PAPER

Analysis of warning letters issued by the US Food and Drug Administration to clinical investigators, institutional review boards and sponsors: a retrospective study

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ABSTRACT

The US Food and Drug Administration (FDA) issues warning letters to all research stakeholders if unacceptable deficiencies are found during site visits. Warning letters issued by the FDA between January 2011 and December 2012 to clinical investigators and institutional review boards (IRBs) were reviewed for various violation themes and compared to similar studies in the past. Warning letters issued to sponsors between January 2005 and December 2012 were analysed for the first time for a specific set of violations using descriptive statistics. Failure to protect subject safety and to report adverse events to IRBs was found to be significant compared to prior studies for clinical investigators, while failure to follow standard operating procedures and maintain documentation was noted as significant in warning letters to IRBs. Failure to maintain minutes of meeting and to follow written procedures for continuing review were new substantial violations in warning letters issued to IRBs. Forty-six warning letters were issued to sponsors, the most common violations being failure to follow a monitoring schedule (58.69%), failure to obtain investigator agreement (34.78%), failure to secure investigators' compliance (30.43%), and failure to maintain data records and ship documents to investigators (30.43%). Appropriate methods for handling clinical trial procedural violations should be developed and implemented worldwide.

INTRODUCTION

Researchers conducting studies must not forget their moral obligations towards the safety and well-being of their study participants.[1] Instances at Duke University, the University of Pennsylvania, New York Cornell Medical Center, Johns Hopkins University, Fred Hutchinson Cancer Research Center, the National Institute of Mental Health, the University of Maryland and Harvard in China[2] have underlined ethical concerns about research involving human participants and emphasised the necessity of conducting clinical trials ethically.[1] All research must be ethically reviewed to reassure participants and the community about the conduct of the study.[3] In the USA, federal regulations govern research involving human participants.[4] It is the legal responsibility of authorised officials in regulated organisations to follow the required procedures and ensure that their products, practices and other activities comply with the regulations.[5] The US Food and Drug Administration (FDA) undertakes vigorous measures to ensure the maintenance of research integrity by clinical investigators, institutional review board (IRB) members, pharmaceutical/device/biotechnology companies, sponsors, etc., especially in light of the growing number of research projects and study participants.[6] The FDA developed its Bioresearch Monitoring Program to safeguard the rights, welfare and safety of human subjects and the quality and integrity of data submitted to the regulatory body, in addition to conducting site visits to IRBs, clinical investigators, sponsors, monitors, contract research organisations, non-clinical (animal) laboratories and bioequivalence analytical laboratories.[7]

All research stakeholders have a fundamental responsibility to conduct ethical clinical trials following the principles of good clinical practice.[8]

FDA investigators are authorised to access, copy and verify any documents created by the clinical investigator. The FDA carries out inspections of clinical investigator sites to authenticate the precision and trustworthiness of the data submitted to the agency: (1) if there is grievance about the conduct of a study at a specific site; (2) in reply to sponsor concerns; (3) on termination of the clinical site; (4) to provide real-time evaluation of the investigator's conduct of the trial and the safety of subjects; (5) on request by the FDA review division; and (6) in connection with certain categories of investigational products that the FDA has acknowledged as current products of extraordinary importance.[9] If a clinical investigator is found to have breached FDA regulations, the FDA informs the investigator of the violations and takes suitable action.[10]

According to the FDA, 'an institutional review board is responsible for evaluating a trial to determine, among other things, whether "risks to subjects are minimized" and "risks to subjects are reasonable in relation to anticipated benefits" '.[11] IRBs must assess a trial to verify whether risks to trial participants are minimised through reliable procedures with sound research plans and are appropriate given the predicted benefits.[12] FDA inspections of IRBs generally fall into one of two categories: (1) surveillance inspections that include intermittent, planned inspections to assess overall IRB procedures and operations; and (2) directed inspections which involve unannounced inspections focusing on the IRB's evaluation of specific clinical trials, and which generally arise from a complaint,

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clinical investigator misconduct or safety issues regarding a trial or site. If an IRB does not take suitable remedial action, the FDA may: (1) withhold consent for new studies conducted at the organisation or reviewed by the IRB; (2) refuse permission for the addition of new subjects to ongoing studies; (3) close down studies to safeguard subject well-being; and (4) inform the relevant state and federal regulatory agencies of the IRB deficiency in cases where non-compliance generates a significant risk to subjects' rights and welfare.[7]

A sponsor is an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.[8] Hence, clinical trial sponsors are held legally accountable by the FDA. The primary duties of a sponsor are to recruit qualified, experienced and capable investigators, submit Investigational Device Exemption and Investigational New Drug applications to regulators, identify the best resources available for monitoring the trial, ensure IRB approval and review, and hire experienced clinical practice professionals to audit and provide feedback on the quality of the data and the adequacy of the monitoring, etc.[13]

The FDA issues warning letters for violations of significant regulations to individuals and organisations, to encourage voluntary compliance through deliberate and rapid corrective action before an enforcement action is initiated.[5] The FDA defines a warning letter 'as an informal advisory to a firm communicating the Agency's position on a matter but does not commit the FDA to taking enforcement action'.[14] Regulated organisations have an official responsibility to implement mandatory procedures to guarantee that their products, practices or other activities comply with the law.[15]

Bramstedt and colleagues previously studied warning letters issued to clinical researchers from February 2002 to February 2004[16] and to IRBs from January 1997 to July 2004.[17] Subsequently, Gogtay *et al* studied warning letters issued to IRBs and clinical investigators from January 2005 to December 2010.[18] We studied warning letters issued by the FDA to clinical investigators and IRBs from January 2011 to December 2012. As there were no previous studies on warning letters issued to sponsors, we selected the period January 2005 to December 2012 and analysed the data in order to examine trends.

METHODS

This was a retrospective study which included an analysis of 2 years of data (January 2011 to December 2012) for clinical investigators and IRBs and 8 years of data (January 2005 to December 2012) for sponsors. The IRB (IRB(I)/OUT/273/15th March 2013) of Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital, Mumbai approved this study. Warning letters by year are listed online in the FDA Warning Letter Index.[19]

All warning letters were searched manually and categorised into those issued to clinical investigators, IRBs and sponsors and were further classified as referring to drug-related or device-related studies.

The warning letters to clinical investigators were evaluated for the following violations: (1) deviation from investigational plan; (2) failure to maintain adequate and accurate case records; (3) informed consent issues; (4) regulatory non-compliance; (5) violations related to the investigational product; (6) lack of personal supervision of study conduct; (7) failure to protect subject safety and report adverse events to IRBs; (8) failure to obtain IRB approval; and (9) submission of false information to the FDA and sponsors.

The violations for which warning letters were issued to IRBs were categorised as: (1) failure to follow standard operating procedures and maintain documentation; (2) inappropriate membership, quorum issues, lack of a layperson in meetings and misuse of expedited review; (3) informed consent issues; (4) failure to follow regulatory requirements; (5) failure to address conflicts of interest; (6) failure to protect vulnerable participants and address risk minimisation; (7) failure to inform institutional officials regarding study status; (8) failure to maintain minutes of meetings; (9) lack of a qualified clinical investigator; and (10) failure to follow written procedures for continuing review.

Sponsors were issued warning letters under the following headings: (1) failure to follow monitoring schedule; (2) failure to obtain investigator agreement; (3) failure to secure investigator compliance; (4) failure to maintain data records; (5) failure to ship/maintain records of the investigational product to the clinical investigator; (6) failure to submit an Investigational Device Exemption or Investigational New Drug Application to the FDA; (7) failure to review, evaluate and submit adverse drug event reports to the FDA; (8) failure to ensure informed consent document received from study participants; (9) failure to submit progress reports to the IRB; (10) failure to ensure that an investigation was conducted in accordance with the investigational plan; (11) failure to provide investigators with the information needed to conduct the study appropriately; (12) failure to ensure IRB review; (13) lack of trained monitors; (14) failure to include elements in informed consent document; (15) failure to ensure proper device labelling; (16) failure to inform the reviewing IRB and the FDA of new information; (17) failure to obtain prior permission for (online) advertisement; (18) failure to notify the FDA of the termination of an investigation; (19) failure to allow FDA inspection; (20) failure to provide the current investigator list; (21) failure to obtain IRB approval; and (22) failure to include reports of previous testing of the device.

Two individuals coded each warning letter separately. Whenever there was a discrepancy between the two coders, consensus was reached after detailed discussion. The findings from the warning letters to clinical investigators and IRBs were compared with the results of Bramstedt and colleagues and Gogtay *et al* using GraphPad V.3.06. Significance was set at 5%. The χ^2 test was used since the data sets were categorical binomial data sets. Whenever one of the two outcomes possible had a value of ≤ 5, then Fisher's exact test was used. Warning letters issued to sponsors were analysed using descriptive statistics.

RESULTS

A total of 84 warning letters issued by the FDA were reviewed.

Warning letters issued to clinical investigators

Twenty warning letters were issued to clinical investigators. Of these, 16 (80%) were related to new investigational drug studies and four (20%) were device related. The most common violation was deviation from the investigational plan (19/20; 95%), with 15/16 (93.75%) letters being issued for drug-related research and 4/4 (100%) for device-related research. Failure to protect subject safety and report adverse events to the IRB was the next most common violation (11/20; 55%) with 8/16 letters (50%) related to drug-related research and 3/4 (75%) to device-related research.

Violations such as failure to maintain accurate and adequate case histories, failure to retain records for inspection, inability to produce records for inspection and regulatory non-compliance were documented in 8/20 warning letters (40%).

Table 1 Warning letters issued to clinical investigators

Item no.	Violation theme	Current study Drug-related N=16 (%)	Current study Device-related N=4 (%)	Current study Drug- and device-related N=20 (%)	Gogtay study[18] Drug- and device-related N=129 (%)	Bramstedt study[16] Drug- and device-related N=36 (%)	p Value
1	Deviation from investigational plan	15 (93.75)	4 (100)	19 (95)	104 (80.6)	32 (88.9)	0.17
2	Maintaining adequate and accurate case records and histories and failure to retain records or produce records for inspection	7 (43.75)	1 (25)	8 (40)	75 (58.1)	Not reported	0.15
3	Informed consent	5 (31.25)	2 (50)	7 (35)	62 (48)	24 (66.7)	0.05
4	Regulatory non-compliance	4 (25)	4 (100)	8 (40)	50 (38.8)	Not reported	1
5	Violations related to investigational product	3 (18.75)	0	3 (15)	38 (29.4)	Not reported	0.28
6	Failure to personally supervise the study	6 (37.5)	0	6 (30)	27 (20.9)	02 (5.6)	0.04*
7	Failure to protect subject safety or report adverse events to institutional review boards	8 (50)	3 (75)	11 (55)	30 (23.2)	17 (47.2)	0.001*
8	Failure to obtain institutional review board approval	2 (12.5)	0	2 (10)	Not reported	Not reported	–
9	Submission of false information to the FDA and sponsors	1 (6.25)	0	1 (5)	Not reported	Not reported	–

*p<0.05 using Fischer's exact test.
FDA, US Food and Drug Administration.

Issues related to informed consent were mentioned in 7/20 warning letters (35%).

Other violations were related to the investigational product (3/20; 15%), failure to obtain IRB approval (2/20; 10%) and failure to personally supervise the study (6/20; 30%). All warning letters mentioned at least two of the nine violation categories, while two mentioned five and one mentioned six.

Data comparing the present research with the earlier studies are presented in table 1 and the trend of important violations is depicted in figure 1.

Warning letters issued to IRBs

Eighteen warning letters were issued to IRBs. Of these, 12 (66.67%) were related to new investigational drug studies and six (33.33%) were device related. The most common violation (11/18; 61.11%) was failure to follow written procedures for continuing review; 7/12 (58.33%) of these letters were issued for drug-related research and 4/6 (66.67%) for device-related research. The next most common violations (10/18; 55.56%) were failure to maintain minutes of meeting, inappropriate membership, quorum issues, misuse of expedited review and lack of a layperson in meetings; 7/12 (58.33%) of these violations were for drug-related research and 3/6 (50%) for device-related research.

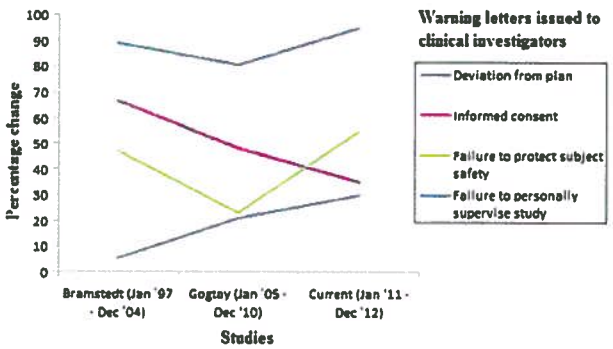

Figure 1 Trends in warning letters issued to clinical investigators.[16 18]

Failure to follow regulatory requirements and failure to follow standard operating procedures and maintain documentation were each noted in 8/22 warning letters (44.44%); 6/12 (50%) of these were for drug-related research and 2/6 (33.33%) for device-related studies, while 4/12 (33.33%) were for drug-related research and 4/6 (66.67%) for device-related studies, respectively. Failure to address risk minimisation and protect vulnerable subjects was mentioned in 4/18 warning letters (22.22%). Conflicts of interest and informed consent issues were raised in 5/18 (27.78%) warning letters, while one IRB (5.55%) failed to appoint a qualified investigator. Nine out of 18 warning letters (50%) documented three violations.

Data comparing these results with those from the previous studies are shown in table 2, while trends are shown in figure 2.

Warning letters issued to sponsors

A total of 46 warning letters were issued to sponsors between January 2005 and December 2012. Of these, 11 (23.91%) were related to new investigational drug studies and 35 (76.09%) to devices.

The most common violation (27/46; 58.69%) was failure to follow the monitoring schedule; 6/11 (54.54%) of these letters were issued for drug-related research and 21/35 (60%) for device-related research. The next most common violation was failure to obtain investigator agreement (16/46; 34.78%), all regarding device-related research (16/35; 45.71%). Failure to secure investigators' compliance was documented in 14/46 warning letters (30.43%); 2/11 (18.18%) of these were for drug-related research and 12/35 (34.29%) for device-related studies. Failure to maintain records of study data and failure to maintain records of the shipping of the investigational product to the investigator was noted in 14/46 (30.43%) warning letters. Thirteen of 46 warning letters (28.26%) indicated failure of the sponsor to submit an Investigational Device Exemption or Investigational New Drug application to the FDA. Eleven of 46 warning letters (23.91%) to sponsors documented failure to review, evaluate and submit adverse drug event reports to the FDA. Two sponsors failed to allow FDA inspection. One sponsor failed to obtain IRB approval. Fifteen of the 46 warning letters (32.60%) documented four violations and 12

Table 2 Warning letters issued to institutional review boards

Item no.	Violation theme	Current study Drug-related N=12 (%)	Current study Device-related N=6 (%)	Current study Drug- and device-related N=18 (%)	Gogtay study[18] Drug- and device-related N=32 (%)	Bramstedt study[16] Drug- and device-related N=52 (%)	p Value
1	Failure to follow standard operating procedures and maintain documentation	4 (33.33)	4 (66.67)	8 (44.44)	30 (93.8)	50 (96.1)	0.0001*
2	Inappropriate membership, quorum issues, misuse of expedited review, lack of a layperson in meetings	7 (58.33)	3 (50)	10 (55.56)	19 (59.4)	30 (58)	0.96
3	Informed consent issues	3 (25)	2 (33.33)	5 (27.78)	15 (46.9)	19 (37)	0.38
4	Failure to follow regulatory requirements	6 (50)	2 (33.33)	8 (44.44)	7 (21.9)	Not reported	0.11
5	Failure to address conflicts of interest	4 (33.33)	1 (16.67)	5 (27.78)	3 (9.4)	Not reported	0.11
6	Failure to address risk minimisation and protect vulnerable participants	4 (33.33)	0	4 (22.22)	4 (12.5)	11 (21.1)	0.55
7	Failure to inform institutional officials regarding study status	2 (16.67)	2 (33.33)	4 (22.22)	Not reported	Not reported	–
8	Failure to maintain minutes of meetings	7 (58.33)	3 (50)	10 (55.56)	Not reported	Not Reported	–
9	Lack of a qualified clinical investigator	1 (8.33)	0	1 (5.55)	Not reported	Not Reported	–
10	Failure to follow written procedures for continuing review	7 (58.33)	4 (66.67)	11 (61.11)	Not reported	Not reported	–

*p<0.05 using Fisher's exact test.

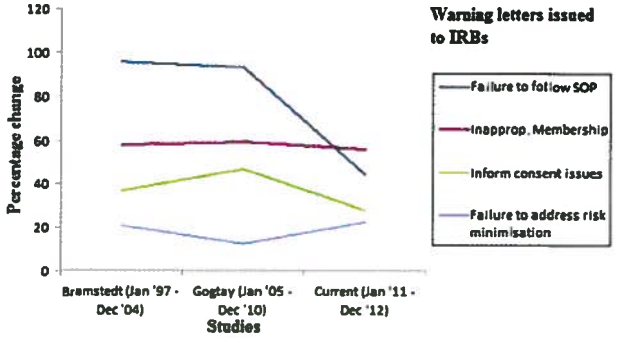

Figure 2 Trends in warning letters issued to institutional review boards (IRBs).[17 18] SOP, standard operating procedures.

warning letters documented 11 violations. Table 3 gives the results of data analysis for warning letters issued to sponsors.

DISCUSSION

Fair and appropriate procedures for handling violations during clinical trials need to be developed and implemented globally in order to protect human rights, well-being and safety, and to raise awareness of ethical behaviour. The FDA practice of issuing warning letters could be copied worldwide by regulatory agencies overseeing clinical trials.

The warning letters were studied in order to determine violations by clinical investigators, IRBs and sponsors.

Compared to the results of Bramstedt and colleagues and Gogtay *et al*, the current study showed that the percentage of warning letters issued to clinical investigators for failure to protect participant safety, report adverse events to IRBs and personally supervise the study, was statistically significant. Other findings showed that although study supervision by investigators worsened over the years, deviation from the investigational plan, maintenance of adequate and accurate case records and histories, retention of and production of records for inspection, issues relating to informed consent, regulatory non-compliance and violations related to the investigational product have all improved; record maintenance, regulatory non-compliance and violations related to the investigational product were not reported on by Bramstedt and colleagues. If the primary duty of a clinical investigator to follow the protocol is violated, study participants can be exposed to needless risk despite the fact that good clinical practice seeks to protect participants from harm. Two new violations were found in our study: failure to obtain IRB approval and submission of false information to the FDA and sponsors. The two pillars of good clinical practice are independent review of a protocol and the informed consent document; if these are bypassed, study integrity is compromised. The provision of false information to the FDA is research fraud.

IRBs must have standard operating procedures and follow them. The current study found that compared to previous studies, there was a statistically significant trend towards improvement by IRBs in following standard operating procedures and maintaining documents. Violations relating to inappropriate membership, quorum issues, misuse of expedited review and lack of a layperson in meetings were similar in all three studies. In the absence of a layperson, the regulators should make it mandatory for IRBs to supply a replacement, as the layperson represents the study participant or the

Table 3 Warning letters issued to sponsors

Item No.	Violation theme	Drug-related N=11 (%)	Device-related N=35 (%)	Drug- and device-related N=46 (%)
1	Failure to follow monitoring schedule	6 (54.54)	21 (60)	27 (58.69)
2	Failure to obtain investigator agreement	0	16 (45.71)	16 (34.78)
3	Failure to secure investigators' compliance	2 (18.18)	12 (34.29)	14 (30.43)
4	Failure to maintain data records	1 (9.09)	13 (37.14)	14 (30.43)
5	Failure to ship/maintain records of investigational product to investigator	2 (18.18)	12 (34.29)	14 (30.43)
6	Failure to submit an Investigational Device Exemption or Investigational New Drug application to the FDA	4 (36.36)	9 (25.71)	13 (28.26)
7	Failure to review, evaluate and submit adverse drug event reports to the FDA	2 (18.18)	9 (25.71)	11 (23.91)
8	Failure to ensure informed consent document received from study participants	2 (18.18)	5 (14.28)	7 (15.22)
9	Failure to submit progress report to institutional review board	0	7 (20)	7 (15.22)
10	Failure to adhere to investigational plan	6 (54.54)	1 (2.86)	7 (15.22)
11	Failure to provide investigators with necessary information	1 (9.09)	5 (14.28)	6 (13.04)
12	Failure to ensure institutional review board review	2 (18.18)	4 (11.43)	6 (13.04)
13	Failure to use trained monitors	2 (18.18)	3 (8.57)	5 (10.87)
14	Failure to include elements in informed consent document	1 (9.09)	3 (8.57)	4 (8.69)
15	Failure to ensure proper labelling of device	0	4 (11.43)	4 (8.69)
16	Failure to inform reviewing institutional review board and the FDA of new information	0	3 (8.57)	3 (6.52)
17	Failure to seek prior permission for advertisement (online)	0	3 (8.57)	3 (6.52)
18	Failure to notify the FDA of termination of an investigation	0	2 (5.71)	2 (4.35)
19	Failure to allow FDA inspection	1 (9.09)	1 (2.86)	2 (4.35)
20	Failure to provide current investigator list	0	1 (2.86)	1 (2.17)
21	Failure to obtain institutional review board approval	0	1 (2.86)	1 (2.17)
22	Failure to include reports of prior testing of the device	0	1 (2.86)	1 (2.17)

FDA, US Food and Drug Administration.

community. Informed consent is crucial for any clinical research, and if it is violated the entire tenet of good clinical practice is breached. Failure to follow regulatory requirements and failure to address conflicts of interest has worsened over the period. Failure to declare a conflict of interest in the present study was mentioned in 5/18 warning letters (27.78%) compared to 3/32 warning letters (9.4%) in the study by Gogtay *et al.*[16] A study conducted by Warner revealed that the rate of disclosure of conflicts of interest was as low as 2% in biomedical research.[20] If conflict of interest is not declared by an individual or organisation, it could possibly corrupt the motivation of conducting the trial. Important new violations noted were failure to follow written procedures for continuing review, lack of maintenance of minutes of meetings, failure to inform institutional officials regarding study status and lack of a qualified clinical investigator.[8]

Warning letters issued to sponsors by the FDA have not previously been scrutinised. The current study found violations in all sponsor responsibilities. Most sponsors did not follow the monitoring schedule, which is an important component of quality assurance in a clinical trial. Failure to obtain the agreement of investigators and secure their compliance was found to be quite common among sponsors. This can reflect poorly on the sponsor, because if there is no agreement, then an investigator is not liable to follow and complete the trial. There was a failure to maintain data records and records of shipping the investigational product to the investigator. One of the basic principles of good clinical practice states that whatever is written and recorded is done.[8] The trial must receive regulator permission before it begins, but many sponsors had not submitted an Investigational Device Exemption or Investigational New Drug application, and some did not have IRB approval.

Initiating a study without IRB approval also has legal implications. Incomplete informed consent documents suggest study results are unreliable, while failure to maintain study data raises doubts about data credibility. The submission of false information to the FDA is illegal. A gross legal violation of refusing to allow an FDA inspection was observed with two sponsors. In addition, several sponsors: (1) did not inform regulators of new information; (2) failed to review, evaluate and submit adverse drug event reports; (3) failed to submit progress reports to the IRB; and (4) did not notify the FDA regarding the termination of a trial. The improper labelling of a device mentioned in few warning letters can raise doubts about the execution of the trial. Failure to adhere to the study plan affects the implementation of a study protocol.

In the six investigator-initiated studies where the investigator was also the sponsor, the deviations were the same as in sponsored studies. In such cases where there is no external monitor, there is a higher probability that the investigator will violate regulations; and hence, the monitoring by IRBs and regulators becomes crucial. Regulators expect sponsors to be totally compliant with the protocol. The consequences of not following protocol specifications on any given trial are increased cost, increased time to completion and lack of confidence in the study and public health at large.

Despite stringent regulation in the USA, there are violations by clinical research stakeholders. In order to curb the frequency of violations in the USA and worldwide, regulations must be enforced through timely and proper monitoring of all stakeholder sites. Every research participant is responsible for adhering to uniform standards and maintaining ethical principles. A culture of research must be developed in order to retain public confidence and the link between public health and community trust.

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