Original Investigation

Research Misconduct Identified by the US Food and Drug Administration

Out of Sight, Out of Mind, Out of the Peer-Reviewed Literature

Charles Seife, MS

IMPORTANCE Every year, the US Food and Drug Administration (FDA) inspects several hundred clinical sites performing biomedical research on human participants and occasionally finds evidence of substantial departures from good clinical practice and research misconduct. However, the FDA has no systematic method of communicating these findings to the scientific community, leaving open the possibility that research misconduct detected by a government agency goes unremarked in the peer-reviewed literature.

OBJECTIVES To identify published clinical trials in which an FDA inspection found significant evidence of objectionable conditions or practices, to describe violations, and to determine whether the violations are mentioned in the peer-reviewed literature.

DESIGN AND SETTING Cross-sectional analysis of publicly available documents, dated from January 1, 1998, to September 30, 2013, describing FDA inspections of clinical trial sites in which significant evidence of objectionable conditions or practices was found.

MAIN OUTCOMES AND MEASURES For each inspection document that could be linked to a specific published clinical trial, the main measure was a yes/no determination of whether there was mention in the peer-reviewed literature of problems the FDA had identified.

RESULTS Fifty-seven published clinical trials were identified for which an FDA inspection of a trial site had found significant evidence of 1 or more of the following problems: falsification or submission of false information, 22 trials (39%); problems with adverse events reporting, 14 trials (25%); protocol violations, 42 trials (74%); inadequate or inaccurate recordkeeping, 35 trials (61%); failure to protect the safety of patients and/or issues with oversight or informed consent, 30 trials (53%); and violations not otherwise categorized, 20 trials (35%). Only 3 of the 78 publications (4%) that resulted from trials in which the FDA found significant violations mentioned the objectionable conditions or practices found during the inspection. No corrections, retractions, expressions of concern, or other comments acknowledging the key issues identified by the inspection were subsequently published.

CONCLUSIONS AND RELEVANCE When the FDA finds significant departures from good clinical practice, those findings are seldom reflected in the peer-reviewed literature, even when there is evidence of data fabrication or other forms of research misconduct.

Editorial

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Author Affiliation: Arthur L. Carter Institute of Journalism at New York University, New York.

Corresponding Author: Charles Seife, MS, Arthur L. Carter Institute of Journalism at New York University, 20 Cooper Sq, Ste 628, New York, NY 10012 (charles.seife@nyu.edu).

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As part of the drug approval process, the US Food and Drug Administration (FDA) regularly inspects clinical trial sites involved in FDA-regulated research to determine the degree to which these sites conform to regulations. The FDA regulations intend to ensure, among other things, that scientists adhere to good clinical practice and that they protect the rights of human participants. Such inspections often yield useful information about the reliability and quality of the clinical data produced at a clinical trial site.

An FDA inspection typically involves officials visiting a trial site and auditing the records kept at that site. During the course of several days, the inspectors verify that, among other things, the investigators adhered to the trial protocol, the participants had given informed consent, and the research had been duly approved by an institutional review board. The inspectors may also audit the data comparing, for example, an investigator's progress notes in hospital records with data reported to the study sponsor to ensure that there are no irregularities.[1]

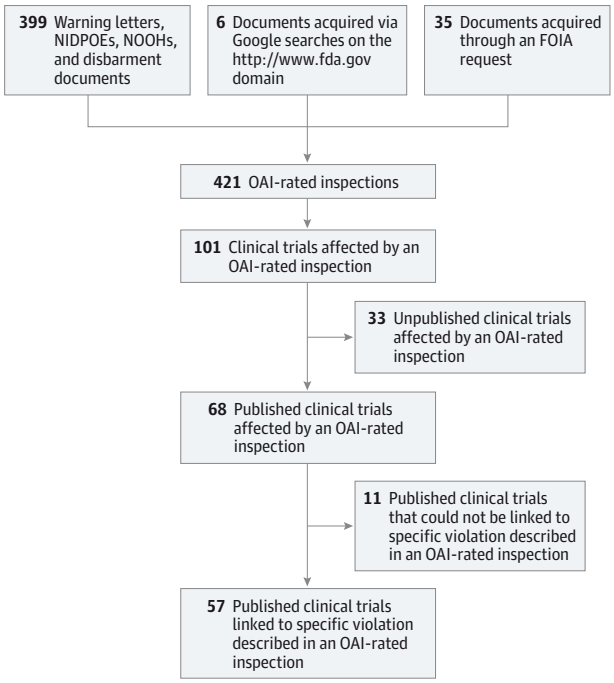
The FDA classifies its inspections in 1 of 3 ways, depending on the gravity of violations found. *No action indicated* indicates that there were no substantial violations. *Voluntary action indicated* means that inspectors have found violations of good clinical practice, but the nature and extent of those problems are not serious enough to require sanction. The most severe classification, *official action indicated* (OAI), is reserved for cases in which the inspection identified objectionable conditions or practices significant enough to warrant regulatory action.[2] In the 2013 fiscal year, approximately 2% of the 644 inspections of trial sites carried out by the FDA's Bioresearch Monitoring organization were classified as OAI.[3] The nature and extent of the OAI violations, which include submission of false information and failure to report adverse events to the appropriate bodies, often raise questions about the validity and accuracy of the clinical trial site's data. Consequently, the FDA typically excludes data from a site that received an OAI when judging the safety or efficacy of a new drug.

The goals of the present study were to identify publications describing clinical trials that the FDA had determined had an OAI violation, to describe the violations, and to determine whether the published article or any subsequent correction acknowledged the violation.

Methods

A multipronged approach was used to identify clinical trials with an OAI violation (**Figure**). The process began by attempting to identify clinical trial sites and principal investigators who had received an OAI violation. Although there is no public canonical list of OAI inspections, the FDA maintains a database containing the results of some of its inspections.[4] In July 2012, the database was searched for clinical investigators who had received an OAI. To obtain documents (form 483s and Establishment Inspection Reports) that provide details about a given inspection, Freedom of Information Act requests were made to the FDA. The request yielded documents related to 20 OAI-rated inspections, all dated before August 8, 2012, when the Freedom of Information Act request was submitted.

Figure. Relevant Clinical Trials



Identification of relevant clinical trials linked to specific violations described in an official action indicated (OAI)–rated inspection. Between October 7 and December 9, 2013, all warning letters that were issued to a clinical investigator after January 1, 1998, as well as all Notices of Disqualification Proceedings and Opportunity to Explain (NIDPOEs), Notices of Opportunity for a Hearing (NOOHs), and disbarment decisions that were on the US Food and Drug Administration's website, were reviewed. FOIA indicates Freedom of Information Act.

To supplement the data obtained from the searches of the FDA database, Google searches of the http://www.FDA.gov domain were performed. The most effective searches used combinations of phrases and their variants that were contained in documents describing OAI-rated inspections of clinical sites (eg, *classified as OAI*, *inspection summary*, *received an OAI*, *inspected*, *OAI classification*, and *inspection*). This strategy yielded documents related to 21 OAI-rated inspections.

The best source of documentation of OAI-rated inspections came from instances in which the FDA took regulatory action against clinical investigators. Such actions occur only when the failure to adhere to research regulations is considered particularly grave. In such cases, the FDA often issues 1 or more documents that detail the problems found in an inspection: warning letter, Notice of Disqualification Proceedings and Opportunity to Explain, Notice of Opportunity for Hearing, and official notification of disbarment or sanctions. Between October 7 and December 9, 2013, all warning letters that were issued to a clinical investigator after January 1, 1998 (letters regarding 298 inspections), as well as all Notices of Disqualification Proceedings, Notices of Opportunity for Hearing, and disbarment decisions that were on the FDA's website (documents concerning 82 inspections), were reviewed.

The 3 methods of search yielded 421 OAI-rated inspections. We then attempted to link the sites and investigators described in the related inspection documents to specific clinical trials. Heavy redactions in most of these documents prevented this linkage in most cases (eAppendix in the Supplement). However, whenever we were able to identify a clinical trial that received an OAI finding, we searched the peer-reviewed literature for any resultant publications. If such publications were found, they were independently reviewed by the author and by a second reader with the goal of identifying any written acknowledgment about the violations identified by the FDA. Agreement between the 2 reviewers was high (κ = 0.85). One article noted that data "were either missing, or were considered unreliable by the investigator due to problems collecting accurate data."[5(p3)] The 2 reviewers disagreed about whether the unreliability might have been an oblique reference to problems found during an inspection. However, the inspection documents[6] detailed failures to obtain informed consent, falsified information, misreporting the dosage of drugs for at least 7 patients, and failure to record data on 10 patients. After discussion, the reviewers concurred that the language in the article was not an acknowledgment of the inspection findings.

PubMed and Thomson-Reuters' Web of Science were searched for any corrections, retractions, expressions of concern, or other comments in which those violations might have been aired after the article was published. Food and Drug Administration–related documents obtained in this investigation are available.[7]

Results

General Findings

There were approximately 600 clinical trials mentioned in the documents we gathered; owing to redactions, most of these trials could not be identified. However, in some cases, key information was not redacted from the documents, allowing us to identify 101 trials in which at least one clinical trial site received an OAI grade on an inspection (Figure).

Of those 101 clinical trials, we identified 68 for which results had been published in the peer-reviewed literature, resulting in a total of 95 publications. For 11 of the clinical trials that had been published, the documents were not sufficiently detailed for us to prove that the violations described in the document were specific to the trial in question, so they were excluded from the primary analysis (**Table 1**).* For example, 1 warning letter[8] and 1 Notice of Disqualification Proceedings and Opportunity to Explain[9] detailed violations in 7 clinical trials of stem cell therapies, which then resulted in 4 publications.[10,35-37] Because of the redactions in those documents, there was ambiguity about which of the 7 trials was linked to which violation described in the documents. It was possible to tie specific violations to only 3 of the 4 published trials[38-40]; the fourth trial[41] was therefore excluded from analysis.

For each of the 57 remaining trials, 1 or more FDA inspections of a trial site had uncovered evidence of significant departures from good clinical practice, such as underreporting of adverse events, violations of protocol, violations of recruitment guidelines, and various forms of scientific misconduct.

In 22 of these trials (39%), the FDA cited researchers for falsification or submission of false information; in 14 (25%), for problems with adverse events reporting; in 42 (74%), for failure to follow the investigational plan or other violations of protocol; in 35 (61%), for inadequate or inaccurate recordkeeping; in 30 (53%), for failure to protect the safety, rights, and welfare of patients or issues with informed consent or institutional review board oversight; and in 20 (35%), for violations not otherwise categorized. Examples of uncategorized violations include cases in which the investigators used experimental compounds in patients not enrolled in trials, delegated tasks to unauthorized personnel, or otherwise failed to supervise clinical investigations properly.

The 57 clinical trials in our analysis resulted in 78 articles published in the peer-reviewed literature (**Table 2**). Of these 78 articles, only 3 publications (4%) included any mention of the FDA inspection violations despite the fact that for 59 of those 78 articles (76%), the inspection was completed at least 6 months before the article was published. Researchers are usually given a form 483 within a day of the inspection, with the form detailing any problems found by the inspector.

For the 3 articles that mentioned the inspection violations, 1 stated that 1 of the trial sites "was found to have allegedly entered fraudulent data and was dropped from participation."[121(p390)] (References 76 through 184 are listed in the eReferences in the Supplement.) The research misconduct involved falsified laboratory test results in a phlebotomy trial. In the second instance, the article noted that the data from 1 clinical trial site were excluded owing to "protocol adherence and data quality issues."[111(p78)] According to the FDA documents, the researcher apparently eliminated the blinding in a randomized protocol so she "could control drug treatment assignments"[168(p7)] of her patients; she was also cited for falsification of data in 2 other protocols. In the third instance, an article explained that data from several patients were excluded from the efficacy analysis because "site monitoring raised questions in regard to certain data at 1 study site."[65(p431)] The FDA documents[64] allege that none of the individuals enrolled at 1 study site had met the inclusion criteria and that the responsible researcher had fabricated chest radiographs of participants and committed other forms of misconduct.

In no other instance did we find acknowledgment of problems found during an FDA inspection. In addition, we were unable to identify any corrections, retractions, comments, or notifications of concern published after FDA identification of the violations.

Examples of Unreported Violations

To illustrate the importance of the unreported inspection violations, 4 cases cut examples are provided herein.

Case 1

A publication describing a stem cell trial in 26 patients with ischemic limbs stated that "all patients recognized and were aware of major clinical improvements in the treated (more is-

*References 12-16, 18-21, 24-26, 28, 29, 33, 34

Table 1. Clinical Trials and Publications With Possible but Not Definitive Instances of OAI-Rated Violations Excluded From the Primary Analysis[a]

Drug/Biologic/ Procedure	Clinical Trial No.	Other Protocol Name	Source Document/ Publication Affected	Falsification[b]	Protocol[c]	Record-keeping[d]	Safety[e]	Other[f]
Autologous stem cells	NCT00548613	2007-02-I	NIDPOE,[8] warning letter[9]/ Lasala et al[10]	...	...	...	P	Y
Bevacizumab	NCT00109070/ NCT00109226	AVF2107g/ AVF2192g	NIDPOE[11]/Scappaticci et al[12]	P	...	...	P	P
Bevacizumab	NCT00109070/ NCT00109226	AVF2107g/ AVF2192g	NIDPOE[11]/Kabbinavar et al[13]	P	...	...	P	P
Bevacizumab	NCT00109070/ NCT00109226	AVF2107g/ AVF2192g	NIDPOE[11]/Kabbinavar et al[14]	P	...	...	P	P
Docetaxel	...	TAX326	NIDPOE[11]/Belani et al[15]	P	...	...	P	P
Docetaxel	...	TAX326	NIDPOE[11]/Fossella et al[16]	P	...	...	P	P
Etanercept	NCT00116714	Radius-1	NIDPOE[17]/Gibofsky et al[18]	...	...	P	P	...
Etanercept	NCT00116714	Radius-1	NIDPOE[17]/Weaver et al[19]	...	...	P	P	...
Etanercept	NCT00116714	Radius-1	NIDPOE[17]/Markenson et al[20]	...	...	P	P	...
Etanercept	NCT00116714	Radius-1	NIDPOE[17]/Gibofsky et al[21]	...	...	P	P	...
Lumiracoxib	NCT00366938	...	NIDPOE,[22] form 483[23]/ Dougados et al[24]	P	P	...	...	...
Lumiracoxib	NCT00366938	...	NIDPOE,[22] form 483[23]/ Sheldon et al[25]	P	P	...	...	...
Naproxcinod	NCT00504127	...	NIDPOE,[22] form 483[23]/ Schnitzer et al[26]	P	P	...	...	...
Quetiapine	NCT00090324	112	Clinical Review[27]/ Findling et al[28]	...	...	...	...	...
Quetiapine	NCT00090311	149	Clinical Review[27]/ Pathak et al[29]	...	...	...	...	...
Telithromycin	...	3005	Form 483 and EIR,[30] NIDPOE,[31] NOOH[32]/ Luterman et al[33]	P	P	...	...	...
Telithromycin	...	3007	Form 483 and EIR,[30] NIDPOE,[31] NOOH[32]/ Zervos et al[34]	P	P	...	...	...

Abbreviations: ADE, adverse drug event; ellipses, not applicable; OAI, official action indicated; P, violation identified but no definitive link; Y, definitive link.

[a] None of the clinical trials listed herein had violations having to do with reporting of ADEs.

[b] Falsification and/or submission of false information.

[c] Protocol issues included failure to follow investigational plan and/or other violations of protocol.

[d] Record-keeping issues included inadequate and/or inaccurate records.

[e] Safety issues included failure to protect rights, safety, and welfare of patients and/or issues related to informed consent or institutional review board notifications.

[f] Other issues were violations not otherwise categorized.

chemic) leg, despite no significant clinical changes in the control (less ischemic) leg."[37(p381)] However, an FDA document[169] revealed that 1 patient had a foot amputated 2 weeks after administration of the stem cells. We found no correction or retraction.

Case 2

Eight of 16 FDA inspections of sites involved in a clinical trial of rivaroxaban,[170] a novel anticoagulant, had been rated OAI. These inspections had uncovered evidence of various transgressions, such as "systemic discarding of medical records,"[171(p3)] unauthorized unblinding, falsification, and "concerns regarding improprieties in randomization."[172(p211)] Consequently, the entire study, RECORD 4 (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep-Venous Thrombosis and Pulmonary Embolism 4), was deemed unreliable by the FDA.[171] These problems are not mentioned in the article describing the study's results[142] or in other publications associated with the trial.[144,145]

Case 3

A researcher was caught falsifying documents in a number of trials,[173-176] in part because those falsifications led to the death of a patient undergoing treatment in a clinical trial comparing 2 chemotherapy regimens. The researcher had falsified laboratory test results to hide the patient's impaired kidney and liver function, and the first dose of the treatment proved to be fatal. The researcher pleaded guilty to fraud and criminally negligent homicide and was sentenced to 71 months in prison. Although this episode is described in detail in FDA documents[11,67] as well as court documents,[177] none of the publications in the peer-reviewed literature associated with the chemotherapy study in which the patient died[70-72,178] have any mention of the falsification, fraud, or homicide. The publications associated with 2 of the 3 other studies for which the researcher falsified documents also do not report on the violations.[68,73]

Case 4

A clinical site in China taking part in a large trial of apixaban, a novel anticoagulant, had apparently altered patient records. If one were to exclude the data from the patients at that site, the claim of a statistically significant mortality benefit disappears.[179] For this reason, among others, the FDA wrestled with whether it was appropriate to allow the manufacturer to claim a mortality benefit. None of this discussion appears in the literature. The claim for the mortality benefit, which has

Table 2. Clinical Trials and Publications Affected by Official Action Indicated–Rated Inspections

No.	Drug/Biologic/ Procedure	Clinical Trial No.	Other Protocol Name(s)	Source Document No./ Publication Affected[a]	Falsification[b]	ADE Reporting[c]	Protocol[d]	Record-keeping[e]	Safety[f]	Other[g]
1[h]	Alogliptin	NCT00707993	SYR-322_303	Clinical inspection summary[42]/ Rosenstock et al[43]	...	...	Y	Y	Y	...
2	Amoxicillin/ clavulanic acid extended-release	...	25000/592	NIDPOE,[44] NOOH,[45] debarment order[46]/ File et al[47]	Y	...	Y	...	...	...
3	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Granger et al[38]	Y	Y	...	...	...	...
4[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Lopes et al[50]	Y	Y	Y	Y	Y	
5[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/McMurray et al[51]	Y	Y	Y	Y	Y	
6[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Wallentin et al[52]	Y	Y	Y	Y	Y	
7[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Garcia et al[53]	Y	Y	Y	Y	Y	
8[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Alexander et al[54]	Y	Y	Y	Y	Y	
9[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Alexander et al[55]	Y	Y	Y	Y	Y	
10[h]	Asenapine	NCT00145470	A7501008, P05844	Warning letter[56]/Szegedi et al[57]	...	...	Y	Y	...	...
11[h]	Autologous dendritic cells	...	1997-064	NOOH[58]/Redman et al[59]	...	...	Y	Y	...	...
12	Autologous stem cells	NCT00518401	2007-01-I	NIDPOE,[8] warning letter[9]/ Lasala et al[35]	...	...	...	...	Y	Y
13[h]	Autologous stem cells	NCT00721006	2008-01-II	NIDPOE,[8] warning letter[9]/ Lasala et al[37]	...	Y	...	...	Y	Y
14	Autologous stem cells	NCT00643981	2007-03-I	NIDPOE,[8] warning letter[9]/ Lasala et al[36]	...	...	Y	...	Y	Y
15	Autologous tumor cells	...	1995-243	NOOH[58]/Chang et al[60]	...	...	Y	Y	...	...
16[h]	Budesonide/ formoterol	NCT00206167	D5899C00001	NIDPOE[61]/Bleecker et al[62]	...	...	...	Y	...	...
17	Budesonide/ formoterol	NCT00206167	D5899C00001	NIDPOE[61]/Rennard et al[63]	...	...	...	Y	...	...
18[h]	Cd34+ Cells	NCT00300053	ACT34-CMI	NIDPOE[64]/Losordo et al[65]	Y	Y	Y	Y	...	Y
19[h]	Cd34+ cells	NCT00300053	ACT34-CMI	NIDPOE[64]/Povsic et al[66]	Y	Y	Y	Y	...	Y
20[h]	Dfmo	NCT00003814	ILEX-DFMO341	NIDPOE,[67] NOOH[11]/Messing[68]	Y	...	Y	P	P	Y
21	Docetaxel	NCT00290966	TAX325	NIDPOE,[11] NOOH,[67] NOOH [69]/ Ajani[70]	Y	...	Y	Y	Y	...
22	Docetaxel	NCT00290966	TAX325	NIDPOE,[11] NOOH,[67] NOOH [69]/ Ajani[70]	Y	...	Y	Y	Y	...
23[h]	Docetaxel	NCT00290966	TAX325	NIDPOE,[11] NOOH,[67] NOOH [69]/ Ajani et al[71]	Y	...	Y	Y	Y	...
24[h]	Docetaxel	NCT00290966	TAX325	NIDPOE,[11] NOOH,[67] NOOH [69]/ Van Cutsem et al[72]	Y	...	Y	Y	Y	...
25[h]	Docetaxel	...	TAX327	NIDPOE,[11] NOOH,[67] NOOH [69]/ Tannock et al[73]	Y	...	Y	Y	Y	...
26	Erlotinib	NCT00081614	AVF2938	Warning letter [74]/ Bukowski et al[75]	...	...	Y	...	Y	...
27[h]	Esomeprazole/ naproxen	NCT00527787	PN400-301	NIDPOE,[22] form 483[23]/ Goldstein et al[76]	Y	P	P	Y	...	...
28	Etanercept	NCT00116727	Radius-2	NIDPOE[17]/Gibofsky et al[18]	...	...	Y	Y	Y	...
29	Etanercept	NCT00116727	Radius-2	NIDPOE[17]/Weaver et al[19]	...	...	Y	Y	Y	...
30[h]	Etanercept	NCT00116727	Radius-2	NIDPOE[17]/Markenson et al[20]	...	...	Y	Y	Y	...
31[h]	Etanercept	NCT00116727	Radius-2	NIDPOE[17]/Gibofsky et al[21]	...	...	Y	Y	Y	...
32	Faropenem daloxate	...	100288	Form 483 and EIR,[77] warning letter,[78] warning letter[79]/ Upchurch et al[80]	...	...	Y	Y	P	...
33[h]	Ferric carboxymaltose	NCT00982007	1VIT09031	Warning letter[81]/ Onken et al[82]	...	...	Y	...	...	...
34[h]	Fondaparinux	NCT00038961	APOLLO	NIDPOE[83]/Turpie et al[84]	...	...	Y	Y	Y	Y

(continued)

Table 2. Clinical Trials and Publications Affected by Official Action Indicated–Rated Inspections (continued)

No.	Drug/Biologic/ Procedure	Clinical Trial No.	Other Protocol Name(s)	Source Document No./ Publication Affected[a]	Falsification[b]	ADE Reporting[c]	Protocol[d]	Record-keeping[e]	Safety[f]	Other[g]
35	Ibuprofen	NCT00225732	008a, CPI-CL-008	Warning letter,[85] clinical inspection summary[86]/ Southworth et al[87]	...	Y	Y	Y	...	Y
36[h]	Ibuprofen	NCT00225732	008b, CPI-CL-008	Warning letter,[85] clinical inspection summary[86]/ Kroll et al[88]	...	...	Y	Y	...	Y
37[h]	Indiplon	...	NBI34060-MR-0212	NIDPOE[89]/Lydiard et al[90]	Y	...	Y	Y	...	...
38[h]	Leuprolide acetate	...	...	Form 483,[91] EIR,[92] letter,[93] NIDPOE[94]/ Crawford et al[95]	Y	...	Y	Y	Y	Y
39[h]	Ly518674	NCT00133380	H8D-MC-EMBF	Warning letter[96]/ Nissen et al[97]	...	...	Y	P	P	Y
40[h]	Modified lymphocytes	...	1990-489	NOOH[58]/Chang et al[98]	...	...	Y	Y	Y	...
41	Modified lymphocytes	...	1995-318	NOOH[58]/DeBruyne et al[99]	...	...	Y	Y	...	...
42[h]	Nebivolol	NCT00200460	NEB302	NIDPOE[100]/Weiss et al[101]	Y	Y	Y	Y	...	Y
43	Ofloxacin	...	PRT002/ PRT003	NIDPOE,[102] NOOH,[103] proposal to debar/ NOOH,[104] debarment,[105] warning letter,[106] warning letter[107]/ Jones et al[108]	Y	...	Y	Y	Y	...
44[h]	Olanzapine	...	FID-US-HGGD/ 2325	NIDPOE,[109] Proposal to debar/ NOOH[110]/Tunis et al[111]	...	...	Y	...	P	...
45[h]	Olanzapine	...	FID-US-HGGD/ 2325	NIDPOE,[109] Proposal to debar/ NOOH[110]/ Ascher-Svanum et al[112]	...	...	Y	...	P	...
46[h]	Olanzapine	...	FID-US-HGGD/ 2325	NIDPOE,[109] Proposal to debar/ NOOH[110]/Faries et al[113]	...	...	Y	...	P	...
47[h]	Olanzapine	NCT00103571	F1D-US-HGLS	Warning letter[114]/Kinon et al[115]	...	...	Y	P	Y	...
48[h]	Oxycontin extended-release	NCT01559701	PTI-821-CM	NIDPOE[116]/Friedmann et al[117]	P	...	Y	Y	Y	...
49[h]	Paliperidone palmitate	NCT00111189	CR004198, R092670PSY300	Warning letter[56]/ Kozma et al[118]	...	Y	Y	Y	Y	...
50[h]	Paliperidone palmitate	NCT00111189	CR004198, R092670PSY300	Warning letter[56]/ Hough et al[119]	...	Y	Y	Y	Y	...
51[h]	Paroxetine	...	704	NIDPOE,[109] proposal to debar, NOOH[110]/Geller et al[120]	Y	...	Y	Y	Y	...
52[h]	Phlebotomy for atherosclerosis	NCT00032357	FeAST	NIDPOE,[11] NOOH,[67] NOOH[69]/ Zacharski et al[121]	Y	...	...	...	...	...
53[h]	Pomalidomide	NCT00072722	...	Warning letter [122]/ Amato et al[123]	...	...	P	P	Y	...
54[h]	Ranibizumab	NCT00445003	LRTforDME +PRP	Warning letter,[124] form 483 and EIR,[125] warning letter[126]/ Googe et al[127]	Y	...	Y	...	...	Y
55[h]	Ranibizumab	NCT00445003	LRTforDME +PRP	Warning letter,[124] form 483 and EIR,[125] warning letter[126]/ Gangaputra et al[128]	Y	...	Y	...	...	Y
56	Ranibizumab	NCT00445003	LRTforDME +PRP	Warning letter,[124] form 483 and EIR,[125] warning letter[126]/ Bhavsar et al[129]	Y	...	Y	...	...	Y
57[h]	Ranibizumab	NCT00891735	HARBOR	Warning letter[130]/ Busbee et al[131]	...	...	Y	Y	Y	...
58[h]	Reduced glutathione	...	...	Warning letter[132]/ Bishop et al[133]	...	...	...	...	Y	Y
59	Rivaroxaban	NCT00329628	RECORD 1	Compliance review,[134] medical review,[135] other review[136]/ Eriksson et al[137]	...	Y	Y	Y	...	...
60[h]	Rivaroxaban	NCT00332020	RECORD 2	NIDPOE,[48] Compliance review,[134] medical review,[135] other review[136]/ Kakkar et al[138]	Y	Y	Y	Y	Y	...

(continued)

Table 2. Clinical Trials and Publications Affected by Official Action Indicated–Rated Inspections (continued)

No.	Drug/Biologic/ Procedure	Clinical Trial No.	Other Protocol Name(s)	Source Document No./ Publication Affected[a]	Falsification[b]	ADE Reporting[c]	Protocol[d]	Record-keeping[e]	Safety[f]	Other[g]
61	Rivaroxaban	NCT00361894	RECORD 3	Compliance review,[134] medical review,[135] other review[136]/ Lassen et al[139]	...	Y		Y	Y	...
62[h]	Rivaroxaban	NCT00362232	RECORD 4	Compliance review,[134] medical review,[135] other review,[136] form 483,[140] EIR[141]/ Turpie et al[142]	Y	Y	Y	Y	Y	Y
63[h]	Rivaroxaban	NCT00329628/ NCT00332020/ NCT00361894	RECORD 1, 2, 3	Compliance review,[134] medical review,[135] other review[136]/ Eriksson et al[143]	Y	Y	Y	Y	Y	...
64[h]	Rivaroxaban	NCT00329628/ NCT00332020/ NCT00361894/ NCT00329628	RECORD 1, 2, 3, 4	NIDPOE,[48] compliance review,[134] medical review,[135] other review,[136] form 483,[140] EIR[141]/ Eriksson et al[144]	Y	Y	Y	Y	Y	Y
65[h]	Rivaroxaban	NCT00329628/ NCT00332020/ NCT00361894/ NCT00329628	RECORD 1, 2, 3, 4	NIDPOE,[48] compliance review,[134] medical review,[135] other review,[136] form 483,[140] EIR[141]/ Lassen et al[145]	Y	Y	Y	Y	Y	Y
66[h]	Rocuronium	NCT00124722	P05797	Warning letter,[146] letter[147]/ Pirotta et al[5]	...	...	...	P	Y	Y
67[h]	Rofecoxib	NCT00060476	2006_414, Formally P30A03LD, MK0966-201	NIDPOE[83]/ van Adelsberg et al[148]	...	...	P	...	...	Y
68[h]	Roflumilast	NCT00297102	BY217/M2-124	NIDPOE[61]/Calverley et al[149]	...	...	Y	Y	Y	Y
69[h]	Ropinirole	...	SKF-101468/ 191	NIDPOE[89]/Allen et al[150]	Y	...	Y	Y	...	...
70	Sodium oxybate	...	OMC-GHB-2	Form 483 and EIR,[151] NIDPOE,[152] medical review[153]/ US Xyrema Multicenter Study Group[154]	P	P	...	P	P	Y
71[h]	Sodium oxybate	...	OMC-GHB-3	Form 483 and EIR,[151] NIDPOE,[152] medical review[153]/ US Xyrema Multicenter Study Group[155]	P	P	...	P	P	Y
72[h]	Sodium oxybate	...	OMC-SXB-21	Form 483 and EIR,[151] NIDPOE,[152] medical review[153]/ US Xyrema Multicenter Study Group[156]	P	P	...	P	P	Y
73[h]	Thrombo-spondin-1	NCT00073125	...	Warning letter[122]/ Ebbinghaus et al[157]	...	...	P	P	Y	...
74[h]	Tramadol extended-release	NCT00348010	...	NIDPOE,[158] NOOH[159]/ Babul et al[160]	Y	Y	Y	Y	Y	...
75[h]	Tramadol extended-release	NCT00347685	...	NIDPOE,[158] NOOH[159]/ Pascual et al[161]	Y	Y	Y	Y	Y	...
76[h]	Valsartan	NCT00154271	CVAH631DUS02	NIDPOE[162]/ Everett et al[163]	Y	Y	Y	Y	Y	...
77[h]	Velimogene aliplasmid	NCT00044356	VCL-1005-208	Warning letter[164]/ Bedikian[165]	...	Y	Y	...	Y	...
78[h]	Zolpidem modified-release	...	EFC4529/ ZOLADULT	NIDPOE,[89] medical review[166]/ Roth et al[167]	Y	...	Y	Y	...	...

Abbreviations: ADE, adverse drug event; ellipses, not applicable; P, violation identified but no definitive link; Y, definitive link.

[a] References 76 through 167 are listed in the eReferences in the Supplement.

[b] Falsification and/or submission of false information.

[c] Violations having to do with reporting of ADEs.

[d] Protocol issues included failure to follow investigational plan and/or other violations of protocol.

[e] Record-keeping issues included inadequate and/or inaccurate records.

[f] Safety issues included failure to protect rights, safety, and welfare of patients and/or issues related to informed consent or institutional review board notifications.

[g] Other issues were violations not otherwise categorized.

[h] The article was published at least 6 months after the inspection was completed.

appeared in the literature since 2011,[50,52,180] consistently relies on the full data set, including data from the site at which the research misconduct allegedly occurred. This is true even for an article that was published[52] nearly 18 months after the alleged research misconduct was discovered. In addition, the mortality benefit analysis of the FDA-approved drug label as of August 31, 2014, is also based on the full data set[181] despite a recommendation from the FDA's Office of Scientific Investigation that data from not just the problematic site but 23 additional suspect Chinese sites be excluded.[182] Despite the fraudulent data, when all the suspect Chinese sites are excluded rather than just the one at which the evidence of alleged research misconduct was found, the mortality benefit becomes statistically significant at the $P = .05$ level once again.[182] One FDA analyst, commenting on the "data quality issues" in this clinical trial, complained about the agency's lack of transparency and poor handling of evidence of problems with trial data: Some of the responsibility for the data quality issues rests with us, the FDA: We have approved drugs ignoring similar data quality issues, granting superiority claims, and not discussing in the labels the data quality issues. We must stop doing this.[182(p19)]

Discussion

Our study has some limitations. The data are descriptive rather than quantitative. We do not know how many publications derive from trials that received an OAI finding or whether a full sample of such publications would show a higher or lower rate of acknowledging inspection violations. Our search strategy was limited by the information publicly available. For example, the FDA database of clinical inspections is infrequently updated. In addition, documents from certain time periods and certain regions of the country were harder to locate than others, indicating that our search was biased. Moreover, the records that the FDA makes available are incomplete and often heavily redacted. The nature of the redactions—and thus, our likelihood of linking a given document to a specific clinical trial—also varied depending on which FDA officer was performing the redaction and the year in which the redactions were performed. All of these limitations prevent generalization of our findings to the entire population of clinical trials. Finally, problems uncovered during inspections of clinical trial sites represent only a fraction of the departures from good clinical practice of which the FDA becomes aware. For example, the FDA sometimes learns of departures from good clinical practice through communications with and inspections of organizations sponsoring and responsible for conducting clinical trials; these instances were not part of our investigation.

Even though several inspection documents reviewed here described major violations of good clinical practice, including allegations of fabrication and other forms of research misconduct, it was rare that objectionable conditions or practices uncovered by the FDA were reflected in the peer-reviewed literature.

Of course, not all violations are of equal severity. When a clinical trial site receives an OAI, it does not mean that the violations need be acknowledged in an article or, if discovered after publication of the study, warrant a correction. Even in the case of data fabrication, there is occasional ambiguity. For example, in a clinical trial[183] of a drug administered via intravitreal injection, a researcher apparently fabricated images of patients' retinas. Although one might argue that an article in which those images were used as data[128] might require a correction, it is unclear whether another article that addresses the study's infection rates associated with intravitreal injections,[129] without relying on the retinal images to support the findings, would be similarly affected. Furthermore, data are sometimes excluded from peer-reviewed publications, occasionally without explanation. Consequently, in some of the articles (Table 2), tainted data might be handled properly, even if not explicitly remarked upon in the publication; it was not possible in the present study to determine how often this occurred.

Conclusions

The findings presented in this study should give us pause. This investigation has found numerous studies for which the FDA determined there was significant evidence of fraudulent or otherwise problematic data. Such issues raise questions about the integrity of a clinical trial, and mention of these problems is missing from the relevant peer-reviewed literature. The FDA does not typically notify journals when a site participating in a published clinical trial receives an OAI inspection, nor does it generally make any announcement intended to alert the public about the research misconduct that it finds. The documents the agency discloses tend to be heavily redacted. As a result, it is usually very difficult, or even impossible, to determine which published clinical trials are implicated by the FDA's allegations of research misconduct.

The FDA has legal as well as ethical responsibilities regarding the scientific misconduct it finds during its inspections. When the agency withholds the identity of a clinical trial affected by scientific misconduct, it does so because it considers the identity to be confidential commercial information, which it feels bound to protect.[184] However, failing to notify the medical or scientific communities about allegations of serious research misconduct in clinical trials is incompatible with the FDA's mission to protect the public health. Such allegations are relevant to include in the peer-reviewed literature on which physicians and other medical researchers rely to help them choose treatments that they offer to patients and other research participants.

To better serve the public health, the FDA should make unredacted information about its findings of research misconduct more readily available. The agency should make sure that any substantial evidence of misconduct is available to editors and readers of the scientific literature. One possible mechanism for this would be to use the national clinical trials database: any OAI inspection affecting a trial site should be promptly noted at http://www.clinicaltrials.gov. The FDA should also create a website or a publicly available database that lists all OAI-rated inspections of

clinical sites and provides links to copies of the relevant, unredacted, inspection-related documents.

The FDA should be more transparent about its findings of research misconduct; however, most of the burden for ensuring the integrity of the research in the peer-reviewed literature falls to the authors of the articles submitted to peer-reviewed journals. Currently, there is no formal requirement for authors seeking to publish clinical trial data to disclose any adverse findings noted during FDA inspections. Journals should require that any such findings be disclosed. Voluntary disclosures are never foolproof, but, as with conflict-of-interest statements, requiring authors and journals to be forthcoming about significant departures from good clinical practice will help raise the standard for the reporting of research toward greater transparency.

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