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An Analysis of United States Food and Drug Administration Warning Letters Issued to Clinical Investigators from 1996 through 2011

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Abstract

The warning letter is a communication sent to sponsors, manufacturers and clinical investigators resulting from inconsistencies and inaccuracies found during FDA audits of clinical research-related activities. Warning letters to investigators can have a major impact on that physician's practice and their affiliated institution. The objective of this research was to analyze the publicly available warning letters that were sent to clinical investigators during the years 1996 to 2011 to identify areas of deficiencies and educate current and future clinical investigators. The data was extracted from letters to Clinical Investigators published in the Electronic Reading Room on the FDA's website.The specific regulationslisted in the letters that were deemed violated by the respective FDA auditor were used for data analysis and termed "infractions".Between 1996 and 2011, 1,404 infractions were noted for 237 Clinical Investigators (mean = 5.14). The vast majority of these infractions occurred in 21 Code of Federal Regulation, parts 50, 312 and 812 (n= 215, 523 and 650 infractions, respectively) and reflected violations in the areas of informed consent, documentation and investigator responsibilities.During this timeframe, the average number of infractions per investigator per year did not decrease. Finally, the number of investigator warning letters that were issued was not correlated to the number of investigator audits. This data shows common deficiencies in clinical research programs and can assist investigators in developing preventative measures for future clinical research.

Keywords: Bioresearch monitoring program; United States Food And Drug Administration; Clinical investigators; FDA audits; Warning letters

Introduction

To ensure that clinical trials are conducted in compliance with federal regulations, the Food and Drug Administration (FDA) conducts audits of clinical trial sites under its Bioresearch Monitoring Program (BIMO), part of the Division of Scientific Investigations (DSI) [1]. The BIMO Program was initiated in 1977 to fulfill the FDA's obligations to provide oversight to the conduct of clinical studies involving FDA-regulated products such as drugs, biologics and devices. This compliance program provides uniform guidance and specific instructions for inspections and audits of Clinical Investigators and other persons or facilities involved in the development and manufacturing of drugs, biologics and devices.2 The regulations that clinical investigators are bound to follow and which the BIMO program enforces, namely 21 CFR 312 and 812, became effective in 1987 and 1980, respectively. By enforcing these regulations,

"The BIMO program helps to:

1. To protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials;

2. To verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications; and

3. To assess compliance with FDA's regulations governing the conduct of clinical trials [2,11]".

There are several types of audits, each warranted for a specific reason; however, pertaining to clinical investigators (e.g., those persons in charge of the conduct of a study at a particular site) the "study and/or investigator-type audit" is conducted to determine the validity and integrity of the data, to assess the adherence to regulations and guidelines and, finally and most importantly, to determine that the rights and welfare of the subjects who participated in the study were protected.3These types of audits can beroutine or "for cause" and can happen at any point during the drug and device development process [1].

If it is found during the audit that the investigator did not comply with the regulations a form 483, which details the deviations, will be issued to the investigator. Subsequently, several things may happen: (1) a recommendation to reject the data, (2) a recommendation to disqualify the clinical investigator or (3) a referral to criminal prosecution, however, most typically (4) a notice of that violation in the form of a "warning letter" is sent to the investigator from the agency overseeing that particular trial [1].

As it states on the Center for Drug Evaluation and Research website, warning letters are informal correspondences and are sent only when the FDA has detected a significant violation of the Federal Food Drug and Cosmetic Act (FD&C) within an investigator's facility during an audit [4,5]. These differ from more formalletters resulting from inspections that would require an investigator to take prompt action, specifically, the Official Action Indicated (OAI) letter. The other formal letters which require either no or voluntary changes are the No Action Indicated (NAI) or Voluntary Action Indicated (VAI), respectively [6].

The FDA views the warning letter as a tool to help the audited investigator correct the violations found at their site rather than a

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mandate for enforcement action. However, the letter clearly states that enforcement action may be taken if the violations are not promptly and adequately corrected [5]. The ramifications of this stance are primarily of a litigious nature in that "the FDA does not consider Warning Letters to be final agency action on which it can be sued" and it should be further noted that the agency is "under no legal obligation to warn individuals (or firms) that they (or their products) are in violation of the law before taking enforcement action [5].

The issued warning letter is typically structured so that the receiving party is made aware of the specific regulation that he/she violated (usually bolded), and further, how it was violated and on which occasions. For example:

"1. You failed to obtain informed consent of subject involved in research in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60]. … a. There were no signed and dated informed consent documents on file for subjects [redacted] and [redacted] enrolled in study [redacted]."

The violation mentioned can pertain to a single incident or many incidents within that same violation. Additionally, that same violated regulation may be cited more than one time for a single investigator if the auditor finds the investigator to have been either particularly negligent or negligent in different ways within the scope of that regulation. To justify the citation, auditors may insert redacted charts, diagrams or other images directly from case report forms or other documents (e.g., blood work).

After the auditor lists all of the violations and details corresponding to these occurrences, the letter is typically closed with the statement that:

"[The] letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug (device). It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations."

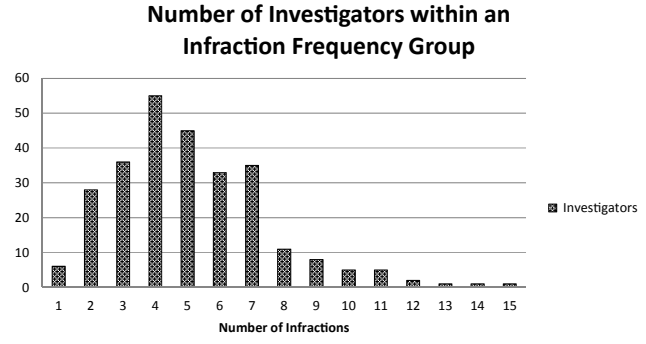

Figure 1: The number of investigators cited for a particular number of infractions. 1996 – Early 2011

This statement further highlights the FDA's hope and expectation that individuals and firms will voluntarily comply with the law [7]. Indeed, investigators conducting clinical trials that fall under the purview of the FDA are requiredto sign "Form 1572", the Statement of Investigator, which gives the FDA, among other information, the assurance that the investigator"will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic" [8,9].

Due to the fact that so many federal regulations are in force when a clinical investigator takes on a trial, an understanding of which regulations that are most often violated will help not only current, but future investigators identify the potential pitfalls within their research programs and assist in compliance with the regulations which they are bound to follow. It is the hope of this researcher to fully demonstrate the regulations that have been violated since 1996, the frequency with which they are violated and the consequences of those violations.

Material and Methods

Data were collected by systematic review of warning letters posted on the FDA's Electronic Reading Room website, a public website provided in accordance with the Freedom of Information Act [10,[a]]. The specific letters used in this study were found under the hyperlink for "Clinical Investigator". It should be noted that the category "Clinical Investigator (Sponsor)" was not used for this data set.

The originallist of warning letters from the website provides the names of 322 clinical investigators; however, several of these letters were not incorporated into the data set for the following reasons: (1) the letters were duplicates (n=31), (2) the letters did not clearly state which regulations were in violation (n=13), (3) the incorrect letter was uploaded to the website (n=3) and (4) two clinical investigators were noted separately within the list, but shared the same letter. In this instance, the letter was counted once. Letters were also excluded as a result of the investigator being incorrectly placed under the category of "Clinical Investigator" (n=1).

The clinical investigator letters dating from 1996 through March 2011 were reviewed for the phrase stated earlier in the introduction. The sentence typically started with "You failed to", followed by a description of the violation and ending with the exact regulation violated in brackets or parentheses (e.g., [21 CFR 50.27]). The other elements of the letters were too variable to provide a standardized metric for analysis.Each and every occurrence of a bracketedregulation that followed this format was counted in the data set and, from here are deemed infractions. Occasionally, a regulation was listed that was not legitimate, likely due to a typographical error or other editing/transcribing error. These, of course, were excluded from the data set.

The number of infractions that appeared in each letterwas tallied for each investigator.Concurrently, the number of infractions of a specific regulation was tallied to gain insight as to which regulations were most frequently violated.These data were compiled and analyzed using Microsoft Excel. Simple linear regression was used to determine if there was an increasing trend of number of infractions per investigator over time.It should be noted that the year 1996 was excluded from this data set because only one letter was published by the FDA for this year.

The data for number of inspections for years 2007 through 2010 were abstracted from BIMO Metrics on the FDA Website and included only those inspections originating in CDER, CBER and CDRH.11Correlation was used to characterize the association between number of inspections per year and the number of warning letters issued.

In regard to human subject research: IRB approval to conduct

[a]Occasionally this link does not directly provide access to the exact data reviewed for this paper. To find the webpage proceed via the following these links: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm→ Browse Warning Letters by Subject → Clinical Investigator. The link to Clinical Investigator (Sponsor) was not used in this data set.

Regulatory Scope	Individual Subpart	Subpart Title	21 CFR Section	Number of Infractions	Number of Subsections the Infractions Cover
Protection of Human Subjects		General	§50	63	1
	Subpart B	Mandate to Obtain Informed Consent	§50.20	59	1
		Exception from General Requirements	§50.23	2	1
		Exception from General Requirements - Emergency Research	§50.24	1	1
		Elements of Informed Consent	§50.25	34	10
		Documentation of Informed Consent	§50.27	55	3
	Subpart D	Documentation of Permission by Parents/Legally Authorized Representative	§50.55	1	1
		General - IDE	§812	3	1
IDE	Subpart A	Labeling of Investigational Devices	§812.5	1	1
		Requirement for FDA & IRB Approval	§812.18	1	1
	Subpart B	IDE Application	§812.20	1	1
		Investigational Plan	§812.25	3	2
		Supplemental Actions	§812.35	6	3
	Subpart C	General Responsibilities of Sponsors	§812.40	10	1
		FDA and IRB Approval	§812.42	6	1
		Selecting Investigators and Monitors	§812.43	11	5
		Monitoring Investigations	§812.46	3	1
	Subpart D	IRB Approval	§812.62	2	1
		IRB's Continuing Review	§812.64	1	1
	Subpart E	General Responsibilities of Investigators	§812.100	170	2
		Specific Responsibilities of Investigators	§812.110	147	6
	Subpart G	Records	§812.140	191*	18
		Inspections	§812.145	3	2
		Reports	§812.150	91	15
IND	Subpart A	Promotion of an investigational new drug	§312.7	1	1
	Subpart B	Requirement for an IND	§312.20	8	3
		IND Content and Format	§312.23	2	2
		Protocol Amendments	§312.30	1	1
		IND Safety Reporting	§312.32	2	2
		Annual Reports	§312.33	4	3
	Subpart C	General Requirements for Use of an IND in a Clinical Investigation	§312.40	8	3
		Clinical Holds and Requests for Modifications	§312.42	1	1
	Subpart D	General Responsibilities of Sponsors	§312.50	7	1
		Selecting Investigators and Monitors	§312.53	17	11
		Informing Investigators	§312.55	1	1
		Review of Ongoing Investigations	§312.56	8	4
		Recordkeeping and Record Retention	§312.57	8	3
		Inspection of Sponsor's Records and Reports	§312.58	1	1
		General Responsibilities of Investigators	§312.60	216	1
		Investigator Recordkeeping and Retention	§312.62	160	4
		Investigator Reports	§312.64	11	3
		Assurance of IRB Review	§312.66	65	1
		Disqualification of a Clinical Investigator	§312.70	2	1

Table 1: Detail of Infractions within the Data Set. The majority of infractions lie within responsibilities of investigators, record keeping and obtaining/documentation of informed consent.1996-Early 2011 *Note: This section has been broken down in Table 2.

exempt research per regulation 45 CFR 46 was gained from the University of Tennessee Institutional Review Board.

Results

Across all of the warning letters included in the data set (n=273), 1,404 infractions were cited by FDA auditors. These infractions covered 140 different specific regulations (data not shown) with the mean number of infractions per clinical investigator being 5.14 (mode = 4, median = 5). The infractions originated from warning letters sent by CDRH (n=129), CDER (n=84) and CBER (n=60). Figure 1 shows the number of clinical investigators who had a particular number of infractions. As one can see, the distribution is skewed to the left due to only a handful of clinical investigators having greater than 10 infractions.

The vast majority of the infractions cited by FDA auditors came from violations of regulations pertaining to the Protection of Human Subjects (21 CFR 50, n=215, 15.3% of total infractions), the Investigational New Drug Application (IND) (21 CFR 312, n=522, 37.2% of total infractions) and the Investigational Device Exemption (IDE) (21 CFR 812, n=650, 46.3% of total infractions), with IDEs accounting for about half of the total infractions cited (Figure 2). When the major regulatory parts are broken down into their subparts (e.g., 21 CFR 50 Subpart B), a better understanding of the specific violations is

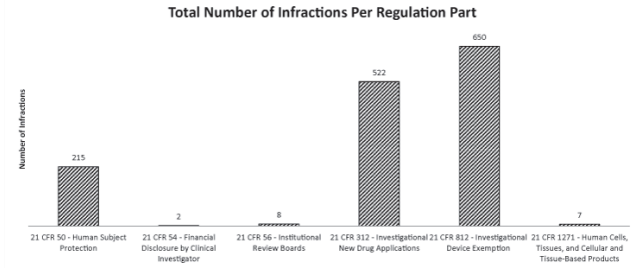

Figure 2: The total number of infractions per broad regulatory "Part". These numbers were derived by combining the more specific regulatory infractions into their broad "Part". 1996-Early 2011

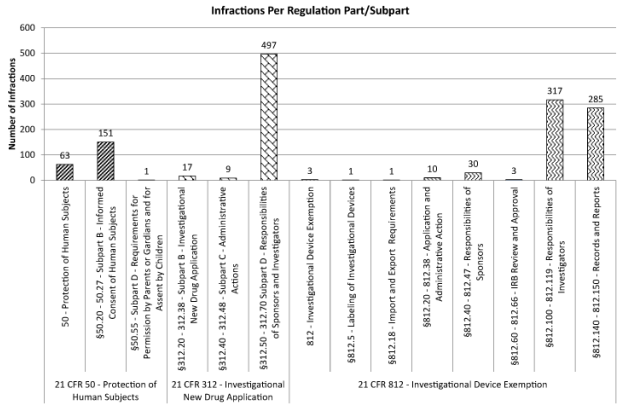

Figure 3: Infractions per regulatory subpart. These subparts are defined by the FDA in the Code of Federal Regulations. The number above the bar indicates the total number of violations of that particular subpart from all of the warning letters utilized in the data set. 1996-Early 2011

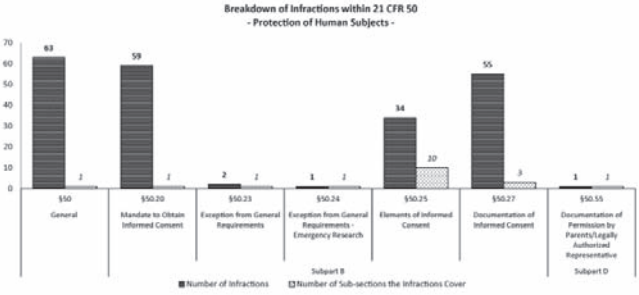

Figure 4: Breakdown of Infractions within 21 CFR 50: Protection of Human Subjects. Most infractions seen within warning letters reside within the subparts that regulate the obtaining and documentation of informed consent. 1996-Early 2011

established (Figures 3,4). Under the Protection of Human Subjects Part of the CFR, there is a strong incidence of violations of the informed consent subpart versus other subparts of the regulation (Figure 3). Within the scope of IND and IDE regulations, infractions occurred most frequently in subparts governing responsibilities of investigators and their record keeping (Figure 3).

When the smaller sections (§) of the regulatory subparts that carry infractions are examined, specific trends are seen. In Subpart B of 21 CFR 50 (Figure 4), there was an almost equal split between the number of infractions for failing to obtaininformed consent and for failing to document that informed consent (59 and 55 infractions, respectively).

In Subpart D of 21 CFR 312 which covers IND applications, the majority of infractions are under the following sections: §312.60 (General Responsibilities of Investigators, n=216), §312.62 (Investigator Recordkeeping and Retention, n=160) and §312.66 (Assurance of IRB Review, n=65)(Table 1).Similar clustering of infractions occurred within IDE applications (21 CFR 812): the majority of the infractions are found within the sections covering General Responsibilities of Investigators (§812.100, n=170), Specific Responsibilities of Investigators (§812.110, n=147), Records (§812.140, n=191) and Reports (§812.150, n=91) (Table 1).

Table 1 also shows the number of regulatory sub-sections the infractions come from, specifically. It is not uncommon to have all infractions covering an entire section without specifying a specific sub-section, as in the case of 21 CFR 50.20 which had 59 infractions. However, several auditors specifically noted many sub-sectionswithin the warning letters as is the case with the Records portion of IDE Subpart G (21 CFR 812.140). This section had 191 infractions covering 19 sub-sections out of a total of 28 sub-sections defined within the regulation. Table 2 shows the breakdown of the where the infractions occurred within the investigators' clinical research programs – namely that they frequently failed to document device receipt, subject case histories and informed consent.

Taking into account the known specific deficiencies, the study finally tried to address any trend over time regarding the number of infractions per investigator. As can be seen in Figure 5, the number of infractions for various investigators during a specific year has not significantly changedfrom 1997 through the spring of 2011 (p= 0.258, 95% confidence interval of the beta-coefficient -0.1248 and 0.03335 [i.e. the increase in the number of infractions per investigator per year]). Note that the number of warning letters issued/investigators for a given year is detailed under the specific year (e.g. 2002 had 17 warning letters, etc.) Also, among the agencies that most frequently issue warning letters to clinical investigators (i.e., CDER, CBER, CDRH), it seems as if there is no correlation between the number of investigations of clinical investigators and the number of warning letters written during years 2007 through 2010 (correlation = 0.29, p=0.7085) (Figure 6).

It is important to note that this study is limited in its ability to report based on what was publicly available on the FDA's website and correlations between numbers of infractions, actual audits and other more formal correspondence is lacking. Readers should also note that because the warning letter specifically states that the list is NOT comprehensive of all of an investigator's failings, the data is only applicable to what particular auditors were able to discover. Therefore, possibly more infractions were there, but were not addressed. Further, due to regulatory evolution and guidance review, the way in which auditors assess a clinical investigator is sure to have changed and that cannot be accounted for within this paper and is far outside the scope of the study.

Discussion

It cannot be overstated how important it is to have a well-planned and executed clinical research program. The ramifications of regulatory violations on a researcher and their corresponding institution can affect their funding as well as their reputation. A recent example of this systemic clinical research failure is exemplified within the retraction

Subsection	Subsection Details	Infractions
812.140	Records - Covers all subsections including those below	7
812.140(a)	Investigator Records	28
812.140(a)(1)	All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports	8
812.140(a)(2)	Records of receipt, use or disposition of a device	38
812.140(a)(2)(i)	The type and quantity of the device, the dates of its receipt, and the batch number or code mark.	3
812.140(a)(2)(ii)	The names of all persons who received, used, or disposed of each device	2
812.140(a)(2)(iii)	Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of	3
812.140(a)(3)	Records of each subject's case history and exposure to the device	52
812.140 (a)(3)(i)	Documents evidencing informed consent […]	21
812.140(a)(3)(ii)	All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests	11
812.140(a)(3)(iii)	A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy	2
812.140(a)(4)	The protocol, with documents showing the dates of and reasons for each deviation from the protocol	5
812.140(a)(5)	Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation	1
812.140(b)	Sponsor records	1
812.140(b)(2)	Records of shipment and disposition	2
812.140(b)(5)	Records concerning adverse device effects (whether nticipated or unanticipated) and complaints and	1
812.140(d)	Retention period	3
812.140(e)	Records custody	2

Table 2: Detail of Infractions within Subsection 21 CFR 812.140. The range of infractions within this subsection can be generalized to documentation of device receipt, case histories and informed consent. 1996-Early 2011

comments from the editor of *Journal of Clinical Oncology (JCO)*. In 2010, the journal published an article by researchers at Saitama Medical University which detailed a clinical research study entitled, "Prospective Analysis of Hepatitis B Virus Reactivation in Patients With Diffuse Large B-Cell Lymphoma After Rituximab Combination Chemotherapy" which was subsequently retracted.13 In his retraction statement, the editor states that the authors,

"Did not comply with standard ethical principles of clinical investigation, despite claims to indicate otherwise in the published article. Specifically, Saitama Medical University determined that the authors failed to obtain Institutional Review Board approval for the research and failed to obtain written informed consent from all of the participants. Accordingly, JCO formally retracts this article" [14].

In response to this article, the entire body of the University was made aware of the situation and the authors were formally reprimanded [15].

Even more striking is the case of Joachim Boldt, a German

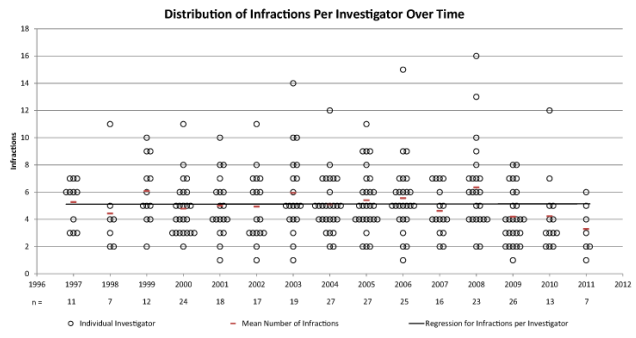

Figure 5: Distribution of infractions for investigators during a specific year.Each circle represents an individual clinical investigator's warning letter. The small lines represent the average number of infractions found in warning letters during a specific year. 1997-Early 2011.

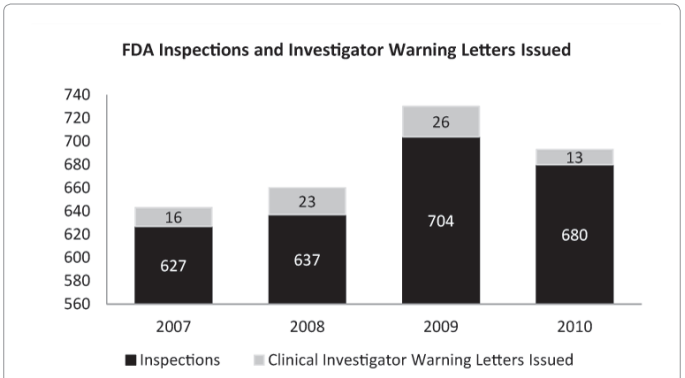

Figure 6: FDA Inspections and Clinical Investigator Warning Letters: Years 2007-2010. The number of warning letters issued does not correlate with number of clinical investigator audits during that year.

anesthesiologist who was stripped of his professorship in February 2011 by the University of Geissen and the university is further investigating his research practices [16]. Surrounding the issue are instances of suspected fraud and lack of ethics board approval. Earlier this year, Reuters reported thatThe Association of Surgeons of Great Britain and Ireland (ASGBI) was made aware of the situation regarding Dr. Boldt and was reviewing guidelines for their research which will no doubt affect the other researchers under their jurisdiction. Additionally, 16 editors were retracting 89 of Boldt's papers because the Rheinland State Medical Boardstated that there was no IRB approval for the articles, which included 22 published in between 1999 and 2009 [17].

Similar errors happen under the oversight of the US FDA every year and can be seen in the data presented within this paper. Within the regulations for the Investigational New Drug there were 65 infractions for the requirement for IRB review (Table 1). Institutional review boards, and their international counterparts, exist to maintain patient safety and have for decades. It is a tremendous breach of medical and societal ethics to refrain from applying for IRB review as is mandated by governmental and, when applicable, institutional agencies (see 21

CFR 312.66). In its code of ethics, the American Medical Association touches on the subject stating that "the ultimate responsibility for ethical conduct of science resides within the institution which conducts scientific research and with the individual scientist. [18]"

Yet when IRB approval is sought and gained, many of the researchers who received warning letters fail to document the informed consent process even if they did obtain consent in the first place (Figure 4). As far as the FDA is concerned, documentation is key to verifying how and when a clinical research activity proceeded and is a necessary part of any investigation [19,20]. The commonly used phrase 'if it isn't documented, it didn't happen' is derived directly from this principle.

Aside from absence of documentation, one of the most commonly violated regulatory sections has to do with the general conduct of a study [21 CFR 312.60] which states:

"An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An investigator shall, […], obtain the informed consent of each human subject to whom the drug is administered, except as provided in §§50.23 or 50.24 of this chapter. […]."

In a 2004 paper investigating 36 warning letters, Bramstedt found deviations from investigational plans to be the most prevalent violation, whether drug or device related [21]. Deviations (a.k.a. protocol violations) in a research protocol have been divided in to minor and non-minor categories by the National Institutes of Health IRB based on whether they satisfy certain criteria: human subject protection (i.e. whether the subject was exposed to further harm) or data fallibility (i.e. scientific integrity was compromised) [22]. In the case of those that expose the patient to further harm, deviations can be typified by patients receiving a dose that is not prescribed by the protocol, the subject meeting withdrawal criteria and continuing in the study or concomitant medications being allowed. Each of these exposes the subject to various harms.

Data-related deviations, such as enrolling ineligible subjects or generally ignoring the investigational plan can result in type I or type II error, possibly introducing a drug or device into the population that was shown to be effective, but in reality isn't or withholding a drug/device from marketthat is effective when the data showed it wasn't [23]. The first error exposes the general population to side effects without a promise of treatment while the second error possibly eliminates a promising new treatment. For these reasons, the marketing application of a drug may be delayed or suspended if a study at a particular site is invalidated, especially if the site was a high patient enroller [3].

Data regarding the obtaining and documenting of the informed consent process is one that does, indeed, overlap widely. For instance, an entire Subpart of 21CFR50 (B: Informed Consent of Human Subjects) fully addresses the regulations surrounding consent. However, the regulations further reiterate the necessity for informed consent by placing it directly within the responsibilities of the investigators under an IND or IDE. Some auditors did cite regulations from both the Protection of Human Subject part and the IND (or IDE), however some did not, possibly thinking that one citation was enough to get the point across. The Regulatory Procedures Manual does not detail to what length a violation should be noted and it is assumed after review of the published letters, that the auditors might be given individual authority to determine what is necessary based on what he/she finds during the audit.

In conclusion, a clinical investigator takes on an enormous responsibility when undertaking a clinical research trial. During the hustle of clinic responsibilities, there are many opportunities for the requirements of a trial to fall by the wayside. It is important for any investigator to employ whatever means necessary to keep their regulatory documents in order and up to date. This may come in the form of a certified research coordinator or nurse who is given the authority and autonomy to carry out the details of the study under the investigator's direction or, in the absence of a research team, it may necessitate the investigator setting aside a designated time to make sure all documents are in place. Several organizations exist specifically for the training and certification of clinical trials personnel, such as the Society of Clinical Research Associates, Inc. (SOCRA) or the Association of Clinical Research Professionals (ACRP) and, for a fee, staff can achieve individual certification in the regulations and conduct of clinical trials. There are also many other private organizations which hold free and/or paid webinars on clinical research and should definitely be consulted by the investigator who is new to clinical research or who has entered a new area of research (e.g. drug vs. device trials).

Whatever the educational method, being familiar with and following the regulations surrounding a clinical research study will keep the investigator out of trouble and will assist the sponsor in getting their product to market.

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