# Clinical Research Compliance: A Daunting Task Gets Harder

*Bethany J. Hills, JD, MPH*
*Hodgson Russ LLP*
*Buffalo, NY*

Appreciating the matrix of complex regulations that govern clinical research conducted in the United States is an ever important exercise as enforcement actions increase against investigators, institutions, and institutional review boards (IRBs). Many of the day-to-day compliance obligations fall upon the investigator and the IRB, yet they may not fully understand the scope of their responsibilities or the impact of their activities. This disconnect is particularly true for adverse event reporting and financial disclosure responsibilities, and may explain why these areas are the recent focus of oversight agencies.

In this article, we will identify examples of research activities that trigger compliance, review existing sources of regulatory requirements, and assess the multitude of regulatory oversight agencies. Two recent actions by regulatory oversight agencies will then be analyzed to demonstrate the principal public health motives driving this complex regulatory scheme: ensuring the safety of human subjects participating in the research and promoting quality data derived from the clinical research.

## Clinical Research Requirements

The complex set of rules that impact clinical research may be triggered by any number of activities. Often, determining whether the activity even constitutes "research" regulated by these requirements is a lengthy assessment in and of itself. If the activity is a systematic investigation designed to develop or contribute to knowledge applicable to other areas, involves obtaining information about living individuals, and includes an interaction or intervention with the individual, then the activity is considered to be "research" involving human subjects.[1]

This definition of "human research" raises some interesting questions—does a physician who prescribes a drug for an off-label use (not Food and Drug Administration (FDA) approved) need to comply with the clinical research requirements? What if the physician prescribes it to more than one patient and shares the findings with colleagues at an academic meeting? Answering these questions is not an easy task.

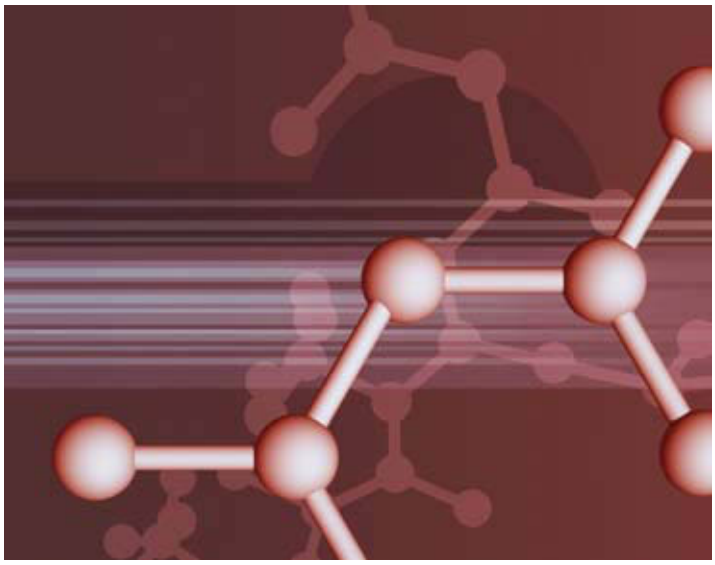
Nonetheless, the answers to those questions may be more obvious when a pharmaceutical, biotechnology, or medical device company (or their discovery and development service provider) seeks the assistance of a clinical investigator to participate in or be principally responsible for clinical research involving new intended uses of a product. In such cases, the clinical investigators and research institutions (usually universities or centralized research branches of healthcare facilities such as hospitals) need to continually assess their research activities to determine whether compliance with the clinical research requirements is warranted.

Indeed, there are hosts of regulatory requirements that may apply to the conduct of clinical trials involving human subjects.[2] Often, clinical research is not conducted in full compliance with *all* regulatory requirements. For example, if clinical research is initiated at a research institution by a clinical investigator without initial input from an industry sponsor such as a pharmaceutical or medical device company, the focus may not be on compliance with the separate set of FDA requirements. In that case, the investigator or research institution (or industry sponsor later interested in commercializing the drug or device used in the clinical research) may be prohibited from relying upon the clinical research data in a later submission to the FDA. The point is simple: regardless of how the investigator arrives at conducting clinical research, one must evaluate *all* of the potential regulatory requirements to identify complete compliance responsibilities and assess the risks of non-compliance.

Unfortunately, this is not necessarily an easy task. Determining which requirements apply depends on (1) whether the research will be used to support FDA submissions, and (2) whether the research is supported by federal funding.[3] The types of applications and submissions triggering the FDA jurisdiction (FDA covered research) include those identified in sections 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act, or under section 351 of the Public Health Service Act (PHS) and known as New Drug Applications (NDA); Abbreviated New Drug Applications (ANDA, also known as generic applications); Investigational New Drug applications (IND); Pre-Market Notifications (510(k) submissions); Pre-Market Applications (PMA); or Investigational Device Exemption (IDE) submissions.

Federally funded research that will not be used to support FDA submissions need only comply with 45 C.F.R. Part 46 (Protection of Human Subjects) and 42 C.F.R. Part 50, subpart F (Promoting Objectivity in Research), and any specific grant agency requirements.[4] Similarly, research conducted to support an FDA submission but receiving no federal funding need only comply with the FDA requirements in 21 C.F.R. Part 50 (Informed Consent), 21 C.F.R. Part 54 (Financial Disclosure of Investigators), 21 C.F.R. Part 56 (IRB and research institutions), and 21 C.F.R. Parts 312 and 812 (Investigational New Drug and Investigational Device Exemptions).[5] Compliance with both sets of requirements is required when research is federally funded *and* used to support an FDA submission. Caution is warranted in these circumstances because the requirements may differ slightly. For example, the standards for financial disclosure for FDA covered trials in 21 C.F.R. Part 54 differ from the standards for financial disclosure for PHS-funded research in 42 C.F.R. pt. 50, subpart F.

Adding to the difficulty in attaining compliance is the realization that once the applicable set of rules has been identified, one must determine what the rules actually require. In this regard, it is important to note that compliance obligations are subject to varying interpretations by a host of regulatory oversight agencies, making compliance all the more difficult. Indeed, more clinical research oversight agencies exist than many clinical investigators



(or their legal counsel) may realize. Understanding the role and jurisdiction of these oversight agencies is important and helps to inform proactive approaches to compliance.

## Key Agencies in Regulatory Oversight

The majority of clinical research compliance oversight resides in the United States Department of Health and Human Services (HHS). The primary agencies within HHS that are involved in the oversight of clinical research are the Office of Human Research Protections (OHRP), Office of Research Integrity (ORI), Office of Inspector General (OIG), National Institutes of Health (NIH), and FDA.

Often overwhelming and duplicative, the clinical research regulations enforced by these agencies can be summarized in two public health goals. First is the protection of human subjects by: (1) application of informed consent principles, (2) IRB requirements, and (3) adverse event reporting requirements.[6] Second is ensuring that clinical research data is reliable and of high quality, meaning that it is not affected by inappropriate financial arrangements or compromised data.[7] Invariably, agencies' policy guidance and enforcement priorities are designed to accomplish these two public health goals.

### OHRP

The first of these oversight agencies is OHRP—the primary oversight agency for non-FDA-covered clinical research.[8] OHRP compliance oversight activities are handled in the Division of Compliance Oversight (DCO) and ensure compliance with HHS regulations governing the protection of human research subjects. OHRP conducts both for-cause and not-for-cause compliance oversight evaluations. Allegations of non-compliance may come from any number of sources, including research subjects, investigators, institutional officials, or even research publications. But for OHRP to proceed under the "for-cause" evaluation, allegations of non-compliance must be in writing and contain a substantive allegation. Not-for-cause evaluations by OHRP may be because of any number of factors, including a high volume of HHS-funded research or concerns raised by other agency evaluations (such as an FDA inspection).

OHRP evaluations focus mainly on:

- *The IRB procedure*. For example, was continuing review of the research conducted by the IRB? Are the IRB expedited review procedures acceptable? Are the IRB written procedures in compliance with HHS requirements? Are reported adverse events properly evaluated?
- *Informed consent procedure*. For example, was informed consent obtained? If informed consent was waived, were appropriate procedures used?[9]

OHRP also derives oversight authority from 45 C.F.R. § 46.103(a), which requires each institution engaged in non-exempt human subjects research to provide written assurance that it will comply with the requirements of the HHS regulations.[10] OHRP reviews and approves these assurances. An institution's assurance may be withdrawn if an OHRP evaluation determines that an institution was not in compliance with HHS regulations.

### OIG

In November 2005, the OIG initiated its direct involvement in oversight of HHS-funded clinical research by publishing draft compliance program guidance for HHS grant recipients. The compliance program guidance was intended to address three primary risk areas: (1) time and effort reporting, (2) proper allocation of charges to award projects, and (3) reporting of financial support from other sources.[11] On June 7, 2006, the OIG draft compliance program guidance was withdrawn, and OIG announced a joint initiative among federal agencies to prepare a compliance program guidance applicable to *all* recipients of federal research funding, not just HHS grant recipients.[12] This multi-agency guidance has yet to be released, so clinical investigators and research institutions often continue to review the 2005 OIG draft guidance when assessing compliance responsibilities.

### FDA

Clinical research that is FDA covered is subject to the FDA Bioresearch Monitoring Program. Known as BIMO inspections, this coordination program allows the FDA to evaluate all aspects of covered clinical research, including clinical investigators, sponsors, monitors, IRBs, analytical laboratories, and clinical research organizations. The FDA conducts both routine and directed BIMO inspections. Directed inspections may be the result of a complaint, but may also be part of an FDA-targeted review of certain issues. BIMO inspections assess:

*Study recruitment and enrollment practices*[13]

- Are study subjects eligible according to the IRB approved protocol?
- Was consent obtained before or after enrollment?
- Are informed consent records available?

*Compliance with FDA approval requirements*

- Was IRB review conducted and IRB approval obtained?
- Were IND or IDE applications submitted and approved by the FDA as necessary?

*Adverse event reporting compliance*[14]

- Are adverse event reports submitted when required?
- Are reportable protocol deviations reported?

*Test article compliance*

- Are applicable manufacturing practices implemented?
- Are investigational drugs or devices tracked?

The FDA's BIMO inspectors also will assess general documentation deficiencies such as inconsistencies between FDA applications and subject records, insufficient drug/device accountability (shipping, use, etc.) records,[15] and inaccurate documentation of delegation during the clinical research. FDA Warning Letters are a good source of information on what BIMO inspectors may focus on during inspections.[16]

## Recent Developments

The two public health goals of the oversight agencies (discussed above) appear to be the driving forces behind recent developments in adverse event reporting and financial disclosure requirements. While these public health goals are worth pursuing, the recent developments have added complexity to those seeking compliance with the clinical research requirements.

### Adverse Event Reporting

On January 15, 2009, the FDA released a "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs—Improving Human Subject Protection" (January 2009 Guidance).[17] A draft guidance released in April 2007 aimed to address concerns raised by IRBs that adverse event reporting processes made it difficult to protect human subjects. Researchers also worried that adverse event reporting in early stage (phase I) studies could overstate the true risks and hinder further research. Furthermore, confusion about the requirements relating to adverse event reporting was widespread. The FDA uses different terms when referring to adverse events—*adverse effect* in 21 C.F.R. § 312.64, *adverse experience* in 21 C.F.R. § 312.32, *unanticipated problem* in 21 C.F.R. § 312.66, and *unanticipated adverse device effect* in 21 C.F.R. § 812.3(s). This final guidance addresses these concerns by clarifying both what constitutes a reportable "unanticipated problem," and how it should be reported to the IRB.

First, the FDA explains that an adverse event should be considered an unanticipated problem involving risk to human subjects and reported to the IRB "***only*** when it is unexpected, serious and has implications for the conduct of the study (*e.g.*, requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure)."[18] Second, the FDA clarified its policy on adverse event reporting for multi-center clinical research. FDA regulations require the clinical investigator to report unanticipated problems.[19] But the FDA now recognizes that the study sponsor may be in the best position to analyze information from all study centers and to determine whether the event is "unanticipated" and also a "problem" for the study. These new FDA policy explanations lay the groundwork for meaningful, aggregated event reporting to the IRBs and multi-center analysis of events, the lack of which were perceived as existing problems in the regulatory structure.

What the January 2009 Guidance did *not* do is simplify the process for attaining compliance with *both* HHS and FDA rules. An existing OHRP policy titled "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" remains in effect and contains slightly different reporting requirements.[20] Investigators conducting clinical research that is FDA covered *and* federally funded will still need to consider both guidance documents when determining whether to report an adverse event to the IRB.

### Financial Disclosures

On January 12, 2009, an OIG Report titled, "The Food and Drug Administration's Oversight of Clinical Investigators' Financial Information" (OIG Report), addressed financial disclosures, which are another perceived problem in the existing regulatory structure. Since 1999, the FDA has required that financial disclosures be included with the submission of marketing applications that contain clinical research demonstrating safety or efficacy.[21] Much attention has been paid to the types of financial arrangements that trigger disclosure and the processes by which financial disclosures are made.[22]

The OIG Report went beyond these discussions and identified two problems with the existing disclosure requirements. First, it identified that financial disclosures are likely not being submitted as required (*e.g.*, 42% of marketing applications submitted to the FDA were missing the financial disclosure information). The OIG Report also appears skeptical that of the 29,691 clinical investigators identified in those financial disclosure forms accompanying marketing applications, only 206 identified a reportable financial arrangement. Second, the OIG Report is critical of the FDA's failure to use the financial disclosure information in evaluating the marketing applications. The FDA's review of the marketing applications did not even consider the financial disclosure in 31% of the applications. The OIG Report also identified that where action on the financial disclosure was warranted, neither the FDA nor the trial sponsor took action in 20% of cases.

The OIG Report recommendations foreshadow upcoming changes for the financial disclosure process in FDA-covered clinical research. The OIG recommends (1) tightening the "due diligence" exemption that permits sponsors to forego financial disclosures,[23] and (2) including a review of financial arrangements as part of the BIMO inspection process. The OIG also recommends that financial disclosure be required as part of the investigational application process (IND or IDE) rather than the subsequent (and much later) marketing application. Finally, the OIG recommends that the FDA prepare guidelines for FDA reviewers that would outline actions to be taken in response to financial arrangements disclosure.

## Conclusion

Although the multitude of rules and the overlapping oversight agencies have common public health goals, compliance with

clinical research requirements remains a daunting task. Investigators, research institutions, and industry sponsors must review the entire universe of requirements and identify the applicable set of rules each time research is initiated. Ongoing compliance requires a working knowledge of the oversight agencies, guidance documents, and enforcement priorities. And despite clarification or changes in policy by one oversight agency, true compliance requires following all rules and agency policy, even if duplicative or conflicting.

1 45 C.F.R. §46.102(d), (f), (f)(1) and(2).

2 The following topics, although important to clinical research, are not directly analyzed here: clinical research coverage and reimbursement, clinical research misconduct, and off-label use of FDA-regulated products. It should also be noted that state, local, and international laws and regulations may also apply to the clinical research, and these requirements should be considered to ensure overall compliance.

3 42 U.S.C. § 289b; 45 C.F.R. § 46.101(a)(1).

4 Additional requirements relating to clinical research misconduct are not addressed here but may be found in 42 C.F.R. Part 93.

5 Additional requirements relating to good practices in manufacturing and laboratory research are not addressed here but may be found in 21 C.F.R. Part 26, Part 210, Part 820 and Part 58. If electronic records are used, compliance with 21 C.F.R. Part 11 is also required.

6 Protection of Human Subjects rules, 45 C.F.R. Part 46 and 21 C.F.R. Part 50; Informed Consent rules, 21 C.F.R. Part 50 (50.20, 50.23, 50.24, 50.25, 50.27) and 45 C.F.R. Part 46 (46.116); IRB requirements, 21 C.F.R. Part 56 and 45 C.F.R. Part 46; and Adverse Event Reporting rules, 21 C.F.R. § 312.64(b), § 312.53(c)(1)(vii), § 312.66, § 312.32(c), § 56.108(b)(1), § 812.3(s), § 812.46, § 812.150; 45 C.F.R. § 46.103(b)(5), § 46.103.(a), § 46.111(a)(1), § 46.11(a)(6), § 46. 109(e), and § 46.113.

7 42 C.F.R. Pt. 50, Subpt. F. "Responsibility of Applicants for Promoting Objectivity in Research for which Public Health Service Funding is Sought"; 21 C.F.R. Part 54, "Financial Disclosure by Clinical Investigators"; 21 C.F.R. §§ 312.68 and 812.145. *See also* The Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: FDA Inspections of Clinical Investigators, dated January 2006, *available at* www.fda.gov/OC/OHRT/IRBS/investigator.pdf. This Guidance clarifies that FDA inspections will compare data submitted with records relating to the clinical investigation, including case report forms and medical records (physician's notes, nurses' notes) to evaluate the quality of the data generated by the clinical research study.

8 ORI and NIH also oversee non-FDA-covered research. The ORI primarily investigates scientific misconduct ("the fabrication, falsification, or plagiarism in proposing, performing, or reviewing research or in reporting research results") (42 C.F.R. § 93.103), which is not addressed here. Additionally, NIH oversight of clinical research provides one example of the grant agency specific requirements that is not discussed in detail here.

9 Additionally, OHRP may determine whether the HHS clinical research regulations apply to the activities at the institution. See OHRP Determination Letter to John Hopkins University School of Medicine, John Hopkins Bloomberg School of Public Health, and Johns Hopkins University date July 19, 2007, *available at* www.hhs.gov/ohrp/detrm_letrs/YR07/jul07d.pdf.

10 Also known as Federalwide Assurance or FWA.

11 70 Fed. Reg. 71313 (Nov. 28, 2005), *available at* www.oig.hhs.gov/fraud/docs/complianceguidance/PHS%20Research%20Awards%20Draft%20CPG.pdf. The draft compliance program guidance was focused on grant compliance and administration in an effort to identify and address government overpayments.

12 OIG News Release, NSTC Launches Government-wide Initiative Based on OIG Draft Guidance for HHS Research Grants, *available at* www.oig.hhs.gov/publications/docs/press/2006/ResearchCPG-finalrelease06072006.pdf.

13 *See, e.g.,* Hilton Becker, M.D. Warning Letter, dated Mar. 13, 2008.

14 *See, e.g.*, William D. Tobler, M.D. Warning Letter, dated Sept. 4, 2007.

15 *See e.g.*, Saroj Brar, M.D. Warning Letter, Ref: 08-HFD-45-0301.

16 *Available at* www.fda.gov/foi/warning.htm. One thing made clear in recent Warning Letter trends is that clinical investigators and IRBs—not industry sponsors—are the focus of FDA inspectional activities.

17 *Available at* www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2007-D-0202-gdl.pdf.

18 Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs – Improving Human Subject Protection, *available at* www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2007-D-0202-gdl.pdf.

19 21 C.F.R. §§ 312.66, 312.53(c)(1)(vii), and 56.108(b)(1).

20 *Available at* www.hhs.gov/ohrp/policy/AdvEvntGuid.htm#Q3.

21 62 Fed. Reg. 5250 (Feb. 2, 1998; effective Feb. 2, 1999).

22 Note, financial disclosure requirements in 21 C.F.R. Part 54 differ from those applicable to federally funded clinical research in 42 C.F.R. Part 50 subpt. F.

23 21 C.F.R. § 54.4.