegations or who is the subject of the assertions, or that there is probability the alleged misconduct will be the subject of a public report. If there is a "reasonable indication" of criminal violation, the research institution must
report it to ORI within 24 hours of learning the information. ORI, in turn, must then turn
the matter over to the OIG.

ORI makes recommendations to the Assistant Secretary of Health regarding
administrative actions to be taken on research misconduct. If the Assistant Secretary
accepts the recommendations of ORI, the "respondent" [culpable individual] is given the
opportunity to have a hearing before a Department Appeals Board on the finding of
misconduct and administrative actions. If the appeal is not taken, then the misconduct
findings become final and, along with the administrative actions, the information is
published in the Federal Register, the NIH Guide for Grants and Contracts, the ORI
Newsletter, and the ORI Annual Report. Debarments can be found in the List of Parties
Excluded from Federal Procurement and Nonprocurement Programs published by the
General Services Administration.

The administrative actions taken are dependent on a number of factors. The seriousness
of the misconduct and its impact are considered along with whether or not it is part of a
pattern of behavior. Administrative sanctions range from one to ten years and can include
any of the actions by the Office for Human Research Protections discussed below.

**Office for Human Research Protections**

The Office for Human Research Protections (OHRP) is the successor to the Office of
Protection from Research Risks (OPRR). Whereas OPRR was housed within NIH, OHRP
is now in the office of the Secretary of HHS. OHRP is responsible for protection of
human subjects in any research conducted or supported by any component of HHS. It is
tasked to coordinate HHS regulations, policies, and procedures within the Department
and with other federal departments and agencies.

OHRP has other responsibilities as well, e.g., to develop and to implement educational
programs and materials and to enhance and improve research subject safety. The Office
of the Director of OHRP directs compliance oversight. The Division of Policy and
Assurance negotiates Assurances of Compliance with research facilities. The Division of
Compliance Oversight inquires into and investigates alleged noncompliant activities. It
can recommend corrective action and oversee a compliance program for a grantee. The
Division of Education and Development produces and coordinates conferences and
workshops that focus on human research subject protection.

OHRP has developed a set of procedures for compliance oversight activities. By
submitting a written Assurance of Compliance, the facility agrees to full compliance with
the law on the part of its personnel and the institution. OHRP places considerable
responsibility on the clinical researcher, institutional officials, and others to make certain
that there is compliance with the regulations and to protect the rights and welfare of
human subjects under § 491 of the Public Health Service Act.
In a compliance oversight evaluation, institutional authorities are apprised in writing by OHRP of what they are likely to find during the course of a review. In most instances, OHRP will not take action against a facility without first giving the facility the opportunity to rebuff suggestions of noncompliance or to take corrective action. OHRP may decide to restrict the Assurance of Compliance by suspending some or all research projects pending the institution achieving compliance. In some instances, OHRP may review some or all of the research projects under the entity's Assurance of Compliance. Corrective action may include education for committee members and institutional officials. In some cases, OHRP may withdraw its approval of an entity's Assurance of Compliance. The consequence is that HHS cannot fund any of the institution's research projects until there is compliance. At the far end of the scale, corrective action may necessitate the removal of the researcher temporarily or permanently from participation in the research. Debarment is also a recourse in which an institution or a researcher is declared ineligible to take part in HHS-supported research. A debarment is usually government wide.

Other federal departments and entities have the capacity to handle research misconduct under their authority, including the National Science Foundation, the Department of the Navy, the Veterans Administration, and others.

Possible New Requirements for Responsible Research

The Public Health Service (PHS) published a document entitled, "PHS Policy for Instruction in the Responsible Conduct of Research. However, the new policy was suspended indefinitely in February 2001 in accordance with the President's Regulatory Review Plan. This was done to enable the new Administration to review the substantive portions of the policy and the procedure followed in adopting it. The suspension included no definite time limit.

The new policy places considerable emphasis on education, including the following core educational areas:

- data acquisition, management, sharing, and ownership
- mentor/trainee responsibilities
- public practices and responsible authorship
- peer review
- collaborative science
- human subjects
- research involving animals
• research misconduct

• conflict of interest and commitment

Aside from the core content, the institution must submit a written assurance that the entity has an education plan and a written description of the program. This assurance must accompany requests for PHS funds for research.

It is unclear when and if the new policy will take effect because members of the U.S. House of Representatives expressed concern about the way in which the new policy was adopted. Because of congressional concern, coupled with the Regulatory Review Plan implementation, the new policy may take some time to become operational. Even at the operational stage, the policy incorporates a phase-in approach to implementation.

Many research entities are not waiting for a final disposition on the policy. They have begun to establish practical educational programs premised on the "core content" required in the PHS plan. I recommend that we implement the core content of the plan as the content of the policy is not in question but how it was approved.

Looking further ahead, many observers believe that further inroads can be expected by the federal government. One idea is the creation of a National Office of Human Research Oversight, which came from a draft report of the National Bioethics Advisory Committee. Still others, may be considered.

The key point is that there are a number of regulatory bodies already using existing laws, policies, and guidance to exercise authority geared to clinical trials compliance. Much more can be done within the present envelope of regulation. Self monitoring, surveillance, education, corrective action, and discipline within research organizations may obviate the need for further regulatory intervention. Achieving a balance between regulatory oversight and internal surveillance and persistence may help to reduce onerous corrective action plans and possible civil and criminal liability.

Government Enforcement of Clinical Research Compliance

A number of government departments and agencies have oversight and enforcement responsibilities. Documentation deficiencies that do not impact billing, accounting, or research subject safety may merit an on-site review, assistance with education, and follow-up compliance visits from an oversight agency. When, however, research subject safety is of prime concern, much more intrusive action is warranted: performing on-site evaluations, suspending trials, working with the entity to develop and implement a corrective action plan, and then doing follow-up monitoring may be the hallmarks of government intervention. The Department of Justice may take action against false claims, false statements, or fraudulent assurances made as the basis for federal research funds. Fraud and abuse in terms of managing research funds, "double-dipping" in terms of
Medicare or Medicaid payments for a treatment paid for under study grants, and misappropriation of federal research funds are likely to engender a criminal investigation and possibly indictments. Certainly, credible whistle-blower assertions will trigger careful review, whether for scientific misconduct, research subject safety issues, or allegations of fraud in the management of research funds.

Once a major issue does bubble up to the surface, it may be seen as a marker requiring further scrutiny of the researcher or entity. For example, significant noncompliance with a Food and Drug Administration test article might trigger inquiries by the Office for Human Research Protections (OHRP) or the Office of Management Administration if the same study comes within their respective jurisdictions. Sometimes too, the marker event may have nothing to do with clinical trials. The health care entity may be the subject of an Internal Revenue Service probe looking into possible tax evasion. In the course of an audit, discrepancies that can be traced back to federally funded research may be detected. Such discrepancies may signal a "back door" investigation into potential research irregularities. On other occasions, the actions of a sponsor or an accrediting body may spark a federal regulatory agency into action. A sponsor may report serious concerns regarding research subject safety or a reviewable event may occur involving serious harm to a subject-patient, triggering the need for a root cause analysis under the Joint Commission on Accreditation of Healthcare Organizations (Joint Commission). If the event is serious enough, the Joint Commission may take stem action with respect to the facility, including placing of the entity on accreditation watch. Since a facility depends upon its Joint Commission accreditation to participate in Medicare or Medicaid, significant accreditation action may set the stage for regulatory reviews by the Centers for Medicare and Medicaid Services (CMS), formerly the Health Care Financing Administration. Because the event involved research subject safety, a federal agency may look into research compliance.

The key point is that there are a number of ways in which a federal department or agency might pursue allegations of noncompliance in clinical trials. Depending upon the outcome of its investigations, a federal agency may stop the research, debar a researcher, and seek prosecution under the False Claims Act, suspend a clinical trial, or impose a corrective action plan. The facts of the case will play a large role in deciding what action is appropriate in the circumstance.

The way federal enforcement authorities respond to noncompliance by a health care organization depends on whether the deficiency is extensive and whether the matter arises in a request for assistance to rectify less-than-acceptable practices or is discovered within the scope of an enforcement effort. With the changes announced in 2000 and the shift of Office for Protection from Research Risks from the National Institutes of Health to the transformed OHRP in the Office of the Secretary of HHS, there is now a definite effort to provide assistance and also to pursue a traditional regulatory framework. The assistance component involves education, help in rectifying deficiencies, and workshops. Some have even turned this into a "partnership" approach between government and the private sector. At the same time, the regulatory model is in operation. Agencies and departments tasked with enforcement responsibilities will use an array of tools to deter
fraud and abuse, to punish those who engage in such activities, and to preclude those who are found culpable of scientific conduct from engaging in federally funded or sponsored clinical trials. Even for the latter group, the debarment may be time limited. Thus, the federal approach is a blend of assistance and enforcement in clinical trials.

**Core Elements of a Clinical Research Compliance Plan**

Aside from the traditional "seven elements" of a compliance plan, specific aspects should be included in a program targeting clinical trials. Structural issues also affect the type of compliance plan put in place for clinical trials research. The special elements of a research compliance plan are addressed first and then the structural considerations.

For a research compliance plan, a number of specific elements should be considered.

**Written Policies and Procedures**

- definition of research compliance
- definition of noncompliance in clinical research
- research compliance role and responsibility of Institutional Review Board members, researchers, and clinical research staff
- means of reporting known or suspected noncompliance
- means of reporting known or suspected scientific misconduct
- nominalization for good-faith reporting
- means of reporting known or suspected unsafe conditions or research practices
- acceptable investigatory methods
- surveillance and monitoring practices
- incorporation by reference of the "Model Policy for Responding to Allegations of Scientific Misconduct" and the "Model Procedures for Responding to Allegations of Scientific Misconduct" of the Office of Research Integrity as part of a due process-oriented method for investigating and managing noncompliant practices
- management of research subject safety issues (adverse events, unanticipated outcomes, relationship to and involvement of data safety monitoring board)
- acceptable corrective action methods
Appointment of a High-Level Individual as the Compliance Officer

- role of the research compliance or integrity officer
- authority
- chain of command
- reporting hierarchy
- responsibilities of the corporate compliance officer and committee with respect to clinical trials research compliance
- responsibilities of the corporate research compliance or integrity officer in relation to the general counsel, outside counsel, and senior management of the health care entity or organization

Education and Training

- general compliance requirements
- specific research compliance requirements - research design (use of placebo, randomization, double-blind studies)
  - research subject recruitment and selection
  - informed consent practices
  - documentation of the consent process
  - confidentiality of individually identifiable research subject information
- responsible conduct of research requirements - acceptable methods for education and training
  - documentation of participation in mandatory education
  - measurement of understanding of core requirements
  - documented participation in continuing education programs on responsible conduct of research practices
- core content curriculum development
Establishment of an Effective Communication System for Reporting Suspected Violations of the Law or the Compliance Plan

• research compliance hotline system

• research compliance suggestion box

• process for handling complaints, expressions of concern, or allegations of noncompliance (anonymous reporting or anonymous reporting with a "tag" number for follow-up discussion)

• timeline for processing allegations of suspected noncompliance

• Development of a Clearly Written Disciplinary System to Punish those who violate the applicable standards or Law

• notice provision in employment application and application for clinical privileges regarding consequence of scientific misconduct or noncompliance regarding consequence of scientific misconduct or noncompliance

• bylaw provisions that delineate recourse for health professional found culpable of scientific misconduct or sanctioned for regulatory noncompliance

• recourse under collective agreements for handling scientific misconduct or regulatory noncompliance by union members

• notice provision in employee handbook and human resources regarding consequence of scientific misconduct or noncompliance
• contractual terms and conditions for management of noncompliance or debarment of clinical research contractor

• terms and conditions for exclusion of research fellows, residents, and interns found accountable for scientific misconduct by a federal agency or department, a state agency, or an academic program

Implementation of Ongoing Monitoring Audits and Surveillance Methods to Identify Noncompliant Activities

• monitoring of consent process

• audits of consent documentation

• randomized record audits of research files

• unannounced audits

• bioresearch monitoring for human drugs and medical devices under Food and Drug Administration-sponsored or funded clinical trials

• coordinated billing, coding, and accounting practices for use of research funds with ongoing clinical studies

• coordinated billing, coding, and accounting practices for Medicare-Medicaid funds used to support clinical trials

• coordinated billing, coding, and accounting practices for clinical trials in which research subjects are also recipients of routine medical services

• audits of adverse events documentation and reporting practices

• audits of research subject complaints

Establishment of an Effective Mechanism to Respond to Identified Noncompliance and to Correct It so that It Does Not Reoccur in the Future

• acceptable investigatory practices (interviews, collection of data)

• use of "investigation committees" and hearings

• preparation of an "investigatory report" with recommendations
• report to outside entities of investigatory findings
  - scientific misconduct
  - request to retract published findings
  - professional licensure bodies
  - accreditation bodies
  - regulatory bodies
  - funding agencies
  - sponsors
  - multicenter coordinators
  - insurance carrier or captive manager if litigation is anticipated for termination of study, termination of researcher, or contract with outside vendor

• lessons learned
  - inclusion in ongoing education
  - inclusion in enhanced policies and procedures
  - inclusion in ongoing surveillance and monitoring strategies

**Responsibility of Corporate Compliance Officer for Research Compliance**

There is no one set formula for determining whether a facility compliance officer should also be responsible for research compliance. A number of considerations need to be weighed in making a decision: budget, reporting structures, the volume of research activities, the funding sources for clinical trials research (private versus public or a blend of both), and the specifications found in sponsorship contracts. The inherent responsibilities of the corporate compliance officer should be carefully considered, especially if the demands are such that the research compliance component will receive little attention if added to an already challenging portfolio. While the position should not be dependent upon the officeholder, a practical reality needs to be considered. If the job description of the corporate compliance officer is heavily dependent upon financial acumen, the officeholder may have a difficult time dealing with the nuances of study design, research assurance information, and clinical trials information. Certainly, these challenges can be overcome with input from individuals with a blend of appropriate skill sets. However, in contemporary health care circles, the development of such a critical
mass of personnel can be burdensome when the personnel, in turn, are drawn in several different directions. Thus, many health care organizations and clinical research organizations (CRGs) place considerable credence on the clinical health care background of the person responsible for research compliance.

At the very least, the research compliance officer must have a solid orientation to the various laws, regulations, and guidelines for clinical trials research. The individual needs a thorough understanding of scientific and professional misconduct in clinical trials research, conflict-of-interest principles as applied to clinical research, and the type of investigatory skills required for teasing out honest mistakes from fraud, abuse, and other improprieties stemming from clinical trials. This knowledge requirement is in addition to the challenging informational requirements for traditional corporate compliance. Some may argue that the research compliance officer should be a specialist or hold a deputy position to the overall compliance officer of the health care organization or ERO. This idea may have merit in some instances as it ensures a strong organizational communications and operational linkage for purposes of compliance. The actual structure will depend upon the nature of the entity and its corporate culture regarding compliance.

**Research Integrity Officer Versus Compliance Officer**

In both the "Model Policy for Responding to Allegations of Scientific Misconduct" and the "Model Procedures for Responding to Allegations of Scientific Misconduct," the Office of Research Integrity (ORI) defines the "Research Integrity Officer" (RIO) as "the institutional official responsible for assessing allegations of scientific misconduct and determining when such allegations warrant inquiries and for overseeing any inquiries and investigations." Given the description of the duties of the RIO, it is quite possible that the RIO may be one and the same as the corporate compliance or research compliance officer, depending upon the organizational structure. If, for example, a particular matter necessitates specialized skills, a qualified individual may be specifically designated as the RIO. In other instances, the research compliance officer may "call upon" additional resources to assist him or her when acting in the capacity of the RIO.

The ORI model policy and procedures stress the importance of affording due process to those under review for scientific misconduct. Thus, someone acting in the capacity of RIO should not be the same individual termed the "deciding officer" who makes the final determination on allegations regarding scientific misconduct and the response of the organization to it.

**Areas of Risk in Research Compliance Programs**

In September 2000, the Division of Compliance Oversight of Office of Human Research Protection (OHRP) published a very useful tool to assist institutional review boards (IRBs), researchers, and research compliance officers in pinpointing high-risk areas. An
OHRP report, "OHRP Compliance Activities: Common Findings and Guidance," highlights eight key areas:

1. initial and continuing review
2. expedited review procedures
3. reporting of unanticipated problems and IRB review of protocol changes
4. application of exemptions
5. informed consent
6. IRB membership, expertise, staff, support, and workload
7. documentation of IRB activities, findings, and procedures
8. miscellaneous OHRP guidance

Within each broad category, OHRP has identified very specific issues. In total, 75 areas were identified by OHRP. Working back from this list and the "suggested guidance" provided, IRBs, research compliance officers, sponsors, health care organizations, and clinical research organizations (CROs) can develop strong compliance plans. The information can be used as a self-assessment tool. For example, one of the risk areas is entitled "Documentation of Required IRB Findings in IRB Minutes." By turning this demonstrative statement into a question on a self-assessment tool, an IRB can do its own compliance "systems check." Similarly, the research compliance officer could use the "question" to evaluate the IRB's performance relative to existing policy and procedure as well as OHRP expectations. As OHRP publishes additional reports, the information can be used to conduct a systems analysis with a view to compliance improvement.

At the same time, it is important for each institution, IRB, and CRG to evaluate its own "high-risk" areas. This can be done by means of a "compliance inventory" that includes information gleaned from hotlines, frequently asked questions, compliance audits, monitoring, and surveillance, as well as the results of scientific misconduct investigations. Using the GHRP report as an audit tool may reveal that a CRG is in fine shape; however, its own review may disclose much more pressing risk-prone areas that merit immediate attention. Thus, it is a combination of both "national experience" and local knowledge that helps to pinpoint high-risk compliance issues.

**Documentation Issues in Clinical Research Compliance**

Lawyers, compliance officers, and risk managers often talk in terms of a "paper trail" to substantiate compliance with rules, regulations, policies, and procedures. Indeed, in the therapeutic context, there is an old expression to the effect, "If it is not charted, it was not
done." The same rationale applies to clinical trials research administration and compliance.

There are a number of practical documentation procedures to use in demonstrating not only compliance, but sound research practices. The key is not to overwhelm researchers, sponsors, clinical research organizations (CRGs), and institutional review board (IRB) members with paper, since the sheer volume of documentation could obscure serious risk issues. Indeed, setting the bar too high in terms of documentation may create its own problem. The failure to complete a report or a series of documents could be construed as substandard practice.

A useful exercise may be to look at what other institutions or CRGs use for documentation practices. However, what others use may not match the particular needs of the local facility, CRG, or IRB. The following are some practical strategies to use with regard to clinical trials documentation.

_A List of Mandatory Documentation for Clinical Trials Research Should be Created_

A mandatory documentation list can be made by gleaning information from mandatory reporting forms found in grants, contracts, regulations, and statutory law. The scope should not be too limited, thus, requirements for documenting the "Final National Coverage Decision" for Medicare coverage of aspects of a clinical trial should be part of the documentation package if it is pertinent to the local human research enterprise. Some of the more common documentary information should include the following (other documentation will be dependent upon local needs and requirements):

- adverse event reports
- annual reports on ongoing studies
- audit reports (financial, research subject safety, and specially required reports for data safety, compliance, etc.)
- conflict-of-interest documentation (including mandatory education attendance, declarations as part of research trial applications, etc.)
- consent monitoring reports (especially of same surveillance practices or special risk subjects)
- field reports
- IRB minutes
- IRB follow-up actions
• modification of study requests and disposition

• monitoring reports

• wrap-up reports for concluding or terminating studies

**Documentation Audit Results Should Be Recorded**

The "paper trail" should demonstrate that the documentation has been reviewed. A designated person should sign off or attest to the fact that the documentation has been evaluated for completeness. The documentation audit may reflect glaring gaps or inconsistencies with established procedures or compliance requirements. If this is the case, this "audit safety net" should trigger appropriate follow-up action to ensure compliance. If documentation is acceptable, the signoff or attestation should reflect this fact.

**Decision Trees Can Be Useful Documentation Tools**

When trying to decide whether an event requires reporting to a sponsor or regulatory body, or when trying to determine whether an item comes within Medicare clinical trials coverage, "decision trees" can be useful tools. A stylized flowchart, the decision tree consists of a series of "Yes" and "No" answers to a series of objective questions. Depending upon the answers, a decision maker may make a determination to report an event or to disallow coverage of a service under the Medicare program. This objective approach can foster consistency in making determinations. It eliminates possible subjective information that could lead to inappropriate decision making. Moreover, it can reduce the time required to generate a report and can lessen the opportunity for conjecture, speculation, and needless information to be recorded in documentation.

**Whistle-blowers in Clinical Research**

In the research compliance context, a "whistleblower" may mean a person who makes an allegation regarding scientific misconduct. It also has a similar connotation albeit dealing with the False Claims Act. Under the False Claims Act any person may bring an action. When "any person" is a private individual or entity, it is known as a "qui tam" action and the party initiating it is referred to as the "qui tam relater." Once the lawsuit is filed, the government must be furnished with information about the action. The complaint is sealed for at least two months, providing time for the government to decide if it wants to join the claim. Even if at this stage the government decides not to participate, it can decide to do so at a later stage. Qui tam realtor actions may involve clinical trials research fraud for falsifying information or submitting false claims. Whether pursued as a matter of scientific misconduct under the Office of Research Integrity (ORI) model policies and procedures or the False Claims Act, whistle-blowers may have some level of protection.
against retaliation for bringing the claim. Section 3730(h) of the False Claims Act protects "any employee who is discharged, demoted, suspended, threatened, harassed, or in any other manner discriminated against" for bringing a False Claims Act action. Such protection may mean reinstatement with the same seniority and same degree of compensation. By comparison, under the OR! model policies and procedures, the whistle-blower protection goes beyond employees. ORI policy states:

The Research Integrity Officer will monitor the treatment of individuals who bring allegations of misconduct or of inadequate institutional response thereto ... and will ensure that these persons will not be retaliated against in the terms and conditions of their employment or other status at the institution ...

In addition, the ORI model policy and procedures address the issue of privacy protection for the whistleblower and the individual's integrity by stating very clearly that "Institutions are required to undertake diligent efforts to protect the positions and reputations of those persons who, in good faith, make allegations."

The rationale for whistle-blower protection is the same whether under the False Claims Act or the ORI model policy and procedures. Those with knowledge of serious noncompliance are encouraged to step forward and take appropriate action to curb such improprieties. Both the False Claims Act and the ORI model policy and procedures serve as ways in which the knowledgeable individual can take appropriate action. Providing antiretaliation protections helps make it easier for the individual to blow the whistle on scientific misconduct or false claims. Under the False Claims Act, the successful qui tam relater is entitled to a substantial portion of what is recovered or reached in settlement. The amount varies depending upon whether the government intervenes in such cases. However, the prospect of substantial financial gain may also serve as an incentive for someone to be a qui tam relater.

**Health Care Organizations Response to Noncompliance**

An allegation of noncompliance requires careful analyses of the assertion. Facts must be gathered and evaluated. Conjecture, speculation, or idle gossip are insufficient grounds for making a determination of noncompliance. Much more is needed.

A good approach to handling allegations of "noncompliance" can be found in the Office of Research Integrity (ORI) "Model Policy for Responding to Allegations of Scientific Misconduct" and the "Model Procedures for Responding to Allegations of Scientific Misconduct." A logical step-by-step process is mapped out by the ORI, from an inquiry through an investigation to administrative action recommended and then taken by the person tasked with making the decision on behalf of the institution or organization. The nature of the alleged misconduct may merit inclusion of others in the process. For example, if a whistle-blower makes an allegation of Medicare fraud involving clinical trials research, an outside forensic auditor may need to ascertain the validity of the claim. An allegation of misconduct involving data falsification or manipulation may necessitate...
an evaluation by a neutral, objective expert in biostatistics or epidemiology. The compliance investigatory rules should enable the clinical research organization or facility to make use of such outside experts under pertinent laws for peer review or, when appropriate, attorney-client privilege.

The rights of the alleged perpetrator must be respected. The individual should be afforded due process. If culpability is found, appropriate action must be taken to redress noncompliance. The following example demonstrates what is involved in such cases.

A researcher signed a conflict-of-interest statement indicating that she had no financial ties or stock holdings in the company sponsoring the test article under investigation. The Institutional Review Board (IRB) received all relevant documentation for the study, including the signed conflict-of-interest statement. Nothing in the documentation suggested that there was any impropriety in the funding for the study and the clinical researcher's relationship with the sponsor.

Six months later, the research compliance officer received an anonymous voice mail on the compliance hotline suggesting that the principal researcher had given a false assurance regarding conflict of interest. Following an inquiry and investigation, the IRB determined that the principal researcher would receive 500 shares of stock from the sponsor contingent upon the study being successfully completed within a 15 percent savings of the specified budget for the research trial. IRB minutes documenting the review of the original protocol noted that the study involved more than minimal risk and that the IRB had insisted that additional protections be put in place for study subjects. The researchers had promised to do so. None of these measures was put in place. The IRB later learned that the added protections would have caused the researcher to exceed the 15 percent budget savings and would preclude her from receiving the stock. This was seen as a conflict of interest for which the researcher could not profess ignorance.

The IRB decided to suspend the clinical trial, to prohibit the researcher from conducting studies on the premises for three years, and to complete a mandatory course in bioethics. A letter of reprimand was sent to the study sponsor indicating that the institution would not accept any further studies unless the financial structure did not create conflicts of interest for investigators or otherwise jeopardize the well-being of study subjects. The final outcome regarding the matter was reported to the ORI. Thus, the action taken against the researcher was reported to the ORI, and information about possible "unprofessional conduct" stemming from the clinical trial was also sent to the state board of medicine. The institution also gave the ORI a copy of the letter sent to the sponsor. In addition, the institution outlined its plan for corrective action, which included advance training on conflict of interest for research investigators, development of a new screening tool for "conflict of interest" in contracts, and a notification letter regarding conflict of interest to be sent to all existing and new sponsors.

The case example shows what can be done in a serious noncompliance matter. Not only was there a thorough investigation, but there was a clear plan of action for the handling the misconduct identified and practical steps to prevent similar cases in the future.
Taking such an approach signals a strong commitment to compliance, an important consideration when federal regulators are notified of misconduct on the part of a clinical researcher. Preventing the institution from being seen as a noncompliant organization is important so that the institution does not lose the opportunity for grants in the future or experience a surge of new investigations looking for "other noncompliant" practices.

**Sanctions for Noncompliance in Clinical Research**

Several ripple effects can occur as a consequence of noncompliance. The actions taken may be either limited or more pronounced in certain cases depending on the nature of the noncompliant practices, for example:

- exclusion from future research for a period of time
- civil monetary penalties under civil False Claims Act litigation
- criminal actions for fraud or abuse
- removal of officials responsible for the stewardship of the clinical trials program
- imposition of a corrective action plan
- public notice of regulatory action taken with regard to noncompliance
- cancellation by sponsors of contracts for noncompliance
- civil lawsuits for breach of contract involving clinical research organizations or sponsors
- termination of a health care organization's participation in a multicenter trial, as a "noncompliant" entity and therefore unacceptable to continue in a study
- loss of funds, and, in some instances, a requirement to repay funds provided for studies that are terminated or suspended
- larger compliance probes involving one or more of the federal fraud and abuse control programs or a state agency

**Medicare Funding for Clinical Trials Research**

Under the Final National Coverage of Clinical Trials Program, Medicare will cover some routine costs of a clinical trial, as well as "reasonable and necessary" items and services needed to diagnose or treat complications that arise from participation in clinical trials.
CMS has developed some guidance regarding what is and what is not covered. This guidance applies to Medicare carriers, fiscal intermediaries, preferred provider organizations, health maintenance organizations, and Medicare Advantage organizations.

There are probably many situations in which careful evaluations will have to be made in order to determine the propriety of Medicare coverage. The risk that this coverage could be abused demands meticulous analysis to avoid noncompliance in such financial matters.

A major financial compliance issue for clinical research institutions is separating out what is an appropriate routine billing for a Medicare "patient" from what is an allowable cost under a grant. Whether the grant is from a private sponsor or a government agency should not make any difference. Coding, accounting, and billing practices should be set up to track items for appropriate allocation. Accounting and billing officials should document the assumptions for the coding and billing practices. If there is any concern or question about the practice prior to implementing it, a formal written inquiry should be made to the fiscal intermediary, CMS, private sponsors, or any other relevant party to validate that the proposed system is acceptable. If it is not acceptable, advance knowledge can enable the institution to develop a permissible methodology. However, all relevant parties (private and public) should agree to the methodology to avoid problems at a later time.

Audits should be structured to evaluate and verify that good accounting practices have been used to properly handle the Medicare component as compared to the grant funds. The same would be true for Medicaid and other federal health plans.

**Conclusion**

Compliance is a major topic for clinical trials research. It goes beyond traditional compliance issues dealing with financial matters. Scientific misconduct, research subject safety, research ethics, and the integrity of the health care organization are all important aspects to a compliance program. A plan requires careful review and upgrading. As laws and regulations change, so too should the compliance plan to keep it current. When the compliance plan is updated, educational opportunities should be provided to everyone, in much the same way that "responsible conduct in research" initiatives are designed to thwart scientific misconduct. Taking these steps can go a long way toward avoiding rigorous scrutiny by regulators, adverse publicity, and possible litigation. These concerns and the desire to do the right thing make a compelling argument for designing and implementing a comprehensive research compliance program.