

Original Investigation

Research Misconduct Identified by the US Food and Drug Administration

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

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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.

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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

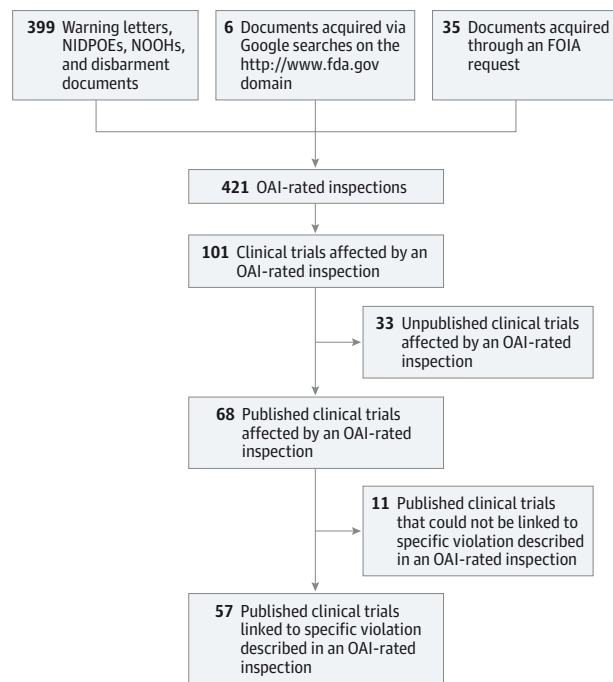
The FDA classifies its inspections in 1 of 3 ways, depending on the gravity of violations found. *No action indicated* indicates that there were no substantial violations. *Voluntary action indicated* means that inspectors have found violations of good clinical practice, but the nature and extent of 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

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.

OAI-rated inspections, all dated before August 8, 2012, when the Freedom of Information Act request was submitted.

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 ($\kappa = 0.85$). 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 documents⁶ 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 letter⁸ and 1 Notice of Disqualification Proceedings and Opportunity to Explain⁹ 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 trials³⁸⁻⁴⁰; the fourth trial⁴¹ 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 de-

partures 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 documents⁶⁴ 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 | 2007-02-1 | 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 | ... | ... | ... |
| Naproxinod | 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 document¹⁶⁹ 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 results¹⁴² 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 /Bleeker 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 / Pirota 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 alipiasmid | 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 published⁵² 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 set¹⁸¹ 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 vio-

lations 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 trial¹⁸³ 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 data¹²⁸ 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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