ORIGINAL RESEARCH

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Warning Letters to Sponsor- Investigators at Academic Health Centres – The Regulatory “Canaries in a Coal Mine”

Abstract

Purpose: This study highlights Warning Letter (WL) findings issued to sponsor-investigators (S-Is) by the Food and Drug Administration (FDA).

Methods: The online index of WLs issued from October 1, 2007 through September 30, 2012 was reviewed [1]. Through a manual screening process, letters were evaluated if specifically issued to ‘clinical investigators’, ‘sponsors’ or ‘sponsor-investigators’. A particular focus was given to S-Is at Academic Health Centres (AHCs). Each letter was scored for the presence of violations in 40 general regulatory categories.

Results: A review of FDA WLs issued over a five-year period (FDA Fiscal Years 2008-2012) revealed that WLs to S-Is represent half of the WLs issued to all sponsors (16 of 32 letters). A review of these letters indicates that S-Is are not aware of, or simply do not meet, their regulatory responsibilities as either investigators or sponsors. In comparing total sponsor letters to those of S-Is, the most cited violation was the same: a lack of monitoring. A review of publicly available inspection data indicates that these 16 letters merely represent the tip of the iceberg.

Conclusion: This review of the WL database reveals the potential for serious regulatory violations among S-Is at AHCs. Recent translational funding initiatives may serve to increase the number of S-Is, especially among Academic Health Centres (AHCs) [2]; thus, AHCs must become aware of this S-I role and work to support investigators who assume both roles in the course of their research.

Manuscript submitted 1st July, 2013

Manuscript accepted 10th November, 2013

Clin Invest Med 2013; 36 (6): E290-E296.

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The United States Food and Drug Administration (US FDA) is charged with protecting the public health by overseeing several areas, including drugs, medical devices, biologics, cosmetics, radiation-emitting electronic products, veterinary products and foods. Part of this responsibility includes oversight of the conduct of clinical studies involving FDA-regulated products. The FDA expects clinical research professionals, including sponsors, investigators and Institutional Review Boards (IRBs), to comply with all applicable regulatory requirements. These requirements are broad and include good clinical practices, regulations and regulatory guidance documents.

One mechanism used by the FDA for ensuring compliance is the inspection process run under FDA's Bioresearch Monitoring (BIMO) Program. If an inspection reveals significant deficiencies the agency may issue a Warning Letter (WL) that details the findings and specifically cites the deficiencies and violations. These WLs are published online at the FDA website. This online database of WLs is a useful window into the Agency's thinking on issues of compliance. Several previously published studies have evaluated the database, focusing on letters to investigators and IRBs [3-5] or on device research letters [6-8].

In Academic Health Centres (AHCs) it is not uncommon for an investigator to assume the role of both the regulatory sponsor and the clinical investigator [9, 10]. These sponsor-investigators (S-Is) take on additional regulatory responsibilities above and beyond those normally assumed by clinical investigators when running a trial. Namely, these investigators must also oversee the submission and maintenance of an Investigational New Drug (IND) or Investigational Device Exemption (IDE) application. Both the 'sponsor' and 'investigator' responsibilities are outlined in the Code of Federal Regulations under Title 21, Parts 312 (drugs) and 812 (devices). Increased emphasis on translational research by the National Institutes of Health (NIH) and a push to repurpose pharmaceutical agents are likely to increase the number of S-Is at AHCs [2, 11-14].

The purpose of this communication is first, to review the inspections process that can lead to a WL and second, to present our findings from WLs that were specifically issued to S-Is and AHC S-Is between FDA Fiscal Years 2008-2012.

Review of the FDA Inspections Process

The inspection process is a part of regulatory authority granted to the FDA by the Food and Drug Act. The Bioresearch Monitoring Program (BIMO) is part of the oversight and protection of human subjects in research that was modernized beginning in 2006 [15]. BIMO reviews FDA-regulated clinical trials in addition to other regulatory inspections. These on-site inspec-

tions take place in AHCs as well as other non-academic research sites. Routine inspections are typically announced and include general surveillance assessments of sponsors, clinical sites, IRBs and/or nonclinical laboratories. These inspections may also include an audit of clinical data that were generated at that site as part of a trial. In contrast, 'for cause' inspections are more frequently unannounced and may result from a history of non-compliance or a specific complaint [16].

All inspections begin with the inspector providing Form FDA 482 (Notice of Inspection) and the duration of an inspection can be anywhere from a few days to weeks depending on the size of the study and the specific goals of the inspection [17]. The FDA official(s) review relevant records to audit all aspects of a clinical study, from the general conduct of the trial to the details of data collection and reliability for documentation that the rights, safety and welfare of the subjects are protected and that the quality, reliability, and integrity of the data are assured.

At the close of an inspection, the inspector can issue an FDA Form 483 (Inspectional Observations), often referred to as a "483." This form captures significant deficiencies or deviations observed by the inspectors that constitute violations of the regulations. Its presentation at the close of the inspection allows the investigator or S-I time to formulate a response and plan for corrective action. Following an inspection, the inspector also compiles an Establishment Inspection Report (EIR) that is in a narrative format and describes all of the inspectional findings. The EIR may include comments and/or concerns that did not result in a formal observation on the 483. The EIR also consists of "evidence" collected during the inspection, including samples, photographs and/or documents, to support observations noted by the Agency.

Establishment Inspection Reports (EIRs) can be shared with the S-I, and the narrative portions of the EIR are routinely provided to the inspected establishment once the inspection is closed. Initial delivery of the EIR to the S-I helps to conclude the inspection process and helps ensure the S-I receives the EIR prior to anyone else since other entities can request a redacted EIR through the Freedom of Information Act (FOIA) [18].

After the inspection, the investigator or S-I has 15 days to respond to the observations listed on the 483. While there is no regulatory requirement to respond to the 483, this response is crucial and can mitigate the final outcome of the inspection. In the response, each observation should be addressed separately with a specific acknowledgment of the problem followed by corrective actions that will mitigate the issue in the future. It is also important to evaluate the impact of the problem and determine the cause, if possible.

The Agency will evaluate the EIR, 483 and S-I's response to the findings and then decide if further formal action is required. Specifically, the FDA applies one of the following three categories to the inspection: NAI (no action indicated), VAI (voluntary action indicated), or OAI (official action indicated). Depending on the severity of the deviations/observations and the formal classification above, a WL may be issued. WLs are only issued for OAI classifications; however, receiving an OAI classification does not automatically trigger a WL [19, 20]. The WL is issued to the audited site or individual and describes the violations of the recipient and serves as a mechanism for the FDA to communicate its concerns on the matter. It provides the recipient an opportunity for voluntary compliance and, thus, does not necessarily commit the Agency to subsequent action.

There are some cases where the recipient of a WL fails to make necessary changes and/or has violated the regulations so significantly that the FDA must take enforcement action. The FDA has the authority to "disqualify" someone from conducting future FDA-regulated research when it has been determined that this investigator repeatedly and/or intentionally failed to follow the regulations. In addition to disqualifying an investigator, which effectively removes him/her from serving as a future clinical investigator, the FDA may "debar" a company or individual. Companies or individuals who are convicted of certain product-related felonies or misdemeanors can be subject to debarment (FD&C Act, Ch. III, Sec. 306). Debarred individuals may not provide any services to people or companies holding an approved or pending marketing application.

Although these more severe enforcement actions by FDA are not usually necessary, it is important that AHCs under-

stand the significance of a WL and the implications of each step surrounding a potential inspection in order to help ensure all S-Is are prepared for the responsibilities and implications of holding an IND or IDE.

Methods

For this review, the online index of WLs [1] issued from October 1, 2007 through September 30, 2012 was reviewed. FDA fiscal years 2008-2012 were chosen in order to give recent examples of WLs that represent the Agency's current thinking. This time frame included a total of 3,007 letters. Through a manual screening process, letters were evaluated if specifically issued to 'clinical investigators', 'sponsors' or 'sponsor-investigators'.^A Each letter was scored for the presence of violations in 40 general regulatory categories ranging from informed consent violations to labeling of investigational drug/device violations. In addition, our findings were compared with the BIMO monitoring metrics reported by fiscal year on the FDA website [21].

Results

During the study period, 113 letters met the search criteria, with 81 letters containing only investigator violations, 16 letters containing only sponsor violations and 16 letters containing both sponsor and investigator violations (Table 1). About half of the letters (53.1%) came from inspections performed by the Center for Drug Evaluation and Research (CDER) while a little under half (41.6%) from the Center for Devices and Radiological Health (CDRH). Of the 16 letters to S-Is, eight of them were issued to S-Is at Academic Health

TABLE 1: Summary of Warning Letters (WLs) from the Study Period

Type of Letter	CDER	CBER	CDRH	Total
Investigator-only*	54	4	23	81
Sponsor-only	2	1	13	16
Sponsor-Investigator	4	1	11	16
Total WLs:				113
AHC S-I WLs	2	1	5	8

* These letters were addressed to individuals who had only 'investigator' responsibilities. Since they did not serve as regulatory 'sponsors', these 81 letters are not discussed further in this paper

CDER = Center for Drug Evaluation and Research; CBER = Center for Biologics Evaluation and Research; CDRH = Center for Devices and Radiological Health; AHC = Academic Health Centre; S-I = sponsor-investigator

^A In addition, some sponsor and S-I letters were found under the subject "Investigational Device Exemption".

TABLE 2. Breakdown of Citations from 16 Warning Letters to 'Sponsor-Investigators'

Sponsor Responsibility Cited	Regulation	All Sponsor-Investigators	AHC Sponsor-Investigators†
Monitoring (none or inadequate)	312.56(a), 812.46	10	5
Not Submitting Annual Reports	312.56(c), 812.150(b)(5)	8	4
Did not Obtain 1572s‡ or Investigator Agreement	312.53(c)(1), 812.43(c)	6	5
No IDE or IND	312, 812	4	–
Financial Disclosure	312.53(c)(4), 312.57(b), 812.43(c)(5), 812.140.(b)(3)	4	3
Protocol Changes not submitted to FDA	312.50, 812.40	3	2
Failure to Report Unanticipated Device Effects	812.150(b)(1)	3	1
Inadequate Drug/Device Shipment Records or Practices	312.57(a), 312.59, 812.140(b)(2)	3	1
Failure to Inform Investigators (CIBs etc.)	312.50, 312.55, 312.56(d), 812.45	2	–
Failure to Submit Investigator List at 6 Month Intervals (Device Studies)	812.150(b)(4)	1	1
Inadequate records retention of all correspondence	312.57(c), 812.140(b)&(d)	1	–
Failure to Secure Investigator Compliance	312.56(b), 812.46(a)	1	–
Inappropriately Charged for an Investigational Drug/Device	312.8, 812.7(b)	1	–

* The citation numbers reflect the fact that most Warning Letters contain multiple violations.

† The citations issued to S-Is at Academic Health Centres are a sub-set of those issued to all S-Is.

‡ The Statement of Investigator, Form FDA 1572 (1572), is an agreement signed by the investigator to provide certain information to the sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic [25].

AHC = Academic Health Centre; IDE = Investigational Device Exemption; IND = Investigational New Drug Application; FDA = Food and Drug Administration; CIB = Current Investigator Brochure

Centres (AHCs).^B The other eight S-I letters were issued to health centres, small pharmaceutical companies and individual physicians.

The most commonly cited violations in WLs to S-Is and to S-Is at ACHs are summarized in Table 2. The most commonly cited deficiency for all sponsors was a lack of monitoring as required by 21 CFR 312.56(a) for drug studies and 21 CFR 812.46 for device studies. Other cited violations included not obtaining investigator agreements and not submitting annual reports.

These findings were compared with the general metrics posted online for the Bioresearch Monitoring Program [21].

During fiscal years 2008-2012 the FDA reported that 3247 inspections were performed on clinical investigators while 644 were performed on sponsor/monitors.^C Approximately 2.5% of BIMO inspections resulted in a WL being issued to a clinical investigator (81 letters out of 3247 inspections) while 5.0% of inspections resulted in a sponsor/monitor WL (32 letters out of 644 inspections); thus, it appears that a regulatory sponsor is twice as likely to get a WL as an investigator. Only general comparisons can be made because it is unknown how many of the 644 sponsor/monitor BIMO inspections were specifically aimed at S-Is. Nonetheless, the most common inspectional finding cited for sponsor/monitors matches the most

^B As defined by the Association of Academic Health Centres: An academic health centre consists of an allopathic or osteopathic medical school, one or more other health profession schools or programs (such as allied health, dentistry, graduate studies, nursing, pharmacy, public health, veterinary medicine), and one or more owned or affiliated teaching hospitals or health systems. <http://www.aahcdc.org/About.aspx> (Accessed November 8, 2013)

^C These inspection numbers include only CDER, CBER and CDRH inspections of clinical investigators and sponsor/monitors. CFSAN and CVM inspections are excluded as are all IRB and GLP inspections. The terms 'sponsor/monitor' and/or 'sponsor/monitor/CRO' are used by BIMO in reports to identify parties with the responsibilities of a sponsor.

common WL violation observed for S-Is: inadequate monitoring. Inadequate monitoring has been at the top of the BIMO list for the entire five year period.

Discussion

The FDA considers assuring the protection of research participants and data integrity as its primary responsibility in the oversight of clinical research. This regulatory oversight occurs initially through the review of clinical protocols submitted as part of INDs and IDEs. In addition to this review, the FDA conducts inspections of clinical studies through their Bioresearch Monitoring Program (BIMO); however, the FDA can review only a very small percentage of the total number of FDA-regulated clinical studies. One mechanism to alert others to issues identified through BIMO inspection program is the publication of WLs on their website. This permits a broad dissemination of the compliance issues that have been identified and allows other clinical research professionals to be alerted to similar issues in their studies.

While exact numbers are difficult to extract, metrics available on the FDA website indicate that published WLs represent just the tip of the iceberg when it comes to compliance issues; for example, during FY 2011, CDER received more than 2700 new INDs [22], adding to the thousands of active INDs already in existence. During that same year BIMO conducted just 360 CDER-specific inspections of clinical investigators and sponsor/monitors. These 360 CDER specific inspections in turn resulted in just 13 WLs; thus, the published database of WLs is merely a window into what is happening on a larger scale.

Most Cited Sponsor-Investigator Violations

This WL database review and the online BIMO metrics demonstrate that inadequate monitoring is the most frequently identified deficiency among S-Is. Not obtaining investigator agreements and not submitting annual reports rounded out the top three S-I violations found in the WL database. These differed from what BIMO reported overall for sponsor/monitors with 'failure to bring investigators into compliance' and 'inadequate accountability for the investigational product' rounding out their top three inspectional observations. The BIMO metrics include both sponsors and S-Is which may explain the difference. More importantly, only a minority of inspections result in a WL; therefore, it is not surprising that the inspection metrics do not match the WL metrics. The fact that inadequate monitoring is at the top of both lists is an indicator that this is problematic for all types of sponsors.

Specific Examples from Warning Letters

In one letter, an S-I did not monitor any aspect of a study for over 18 months. Instead, the S-I had been operating under the assumption that appropriate monitoring was provided by the Data Safety Monitoring Board (DSMB). While DSMBs play a role in monitoring adverse events and subject safety, they do not monitor other aspects of the study such as ensuring proper informed consent, verifying eligibility criteria or confirming that the investigation plan is followed. Not monitoring a study can lead to multiple problems that impact subject safety and data integrity. All of the WLs with a monitoring violation had at least one other violation that could have been prevented if the study had been properly monitored.

In another letter, an S-I was cited for not submitting IDE progress reports to the FDA in over two years. This type of omission limits the FDA's ability to properly review the safety and progress of a study. In this case, the S-I was under the assumption that these reports were not needed since the study was no longer enrolling subjects. In fact, ongoing reporting requirements to IND/IDEs, including annual progress reports, do not cease until the IND/IDE has been formally withdrawn or inactivated.

Relevance to Academic Health Centres

Sponsor-investigators at AHCs are held to the same regulatory requirements for holding an IND/IDE as a commercial sponsor. Half of the WLs to S-Is were issued at Academic Health Centres (AHCs). At all of these AHCs, the INDs or IDEs were held by the individual investigators and not the institution. Nonetheless, the institution's name is displayed on the majority of WLs; thus, these types of letters can impact the ability of an investigator to attract funding and can damage the institution's reputation.

As was described above, the published WLs represent only a small sampling of what is happening on a larger scale. The majority of INDs submitted to the FDA are non-commercial or "research" INDs. To illustrate, in 2011, CDER received 2,098 research INDs and 648 commercial INDs [22]. In that same year, CBER, which reviews both INDs and IDEs, reported receiving 172 research applications and 99 commercial applications [23]. Most of these 'research' submissions are assumed to come from S-Is. It is unknown how many of the S-Is come from AHCs but the number is unlikely to be low. Recent translation funding initiatives are likely to increase the number of S-Is at AHCs. These Clinical and Translational Science Awards (CTSA) were first awarded in 2006 to a consortium of

12 different Academic Health Centres. Since then, the award has been expanded to a consortium of 60 different institutions [2]. At Duke University Medical Center alone, the number of S-I held IND/IDEs has increased from 78 in August of 2009 to 118 in October of 2013 with the individual number of S-Is increasing from 38 to 66 (E. O'Reilly, personal communication).

Conclusion

Our review of the WL database at the FDA reveals the potential for serious regulatory violations at Academic Health Centres. AHCs must become aware of this S-I role and work to support investigators who assume both roles in the course of their research. AHCs should consider the available WL findings as an instructive tool for guidance on how to improve their research programs. Our specific recommendations are below:

1. Institutional Recognition of the Issue

It is important that institutional leadership recognize the significance of assuring regulatory compliance when its investigators take on the special role of 'sponsor-investigator'. Support for appropriate programs and tools requires endorsement from the highest levels at an institution. These programs require personnel and funding at levels proportional to the number of S-Is at an institution. Lack of these programs can not only jeopardize subject safety, but can also have a major impact on the quality and integrity of data collected during the study, as well as on the image and credibility of the institution.

2. Sponsor-Investigator Training

Sponsor-Investigators may not be aware of the implications of signing an FDA Form 1571. By signing this form, the S-I agrees to conduct an investigation in accordance with all applicable regulatory requirements; thus, S-I training is an important component in building and maintaining a quality research program within an AHC. A good training program can be instrumental in preventing the kinds of issues that are commonly cited in FDA WLs. Many institutions offer S-I training and/or access to resources [9, 10]. The models of training are tailored to the specific needs of each institution; however, the goals are the same: to provide an overview of the regulations, an understanding of the appropriate oversight and responsibilities of an S-I, as well as provide guidance on how to comply with those responsibilities.

3. Implement Monitoring

Monitoring was the most frequently cited deficiency among both the WL and BIMO metrics. Thus, institutions can prioritize improving their research programs by addressing the need to assist their S-Is with monitoring programs. Ongoing monitoring of a study is an efficient way of identifying problems early in the life of a trial before human subject protection or data integrity issues arise. Too often, at AHCs, the term 'monitoring' is only associated with 'safety monitoring' in relation to adverse events caused by a drug or device. Equally important is 'study monitoring' where the conduct of the study is evaluated. Study monitoring includes verification of proper consent, proper enrollment based on the inclusion/exclusion criteria and proper reporting of safety events among many other issues like drug accountability. The FDA has published a guidance document on developing a risk-based monitoring plan that would be followed throughout the study [24]. A good monitoring plan will minimize mistakes, improve data integrity, improve human research subject protection and can help protect an S-I from being vulnerable to a WL.

Acknowledgments

This paper was supported by the National Center for Research Resources and the National Center for Advancing Translational Science of the National Institutes of Health through Grant Numbers UL1RR024128, UL1RR024982 and UL1TR000157. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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