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Patterns of Regularity Noncompliance Identified by the U.S. Food and Drug Administration and Their Effects on Meta-analyses

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FLORIDA INTERNATIONAL UNIVERSITY

Miami, Florida

PATTERNS OF REGULATORY NONCOMPLIANCE IDENTIFIED BY THE U.S. FOOD AND DRUG ADMINISTRATION AND THEIR EFFECTS ON META-ANALYSES

A dissertation submitted in partial fulfillment of the

requirements for the degree of

DOCTOR OF PHILOSOPHY

in

PUBLIC HEALTH

by

Craig Alexander Garmendia

2018

To: Dean Tomás R. Guilarte
Robert Stempel College of Public Health and Social Work

This dissertation, written by Craig Alexander Garmendia, and entitled Patterns of Regulatory Noncompliance Identified by the U.S. Food and Drug Administration and Their Effects on Meta-analyses, having been approved in respect to style and intellectual content, is referred to you for judgement.

We have read this dissertation and recommend that it be approved.

Mary Jo Trepka

Emir Veledar

Stanislaw F. Wnuk

Purnima Madhivanan, Major Professor

Date of Defense: September 20, 2018

The dissertation of Craig Alexander Garmendia is approved.

Dean Tomás R. Guilarte
Robert Stempel College of Public Health and Social Work

Andrés G. Gil
Vice President for Research and Economic Development
Dean of the University Graduate School

Florida International University, 2018

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DEDICATION

This dissertation is dedicated to the ones who have been my greatest encouragement and support: my mother, Terrie Garmendia; my father, William Garmendia; and my husband, Robert Gonzalez III.

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My deepest appreciation begins with the Department of Epidemiology; its faculty, both past and present; and my dissertation committee, for which this body of work would not have been possible without their instruction, influence, and guidance. Dr. Purnima Madhivanan, for her unwavering commitment to this research and mentoring through my years in the doctorate program, both as an academic advisor and major professor. To my current committee, Drs. Trepka, Veledar, and Wnuk, and former committee member, Dr. Oren D. Williams, for their invaluable feedback and suggestions that sculpted this body of work. One additional former university faculty member deserves my utmost thanks, Dr. Neera Bhansali, without whom this dissertation would not have been possible. And of course, my colleagues Katrina Epnere, Liliana Gorra, and Ana L. Rodriguez for their assistance with the collection and statistical analysis of the dissertation's data.

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I came to the area of public health and epidemiology at a later stage than most. This came about from leaving the field of chemistry and beginning my years of public service with the U.S. Food and Drug Administration. Without my career with the Agency, I would not have discovered my passion for clinical research. I would like to thank all of my colleagues and mentors who provided the inspiration for this research through their sharing of knowledge, including institutional knowledge, and passion for the mission of the Agency.

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"It is never too late to be what you might have been."

- George Eliot (penname for Mary Anne Evans)

ABSTRACT OF THE DISSERTATION

PATTERNS OF REGULATORY NONCOMPLIANCE IDENTIFIED BY THE U.S. FOOD AND DRUG ADMINISTRATION AND THEIR EFFECTS ON META-ANALYSES

by

Craig Alexander Garmendia

Florida International University, 2018

Miami, Florida

Professor Purnima Madhivanan, Major Professor

The objective was to determine the patterns of regulatory noncompliance, as identified by the U.S. Food and Drug Administration (FDA), and their effects on meta-analyses. Three studies were undertaken: analysis of citations issued; analysis of regulatory actions towards clinical researchers; and sensitivity analysis of meta-analyses based on FDA's determination of research misconduct, primarily the falsification of data. Citations were analyzed using Chi-Square analysis based on geographic location of the inspection, type of inspection, and type of violation. Temporal changes in inspection totals and violations cited were analyzed using bivariate Poisson regression models. Bonferroni correction was employed for temporal changes across time. Regulatory actions were analyzed via Chi-Square or Fisher's exact test based on previous publications, temporal changes, and differences between regulatory action types. Sensitivity analysis of meta-analyses identified through a systematic review were assessed qualitatively and quantitatively for the effects of including publications of apixaban trials with regulatory actions, i.e. the comparison of odds ratio point estimate and upper and lower 95% confidence intervals considering the use of falsified data.

From 2007-2015, FDA inspections increased but rate of citation issuance per inspection decreased. One third of violations were related to adherence to investigational procedures. Since 2007, rates of significant deviations had decreased. Lack of researcher supervision and submission of false information were cited more frequently for disqualification proceedings. A sensitivity analysis of meta-analyses found nearly one-third of results changed in the conclusions reported in the original statistical analyses.

In the decade analyzed, violations cited during inspections decreased; however, significant improvements can be made regarding adherence to study procedures, consenting of human subjects, and creation of adequate and accurate study documentation. Disqualification of clinical researchers is more likely to occur when failure to supervise a clinical trial or false information is submitted. Falsified data can make its way into the exploding field of meta-analyses, a method that provides concise and compelling results for the dissemination of medical intervention knowledge; however, this method can be highly unstable and provide biased results. A robust sensitivity analysis that considers data quality from available sources can help ensure calculations of the best estimates.

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ABBREVIATIONS AND ACRONYMS

[50]	Informed Consent of Subjects
AM	Analysis Method
BIMO	Bioresearch Monitoring
CBER	Center for Biologic Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Device and Radiological Health
CI	Clinical Investigator
CFR	Code of Federal Regulations
Est.	Estimate
F	Fixed
FD	Falsified Data
FDA	U.S. Food and Drug Administration
FY	U.S. Governmental Fiscal Year
GCP	Good Clinical Practice
IRB	Institutional Review Board
LCI	Lower 95% Confidence Interval
N	No
N/A	Not Available
NAI	No Action Indicated
NIDPOE	Notice of Initiation of Disqualification Proceedings and Opportunity to Explain
OAI	Official Action Indicated

OR	Odds Ratio
R	Random
Rig	Rights, Safety, and Welfare of the Subject
Sup	Supervision of Clinical Trial
SW	Study Weight
UCI	Upper 95% Confidence Interval
U.S.	United States
VAI	Voluntary Action Indicated
VT	Violation Theme
WL	Warning Letter
Y	Yes

I. INTRODUCTION

It has been stated that due to the uncertainty in data validity, medical journals are unable to adhere to their responsibility of maintaining and improving trust in medical literature (1). Former U.S. Food and Drug Administration (FDA) Commissioner Dr. Robert M. Califf, and his colleagues at Duke University and Stanford University, indicated that this uncertainty in data validity is due in part to important data being commonly omitted from published research (2). Omission of data is one of the five parts that make up the definition of research misconduct, particularly in human research studies: [1] the fabrication of data or results and its recording and reporting; [2] the manipulation of data so that it no longer accurately reflects what was observed; [3] plagiarism; [4] the repeated and systematic deviation from the established protocol; and [5] the violation of human subject rights and protections (3,4).

The definition of research misconduct has evolved over the years to include additional criteria as the research community has become aware of violations that have occurred. One of the first attempts to establish criteria to prevent human subject research misconduct was the 1947 Nuremberg Code. This code was the result of Drs. Leo Alexander and Andrew Ivy's work studying and analyzing human experimentation performed by the Third Reich during the Second World War (5). The experimentation by the Third Reich has been classified into three different categories: [1] increasing the survival of the military; [2] medical treatments for the cure and/or prevention of diseases/illnesses; and [3] the perpetuation of the Nazi's view of race. The overwhelming majority of these research activities were performed on prisoners of the Third Reich, and

without consent from the human subjects (6). The analysis of medical research performed by the Third Reich led to the following ten parts that comprise the Nuremberg Code (5):

1. The voluntary consent of the human subject is absolutely essential.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be conducted so as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serves as a subject.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified individuals. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if they have reached the physical or mental state where continuation of the experiment seems to them to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if they have probable cause to believe, in the exercise of good faith, superior skill, and careful judgment required of them, that continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

The subject of research misconduct took another leap forward in 1964 via the World Medical Association's Declaration of Helsinki. This declaration provided basic principles for human subject research that were an evolution of the Nuremberg Code. The declaration has been revised seven times since 1964, the results of which are categorized into two themes: basic human subject protection and operational aspects of a clinical trial. The declaration can be summarized into the following principles (7):

- Basic Principles
    - Respect of the subject's right to self-determination based on being continually informed of all aspects of the research that may affect the subject.
    - The subject's welfare and need should supersede the needs of the research, including ethical considerations.
    - Special considerations must be given to vulnerable subjects, including consent from the subject's legal guardian.

- Operational Principles
    - The research must be based on scientific knowledge and be methodologically sound.
    - Research protocols should address ethical principles, including proper training of the research personnel and ethical oversight.
    - If new information warrants it, the research should be discontinued.
    - Comparison research should include the best methods currently available, and only under certain circumstance should a placebo or no treatment be utilized.
    - The results of the research should be made available and published.
    - The best interest of the subject should be the research personnel's priority during and after the research, including access to the best-proven care.

However, both the Nuremberg Code and the Declaration of Helsinki were not in the forefront of thought when individuals from the United States Public Health Service performed the Tuskegee Syphilis Study, a study in which individuals were knowingly infected with a deadly bacteria and known effective treatments for the infection were withheld (8). Because of this, in 1978 the United States government established the "National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research". The result of this commission was the Belmont Report; this report included the following categories that should be considered when performing research on human subjects (9):

- Boundaries Between Practice and Research
- Basic Ethical Principles
    - Respecting Human Subjects
    - Beneficence
    - Justice
- Application
    - Informed Consent
    - Assessment of Risk and Benefits
    - Selection of Subjects

These three documents (Nuremberg Code, Declaration of Helsinki, Belmont Report) have guided the course of human subject research, both medical and behavioral studies, in order to prevent egregious research misconduct. In addition, these documents have guided the legislative and executive branches of the U.S. government in passing new laws and enforcing those laws, including the regulations enforced by the FDA.

Dr. Califf and colleagues indicated that FDA-regulated research may be less susceptible to specific kinds of research misconduct (2). The reason for their statement is due to the FDA ensuring research misconduct has not occurred through inspections of researchers, clinical investigators, who have and/or are conducting clinical trials of products (study test articles) that fall under FDA's jurisdiction. The Agency was given this authority via the 1962 Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act (10). The amendment, better known as the Kefauver-Harris amendment, was a direct effect of Dr. Frances Kelsey's work as a reviewer of pharmaceutical applications with the agency. Dr. Kelsey refused to approve the application of the pharmaceutical thalidomide based on insufficient safety data (10). Her skepticism of the

drug's safety profile was proven to be well founded when by 1962 news and media outlets began reporting thousands of children being born in Europe with shortened, missing, or flipper-like arms and legs (10). Outrage ensued when it was discovered that the drug manufacturer, Williams S. Merrill Company, had already distributed thalidomide to approximately 1,200 physicians in the U.S. The Kefauver-Harris Amendment included provisions to not only require a new pharmaceutical be efficacious, as shown through a well-controlled clinical trial performed by qualified experts, but also that these new pharmaceuticals be safe. In addition, study subjects were now required to give their informed consent prior to any study procedures, especially for treatment with a study test article, e.g. an unapproved pharmaceutical (10). It is curious to note that the 1947 Nuremberg Code's first principle is to obtain voluntary consent, but this was not incorporated into the U.S. law until 1962, 15 years later.

In order to assure that clinical trials were, and are, conducted in an appropriate manner for regulatory review, the FDA conducts approximately 700 inspections of researchers within the U.S. and 140 foreign inspections of researchers annually. These inspections take place as part of FDA's Bioresearch Monitoring program (11-19). This program was established in 1977 as a result of a task force that was represented by various FDA divisions that make up the regulatory structure of the agency. As a result, a document known as "Compliance Program 7348.811, Chapter 48 – Bioresearch Monitoring – Clinical Investigators and Sponsor-Investigators" was developed and published (20). The program established the audit of researchers for new products under FDA's purview that are seeking approval for introduction into the U.S. and its territories. These new products are known as study test articles and defined within the regulations as "…any drug (including a biological product for human use), medical device for human

use,…or any other article subject to regulation under the act…" (21). The divisions of the FDA that provide approval for human medical products are: Center for Biologic Evaluation and Research (CBER), whose products include vaccines and other biologically based products; Center for Drug Evaluation and Research (CDER), whose products include human pharmaceutical products; and the Center for Device and Radiological Health (CDRH), whose products include medical and radiation emitting devices. The compliance program requires that the clinical research presented to the agency be conducted according to U.S. regulations and Good Clinical Practice (GCP). In addition, the compliance program requires the governing FDA center to identify the researchers to be audited, and these centers to make the final determination of findings for violations of FDA regulations, including research noncompliance with the Institutional Review Board (IRB) approved protocols, human subject rights violations, and data verification/validation issues, that have been identified by FDA Investigators (20).

As part of the final determination, or classification, of an inspection, the FDA center that has regulatory authority over the study test article, is to classify the inspection into one of three categories: No Action Indicated (NAI); Voluntary Action Indicated (VAI): or Official Action Indicated (OAI). NAI is suggestive of an audit that has found no deviations from the regulatory requirements that are of a concern for the agency. VAI is suggestive of an inspection that has found deviations from the regulatory requirements and the deviations are of concern to the agency, but the violations are not of a nature significant enough to require action by the FDA. OAI is indicative of an audit in which deviations from regulatory requirements have been found and that these deviations are so egregious that regulatory action by the Agency is required. In addition, the data from OAI

inspections are generally not accepted by the FDA and thus will not be allowed for consideration in the application process for a new product. Both VAI and OAI classified inspections result in the issuance of a Form FDA 483, Inspectional Observations (22).

OAI classified inspections are considered the most egregious of violations and constitutes research misconduct. As a result, the FDA initiates regulatory actions against researchers who have had inspections classified OAI. These regulatory actions fall into one of three levels: the lowest level may result in an Untitled Letter (UL); the middle level may result in a Warning Letter (WL); and the highest level may result in a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) letter. The NIDPOE letter will generally include either suspension or outright disqualification of researchers from performing FDA-regulated clinical trials, and occasionally results in prosecutions by local, state, and/or federal agencies. Untitled Letters are not published on FDA's website for researchers and are only available through a Freedom of Information Act (FOIA) request. Unlike ULs, WLs and NIDPOEs are published on the FDA's website, which are freely accessible to all individuals (23).

As would be expected, the clinical trials conducted for FDA approval are considered of the highest quality and are routinely published in medical journals, even though compliance, e.g. quality of the data, may be questionable (24). These studies may then be included in Systematic Reviews and Meta-Analyses. The gold standard for conducting Systematic Reviews is presented by the Cochrane Collaboration. However, in the "Cochrane Handbook for Systematic Reviews of Interventions" there is no mention of assessing study noncompliance, such as compliance with the IRB approved protocol or reporting of data (25).

AIMS OF THE DISSERTATION

An analysis of WLs determined that over 81% were issued in part because researchers failed to adhere to the IRB approved protocol (26-28). However, a review of the literature has found that no study has analyzed all published regulatory actions in regard to study test article type, temporality, or the type of violation cited. A cross reference of WLs and NIDPOEs issued to researchers by the FDA due to significant noncompliance with U.S. regulations and GCP, among other sources documentations, resulted in the identification of 78 publications from 57 different clinical trials. Of the 78 publications identified, only three publications mentioned that the FDA had observed objectionable conditions or practices by the researcher in regard to the conduct of the audited clinical trial (24).

It has been argued that given the uncertainty in data validity, medical journals are unable to adhere to their responsibility, maintaining and improving trust in medical literature (1). Taking this into consideration, a review of the literature has found no study that analyzed the effect of protocol noncompliance on the results of meta-analyses.

The objective of this dissertation was to determine the patterns of noncompliance observed by the FDA and their effects on meta-analyses by examining the following specific aims:

Aim 1: Association of geographical location, researcher type, and/or time trend with the issuance of citations by FDA Investigators.

Aim 2: Association of study intervention type, type of violation and type of violation based on intervention type with regulatory actions taken by the FDA.

Aim 3: Effects of considering significant study noncompliance, as identified by the FDA, in meta-analysis results.

These aims were examined through three separate studies with analyses of data publicly available data from the FDA and research literature. The results of the dissertation research are presented here in three separate manuscripts. The first manuscript is a cross-sectional analysis of FDA inspectional observations in order to describe the paraments of where (geographical), who (researcher type), and when (time trend) the issuance of a Form FDA 483, Inspectional Observations, had occurred. The second manuscript is a cross-sectional analysis of citations in FDA regulatory actions (WLs and NIDPOEs) for the purpose of understanding differences between these two regulatory actions. Finally, the third manuscript is a sensitivity analysis of meta-analyses to understand the effects of significant study noncompliance, i.e. data falsification, on the results of meta-analyses.

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II. MANUSCRIPT 1

Research Deviations in FDA-Regulated Clinical Trials: A Cross-Sectional Analysis of FDA Inspection Citations

ABSTRACT

Background: The U.S. Food and Drug Administration (FDA) ensures clinical trials meet regulatory/ethical standards through inspections. If FDA investigators observe potential violations of regulatory requirements during an inspection, a firm will receive a Form FDA 483, Inspectional Observations. Violations cited have resulted in the death of human research subjects, prosecution of research personnel, and denial of approval for new medical products. Objectives included the standardization of Violation Themes cited for analysis by inspection firm type, geographic location, and Violation Theme citation to provide insight into regulatory violations. **Methods**: Cross-sectional analysis of citations published in public databases between October 1, 2005, and September 30, 2015, by the FDA for inspections under the Bioresearch Monitoring program. For each inspection citation, the main measure was the Code of Federal Regulation cited coded into a standardized Violation Theme for citation analysis. **Results**: Under the Bioresearch Monitoring program, 3,281 inspections received a Form FDA 483 in 2007-2015. FDA inspections have increased over this period but the rate of Form FDA 483 issuance has decreased. On average, Sponsor-Investigators received 4.41 citations per inspection compared to clinical researchers alone receiving 2.21. One-third of violations were related to adherence to investigational procedures followed by informed consent and study records issues. **Conclusions**: In the last decade, the number of violations observed under the Bioresearch Monitoring program has decreased; however, significant

improvements can still be made regarding adherence to study procedures, the consenting of human research subjects, and creation of adequate and accurate study documentation.

Keywords: Bioresearch Monitoring; Code of Federal Regulations; deviation; Form FDA 483; inspection

INTRODUCTION

The Food and Drug Administration Amendments Act of 2007 (FDAAA) requires all clinical trials involving human subjects to be included in ClinicalTrials.gov prior to the beginning of the clinical trial (1). Since the inception of ClinicalTrails.gov in 2000, the registration of clinical trials has increased significantly from 5,632 to 243,111 in 2017. Currently registered studies include clinical trials from all 50 US states and 199 countries. Eighty percent (n = 194,690) of these studies are interventional, while 19% (n = 47,277) are observational. Most of the interventional studies are trials of pharmaceuticals and biologics (n = 117,673; 60.44%), followed by behavioral (n = 57,770; 29.67%), medical device (n = 23,030; 11.83%), and surgical procedure (n = 20,998; 10.79%) clinical trials (each trial can involve more than one type of intervention) (2). Researchers are required to report study summaries, participant information including race and ethnicity, full study protocols, and annual updates. This is meant to increase the transparency and validity of medical research findings, help avoid duplication of studies, and improve study designs (1).

Because of the growing number of research studies and study participants, and the increasing complexity of clinical trials, it is important to regulate and monitor the ethical conduct of clinical trials and to address all researchers and involved stakeholders (3,4). The enforcement of these policies falls under the existing FDA Bioresearch Monitoring program (1). The program was established in 1977 after the passage of the 1962

Amendments to the Federal Food, Drug and Cosmetic Act, better known as the Kefauver-Harris amendment, because of the thalidomide incident (a sedative that was used to treat morning sickness in pregnant women and resulted in birth defects) (5,6). The Bioresearch Monitoring program is responsible for monitoring all aspects of the conduct and reporting of FDA regulated research, including protection of human subjects rights, reliability and quality of clinical data, and compliance with FDA regulations (3,7). Research of new medicines, medical devices, food and food color additives, and veterinary products are all monitored under the Bioresearch Monitoring program (7,8). Monitoring of Tobacco products has recently been added to the Bioresearch Monitoring program as well but is still new and does not significantly contribute to the overall workload of the Bioresearch Monitoring program (9).

US Food and Drug Administration regulations relevant to the Bioresearch Monitoring programs are found under Title 21 of the United States Code of Federal Regulations (21 CFR). For example, 21 CFR Part 50 regulates the informed consent document and process; Part 56 regulates the institutional review of human subject research; Part 312 regulates the studies of pharmaceuticals and biologics; and Part 812 regulates medical device studies (10,11). The Office of Regulatory Affairs is the main entity under the FDA responsible for conducting field inspections to verify and enforce compliance with regulations (12,13). The mission of the Office of Regulatory Affairs is to maximize compliance and minimize the associated risks of FDA-regulated products (14). There are 7 compliance programs, field guides on how inspections should take place, under the Bioresearch Monitoring program: [1] nonclinical testing laboratories in accordance to Good Laboratory Practice (GLP); [2] Good Laboratory Practice Program (Nonclinical Laboratories) EPA Data Audit; [3] Clinical Investigators in accordance to

Good Clinical Practice (GCP); [4] Sponsors/Contract Research Organizations/clinical trial monitors; [5] In vivo bioequivalence facilities; [6] Institutional Review Boards (IRBs); and [7] Radioactive Drug Research Committees (4).

There are several reasons for conducting a FDA inspection: [1] verify accuracy of data submitted to the FDA; [2] respond to a complaint against a firm involved in FDA regulated research; [3] respond to a concern by the sponsor of a trial; and/or [4] determine the protection of research subjects (4). Inspections conducted by the FDA can be announced or unannounced (7). More than a thousand inspections are conducted every year domestically and internationally (15-23). During the period of US Governmental fiscal year 2006-2010, there were a total of 78,242 FDA inspections within 11 manufacturing categories (13). From fiscal years 2007 to 2015, there were 11,149 inspections under the Bioresearch Monitoring program, with 1388 in fiscal year 2015 alone (15-23).

At the beginning of an inspection, FDA Investigators present their credentials and a Notice of Inspection, Form FDA 482. During an inspection, the FDA Investigator verifies compliance with the regulations by direct observation of conditions, equipment, facilities, behavior, labeling, documents, etc. FDA Investigators will also conduct interviews of selected research personnel and perform extensive document review (7,11). During FDA field inspections, deviations or violations of the regulations are documented in a Form FDA 483, Inspectional Observations (7). After receiving the Form FDA 483, the firm has 15 business days to respond. The Form FDA 483 is not the final determination of violation of FDA regulations; it is evaluated along with other supporting documents such as the Establishment Inspection Report, firm's response, and other evidence collected before any further actions are taken (24). In case of no response to the

Form FDA 483, or an insufficient response, a regulatory action may be taken in regard to the regulatory violations observed (11,13).

The final determination of the inspection is sent to firms in the form of a letter; there are 5 types of letters: (1) a letter that states compliance with FDA regulations; (2) an informal letter that identifies deviations from regulations but does not meet the significance criteria for regulatory action; (3) an untitled letter that identifies serious and significant deviations from the regulations but does not reach the level of a published warning letter; (4) a warning letter that identifies serious and significant deviations from statutes that might lead to enforcement action if not properly corrected, and this letter is published on the Agency's website; and (5) a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain that identifies the Agency's intent to disqualify a researcher (Clinical Investigator) from conducting FDA-regulated research in the future; this letter too is published on the Agency's website (7).

Several studies have been conducted to explore the Warning Letters issued to researchers, IRBs, and sponsors. The most common violations from 1996 to 2011 were found to be deviations from the investigational plan; flawed consent process/ document; failure to report adverse events; and inaccurate records and documentation (25-28). Warning Letters are viewed as a tool to help the audited firm to correct violations; however, if the violations are not adequately addressed, additional enforcement action may be taken. The violations mentioned in the Warning Letter can refer to a single incident or many incidents within the same violation or the same regulations might be cited multiple times for the same firm (26). However, these previous studies do not list all the findings of the FDA Investigators. Warning Letters are not the only regulatory action taken from Official Action Indicated classified inspections, and not all citations result in

the issuance of a Warning Letter. Therefore, the literature on Warning Letters is only a small segment of the observations of deviations by the Agency.

We have focused our research on the Bioresearch Monitoring program because violations in the clinical trials conducted under FDA's authority could have devastating consequences. For example, there was a fatality in a gene trial for ornithine transcarbamylase deficiency when compliance with the investigational plan was not strictly adhered to. The researcher of this clinical trial has pointed out the importance of adherence to clinical protocols, reporting of adverse events, disclosure of potential financial conflicts of interest, and oversight of the informed consent process. He also went on to state that all participants of clinical trials deserve a well-designed and strictly compliant clinical trial (29). With the growing popularity of the "Right To Try" movement—allowing terminally ill patients access to medicines that have passed Phase I clinical trials—the expanded use of these still-unproven medical products could be deleterious if proper controls are not in effect (30).

In 2009, President Obama issued the Open Government Initiative; as a result, the FDA has published data from field inspections, including those under the Bioresearch Monitoring program, thus providing the public with information regarding various findings of FDA inspections. This is meant to "improve the public's understanding of how the FDA works to protect the public health, provide the public with a rationale for the Agency's enforcement actions, and to help inform public and industry decision-making allowing them to make more informed marketplace choices and help to encourage compliance" (31). Thus, this study aims to explore the recently published violations of regulations observed during FDA inspections within the Bioresearch Monitoring program. We have grouped the violations into 15 Violation Themes such as

Adverse Events, Consent, Financial Disclosure, Procedures, Records, etc. Exploration of the number of citations and trends for each type of violation over the past 10 fiscal years is sought to identify areas where special attention can be made to improve the conduct of clinical trials by all stakeholders.

METHODS

This manuscript does not contain any studies with human or animal subjects performed by any of the authors.

This cross-sectional study included a secondary analysis of citations recorded on Form FDA 483s within 10 fiscal years (October 1, 2005, through September 30, 2015) (32-41). The original data files are available in Excel format and include 9 variables: "Firm Name" specifies the name of the inspected firm; "City, State, Country/Area" refers to the location of the inspected firm; "Inspection End Date" indicates the date when the inspection was completed; "Program Area" includes one of the Agency's program areas (drugs, foods, biologics, devices, veterinary medicine, human tissue for transplantation, radiological health and bioresearch monitoring); "CFR Number" specifies the section of the Code of Federal Regulations that has been violated/cited by the FDA Investigator; "Short Description" briefly states the violation; and "Long Description" is a more detailed description of the violation cited.

The following transformations to the original data files were performed by CAG, unless otherwise noted. Original data files were merged into one master file containing citation information for all product areas and all fiscal years. We extracted the citations under the Program Areas for Bioresearch Monitoring and Devices; Devices was used because all medical device–specific violations, Good Manufacturing Practice, or Good Clinical Practice were contained in the Device section only. For our analysis, we

manually coded and added 5 variables: “Item Number” was a unique identifier for each citation; “Violation Theme” (VT) was a standardization of themes observed in regard to the Code of Federal Regulation cited based on the “Long Description” text as reviewed by an individual trained in FDA inspections and regulations (CAG; Table 1). Any unusual or ambiguous cases were collectively reviewed by all authors: we referred to the Code of Federal Regulations definition and compared that to the long description of the citation and then a final consensus decision was made. In some cases (n = 150, 1.7%), there were two or more Violation Themes relevant per citation—these cases were carefully reviewed by the complete research team and the additional Violation Themes were captured (8,889 Violation Themes from 8,739 citations). “FDA Districts” was a new variable created based on the original variables of “City, State, Country/Area” corresponding to one of the FDA’s 20 districts (Table 2) (43). For administrative purposes, the US territory has been divided into 19 districts and an additional category for international territories. All international inspections were classified into the same district since the inspections did not take place in an FDA US district and separating based on country would lead to no discernable observation trends from FDA inspections. “Fiscal year” was based on the original variable “Inspection End Date” to create a variable that identifies the US Governmental fiscal year in which the inspection closed; that is, fiscal year 2006 includes all inspections concluded between October 1, 2005, and September 30, 2006. “Firm Type” was coded based on the “Firm Name” and the sections of the Code of Federal Regulations cited (there are specific Code of Federal Regulations for each firm type): (1) Clinical Investigators (an individual researcher who conducts a clinical investigation and under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or in the event of an investigation conducted

by a team of individuals, is the responsible leader of that team); (2) IRBs (a review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection); (3) Sponsor (a person who takes responsibility for and initiates a clinical investigation; the sponsor may be an individual or a company, governmental agency, academic institution, private organization, or other organization); (4) Sponsor-Investigator (an individual who both initiates and conducts an investigation, and under whose immediate direction the test article is administered or dispensed); or (5) Good Laboratory Practices firm (an institution or individual who was cited for Good Laboratory Practices under Part 58 of the Code of Federal Regulations.) (42). Less than 1% of all cases (n = 4, 0.08%) were marked as N/A and excluded from the analysis when looking at the "Firm Types"; that is, N/A was placed if the regulation cited did not match what the firm appeared to be, such as an IRB cited for Clinical Investigator regulations.

All statistical procedures were performed using the SPSS software version 17.0 (IBM Corporation, New York, NY) and SAS software version 9.4 (SAS Institute Inc, Cary, NC). The focus of the analysis was to explore the number of citations under each of the Violation Themes within each Firm Type. Frequencies of the citations were calculated across categorical variables (FDA Districts, Firms Types, Violations Themes). The proportions of citations across these categorical variables were tested using the chi-square test. To examine the changes in number of inspections and citations between fiscal years, we employed bivariate Poisson regression models: we used total number of Bioresearch Monitoring inspections, number of Bioresearch Monitoring inspections receiving a Form FDA 483, and the number of citations as dependent count variables, and fiscal year as the independent categorical variable. Bonferroni correction for multiple

comparisons were used when comparing consecutive fiscal years and changes across 10 fiscal years. The P-value of 0.05 was used to determine statistical significance.

RESULTS

Inspections and Citations: Overall

Between fiscal year 2007 and 2015, the Bioresearch Monitoring inspection metrics reported a total of 11,409 inspections globally, not including Bioequivalence studies. Between fiscal years 2006 and 2015, there were a total of 3,281 inspections under the Bioresearch Monitoring and Device (Bioresearch Monitoring specific) programs that received a Form FDA 483. These forms listed a total of 8,739 citations for deviations from regulatory requirements. The total number of inspections (P value < 0.0001), number of inspections receiving a Form FDA 483 (P value < 0.0001), and the total number of citations (P value < 0.0001) were significantly associated with fiscal year (Figure 1). Overall the total number of inspections increased by 30% between fiscal year 2007 and 2015 (P value < 0.0001), yet the number of inspections receiving a Form FDA 483 has decreased by 36% since 2009 (P value < 0.0001) and the total number of citations has decreased by 31% since 2006 (P value < 0.0001; Figure 1).

Inspections and Citations: Geographically

The number of inspections receiving a Form FDA 483 (P value < 0.0001) and the number of citations per Form FDA 483 (P value < 0.0001) is associated with FDA Districts. Inspections in the Los Angeles and Dallas Districts received the most numbers of Form FDA 483, 314, and 280, respectively. However, the highest number of citations per inspection was received by the Districts of Chicago, Denver, New Orleans, Detroit, and New York; on average, these districts received more than 3 citations per Form FDA 483 (Table 3).

Inspections and Citations: Violation Theme

There were a total of 8,889 Violation Themes recorded across 8,739 citations in the decade analyzed. The number of citations issued differed across the Violation Themes (P value < 0.0001). Almost one-third of the citations were related to Procedures, 16% were related to the Consent process, and almost 15% were related to Study Records (Table 5). Less than 1% of citations were related to Financial Disclosure, Registration, Inspection, Facilities and Equipment, and Declaration of Helsinki (which is a provision in the regulations that allows for waivers to regulatory requirements but still must meet the requirements of the Declaration of Helsinki).

There were a total of 4,768 Violation Themes cited for Clinical Investigators. Almost 40% of these violations were related to Procedures (n = 801), more than 20% were related to the Consent process (n = 1,023), 15% were related to the Investigational Product (n = 25), and 14% were related to study Records (n = 84). Since 2009, the total number of violations per fiscal year has decreased by almost half. Also, the number of violations per fiscal year has been decreasing within each of the themes, with fiscal year 2015 having the lowest or near lowest citation incidents for each Violation Theme (Appendix Table 1). There were few violations recorded for Good Laboratory Practice (n = 26), with half of the citations recorded in fiscal year 2006; almost a third of all violations were related to Facilities and Equipment (Appendix Table 2). In the past decade, IRBs were cited for a total of 2,603 violations, with almost a third of these violations related to Procedures (n = 821). More than 18% of violations were related to Approval (n = 482) and more than 16% were related to Records (n = 433). Overall, the number of violations per fiscal year has decreased by more than 50% since 2010. Similarly, the number of violations within each of the themes has been decreasing, again

with fiscal year 2015's incidents per Violation Theme at the lowest, or near lowest, for the 10 fiscal years analyzed (Appendix Table 3). Sponsors received citations for a total of 769 violations. Monitoring (n = 161, 20.94%), Procedures (n = 121, 15.73%), and Communication (n = 115, 14.95%) were the most commonly cited violations. From a total of 120 violations in 2010, the number of violations cited has decreased to only 28 in fiscal year 2015, the lowest in the past decade (Appendix Table 4). There were a total of 649 violations cited for Sponsor-Investigators in fiscal years 2006-2015. Most violations were related to Procedures (n = 121, 18.64%) and Consent process (n = 111, 17.10%). As with Sponsors, Sponsor-Investigators saw inspections in fiscal year 2015 result in the least amount of citations over the past decade (Appendix Table 5).

DISCUSSION

As we push the boundaries of medical knowledge and innovation further and further, the importance of compliance with ethical and regulatory requirements becomes greater; this compliance can help limit any long-term negative effects a new medical product or procedure may have. This importance has only increased with the "Right To Try" movement that results in the increased number of individuals who have access to new medical products with limited safety and efficacy data. Fortunately, published data allows us to analyze observations of noncompliance in clinical trials that have the most oversight, FDA clinical trials.

If we assume that there have been no significant changes in the process of FDA Bioresearch Monitoring inspections, and no significant change in the workforce conducting these inspections, then the Agency is seeing greater compliance with ethical and regulatory requirements through the past decade, with fiscal year 2015 having the best compliance over all firm types. Our findings are consistent with previous studies that

explored Warning Letters (4, 25-28). Possible reasons for reduction in the number of violations could be (1) outreach by the FDA and other organizations to educate all research stakeholders about requirements of the regulations; (2) regarding Clinical Investigators, reduction in FDA clinical trials because of the economic collapse that could have resulted in sponsors being more selective of Clinical Investigators; and/or (3) if a firm has been inspected historically, it is likely that they will have addressed previously cited violations. Finally, we cannot rule out the possibility that the FDA has changed its standards for the issuance of citations, i.e. a higher threshold is required for a citation to be issued. But all research stakeholders should increase their vigilance with compliance of the investigational plan, consent, adverse events, and study documentation requirements based on our analysis.

Two areas of our analysis, firm types and geographic areas, indicate additional vigilance with compliance is needed. First, Sponsor-Investigators received double the citations per Form FDA 483 as Clinical Investigators alone. This firm type is responsible for two parts of the regulations, the Clinical Investigator part and the Sponsor part. Thus, Sponsor-Investigators must ensure they have enough oversight to ensure compliance with both parts of the regulations. Second, some districts have more clinical sites and more inspections, and thus higher number of citations. For example, inspections in the Dallas District received the most Form FDA 483s and the most citations; however, the New York and Detroit Districts had the most citations per inspection on average. Firms in these 3 geographic areas should increase their vigilance with regulatory compliance to reduce violations and in turn citations by the FDA.

One of the limitations of our study is that this was a secondary analysis of available data sets; no common variable was available to link the inspection observation

data with citation data. This would have allowed for a more comprehensive analysis of Bioresearch Monitoring inspection findings. The structure and format of the data files available on the FDA website are not conducive for efficient data analysis and the information was not always complete. Merging and formatting the files, extracting the necessary information, and manually recording the variables required considerable effort. As no data on Bioequivalence studies was available (21 CFR 320s) this information was not included in this study. In addition to data that might be missing, some Form FDA 483s are prepared manually and are not included in the database or forms might have been updated and not synchronized with the electronic inspection tool (13,31,44). Finally, this study was unable to discern if the differences seen between FDA districts was due to compliance with the regulations for each type of inspection or if differences between districts was related to inspection practices.

Even though this was mainly a descriptive study, we believe that it is the first of its kind to explore all the citations from field inspections under the Bioresearch Monitoring program. Studies have been conducted using data from Warning Letters, but as pointed out earlier, they only captured one part of all observations. Another major contribution of this study is the development of a classification system for Violation Themes from more than 250 sections and subsections of the Code of Federal Regulations classified into 15 Violation Themes. This generalization and simplified classification should help to better understand the nature of citations and point out the critical areas of clinical research where improvements can be made.

Future studies could explore the violations within districts, specific firm types, or within most common violation themes in detail. Other FDA program areas, such as Drugs, Foods, Biologics, and Devices could be studied in addition to Bioresearch

Monitoring. As described in the FDA Program Alignment Bioresearch Monitoring Program FY2016 Action Plan, the Bioresearch Monitoring program needs to be continuously improved, monitored, and evaluated. The Action Plan also states that it is important to improve the analysis and presentation process of the findings (45). We hope that our study will provide information to all research stakeholders, improve the understanding of FDA's Bioresearch Monitoring program, and increase the compliance with Good Clinical Practices, both within and outside of FDA regulated clinical trials.

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TABLES AND FIGURES

Table 1: Classification of Violation Themes

VT	Short Description	Long Description[42]	21 CFR Section	Firm Type Applicability*				
				CI	*GLP*	*IRB*	*S*	*SI*
1	Adverse Events	The documentation and/or reporting of any untoward medical occurrence associated with the use of an investigational product. Observation and protection of human subject safety including but not limited to adverse events. According to CFR Title 21 "Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related"	312.50, 312.55(b), 312.64(b), 312.66, 56.115(a)(1), 812.140(a)(3)(ii), 812.140(b)(5), 812.150(a)(1), 812.150(b)(1), 812.36(e), 812.46(b)(1)	Yes	No	Yes	Yes	Yes
2	Approval	The approval, including documentation of the approval, for any research related activities by a responsible party.	312.66, 50.24(a)(1), 50.24(a)(2), 50.24(a)(3), 50.24(a)(4), 50.24(a)(5), 50.24(a)(6), 50.24(a)(7), 50.27(b)(2), 56.103(a), 56.108(c), 56.109(a), 56.109(f), 56.110(b), 56.110(b)(1), 56.110(b)(2), 56.111(a)(1), 56.111(a)(2), 56.111(a)(3), 56.111(b), 56.111(c), 56.113, 812.110(a), 812.150(a)(4), 812.20(a)(2), 812.35(a)(1), 812.36(d), 812.36(e), 812.40, 812.42, 812.46(c)	Yes	No	Yes	Yes	Yes
3	Communication	The communication of information (sending reports, sharing information, timeliness) to required parties not covered by other violation theme.	312.50 ,312.55(a), 312.56(b), 312.56(c), 312.64(a), 312.64(c), 50.24(e), 56.109(e), 56.109(g), 56.110(c), 56.113, 56.115(a)(1), 56.115(a)(4), 812.140(e), 812.140(b)(1), 812.150(a)(2), 812.150(a)(3), 812.150(a)(4), 812.150(a)(6), 812.150(a)(7), 812.150(b)(2), 812.150(b)(3), 812.150(b)(4), 812.150(b)(5), 812.150(b)(6), 812.150(b)(7), 812.150(b)(8), 812.35(a)(3)(iv), 812.140(a)(1), 812.40, 812.45, 812.66	Yes	No	Yes	Yes	Yes
4	Consent	The approval, procedure to obtain, and/or documentation of the informed consent and assent process.	312.60, 312.62(b), 50.20, 50.23(a), 50.25(a)(1), 50.25(a)(2), 50.25(a)(3), 50.25(a)(4), 50.25(a)(5), 50.25(a)(6),	Yes	No	Yes	Yes	Yes

			50.25(a)(7), 50.25(a)(8), 50.25(b)(1), 50.25(b)(2), 50.25(b)(3), 50.25(b)(4), 50.25(b)(5), 50.25(b)(6), 50.25(c) 50.27(a), 50.27(b)(1), 50.27(b)(2), 50.51 50.52, 50.53, 50.55(a), 50.55(b), 50.55(c) 50.55(e)(2), 50.55(f), 50.55(g), 50.56(b), 56.109(b), 56.109(c)(2), 56.109(h), 56.111(a)(4), 56.111(a)(5), 56.115(a)(1), 56.115(a)(7), 812.100, 812.110(a), 812.140(a)(3)(i), 812.150(a)(5), 812.36(e)					
5	Declaration of Helsinki	The ethical principles stated in the ``Declaration of Helsinki'' and the laws and regulations of the country in which the research was conducted.	312.120(c)	Yes	No	No	Yes	No
6	Facilities & Equipment	The design and maintenance, including any applicable documentation, in regards to a firm's facility or equipment contained within the facility.	58.190(b), 58.43(d), 58.61, 58.63(a), 58.63(b), 58.63(c), 58.81(b), 58.83, 58.90(g)	No	Yes	No	No	No
7	Financial Disclosure	The disclosure or documentation of the disclosure, of any financial conflicts of interest.	312.53(c)(4), 312.57(b), 312.64(d), 812.110(d), 812.140(b)(3), 812.43(c)(5)	Yes	No	No	Yes	Yes
8	Inspection	The impediment of an audit of a clinical trial, or its review or oversight, by any individual or party with authority to conduct such audit.	312.58(a), 312.68, 56.115(b), 812.145(b), 812.150(a)(7)	Yes	No	Yes	Yes	Yes
9	Investigational Product	The distribution of investigational product and/or the documentation of distribution included but not limited to the dosing of study research subjects.	312.53(b), 312.56(b), 312.57(a), 312.59, 312.6(a), 312.61, 312.62(a), 312.69, 312.7(a), 312.7(b), 312.7(d), 56.104(c), 58.105(a), 58.107, 58.113(a)(1), 58.113(a)(2), 812.100, 812.110(c), 812.110(e), 812.140(a)(2)(i), 812.140(a)(2)(ii), 812.140(a)(2)(iii), 812.140(a)(3), 812.140(a)(3)(ii), 812.140(a)(3)(iii), 812.140(b)(2), 812.140(b)(4)(i), 812.140(b)(4)(ii), 812.140(b)(4)(v), 812.18(b), 812.43(b), 812.5(a), 812.7(a), 812.7(b), 812.7(d)	Yes	Yes	No	Yes	Yes
10	IRB Members	The appointment of and service by IRB members.	56.107(a), 56.107(c), 56.107(d), 56.107(e), 56.107(f)	No	No	Yes	No	No

11	Monitoring	The monitoring of a clinical trial and/or the documentation of such monitoring. (Refers to the sponsor)	312.50, 56.109(f), 56.111(a)(6), 312.56(a), 58.35(b)(3), 58.35(b)(5), 812.25(e), 812.40	No	Yes	No	Yes	Yes
12	Procedures	The adherence to an investigational plan, statement of the investigator, Standard Operating Procedures (SOP), or any other required documentation. Signed investigator agreement.	312.50, 312.56(b), 312.60, 56.108(a)(1), 56.108(a)(2), 56.108(a)(3), 56.108(a)(4), 56.108(b)(1), 56.108(b)(2), 56.108(b)(3), 56.115(a)(1), 56.115(a)(6), 58.120(a)(6) 58.120(a)(7), 58.130(a), 58.33(c), 812.100 812.110(b), 812.46(a)	Yes	Yes	Yes	Yes	Yes
13	Qualified Personnel	The selection of individuals qualified for specific tasks which can include qualification by education or experience.	312.50, 312.53(a), 312.53(c)(2), 312.53(d), 56.115(a)(5), 58.29(a), 58.29(b), 812.40, 812.43(a), 812.43(d)	No	Yes	Yes	Yes	Yes
14	Records	The documentation of tasks required under regulations that are not otherwise covered by any other violation theme. Inadequate creation/ maintenance of records including transfer of obligations	312.50, 312.52(a), 312.53(c)(1), 312.57(c), 312.62(b), 312.62(c), 50.52, 50.53, 56.115(a)(1), 56.115(a)(2), 56.115(a)(3), 56.115(b), 58.120(b), 58.130(e), 58.185(a)(8), 58.185(a)(9), 58.195(e), 58.195(g), 58.33(c), 58.90(i), 812.140(a)(3)(ii), 812.140(a)(4), 812.140(a)(5), 812.140(b)(4), 812.140(b)(4)(i), 812.140(b)(4)(iii), 812.140(b)(4)(iv), 812.140(b)(4)(vi), 812.140(b)(6), 812.140(d), 812.43(c), 812.43(c)(1), 812.43(c)(2), 812.43(c)(3), 812.43(c)(4)(i), 812.43(c)(4)(ii), 812.43(c)(4)(iii)	Yes	Yes	Yes	Yes	Yes
15	Registration	The registration of activities with responsible parties, which include but are not limited to clinicaltrials.gov or applications with the FDA.	312.20(a), 312.20(b), 312.20(c), 56.106(a), 56.106(b)(1), 56.106(b)(2), 56.106(b)(3), 56.106(b)(4), 56.106(c), 56.106(e), 812.2(b) 812.2(c), 812.2(c)(3), 812.2(c)(7), 812.20(a)(1), 812.40	No	No	Yes	Yes	Yes

Abbreviations: CI – Clinical Investigator; GLP – Good Laboratory Practice; IRB – Institutional Review Board; S – Sponsor; SI – Sponsor-Investigator; VT – Violation Theme

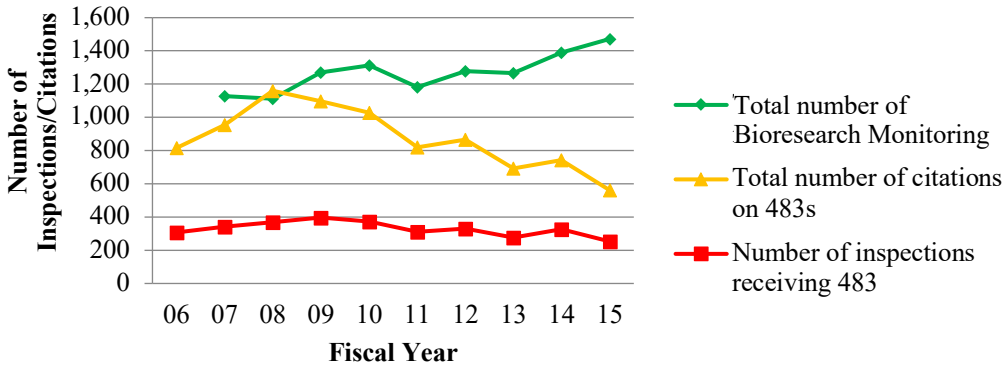
Table 2: Classification of FDA Districts		
Short FDA District Name	**FDA District Name**	**State/Country included in FDA District**
ATL	Atlanta	Georgia, North Carolina, South Carolina
BLT	Baltimore	Maryland, Virginia, Washington, D.C., West Virginia
CHI	Chicago	Illinois
CIN	Cincinnati	Kentucky, Ohio
DAL	Dallas	Arkansas, Oklahoma, Texas
DEN	Denver	Colorado, New Mexico, Utah, Wyoming
DET	Detroit	Indiana, Michigan
FLA	Florida	Florida
INT	International	Any place outside of states and territories listed here.
KAN	Kansas	Iowa, Kansas, Missouri, Nebraska
LOS	Los Angeles	Arizona, South California
MIN	Minneapolis	Minnesota, North Dakota, South Dakota, Wisconsin
NOL	New Orleans	Alabama, Louisiana, Mississippi, Tennessee
NWE	New England	Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont
NWJ	New Jersey	New Jersey
NYK	New York	New York
PHI	Philadelphia	Pennsylvania, Delaware
SAN	San Diego	Hawaii, Nevada, Northern California
SEA	Seattle	Alaska, Idaho, Montana, Oregon, Washington
SNJ	San Juan	Puerto Rico, U.S. Virgin Islands

Table 3: Inspections and Citations per FDA districts, FY 2006-2015					
FDA District	**Inspections receiving Form FDA 483**		**Number of citations**		**Average number of citations per inspection**
	n	%	n	%	
NYK	107	3.26	404	4.62	3.78
DET	193	5.88	680	7.78	3.52
NOL	86	2.62	290	3.32	3.37
DEN	133	4.05	412	4.71	3.10
CHI	105	3.20	318	3.64	3.03
SJN	11	0.34	33	0.38	3.00
SEA	178	5.43	515	5.89	2.89
SAN	170	5.18	491	5.62	2.89
ATL	136	4.15	388	4.44	2.85
NEW	217	6.61	587	6.72	2.71
BLT	180	5.49	478	5.47	2.66
CIN	171	5.21	435	4.98	2.54
NWJ	149	4.54	379	4.34	2.54
DAL	280	8.53	712	8.15	2.54
PHI	92	2.80	229	2.62	2.49
MIN	119	3.63	289	3.31	2.43
FLA	272	8.29	655	7.50	2.41
KAN	90	2.74	216	2.47	2.40
LOS	314	9.57	703	8.04	2.24
INT	278	8.47	525	6.01	1.89
TOTAL	3281	100.00	8739	100.00	

Table 4: Number and Percent of Inspections and Citations by Firm Type – FY 2006-2015					
	Inspections receiving Form 483		Number of citations		**Average number of citations per inspection**
Firm Type	n	%	n	%	
Sponsor-Investigator	143	4.40	631	7.28	**4.41**
IRB	665	20.47	2557	29.51	**3.85**
GLP	8	0.25	26	0.30	**3.25**
Sponsor	272	8.37	688	7.94	**2.53**
CI	2160	66.50	4763	54.97	**2.21**
TOTAL	3248	100.00	8665	100.00	

Table 5: Number and Percent of Citations per Violation Theme, FY 2006-2015		
Violation Theme	n	%
12 Procedures	2881	32.41
4 Consent	1427	16.05
14 Records	1317	14.82
9 Investigational Product	946	10.64
2 Approval	716	8.05
3 Communication	511	5.75
1 Adverse Events	338	3.8
11 Monitoring	231	2.6
13 Qualified Personnel	224	2.52
10 IRB Members	144	1.62
7 Financial Disclosure	84	0.94
15 Registration	41	0.46
8 Inspection	14	0.16
6 Facilities & Equipment	12	0.13
5 Declaration of Helsinki	3	0.03
TOTAL	8889	100

Figure 1: Number of Inspectons and Citations Under FDA Bioresearch Monitoring Program, FY 2006-2015



APPENDIX

Table 1: Clinical Investigator Number and Percent of Citations per Violation Theme Fiscal Year											
Violation Theme	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	TOTAL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1 Adverse Events	30 (6.26)	28 (5.51)	42 (7.20)	28 (4.56)	34 (6.10)	26 (6.07)	24 (5.45)	17 (4.79)	20 (4.46)	19 (5.34)	268 (5.62)
2 Approval	21 (4.38)	20 (3.94)	24 (4.12)	16 (2.61)	27 (4.85)	20 (4.67)	5 (1.14)	6 (1.69)	8 (1.79)	6 (1.69)	153 (3.21)
3 Communication	13 (2.71)	16 (3.15)	11 (1.89)	7 (1.14)	10 (1.80)	8 (1.87)	9 (2.05)	3 (.85)	4 (0.89)	3 (0.84)	84 (1.76)
4 Consent	87 (18.16)	118 (23.23)	127 (21.78)	138 (22.48)	124 (22.26)	80 (18.69)	88 (20.00)	86 (24.23)	103 (22.99)	72 (20.22)	1,023 (21.46)
5 Declaration of Helsinki	-	-	-	-	-	1 (.23)	-	1 (0.28)	-	-	2 (0.04)
6 Facilities & Equipment	-	-	-	-	-	-	-	-	-	-	N/A
7 Financial Disclosure	1 (0.21)	-	6 (1.03)	1 (0.16)	7 (1.26)	1 (.23)	2 (0.45)	-	4 (.89)	2 (0.56)	24 (0.50)
8 Inspection	-	1 (0.20)	-	-	-	-	2 (0.45)	1 (0.28)	-	-	4 (0.08)
9 Investigational Product	79 (16.49)	76 (14.96)	107 (18.35)	87 (14.17)	92 (16.52)	59 (13.79)	73 (16.59)	49 (13.80)	59 (13.17)	44 (12.36)	725 (15.21)
10 IRB Members	-	-	-	-	-	-	-	-	-	-	N/A
11 Monitoring	-	-	-	-	-	-	-	-	-	-	N/A
12 Procedures	174 (36.33)	176 (34.65)	194 (33.28)	240 (39.09)	200 (35.91)	162 (37.85)	171 (38.86)	140 (39.44)	185 (41.29)	159 (44.66)	1801 (37.77)
13 Qualified Personnel	-	-	-	-	-	-	-	-	-	-	N/A
14 Records	74 (15.45)	73 (14.37)	72 (12.35)	97 (15.80)	63 (11.31)	71 (16.59)	66 (15.00)	52 (14.65)	65 (14.51)	51 (14.33)	684 (14.35)
15 Registration	-	-	-	-	-	-	-	-	-	-	N/A
TOTAL n (%)	479 (10.05)	508 (10.65)	583 (12.23)	614 (12.88)	557 (11.68)	428 (8.98)	440 (9.23)	355 (7.45)	448 (9.40)	356 (7.47)	4,768

Table 2: Good Laboratory Practice Number and Percent of Citations per Violation Theme by Fiscal Year											
Violation Theme	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	TOTAL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1 Adverse Events	-	-	-	-	-	-	-	-	-	-	N/A
2 Approval	-	-	-	-	-	-	-	-	-	-	N/A
3 Communication	-	-	-	-	-	-	-	-	-	-	N/A
4 Consent	-	-	-	-	-	-	-	-	-	-	N/A
5 Declaration of Helsinki	-	-	-	-	-	-	-	-	-	-	N/A
6 Facilities & Equipment	5 (38.46)	2 (40.00)	1 (100.00)	-	-	-	-	-	-	-	8 (30.78)
7 Financial Disclosure	-	-	-	-	-	-	-	-	-	-	N/A
8 Inspection	-	-	-	-	-	-	-	-	-	-	N/A
9 Investigational Product	1 (7.69)	1 (20.00)	-	1 (100.00)	-	1 (100.00)	-	-	-	-	4 (15.38)
10 IRB Members	-	-	-	-	-	-	-	-	-	-	N/A
11 Monitoring	-	1 (20.00)	-	-	-	-	1 (100.00)	-	-	-	2 (7.69)
12 Procedures	2 (15.38)	-	-	-	-	-	-	2 (50.00)	-	-	4 (15.38)
13 Qualified Personnel	1 (7.69)	1 (20.00)	-	-	-	-	-	2 (50.00)	-	-	4 (15.38)
14 Records	4 (30.77)	-	-	-	-	-	-	-	-	-	4 (15.38)
15 Registration	-	-	-	-	-	-	-	-	-	-	N/A
TOTAL	13 (50.00)	5 (19.23)	1 (3.85)	1 (3.85)	-	1 (3.85)	1 (3.85)	4 (15.38)	-	-	26

Table 3: IRB Number and Percent of Citations per Violation Theme by Fiscal Year											
Violation Theme	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	TOTAL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1 Adverse Events	2 (0.88)	-	5 (1.69)	-	-	1 (0.33)	-	1 (.52)	1 (0.55)	-	10 (0.38)
2 Approval	42 (18.50)	70 (20.23)	53 (17.97)	68 (23.69)	59 (18.55)	51 (16.67)	47 (15.99)	34 (17.71)	34 (18.58)	24 (15.48)	482 (18.52)
3 Communication	23 (10.13)	34 (9.83)	25 (8.47)	25 (8.71)	28 (8.81)	25 (8.17)	38 (12.93)	19 (9.90)	20 (10.93)	13 (8.39)	250 (9.60)
4 Consent	24 (10.57)	48 (13.87)	23 (7.80)	27 (9.41)	27 (8.49)	29 (9.48)	23 (7.82)	12 (6.25)	22 (12.02)	13 (8.39)	248 (9.53)
5 Declaration of Helsinki	-	-	-	-	-	-	-	-	-	-	N/A
6 Facilities & Equipment	-	-	-	-	-	-	-	-	-	-	N/A
7 Financial Disclosure	-	-	-	-	-	-	-	-	-	-	N/A
8 Inspection	1 (0.44)	-	-	-	-	1 (0.33)	-	1 (.52)	-	-	3 (0.12)
9 Investigational Product	1 (0.44)	2 (0.58)	3 (1.02)	1 (0.35)	4 (1.26)	-	1 (0.34)	2 (1.04)	-	-	14 (0.54)
10 IRB Members	13 (5.73)	19 (5.49)	16 (5.42)	5 (1.74)	19 (5.97)	21 (6.86)	17 (5.78)	9 (4.69)	16 (8.74)	9 (5.81)	144 (5.53)
11 Monitoring	-	-	1 (.34)	1 (.35)	-	1 (.33)	-	-	1 (0.55)	-	4 (0.15)
12 Procedures	76 (33.48)	102 (29.48)	98 (33.22)	89 (31.01)	109 (34.28)	99 (32.35)	95 (32.31)	50 (26.04)	53 (28.96)	50 (32.26)	821 (31.54)
13 Qualified Personnel	11 (4.85)	22 (6.36)	18 (6.10)	22 (7.67)	23 (7.23)	21 (6.86)	23 (7.82)	20 (10.42)	10 (5.46)	12 (7.74)	182 (6.99)
14 Records	34 (14.98)	49 (14.16)	53 (17.97)	49 (17.07)	48 (15.09)	55 (17.97)	45 (15.31)	43 (22.40)	26 (14.21)	31 (20.00)	433 (16.63)
15 Registration	-	-	-	-	1 (.31)	2 (.65)	5 (1.70)	1 (.52)	-	3 (1.94)	12 (0.46)
TOTAL n (%)	227 (8.72)	346 (13.29)	295 (11.33)	287 (11.03)	318 (12.22)	306 (11.76)	294 (11.29)	192 (7.38)	183 (7.03)	155 (5.95)	2,603

Table 4: Sponsor Number and Percent of Citations per Violation Theme by Fiscal Year											
Violation Theme	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	TOTAL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1 Adverse Events	4 (6.90)	2 (3.17)	6 (5.41)	3 (4.23)	-	3 (5.88)	5 (5.38)	3 (3.80)	4 (4.21)	-	30 (3.90)
2 Approval	5 (8.62)	5 (7.94)	8 (7.21)	2 (2.82)	5 (4.17)	3 (5.88)	3 (3.23)	2 (2.53)	5 (5.26)	-	38 (4.94)
3 Communication	11 (18.97)	10 (15.87)	17 (15.32)	9 (12.68)	21 (17.50)	6 (11.76)	10 (10.75)	12 (15.19)	12 (12.63)	7 (25.00)	115 (14.95)
4 Consent	5 (8.62)	1 (1.59)	2 (1.80)	8 (11.27)	7 (5.83)	1 (1.96)	6 (6.45)	-	4 (4.21)	1 (3.57)	35 (4.55)
5 Declaration of Helsinki	-	-	-	-	1 (.83)	-	-	-	-	-	1 (0.13)
6 Facilities & Equipment	-	-	-	-	-	-	-	-	-	-	N/A
7 Financial Disclosure	4 (6.90)	4 (6.35)	14 (12.61)	2 (2.82)	7 (5.83)	1 (1.96)	3 (3.23)	9 (11.39)	6 (6.32)	1 (3.57)	51 (6.63)
8 Inspection	-	1 (1.59)	-	-	-	-	-	-	-	-	1 (0.13)
9 Investigational Product	9 (15.52)	11 (17.46)	11 (9.91)	10 (14.08)	19 (15.83)	4 (7.84)	6 (6.45)	12 (15.19)	9 (9.47)	1 (3.57)	92 (11.96)
10 IRB Members	-	-	-	-	-	-	-	-	-	-	N/A
11 Monitoring	11 (18.97)	13 (20.63)	20 (18.02)	15 (21.13)	23 (19.17)	15 (29.41)	24 (25.81)	14 (17.72)	18 (18.95)	8 (28.57)	161 (20.94)
12 Procedures	2 (3.45)	7 (11.11)	12 (10.81)	13 (18.31)	16 (13.33)	11 (21.57)	23 (24.73)	11 (13.92)	19 (20.00)	7 (25.00)	121 (15.73)
13 Qualified Personnel	2 (3.45)	1 (1.59)	7 (6.31)	3 (4.23)	6 (5.00)	1 (1.96)	5 (5.38)	-	5 (5.26)	-	30 (3.90)
14 Records	5 (8.62)	6 (9.52)	13 (11.71)	5 (7.04)	13 (10.83)	6 (11.76)	7 (7.53)	12 (15.19)	11 (11.58)	3 (10.71)	81 (10.53)
15 Registration	-	2 (3.17)	1 (.90)	1 (1.41)	2 (1.67)	-	1 (1.08)	4 (5.06)	2 (2.11)	-	13 (1.69)
TOTAL n (%)	58 (7.54)	63 (8.19)	111 (14.43)	71 (9.23)	120 (15.60)	51 (6.63)	93 (12.09)	79 (10.27)	95 (12.35)	28 (3.64)	769

Table 5: Sponsor-Investigator Number and Percent of Citations per Violation Theme by Fiscal Year											
Violation Theme	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	TOTAL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1 Adverse Events	3 (6.98)	2 (4.26)	7 (3.95)	5 (4.07)	4 (8.16)	2 (4.55)	1 (2.33)	3 (4.48)	-	2 (8.70)	29 (4.47)
2 Approval	3 (6.98)	4 (8.51)	12 (6.78)	5 (4.07)	-	-	1 (2.33)	5 (7.46)	2 (6.06)	1 (4.35)	33 (5.08)
3 Communication	1 (2.33)	3 (6.38)	22 (12.43)	9 (7.32)	-	9 (20.45)	5 (11.63)	2 (2.99)	2 (6.06)	2 (8.70)	55 (8.47)
4 Consent	8 (18.60)	7 (14.89)	32 (18.08)	15 (12.20)	3 (6.12)	6 (13.64)	9 (20.93)	21 (31.34)	4 (12.12)	6 (26.09)	111 (17.10)
5 Declaration of Helsinki	-	-	-	-	-	-	-	-	-	-	N/A
6 Facilities & Equipment	-	-	-	-	-	-	-	-	-	-	N/A
7 Financial Disclosure	-	-	3 (1.69)	3 (2.44)	-	-	1 (2.33)	2 (2.99)	-	-	9 (1.39)
8 Inspection	-	1 (2.13)	-	1 (0.81)	1 (2.04)	-	-	-	2 (6.06)	-	5 (0.77)
9 Investigational Product	8 (18.60)	10 (21.28)	30 (16.95)	22 (17.89)	5 (10.20)	5 (11.36)	3 (6.98)	6 (8.96)	7 (21.21)	3 (13.04)	99 (15.25)
10 IRB Members	-	-	-	-	-	-	-	-	-	-	N/A
11 Monitoring	5 (11.63)	3 (6.38)	14 (7.91)	11 (8.94)	9 (18.37)	9 (20.45)	4 (9.30)	6 (8.96)	3 (9.09)	-	64 (9.86)
12 Procedures	7 (16.28)	7 (14.89)	31 (17.51)	25 (20.33)	14 (28.57)	5 (11.36)	10 (23.26)	9 (13.43)	7 (21.21)	6 (26.09)	121 (18.64)
13 Qualified Personnel	-	1 (2.13)	2 (1.13)	3 (2.44)	-	1 (2.27)	-	-	1 (3.03)	-	8 (1.23)
14 Records	5 (11.63)	9 (19.15)	21 (11.86)	23 (18.70)	12 (24.49)	7 (15.91)	7 (16.28)	11 (16.42)	1 (3.03)	3 (13.04)	99 (15.25)
15 Registration	3 (6.98)	-	3 (1.69)	1 (0.81)	1 (2.04)	-	2 (4.65)	2 (2.99)	4 (12.12)	-	16 (2.46)
TOTAL n (%)	43 (6.63)	47 (7.24)	177 (27.27)	123 (18.95)	49 (7.55)	44 (6.78)	43 (6.63)	67 (14.29)	33 (5.08)	23 (3.54)	649

III. MANUSCRIPT 2

Research Misconduct in FDA-Regulated Clinical Trails: A Cross-Sectional Analysis of Warning Letters and Disqualification Proceedings

ABSTRACT

Background: The US Food and Drug Administration (FDA) ensures that clinical trials meet regulatory and ethical standards through inspections of researchers, also known as clinical investigators. Inspections with significant regulatory/ethical violations may result in regulatory actions, such as a warning letter or a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE). Objectives included the standardization of regulatory violation themes cited by the FDA for novel analysis of published regulatory actions rate issued by study intervention type, violation theme by intervention type, and violation theme variation between regulatory action type. **Methods**: Cross-sectional analysis of regulatory actions from October 1, 2006, to September 30, 2015, for inspections of researchers. For each FDA regulatory action, the main measure was the Code of Federal Regulations cited coded into a violation theme. Data were paired with FDA's published researcher inspection metrics to perform fiscal year analysis. **Results**: The FDA conducted 6375 domestic inspections of researchers in 2007 to 2015: 360 had significant regulatory violations, and 194 received published regulatory actions. Since 2007, rates of significant deviations have decreased. Medical device researchers had higher rates of warning letter issuance than did biologic product researchers. In contrast, medical device researchers had lower rates of NIDPOE issuance as compared to rates of biologic or pharmaceutical researchers. Lack of researcher supervision and submission of false information were cited more frequently for

NIDPOEs. **Conclusions**: Researcher compliance has significantly improved as evidenced by the reduction in regulatory actions issued by the FDA. Disqualification is more likely to occur when researchers fail to supervise the trial or false information is submitted.
Keywords: clinical investigator, Code of Federal Regulations, disqualification, inspection, regulatory action, warning letter

INTRODUCTION

Research misconduct involving clinical trials may fall into one or more of five categories: (1) the fabrication of data or results and their recording and reporting; (2) the manipulation of data so that data no longer accurately reflect what was observed; (3) plagiarism; (4) the repeated and systematic deviation from the established protocol; and/or (5) the violation of human subject rights and protections (1,2). This definition has evolved over the years as the research community has become enlightened to violations in the past, such as the human experimentation by the Third Reich during the Second World War and the Tuskegee Syphilis Study by the US Public Health Service (3,4). These two incidents of research misconduct led to the creation of three seminal works for the protection of human subjects: the 1947 Nuremberg Code, the World Medical Association's Declaration of Helsinki, and the Belmont Report (3,5,6). In addition, these documents have provided guidance to the legislative and executive branches of the US government in passing new laws, and the regulations to enforce these laws, that help protect human subjects, including the regulations enforced by the US Food and Drug Administration (FDA).

The FDA was given significant oversight of clinical trials, particularly for new medical products, via the 1962 amendments to the Federal Food, Drug and Cosmetic Act, better known as the Kefauver-Harris amendment (7). As part of these and other

amendments, the FDA ensures that clinical trials meet regulatory and ethical standards through inspections of researchers, also known as clinical investigators (8). These inspections are conducted to ensure that researchers received institutional review board (IRB) approval prior to the enrollment of human subjects, the investigational plan was adhered to, informed consent was obtained prior to human subject enrollment, and required reports were submitted to the IRB and sponsor, as well as to verify the adequacy and accuracy of clinical trial documentation (9).

Observations noted on Form FDA 483, Inspectional Observations, from the inspections of researchers are passed through multiple levels of review within the FDA. The inspection is ultimately classified into one of three categories: No Action Indicated, Voluntary Action Indicated, or Official Action Indicated. No Action Indicated is suggestive of an inspection that has found no deviations from FDA regulatory requirements. Voluntary Action Indicated is suggestive of an inspection that has found deviations from the regulatory requirements and the deviations are of concern to the FDA, but the violations are not of a nature significant enough to require action by the FDA. Official Action Indicated is indicative of an inspection in which deviations from regulatory requirements have been found, and these deviations are so egregious that regulatory action by the FDA is required (9). Deviations from regulations that reach the level of Official Action Indicated can have devastating consequences, including the death of human subjects (8,10). Regulatory actions taken as a result of an Official Action Indicated classified inspection can lead to the issuance of a warning letter or a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE), the FDA's most severe regulatory action for researchers. In addition, violations of criminal law may also be identified, resulting in criminal prosecution (8,9). The data from

inspections of clinical investigators classified as Official Action Indicated are generally not accepted by the FDA as these data are considered invalid (9).

Previously, Shetty and Saiyed compared warning letters from 2011 and 2012 to previous studies and found that the incidence of citations for failure to protect subject safety and the reporting of adverse events to the IRB were significantly different from the previously published studies. All three studies failed to include the analysis of FDA inspections with the most severe regulatory action, NIDPOEs (11-13). Another shortcoming of previous analyses was the failure to analyze regulatory actions based on intervention classification, that is, biologic product, pharmaceutical, or medical device. In addition, the lack of violation theme standardization in previous studies limited the accuracy of comparisons in that each study may have used different criteria for each violation theme. For example, failure to communicate with the IRB in one study may have been identified as a deviation from the investigational plan in another study. Despite these limitations, this study compared the most recent warning letters published, US governmental fiscal year (FY) 2013 through 2015, with the previously published studies. Novel analysis included overall inspection classification trends for available FYs (2007 through 2015); in addition, violation theme analysis of warning letters and NIDPOEs was performed. In-depth analysis by intervention classification (i.e., biologic, pharmaceutical, or medical device product) and the variation between the two regulatory actions (i.e., warning letter and NIDPOE) based on the standardized violation themes was performed (14-22). These various analyses aimed to provide insight into research misconduct observed by the FDA and potential areas for limited resources to be strategically applied with the goal of research misconduct reduction and increased data validity.

METHODS

This article does not contain any studies with human or animal subjects performed by any of the authors.

This cross-sectional study included an analysis of three FYs of data (October 1, 2012, to September 30, 2015) for researchers who received warning letters (23-49). The analysis included the comparison of these warning letters to previously published analyses: Shetty and Saiyed (January 2011 to September 2012), Gogtay *et al* (January 2005 to December 2010), and Bramstedt (January 1997 to December 2004) (11-13). In addition, this study included a novel expanded analysis of researchers who received warning letters and/or NIDPOEs, which was performed for nine FYs (October 1, 2006, to September 30, 2015) (23-217).

All warning letters and NIDPOEs were manually searched from the FDA's publicly available databases and categorized by violation theme on April 25 to 29, 2016. The categories were subsequently verified on June 22, 2016, with regulatory actions subclassified based on US governmental FY; intervention type based on the center issuing the regulatory action, that is, Center for Biologic Evaluation and Research (CBER) for biologic products, Center for Drug Evaluation and Research (CDER) for pharmaceuticals, or Center for Device and Radiological Health (CDRH) for medical devices; and the type of regulatory action, that is, warning letter versus NIDPOE. An individual (C.A.G.) trained in FDA inspections and regulations coded each regulatory action into its respective violation theme based on the Code of Federal Regulations (CFR) cited in each regulatory action (Table 1). Depending on applicability, Chi Square or Fisher's exact test was performed, with significance set at 5%, along with 95% confidence intervals, using SAS software version 9.4 (SAS Institute Inc.).

RESULTS

Between US governmental FY 2007 and 2015, the FDA conducted 6,375 inspections of researchers within the United States and its territories, of which 360 (6%) received Official Action Indicated classification, that is, research misconduct. Of these 360 Official Action Indicated classified inspections, 155 (43%) received a warning letter, and 39 (11%) received a NIDPOE. The public database did not include the final action taken by the FDA for 166 (46%) of the 360 Official Action Indicated inspections.

Standardization of Violation Themes

In two of the three previous studies, designated regulatory noncompliance (violation theme 4 [VT4]) was used as a miscellaneous category when the researchers were unable to classify the cited violation into one of the other violation themes. This violation theme was determined to be unnecessary during the development of the standardized violation themes for this study, as all violations cited represent noncompliance with the regulations and all cited violations could be categorized into a violation theme based on the CFR cited (Table 1); thus, the regulatory noncompliance violation theme (VT4) was eliminated from this analysis. In addition, the violation theme for failure to protect subject safety/report adverse events to IRB (VT7) and failure to communicate with the IRB (VT8) used in previous publications were merged for this analysis, given that the sole function of an IRB is to ensure human subject safety.

Warning Letter Violation Theme Comparison

For FY 2013 to 2015, 27 warning letters were issued to researchers. The categorization of citations in those warning letters is presented in Table 2. Statistical analysis found significant deviations in the informed consent process (VT3), regulatory noncompliance (VT4), and failure to protect subject safety/report adverse events to IRB

(VT7) for FY 2013 to 2015 as compared to the previous three studied time periods. The combination of failure to protect subject safety/report adverse events to IRB (VT7) and failure to communicate with the IRB (VT8) were also significantly different between all four studies ($P < 0.01$).

Deviations regarding the informed consent process (VT3) and regulatory noncompliance (VT4) were not significantly different from those reported in the Shetty and Saiyed study (13), indicating the more recent data is showing a decrease in the rate of citations for these two violation themes. Whether failure to communicate with the IRB (VT8) and failure to protect subject safety/report adverse events to IRB (VT7) were combined or not, a significant reduction was shown in the citation of IRB-related noncompliance as compared to the Shetty and Saiyed data. Of note is that in the Shetty and Saiyed study, failure to personally supervise the study (VT6) was significantly different from the previous studies, but this is not the case in the current analysis.

Warning Letter Violation Theme Comparison by Intervention

For FY 2013 to 2015, 22 warning letters were issued to researchers for interventions related to biologic or pharmaceuticals, while five were issued for medical device interventions. The categorization of citations in the warning letters is presented in Table 2. Shetty and Saiyed (13) provided sub-analysis based on the part of the CFR cited, 21 CFR 312 for biologic and pharmaceutical interventions and 21 CFR 812 for medical device interventions.

Three violation themes were significantly different for biologic and pharmaceutical interventions between the Shetty and Saiyed study (13) and the current study: regulatory noncompliance (VT4), failure to personally supervise the study (VT6), and failure to protect subject safety/report adverse events to IRB (VT7). When failure to

protect subject safety/report adverse events to IRB (VT7) is combined with failure to communicate with the IRB (VT8), the incidence of violation themes was also significantly different (n = 2, P = 0.008). In all four of these comparisons, a decrease in the rate of citations was observed between the current study and the Shetty and Saiyed study, showing an improvement in regulatory compliance over time.

A review of medical device warning letters showed the incidence of two violation themes was significantly different: regulatory noncompliance (VT4) and failure to protect subject safety/report adverse events to IRB (VT7). The combination of failure to protect subject safety/report adverse events to IRB (VT7) and failure to communicate with the IRB (VT8) also showed a significant difference (n = 0, P = 0.048). The rate of citation for these three comparisons represents a decrease in the frequency between the Shetty and Saiyed study (13) and the current data.

FY 2007 to 2015: Inspection Classification Analysis

The classification of researcher inspections by FY is presented in Table 3. Official Action Indicated classified inspections, the most serious FDA classification, have significantly decreased over these nine FYs. When year-over-year change for all inspection classifications is compared, FY 2009, 2011, 2012, and 2015 had a significantly lower number of inspections classified as Official Action Indicated as compared with their preceding years. In contrast, a significantly higher number of inspections were classified as Official Action Indicated during FY 2010 and 2014 as compared with their preceding years. However, the overall number of inspections classified as Official Action Indicated decreased from FY 2007 through 2015.

FY 2007 to 2015: Warning Letter Analysis

For biologic interventions, the CBER issued 10 warning letters out of 768 inspections (1%); the CDER issued 89 warning letters out of 3620 pharmaceutical inspections (2%); and for medical device interventions, the CDRH issued 56 warning letters out of 1693 inspections (3%). Comparison analysis determined the rate of warning letter issuance to be significantly different between the intervention types (P = 0.0120). Detailed analysis determined that medical device clinical trial researchers were more likely to receive a warning letter than were biologic clinical trials (P = 0.0043).

Warning letter violation theme citation by intervention type is presented in Table 4. Failure to personally supervise the study (VT6) was found to be significantly different by intervention type. Inter-intervention analysis determined that the incidence of VT6 was significantly lower for medical device trials than for pharmaceutical clinical trials (P = 0.0074). Warning letter violation theme citation by FY is presented in Table 5. Analysis found that deviations with the informed consent process (VT3) were significantly different and the rate of citation decreased over time. A comparison of change from one year to the year immediately following it determined that FY 2008 showed a significant difference (P = 0.016), with an increase in the rate of citation over FY 2007.

FY 2007 to 2015: NIDPOE Analysis

Biologic intervention researchers were issued eight NIDPOEs out of 768 inspections (1%); thirty NIDPOEs out of 3620 inspections (1%) were issued to pharmaceutical researchers; and medical device researchers were issued one NIDPOE out of 1,693 inspections (<1%). Analysis determined that the rate of issuance was significantly different between the different intervention types (P = 0.0002). Inter-

intervention analysis determined that medical device researchers were significantly less likely to receive a NIDPOE as compared with biologic researchers (P = 0.0006) or with pharmaceutical researchers (P = 0.0001).

Violation theme citation for NIDPOEs based on intervention is presented in Table 4. Analysis of NIDPOEs by violation themes by interventions found that submission of false information to the FDA and sponsor (VT9) was significantly different. Inter-intervention analysis determined that biologic intervention researchers were statistically less likely to be cited for this violation theme as compared with pharmaceutical researchers (P = 0.0337). Violation theme citation for NIDPOEs by FY is presented in Table 5. Analysis found that failure to maintain adequate/ accurate source documentation (VT2) significantly decreased over time. A comparison of change from one FY to another determined that this violation theme was cited significantly less in FY 2015 than in FY 2014 (P = 0.0476).

FY 2007 to 2015: Warning Letter/NIDPOE Analysis

Violation theme by regulatory action is presented in Table 6. The incidence of failure to personally supervise the study (VT6) and submission of false information to the FDA and sponsor (VT9) were significantly different between warning letters and NIDPOEs, with NIDPOEs more likely to be cited for these regulatory violations.

DISCUSSION

As medical advances come quicker with each passing year, one of the most significant hurdles to getting these advances to market is approval by the FDA. Approval may come only after clinical trials have been reviewed by the agency and a decision is made that the safety of the medical advancement is acceptable for the given indication and the treatment is efficacious. Researchers must ensure that the clinical trial is

performed in accordance with ethical and regulatory requirements, so that the data obtained are valid and suitable for review by the agency and human subjects are adequately protected.

The findings in this study provide evidence that researchers are striving to improve compliance with ethical and regulatory standards if we are to assume that no significant internal policy changes have occurred within the FDA for the inspection process and inspection classification. We have shown that research misconduct by researchers of FDA regulated clinical trials has decreased over the past nine FYs. In addition, assuming each FDA center issues regulatory actions utilizing the same criteria, biologic and pharmaceutical researchers can improve their operations to bring the most egregious violations into a compliance rate closer to that of researchers of medical device interventions.

Improvement with compliance ultimately rests not only on the researchers but also on all parties. Sponsors and IRBs are also responsible for ensuring data validity and, most important, subject safety. Researchers can achieve this through proper education of their staff and supervision of the clinical trial. Failure to properly supervise a clinical trial may result in a researcher being disqualified and the data generated being eliminated from consideration by the agency. The time and effort of the enrolled subjects are not recognized, and the subjects may have been exposed to unnecessary risk in improperly conducted clinical trials. Disqualification is also extended to researchers who submit, or allow submission of, false information.

This study was focused on FDA inspections of clinical researchers and fails to analyze the role sponsors, monitors, and IRBs play in ensuring subject safety and regulatory compliance. While an improvement over previous studies, the current study

has several limitations. The regulatory actions used to describe Official Action Indicated classified inspections in this study represented only 54% of the 360 domestic Official Action Indicated classified inspections; thus, we do not have a complete representation of the violation themes cited in inspections of researchers engaged in research misconduct. This lack of complete representation was due to the limits of the FDA's publicly available databases. In addition, the current data do not include inspections outside of the United States and its territories because no regulatory actions were contained within the FDA's publicly available databases for foreign researchers; thus, of the 1,016 inspections conducted outside of the United States and classified between FY 2008 and 2015, 19 (2%) were classified Official Action Indicated and were not captured in this study.

The FDA may be able to improve compliance by releasing additional detailed information about researcher noncompliance. This additional information could include all other regulatory actions initiated that are not included in currently available public databases. In addition, detailed analysis could be performed to identify other clinical trial parameters that may have increased rates of noncompliance, such as geographic location of the clinical trial, type of facility performing the clinical trial, and/or medical specialty of the clinical trial. These additional parameters may provide greater insight to the understanding of researcher noncompliance and help improve compliance, thus increasing the assurance of data validity and, above all, subject safety.

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TABLES AND FIGURES

Table 1: Violation Theme Standardization with Code of Federal Regulations						
VT	**Violation Theme**	**CFR**				
1	Deviation from investigational plan	312.60 812.150(a)(4)	312.60[Rig]	812.100	812.110[Rig]	812.110(b)
2	Failure to maintain adequate/accurate source documentation	312.62(b) 812.140(a)(3)	312.62(c) 812.140(a)(3)(ii)	312.305(c)(4) 812.140(a)(4)	812.140(a) 812.140(a)(5)	812.140(a)(1) 812.140(d)
3	Informed consent	50.20 50.27 812.100[50]	50.23 50.27(a) 812.110(a)	50.25 50.27(b) 812.140(a)(3)(i)	50.25(a) 50.55(f) 812.150(b)(5)	50.25(b) 312.60[50]
4	Regulatory non-compliance	N/A				
5	Violations related to investigational product	312.61 812.140(a)(2)	312.62(a) 812.140(a)(2)(i)	312.69 812.140(a)(2)(ii)	312.305(c)(1) 812.140(a)(2)(iii)	812.7(d)
6	Failure to personally supervise the study	312.60[Sup]	812.110(c)			
7	Failure to protect subject safety/report adverse events to IRB	812.150(a)(1)	812.150(a)(2)	812.150(a)(3)		
8	Failure to communicate with the IRB	56.103	312.66			
9	Submission of false information to the FDA and Sponsor	312.70	312.70(a)	812.119	812.119(a)	
10	Failure to communicate with sponsor	312.64(b)	812.150(a)(6)			
11	Financial Disclosure	812.110(d)				

Abbreviations: CFR – Code of Federal Regulation Title 21 Part; [Rig] – Rights, Safety, and Welfare of the Subject; [50] – Informed Consent of Subjects; [Sup] – Supervision of Clinical Trial

Table 2: Warning Letters Issued to Researchers – Violation Theme Multi-Study Comparison												
		Biologic, Medical Device, and Pharmaceutical Warning Letters					**Biologic & Pharmaceutical Warning Letters**			**Medical Device Warning Letters**		
VT	**Violation Theme**	**Current N=27 (%)**	**Shetty N=20 (%)**	**Gogtay N=129 (%)**	**Bramstedt N=36 (%)**	**p-value**	**Current N=22 (%)**	**Shetty N=16 (%)**	**p-value**	**Current N=5 (%)**	**Shetty N=4 (%)**	**p-value**
1	Deviation from investigational plan	24 (89)	19 (95)	104 (81)	32 (89)	0.327	21 (95)	15 (94)	>0.99	5 (100)	4 (100)	-
2	Failure to maintain adequate/accurate source documentation	16 (59)	8 (40)	75 (58)	-	0.296	13(59)	7 (44)	0.512	4 (80)	1 (25)	0.201
3	Informed consent	9 (33)	7 (35)	62 (48)	24 (67)	0.034	5 (23)	5 (31)	0.713	4 (80)	2 (50)	0.524
4	Regulatory non-compliance	0	8 (40)	50 (39)	-	<0.01	0	4 (25)	0.025	0	4 (100)	0.008
5	Violations related to investigational product	6 (22)	3 (15)	38 (29)	-	0.413	5 (23)	3 (19)	>0.99	2 (20)	0	0.444
6	Failure to personally supervise the study	3 (11)	6 (30)	27 (21)	2 (6)	0.051	2 (9)	6 (38)	0.0498	0	0	0
7	Failure to protect subject safety/report adverse events to IRB	0	11 (55)	30 (23)	17 (47)	<0.01	0	8 (50)	0.003	0	3 (75)	0.048
8	Failure to communicate with the IRB	2 (7)	2 (10)	-	-	>0.99	2 (9)	2 (13)	>0.99	0	0	-
9	Submission of false information to the FDA and Sponsor	1 (4)	1 (5)	-	-	>0.99	0	1 (6)	0.421	0	0	-

Abbreviations: FDA – U.S. Food and Drug Administration; IRB – Institutional Review Board; VT – Violation Theme; p-value < 0.05

Table 3: Inspection Classification										
Classification	**FY07 N=592 (%)**	**FY08 N=705 (%)**	**FY09 N=867 (%)**	**FY10 N=739 (%)**	**FY11 N=611 (%)**	**FY12 N=572 (%)**	**FY13 N=664 (%)**	**FY14 N=803 (%)**	**FY15 N=822 (%)**	**Total N=6,375 (%)**
NAI	308 (52)	353 (50)	416 (48)	340 (46)	324 (53)	320 (56)	372 (56)	466 (58)	526 (64)	3,425 (54)
VAI	237 (40)	289 (41)	399 (46)	333 (45)	250 (41)	235 (41)	279 (42)	297 (37)	271 (33)	2,590 (40)
OAI	47 (8)	63 (9)	52 (6)	66 (9)	37 (6)	17 (3)	13 (2)	40 (5)	25 (3)	360 (6)
p-value	-	0.521	0.026	0.025	0.048	0.011	0.248	0.002	0.046	<0.01

Abbreviations: FY – Fiscal Year; NAI – No Action Indicated; OAI – Official Action Indicated; VAI – Voluntary Action Indicated; p-value < 0.05

Table 4: Violation Themes by Regulatory Action and Study Test Article									
		Warning Letter				**NIDPOE**			
VT	**Violation Theme**	**Biologic N=10 (%)**	**Pharmaceutical N=89 (%)**	**Medical Device N=56 (%)**	**p-value**	**Biologic N=8 (%)**	**Pharmaceutical N=30 (%)**	**Medical Device N=1 (%)**	**p-value**
1	Deviation from investigational plan	9 (90)	84 (94)	52 (93)	0.559	7 (88)	28 (93)	1 (100)	0.556
2	Failure to maintain adequate/accurate source documentation	8 (80)	57 (64)	39 (70)	0.576	7 (88)	23 (77)	1 (100)	0.730
3	Informed consent	6 (60)	36 (40)	33 (59)	0.071	4 (50)	10 (33)	0 (0)	0.637
5	Violations related to investigational product	4 (40)	30 (34)	13 (23)	0.279	4 (50)	13 (43)	0 (0)	>0.99
6	Failure to personally supervise the study	0 (0)	22 (25)	4 (7)	0.008	1 (13)	15 (50)	0 (0)	0.109
7-8	Failure to protect subject safety/report adverse events to IRB/ communicate with the IRB	3 (30)	31 (35)	19 (34)	>0.99	5 (63)	7 (23)	0 (0)	0.079
9	Submission of false information to the FDA and Sponsor	0 (0)	1 (1)	0 (0)	>0.99	2 (25)	22 (73)	1 (100)	0.034
10	Failure to communicate with sponsor	0 (0)	3 (3)	1 (2)	>0.99	0 (0)	0 (0)	0 (0)	-
11	Financial Disclosure	0 (0)	0 (0)	1 (2)	0.426	0 (0)	0 (0)	0 (0)	-

Abbreviations: NIDPOE – Notice of Initiation of Disqualification Proceedings and Opportunity to Explain; VT – Violation Theme; p-value < 0.05

Table 5: Violation Themes by Regulatory Action and Fiscal Year												
Regulatory Action	**VT**	**Violation Theme**	**FY07 N=27 (%)**	**FY08 N=30 (%)**	**FY09 N=26 (%)**	**FY10 N=22 (%)**	**FY11 N=13 (%)**	**FY12 N=10 (%)**	**FY13 N=9 (%)**	**FY14 N=14 (%)**	**FY15 N=4 (%)**	**p-value**
WL	1	Deviation from investigational plan	24 (89)	28 (93)	24 (92)	22 (100)	13 (100)	8 (80)	9 (100)	13 (93)	4 (100)	0.545
	2	Failure to maintain adequate/ accurate source documentation	17 (63)	25 (83)	19 (73)	14 (64)	7 (54)	5 (50)	6 (67)	10 (71)	1 (25)	0.243
	3	Informed consent	12 (44)	23 (77)	15 (58)	8 (36)	3 (23)	5 (50)	5 (56)	4 (29)	0 (0)	0.005
	5	Violations related to investigational product	9 (33)	10 (33)	10 (38)	8 (36)	2 (15)	2 (20)	1 (11)	5 (36)	0 (0)	0.732
	6	Failure to personally supervise the study	6 (22)	3 (10)	3 (12)	5 (23)	5 (38)	2 (20)	0 (0)	2 (14)	0 (0)	0.347
	7-8	Failure to protect subject safety/communicate with IRB	11 (41)	11 (37)	10 (38)	10 (45)	6 (46)	3 (30)	1 (11)	1 (7)	0 (0)	0.157
	9	Submission of false information to the FDA and Sponsor	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)	0.148
	10	Failure to communicate with sponsor	2 (7)	1 (10)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.954
	11	Financial Disclosure	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	>0.99

NIDPOE	VT	Violation Theme	FY07 N=6 (%)	FY08 N=7 (%)	FY09 N=5 (%)	FY10 N=5 (%)	FY11 N=5 (%)	FY12 N=4 (%)	FY13 N= 0	FY14 N=5 (%)	FY15 N=2 (%)	p-value
	1	Deviation from investigational plan	6 (100)	7 (100)	5 (100)	5 (100)	5 (100)	3 (75)	-	3 (60)	2 (100)	0.080
	2	Failure to maintain adequate/ accurate source documentation	6 (100)	6 (86)	3 (60)	3 (60)	5 (100)	3 (75)	-	5 (100)	0 (0)	0.035
	3	Informed consent	5 (83)	3 (43)	0 (0)	1 (20)	2 (40)	2 (50)	-	1 (20)	0 (0)	0.135
	5	Violations related to investigational product	3 (50)	4 (57)	3 (60)	3 (60)	1 (20)	2 (50)	-	1 (20)	0 (0)	0.697
	6	Failure to personally supervise the study	3 (50)	4 (57)	4 (80)	2 (40)	1 (20)	1 (25)	-	0 (0)	1 (50)	0.255
	7-8	Failure to protect subject safety/communicate with IRB	1 (17)	3 (43)	2 (40)	0 (0)	3 (60)	2 (50)	-	1 (20)	0 (0)	0.469
	9	Submission of false information to the FDA and Sponsor	5 (83)	3 (43)	5 (100)	4 (40)	2 (40)	1 (25)	-	4 (40)	1 (50)	0.173
	10	Failure to communicate with sponsor	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-	0 (0)	0 (0)	-
	11	Financial Disclosure	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-	0 (0)	0 (0)	-

Abbreviations: FY – Fiscal Year; NIDPOE – Notice of Initiation of Disqualification Proceedings and Opportunity to Explain; VT – Violation Theme; WL – Warning Letter; p-value < 0.05

Table 6: Violation Themes by Regulatory Action					
VT	**Violation Theme**	**Warning Letter N=155 (%)**	**NIDPOE N=39 (%)**	**p-value**	**95% Confidence Interval**
1	Deviation from investigational plan	145 (94)	36 (92)	0.727	-0.163, 0.188
2	Failure to maintain adequate/accurate source documentation	104 (67)	31 (79)	0.133	-0.295, 0.054
3	Informed consent	75 (48)	14 (36)	0.162	-0.053, 0.295
5	Violations related to investigational product	47 (30)	17 (44)	0.115	-0.307, 0.041
6	Failure to personally supervise the study	26 (17)	16 (41)	0.001	-0.413, -0.069
7-8	Failure to protect subject safety/report adverse events to IRB/ communicate with the IRB	53 (34)	12 (31)	0.686	-0.143, 0.207
9	Submission of false information to the FDA and Sponsor	1 (>1)	25 (64)	<0.01	-0.776, -0.470
10	Failure to communicate with sponsor	4 (3)	0	0.585	-0.150, 0.201
11	Financial Disclosure	1 (>1)	0	>0.99	-0.169, 0.182

Abbreviations: NIDPOE – Notice of Initiation of Disqualification Proceedings and Opportunity to Explain; VT – Violation Theme; p-value < 0.05

IV. MANUSCRIPT 3

Effects of Including Studies Identified by the U.S. Food and Drug Administration as having Research Misconduct on Results of Meta-Analyses: The example of the apixaban trials

ABSTRACT

Background: Previous reports have identified publications in peer-reviewed journals that have used data from studies identified by the U.S. Food and Drug Administration (FDA) as having significant regulatory and Good Clinical Practice (GCP) lapses including falsified data. Furthermore, yearly the FDA cites over 40 individual research sites with significant lapses. Despite this, the effect on the results of meta-analyses which include reports from these problematic studies has not been previously studied. The objective of this study was to assess the effect of including clinical trials with significant regularly and GCP lapses in meta-analyses on results of meta-analyses. **Methods**: A systematic review was performed of meta-analyses of studies of "apixaban" that utilized published clinical trial results of apixaban from clinical trials that the FDA identified as having significant regulatory and GCP violations. Further, a sensitivity analyses was performed to assess the effect of including these problematic publications on the results of the meta-analyses. In addition, previously identified rivaroxaban studies with significant regulatory and GCP violations were included with the apixaban studies in an expanded sensitivity analysis. Sensitivity analysis was performed for each meta-analysis obtained to assess both the qualitative and quantitative effects of including publications of apixaban trials with significant FDA violations on meta-analysis results, i.e. odds ratio point estimate, upper 95% confidence interval, and lower 95% confidence interval. **Results**: Of the 1,162 publications that were retrieved, 99 statistical analyses from 22 meta-analyses were

available for sensitivity analyses. For thirty-two analyses (32.3%), there was a change in the conclusions made from the originally published statistical analyses. Changes could be categorized into one of four sub-categories: (1) the odds ratio point estimate for five analyses (5.1%) crossed 1.0; (2) 22 analyses (22.2%) had the upper confidence interval cross 1.0; (3) both the odds ratio point estimate and the upper confidence interval crossed 1.0 for four analyses (4.0%); and (4) one analysis (1.0%) had the lower confidence interval cross 1.0. Sub-group analyses resulted in statistical changes for 14 analyses (43.8%) while full analyses changed for 18 (26.9%). Model analysis found 18 fixed effects models (43.9%) and 14 random effects models (24.1%) with statistical changes. One-way repeated measure ANOVA of apixaban sensitivity analysis had no statistically significant results. When meta-analyses had both apixaban and rivaroxaban studies removed with significant deviations related to data, no statistical changes were observed.

Conclusions: The exploding field of meta-analyses has provided a concise and compelling method for the dissemination of medical intervention knowledge; however, this method depends on the quality of the studies that are included. A robust sensitivity analysis that considers data quality from available sources can help ensure calculation of the best estimates.

Keywords: FDA; falsified data; meta-analysis; research misconduct; sensitivity analysis; systematic review

INTRODUCTION

The consolidation of medical knowledge through meta-analyses of randomized clinical trials is considered to provide the most compelling evidence for the efficacy of medical interventions (1). Clinical trials conducted in support of medical product applications with the U.S. Food and Drug Administration (FDA) are considered of the

highest quality and are routinely published in the most prestigious medical journals and are subsequently included in meta-analyses; however, the data generated from these clinical trials may be of questionable quality if not performed in compliance with applicable regulations or Good Clinical Practices (GCP) (2). The FDA ensures clinical trials under its purview meet both regulatory and ethical standards via inspections of clinical investigators in order to identify clinical trials that were performed in such a manner that the data are rendered invalid (3). Between October 01, 2006 and September 30, 2015, the FDA conducted 6,375 inspections of clinical investigators within the U.S.; in 2,160 of these inspections, deviations from regulatory requirements were found (4-5). Of the 6,375 inspections, 360 (6%) were considered to have deviated significantly from regulatory violations so that the agency was forced to take regulatory action against the Clinical Investigator (5).

Regulatory actions such as “Warning Letters” and “Notice of Initiation of Disqualification Proceedings and Opportunity to Explain” (NIDPOE) are typically only initiated by the FDA when an inspection of a Clinical Investigator finds significant violations of the regulations that place participants at unreasonable and significant risk of illness or injury; seriously compromise their rights; and/or affect the integrity or reliability of the trial’s data (6). An analysis of Warning Letters and NIDPOEs showed that over 93% cited considerable deviations from the established protocol (5). In addition, data from inspections with these significant regulatory actions are generally not accepted by the FDA, and thus will not be allowed for consideration in the application process for a new product (6). A cross reference of Warning Letters and NIDPOEs issued to clinical investigators by the FDA and other sources with published manuscripts resulted in the identification of 78 publications from 57 different clinical trials that received these

regulatory actions from the FDA (2). Studies of two pharmaceuticals, apixaban and rivaroxaban were identified to have included falsified data, and yet there were no less than seven publications for each of these pharmaceutical agents that included these studies despite the warning from the FDA to the clinical investigators prior to publications (2). These two pharmaceutical agents, apixaban and rivaroxaban, were identified to have the most publications with significant regulatory and GCP violations (2).

The gold standard for meta-analyses has been established by the Cochrane Collaboration through their publication of the *Cochrane Handbook for Systematic Reviews of Interventions* (1,7-8). However, it has been shown that findings from meta-analyses can be highly unstable depending on the methods used (9). Thus, the Cochrane method requires that studies be assessed for quality and that sensitivity analysis be performed to ensure that findings are robust against arbitrary and unclear decisions (8). The example given by the handbook is to consider re-analysis of studies for which information is complete (8). We are unaware of any publication that has performed these sensitivity analyses using FDA inspection results, i.e. study protocol noncompliance. Thus, we aimed to assess the effects of study noncompliance, particularly falsified data, on published meta-analyses.

METHODS

This protocol-based systematic review and sensitivity analysis (PROSPERO: CRD42017055627) was conducted in accordance with the *Cochran Handbook for Systematic Reviews of Interventions* (7). This study was deemed exempted from institutional review board or ethics committee oversight by Florida International

University's institutional review board because this study did not involve direct human subject participation and only included data from publicly available sources.

Data Sources and Searches

One investigator (CAG) with the assistance of a librarian, developed, piloted, and executed the established search criteria (Table 1 in the Appendix). Databases searched included PubMed, EMBASE, CINAHL, Cochrane Library's CENTRAL, and Web of Science's BIOSIS from inception of each database to February 20, 2017. No restrictions were placed as to the location or language of the meta-analysis included. Each unique study record retrieved was assigned a unique identification number.

Study Selection

Studies were included if the publication was a meta-analysis for human clinical trials that included 'apixaban' as an intervention; rivaroxaban studies would be identified later to be included in additional sensitivity analyses. Meta-analyses from observational studies were not included. Meta-analyses were excluded if the publication was a network meta-analysis or if the apixaban clinical trial(s) included in the analysis was not one of the publications identified by Sefie, the only publication to have performed an exhaustive search of FDA documents identifying publications with significant regulatory and GCP violations (2). Two investigators (CAG and LNG) independently evaluated all records for eligibility (Table 2 in the Appendix) and disagreements were resolved by an independent third reviewer (ALR).

Synthesis

Sensitivity analyses were conducted to evaluate the effect of invalid data on the results of each meta-analysis via qualitative (i.e. odds ratio and 95% confidence interval

were examined qualitatively in order to determine if the new summary estimates changed in significance or in direction) and quantitative analysis. Point estimate and 95% confidence intervals, along with meta-analysis statistics (heterogeneity values [χ^2, degrees of freedom, p-value, I^2 value] and overall effect [z-test value and p-value]), were calculated using either a fixed or random effects model outlined in each meta-analysis publication, both with and without the data identified in publications in which the FDA cited the Clinical Investigator for significant regulatory violations (10-23). In order to provide comparison, all point estimates and 95% confidence intervals were calculated in odds ratio, regardless of the cited meta-analysis' original method. In order to obtain the weighted odds ratios, the Mantel-Hanszel statistical method was used for all meta-analyses, regardless of the method used by the original publication.

To perform qualitative analysis comparison, both iterations of the meta-analysis, i.e. the summary estimates and 95% confidence interval, were examined qualitatively in order to determine if the new summary estimates changed in significance or in direction. For quantitative analysis, one-way repeated measure ANOVA was performed to compare both iterations of the meta-analysis using the F-test statistic set at 0.05.

All meta-analyses were performed using Review Manager software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). One-way repeated ANOVA calculations were performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

General Characteristics of the Meta-Analyses

Of the 1,162 records retrieved, 64 meta-analyses met inclusion criteria. Refer to Figure 1 for the flow diagram of publication selection. Only 22 meta-analyses had more than one apixaban study which allowed for sensitivity analysis to be performed with apixaban contributing data after the removal of the previously identified study with data validity issues. The included studies were all published in English between 2012 and 2017; each meta-analysis' characteristics are reported in TABLE 1 (24-45). Concisely, the median number of clinical trials contributing to the full meta-analysis estimates in each publication was 9 (range: 2-28) with the InCite journal impact factor median being 5.658 (range: 3.154-17.202) (46). In addition, the median weight of the publication with data validity issues included in each meta-analysis calculation was 37.3% (range: 7-100%).

Qualitative Apixaban Sensitivity Analysis: Total Meta-Analysis

There were 101 analyses from the 22 meta-analyses ultimately included; however, two calculations lacked sufficient data to perform sensitivity analysis and attempts to contact the authors were unsuccessful. Of the 99 remaining analyses as presented in (Table3 in the Appendix), 32 analyses (32.3%) yielded results that would change the conclusions of the initial meta-analysis; these changes can be classified into four different categories (Figure 2): (1) the odds ratio point estimate for five analyses (5.1%) crossed 1.0, in that the odds ratio went from favoring the intervention to favoring the control; (2) 22 analyses (22.2%) had the upper 95% confidence interval cross 1.0, thus the analysis

went from statistically significant in favor of the intervention to lacking statistical significance; (3) both the odds ratio point estimate and the upper 95% confidence interval crossed 1.0 for four analyses (4.0%), the analysis went from statistically favoring the intervention to favoring the control without statistical significance; and (4) one analysis (1.0%) had the lower 95% confidence interval cross 1.0, thus the study became statistically significant in favor of the control once the study with data validity issues was removed.

Qualitative Apixaban Sensitivity Analysis: Full vs. Sub-Group Meta-Analysis

The analyses were classified based on the level of the analysis, e.g. were the analyses a sub-group of the full analysis or the full analysis itself. Thirty-two analyses were sub-groups with 14 analyses (43.8%) having a noteworthy change in the results. Three analyses (9.4%) had the odds ratio crossing 1.0. The upper confidence interval crossed 1.0 for eight analyses (25.0%). Both the odds ratio point estimate and the upper confidence interval crossed 1.0 for two analyses (6.3%). One analysis (3.1%) had the lower confidence interval cross 1.0.

The remaining 67 analyses were considered to be full analyses, i.e. the final point estimate for the investigation. The final analysis level had 18 analyses (26.9%) suffer from considerable changes in the results. Two analyses (3.0%) had the odds ratio cross 1.0. The upper 95% confidence interval crossed 1.0 for 14 analyses (20.9%). Both the odds ratio point estimate and the upper 95% confidence interval crossed 1.0 for two analyses (3.0%).

Qualitative Apixaban Sensitivity Analysis: Effects Model Meta-Analysis

Analyses were also classified based on the models used in the original analysis, e.g. whether the original meta-analysis used fixed or random effects models. Forty-one analyses used the fixed effect model, of which 18 analyses (43.9%) suffered from a statistical change. Two analyses (4.9%) had the odds ratio cross 1.0. The upper 95% confidence interval crossed 1.0 for 14 analyses (34.1%). Both the odds ratio point estimate and the upper 95% confidence interval crossed 1.0 for two analyses (4.9%).

Random effects model was used in the other 58 analyses, of which 14 analyses (24.1%) resulted in a change in the statistical results. Three analyses (5.2%) had the odds ratio cross 1.0. The upper 95% confidence interval crossed 1.0 for eight analyses (13.8%). Both the odds ratio point estimate and the upper 95% confidence interval crossed 1.0 for two analyses (3.4%). One analysis (1.7%) had the lower 95% confidence interval cross 1.0.

Quantitative Apixaban Sensitivity Analysis: Total Metal-Analysis

No analysis was found to be statistically different using the one-way repeated measures ANOVA testing (Table3 in the Appendix).

Apixaban & Rivaroxaban Sensitivity Analysis: Total Meta-Analysis

There were seven analyses from four meta-analyses included (Table4 in the Appendix); however, one calculation lacked sufficient data to perform sensitivity analysis, and attempts to contact the authors were unsuccessful. Of the remaining six analyses, none of the analyses was observed to have results that would change the

conclusions initially made. In addition, one-way repeated measures ANOVA testing failed to find a statistically significant difference (Table4 in the Appendix).

DISCUSSION

Systematic reviews and meta-analyses are considered the gold standard for medical interventions, especially when performed using the Cochrane method (1,7-8). Still, given the complexity and instability in the reporting of data in medical literature much debate and study continues with meta-analyses. The issue at hand is the contradictory nature of meta-analyses, inclusion of all available data while obtaining the "best estimate" (47). Some have concluded that in order to obtain this "best estimate" that all data obtained in support of FDA applications for new medical products should be included (48). However, our study contradicts this assertion.

Ioannidis has argued that most research findings are false, but this claim is purely from a design point of view and doesn't address that even a perfectly designed study can suffer from poor execution resulting in data integrity issues (49). In this study, we analyzed the effect that data of questionable integrity, particularly falsified data, from one pharmaceutical agent may have on conclusions made from meta-analyses. Conclusions made by the original meta-analyses were affected considerably by the inclusion of questionable data. The effects ranged from the change in statistical significance to the change in overall outcome, or a combination of both, and occurred in 32.3% of the analyses studied. This is in line with previous literature in which 33.7% of researchers admitted to "questionable research practices" (50). However, the quantitative sensitivity analysis found no changes in significance. This was not unexpected as there were only two points (with falsified study data and without falsified study data) of three values

(odds ratio, 95% lower confidence interval, and 95% upper confidence interval) with the changes in values exceedingly small, typically less than a 0.5 change in value.

Effects on conclusions made by previous meta-analyses occurred regardless of the amount of contribution the questionable publication had; study weights ranged from 13.1% to 99.6%. In addition, the level of analysis and the models used could not shield the meta-analysis from these effects with changes to statistical results in 24% or more of the analyses' sub-categories. Sub-group analyses and fixed effects model are less robust given the effect of falsified data, this is expected given the limitations with using fewer studies, i.e. sub-group analysis, and less robust assumption and statistical analyses, i.e. fixed effects modeling. All of these results were derived from one study, the ARISTOTLE study of apixaban. However, another pharmaceutical, rivaroxaban, was studied in the same class of pharmaceuticals that also suffered from significant research conduct issues, including data falsification. Our sensitivity analysis of meta-analyses that included both pharmaceuticals' studies found no change from the results of apixaban only. This lack of change could be attributed to rivaroxaban's much smaller contribution to the meta-analyses, weight ranging from 1.5% to 14.7%.

Limitations

Only falsified data identified and cited by the FDA were used in this study. While the FDA is by far the largest medical regulatory agency in the world, the studies the FDA oversees represent only a fraction of the clinical trials that are monitored by various agencies in the world. In addition, we acknowledge that not all of the data contained in the previously identified studies were falsified, we chose to remove the entire data for two reasons: one, the authors of the identified publications were notified by the FDA that

it had determined the data audited during an inspection had been falsified, and yet the data were still published in medical journals; two, we wanted to replicate the limited access meta-analysis investigators would have to identify the falsified data. In regard to point two, based on reporting by Seife we know that the questionable data was from a clinical investigator in China, however we only knew that 2,916 participants (16.0%) were from the Asia-Pacific region (2,10). Our study is just an example of two pharmaceutical agents, but it highlights the problem of including studies that have used questionable data in meta-analyses. Thus, our findings are not a final conclusion, but rather a spark for discussion on how research misconduct can affect and should be addressed in meta-analyses and even publications as a whole.

Practical Recommendations

With the proliferation of data available to researchers conducting meta-analysis, such as the reporting of clinical trial data through clinicaltrials.gov, and the requirement to assess the quality of studies under the Cochrane Method for meta-analyses, there should be mechanisms to identify data that are of questionable reliability. Seife concluded that the FDA should be more transparent when it finds research misconduct; we agree with him but would argue that all parties involved in clinical research should be more transparent, i.e. other regulatory agencies, sponsors, and medical journals (2). In regards to the reporting of information on clinicaltrials.gov, reporters and those with oversight, i.e. regulatory agencies or institutions, should have a mechanism in order to identify those data points for which data quality cannot be assured, and the reason for the lack of assurance. For medical journals, any submission should be queried for information regarding monitoring or regulatory body inspections. Thus, journals could require authors to publish a statement in the publication itself, possibly next to the

conflict of interest statement, indicating if there was monitoring or regulatory inspections and if so, if there were any significant deviations and what were those deviations. Likewise, meta-analysis researchers should attest to assessing data quality through cross reference with regulatory bodies or other appropriate means.

CONCLUSION

Our sensitivity analysis results have shown that meta-analyses can suffer considerably from the inclusion of falsified data, so much so to the extent that conclusions may be altered. This study contributes to the literature that underscores the need for a robust sensitivity analysis for meta-analyses. In addition, it should add impetus for stronger prevention of publication of data that have been cited as having problems; the questionable data affects not only the original publication, but also any subsequent meta-analyses that use that publication's results.

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Table 1: Meta-Analysis Characteristics

Included Meta-Analysis	Total Apixaban Studies	Total Rivaroxaban Studies	Total Meta-Analysis Studies	Journal Impact Factor
Bruins et al,[24] 2012	2	-	10	5.939
Caldeira et al,[25] 2015	4	-	12	5.735
Caldeira et al,[26] 2014	7	-	25	5.595
Caldeira et al,[27] 2015	3	-	9	4.036
Chai-Adisaksopha,[28] 2014	2	-	12	10.452
Chai-Adisaksopha,[29] 2015	2	-	13	5.565
Chatterjee et al,[30] 2013	2	-	6	N/A
Chatterjee et al,[31] 2014	3	-	7	6.262
Dentali et al,[32] 2012	2	-	12	15.202
Garg et al,[33] 2012	2	-	11	6.189
Holster et al,[34] 2013	12	2	17	13.926
Kundu et al,[35] 2016	2	-	7	6.189
Lega et al,[36] 2014	2	-	9	5.72
Loke et al,[37] 2014	9	-	9	3.878

Miller et al,[38] 2017	10	4	28	N/A
Pancholy et al,[39] 2014	2	-	5	3.276
Pathak et al,[40] 2015	6	-	6	3.154
Sardar et al,[41] 2014	3	-	6	3.711
Sardar et al,[42] 2014	3	-	8	4.572
Sharma et al,[43] 2015	4	-	2	17.202
Tornyos et al,[44] 2015	12	-	12	5.565
Touma et al,[45] 2015	5	-	5	3.154

Abbreviations: N/A – Not Available

Figure 1 – PRISMA Flow Diagram

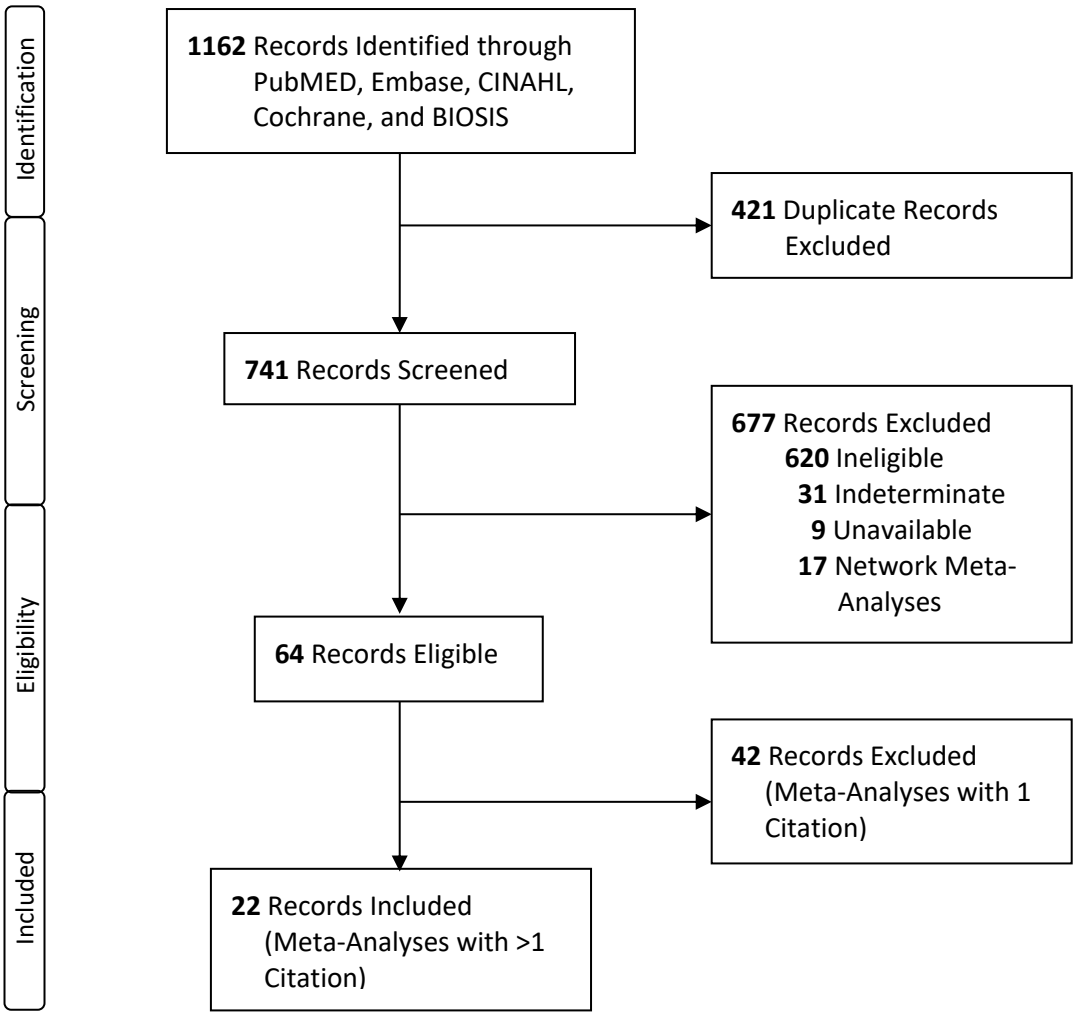
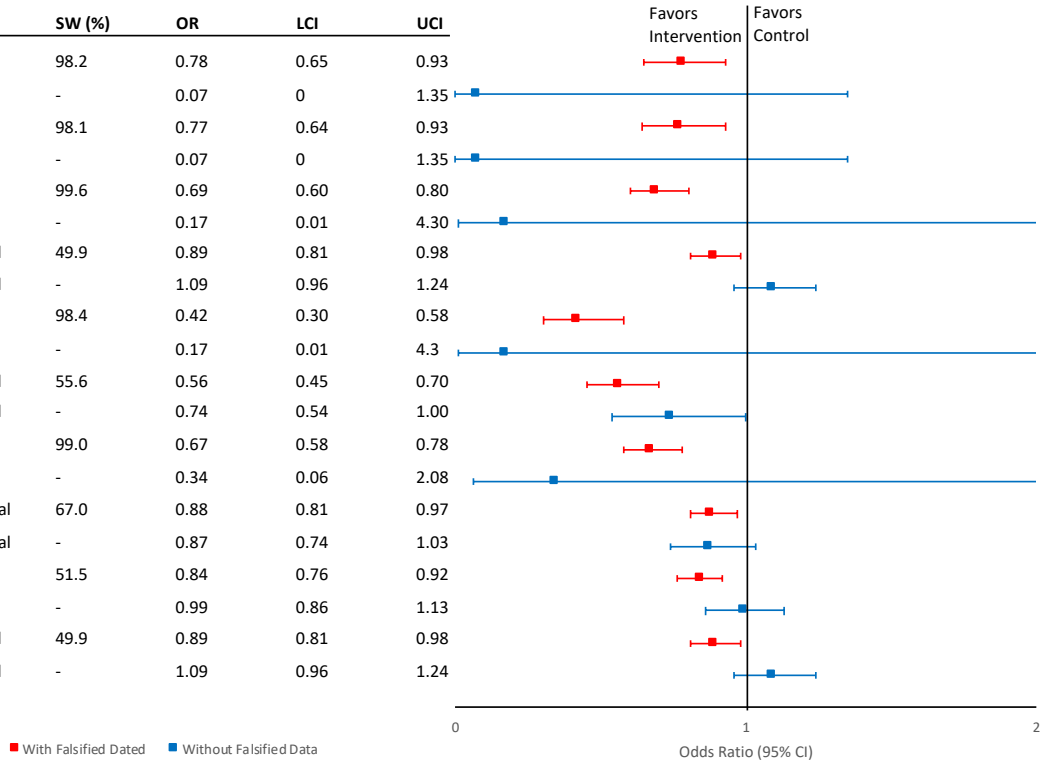


Figure 2 – Meta-Analysis Sensitivity Analysis Results with Qualitative Change

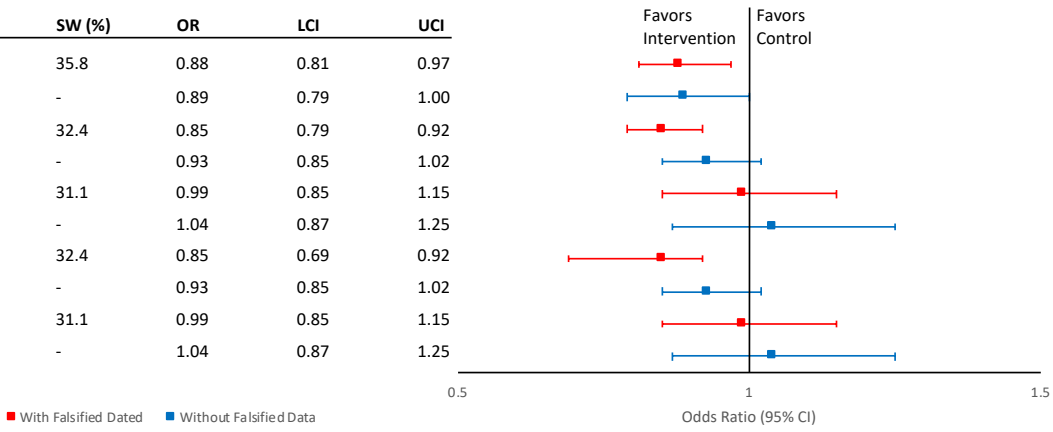
A – Bruins et al,[24] 2012 Publication

Figure	SW (%)	OR	LCI	UCI
1.1-Sub	98.2	0.78	0.65	0.93
1.1-Sub	-	0.07	0	1.35
1.2-Sub	98.1	0.77	0.64	0.93
1.2-Sub	-	0.07	0	1.35
1.6-Sub	99.6	0.69	0.60	0.80
1.6-Sub	-	0.17	0.01	4.30
1.6-Total	49.9	0.89	0.81	0.98
1.6-Total	-	1.09	0.96	1.24
1.7-Sub	98.4	0.42	0.30	0.58
1.7-Sub	-	0.17	0.01	4.3
1.7-Total	55.6	0.56	0.45	0.70
1.7-Total	-	0.74	0.54	1.00
1.8-Sub	99.0	0.67	0.58	0.78
1.8-Sub	-	0.34	0.06	2.08
1.11-Total	67.0	0.88	0.81	0.97
1.11-Total	-	0.87	0.74	1.03
2.2-Sub	51.5	0.84	0.76	0.92
2.2-Sub	-	0.99	0.86	1.13
2.2-Total	49.9	0.89	0.81	0.98
2.2-Total	-	1.09	0.96	1.24



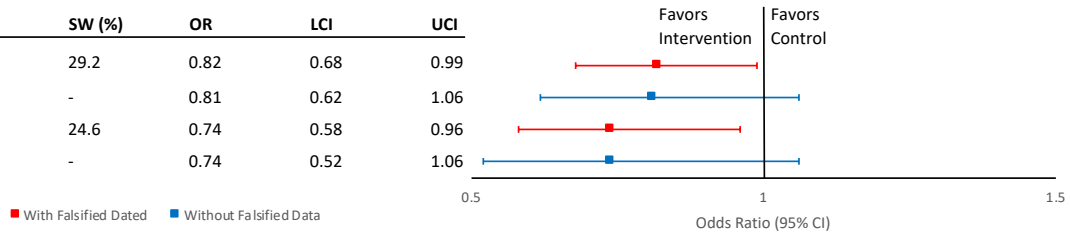
B – Dentali et al,[32] 2012

Figure	SW (%)	OR	LCI	UCI
1B	35.8	0.88	0.81	0.97
1B	-	0.89	0.79	1.00
3A	32.4	0.85	0.79	0.92
3A	-	0.93	0.85	1.02
4	31.1	0.99	0.85	1.15
4	-	1.04	0.87	1.25
Sup. 2	32.4	0.85	0.69	0.92
Sup. 2	-	0.93	0.85	1.02
Sup. 3	31.1	0.99	0.85	1.15
Sup. 3	-	1.04	0.87	1.25



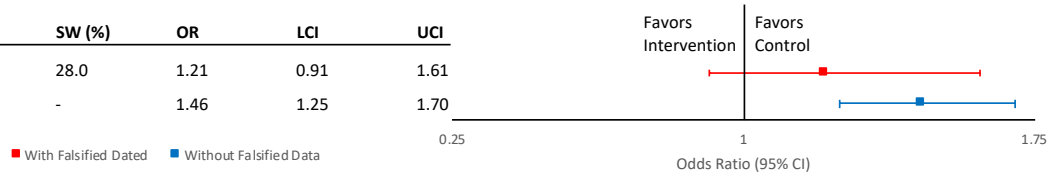
C – Garg et al,[33] 2012

Figure	SW (%)	OR	LCI	UCI
2	29.2	0.82	0.68	0.99
2	-	0.81	0.62	1.06
3-1.1.3	24.6	0.74	0.58	0.96
3-1.1.3	-	0.74	0.52	1.06



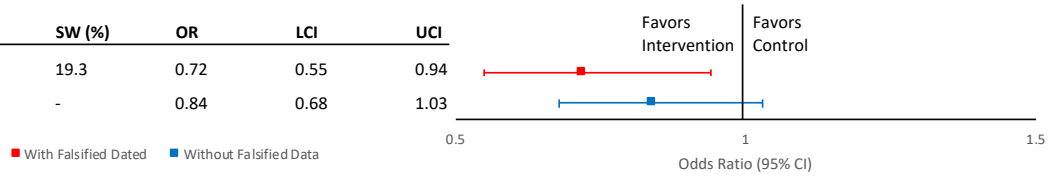
D – Holster et al,[34] 2013

Figure	SW (%)	OR	LCI	UCI
2A-Sub	28.0	1.21	0.91	1.61
2A-Sub	-	1.46	1.25	1.70



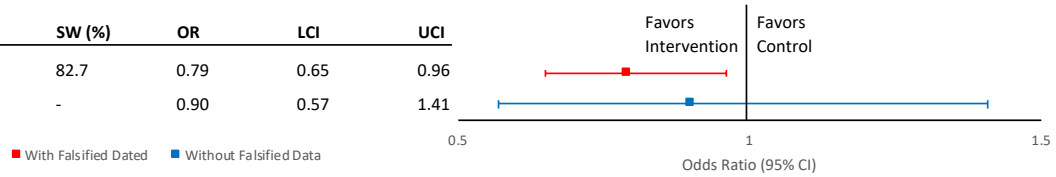
E – Lega et al,[36] 2014

Figure	SW (%)	OR	LCI	UCI
1A	19.3	0.72	0.55	0.94
1A	-	0.84	0.68	1.03



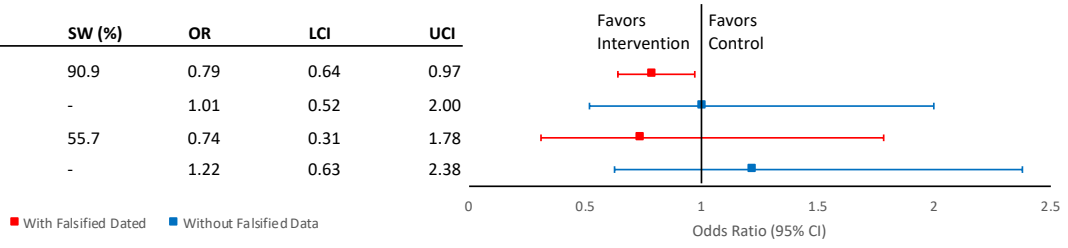
F – Pathak et al,[40] 2015

Figure	SW (%)	OR	LCI	UCI
2	82.7	0.79	0.65	0.96
2	-	0.90	0.57	1.41



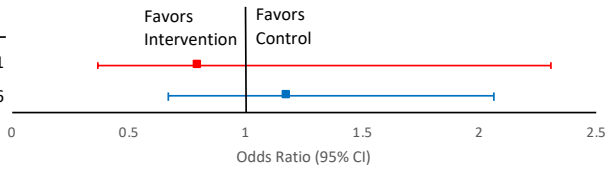
G – Sardar et al,[41] 2014

Figure	SW (%)	OR	LCI	UCI
2-1.1.2	90.9	0.79	0.64	0.97
2-1.1.2	-	1.01	0.52	2.00
4-2.1.2	55.7	0.74	0.31	1.78
4-2.1.2	-	1.22	0.63	2.38



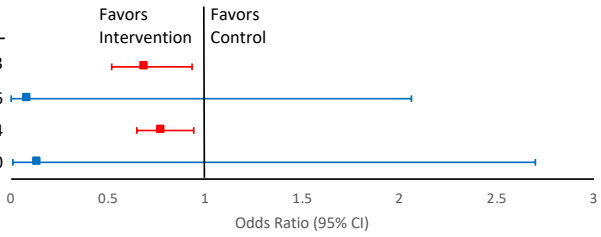
H – Sardar et al,[42] 2014

Figure	SW (%)	OR	LCI	UCI
2-1.2	58.2	0.80	0.43	1.51
2-1.2	-	1.18	0.67	2.06



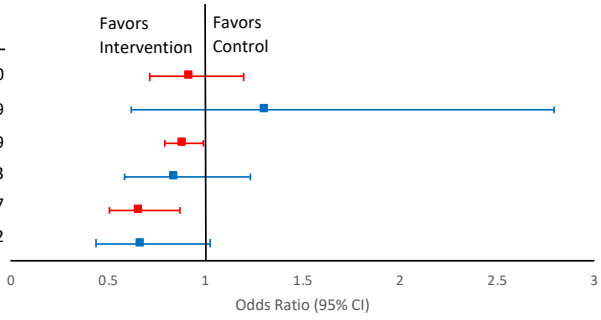
I – Sharma et al,[43] 2015

Figure	SW (%)	OR	LCI	UCI
3-1.1.4	97.0	0.69	0.52	0.93
3-1.1.4	-	0.09	0	2.06
3-2.1.4	98.7	0.78	0.65	0.94
3-2.1.4	-	0.14	0.01	2.70



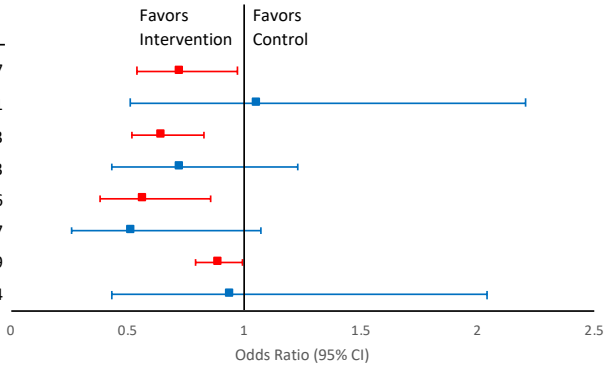
J – Tornyos et al,[44] 2015

Figure	SW (%)	OR	LCI	UCI
1-Sub	87.5	0.92	0.71	1.20
1-Sub	-	1.31	0.62	2.79
2-Sub	91.6	0.89	0.79	0.99
2-Sub	-	0.84	0.58	1.23
3-Sub	23.1	0.66	0.51	0.87
3-Sub	-	0.67	0.44	1.02



K – Touma et al,[45] 2015

Figure	SW (%)	OR	LCI	UCI
2-Sub	86.6	0.73	0.54	0.97
2-Sub	-	1.06	0.51	2.21
2-Total	44.9	0.65	0.52	0.83
2-Total	-	0.73	0.43	1.23
3-Total	42.2	0.57	0.38	0.86
3-Total	-	0.52	0.26	1.07
4-Total	92.7	0.89	0.79	0.99
4-Total	-	0.94	0.43	2.04



Abbreviations: SW – Study Weight; OR – Odds Ratio; LCI – Lower 95% Confidence Interval; UCI – Upper 95% Confidence Interval

APPENDIX

Table 1: Search Strategy for Each Database		
Database	**Keywords**	**Study Type**
BOSIS	Apixaban OR Eliquis	“meta analyses” OR “meta analysis” OR “meta-analyses” OR “meta-analysis”
CINAHL	Apixaban OR Eliquis	(MH+ "Meta Analysis") OR “meta analyses” OR “meta analysis” OR “meta-analyses” OR “meta-analysis”
Cochrane*	Apixaban OR Eliquis	“Meta-Analysis”
Embase	'apixaban'/exp OR Apixaban OR Eliquis	'meta analysis (topic)'/exp OR 'meta analysis'/exp OR “meta analyses” OR “meta analysis” OR “meta-analyses” OR “meta-analysis”
PubMed	"apixaban" [Supplementary Concept] OR Apixaban OR Eliquis	"Meta-Analysis" [Publication Type] AND "Meta-Analysis as Topic"[Mesh] AND "Network Meta-Analysis"[Mesh] OR “meta analyses” OR “meta analysis” OR “meta-analyses” OR “meta-analysis”

*Cochrane: MeSH descriptor: [Meta-Analysis] explode all trees

Table 2: Inclusion/Exclusion Criteria	
Inclusion	Any meta-analysis that includes each of the following:
	Species: Human only
	Age: Any age
	Intervention: Apixaban
	Indication: Any use of the intervention
	Outcomes: Any outcome
	Comparator: Any Comparator
Exclusion	Any meta-analysis that does not include one of the following studies:
	Granger CB, Alexander JH, McMurray JJ, et al; ARISTOTLE Committees and. Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981-992.
	Lopes RD, Al-Khatib SM, Wallentin L, et al. Efficacy and safety of Apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. *Lancet*. 2012;380 (9855):1749-1758.
	McMurray JJ, Ezekowitz JA, Lewis BS, et al; ARISTOTLE Committees and Investigators. Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrialfibrillation: insights from the ARISTOTLE trial. *Circ Heart Fail*. 2013;6(3):451-460.
	Wallentin L, Lopes RD, Hanna M, et al; Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Investigators. Efficacy and safety of apixaban compared with warfarin at different levels of predicted international normalized ratio control for stroke prevention in atrial fibrillation. *Circulation*. 2013;127(22):2166-2176.
	Garcia DA, Wallentin L, Lopes RD, et al. Apixaban versus warfarin in patients with atrial fibrillation according to prior warfarin use: results from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial. *Am Heart J*. 2013;166(3):549-558.
	Alexander JH, Levy E, Lawrence J, et al. Documentation of study

	medication dispensing in a prospective large randomized clinical trial: experiences from the ARISTOTLE Trial. *Am Heart J*. 2013;166(3):559-565.
	Alexander JH, Lopes RD, Thomas L, et al. Apixaban vs. warfarin with concomitant aspirin in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J*. 2014;35(4):224-232.

Table 3: Meta-Analysis Sensitivity Analysis																	
Meta-Analysis Details				**Sensitivity Analysis**											**ANOVA**		
Citation	**Table**	**AM**	**FD**	**Est.**	**LCI**	**UCI**	**Heterogeneity**					**Overall Effect**		**SW**	**F-test**	**df**	**p-value**
							τ	**χ^2**	**df**	**p-value**	**I^2**	**z-value**	**p-value**				
24	1.1-Sub	F	Y	0.78	0.65	0.93	N/A	2.58	1	0.11	61	2.69	0.007	98.2	0.49	1	0.52
			N	0.07	0	1.35	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	1.1-Total	F	Y	0.81	0.72	0.91	N/A	6.91	7	0.44	0	3.5	0.0005	42.2	0.02	1	0.89
			N	0.82	0.7	0.96	N/A	6.78	6	0.34	12	2.47	0.01	-			
	1.2-Sub	F	Y	0.77	0.64	0.93	N/A	2.57	1	0.11	61	2.67	0.008	98.1	0.47	1	0.53
			N	0.07	0	1.35	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	1.2-Total	F	Y	0.78	0.69	0.89	N/A	5.7	7	0.58	0	3.73	0.0002	47.4	0	1	0.97
			N	0.77	0.65	0.93	N/A	5.7	6	0.46	0	2.79	0.005	-			
	1.3-Sub	F	Y	0.9	0.73	1.12	N/A	2.07	1	0.15	52	0.91	0.36	98.1	0.11	1	0.76
			N	0.1	0	2.06	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	1.3-Total	F	Y	0.88	0.76	1.02	N/A	6.19	6	0.4	3	1.7	0.09	46.4	0.06	1	0.82
			N	0.1	0	2.06	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	1.5-Sub	F	Y	0.88	0.44	1.76	N/A	N/A	N/A	N/A	N/A	N/A	N/A	100	N/A	N/	N/A

			N	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-		A	
	1.5-Total	F	Y	0.53	0.32	0.87	N/A	6.01	5	0.3	17	2.51	0.01	38.6	0.91	1	0.39
			N	0.3	0.14	0.65	N/A	2.45	4	0.65	0	3.05	0.002	-			
	1.6-Sub	F	Y	0.69	0.6	0.8	N/A	0.72	1	0.4	0	5	<0.00001	99.6	0.32	1	0.60
			N	0.17	0.01	4.3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	1.6-Total	F	Y	0.89	0.81	0.98	N/A	48.81	9	<0.00001	82	2.34	0.02	49.9	4.62	1	0.10
			N	1.09	0.96	1.24	N/A	29.17	8	0.0003	73	1.32	0.19	-			
	1.7-Sub	F	Y	0.42	0.3	0.58	N/A	0.29	1	0.59	0	5.28	<0.00001	98.4	0.57	1	0.49
			N	0.17	0.01	4.3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	1.7-Total	F	Y	0.56	0.45	0.7	N/A	12.5	5	0.03	60	5.13	<0.00001	55.6	1.57	1	0.28
			N	0.74	0.54	1	N/A	8.5	4	0.07	53	1.97	0.05	-			
	1.8-Sub	F	Y	0.67	0.58	0.78	N/A	0.55	1	0.46	0	5.07	<0.00001	99	0.06	1	0.82
			N	0.34	0.06	2.08	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	1.8-Total	F	Y	1.00	0.93	1.07	N/A	58.69	9	<0.00001	85	0.01	0.94	23.9	2.65	1	0.18
			N	1.1	1.02	1.18	N/A	28.41	8	0.0004	72	2.43	0.01	-			

	1.9-Sub	F	Y	0.88	0.66	1.17	N/A	N/A	N/A	N/A	N/A	0.9	0.37	100	N/A	N/A	N/A
			N	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	1.9-Total	F	Y	0.87	0.73	1.05	N/A	3.16	4	0.53	0	1.43	0.15	42.2	0	1	0.98
			N	0.87	0.68	1.11	N/A	3.15	3	0.37	5	1.12	0.26	-			
	1.11-Sub	F	Y	0.89	0.79	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	100	N/A	N/A	N/A
			N	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	1.11-Total	F	Y	0.88	0.81	0.97	N/A	2.18	4	0.7	0	2.57	0.01	67	0	1	0.95
			N	0.87	0.74	1.03	N/A	2.14	3	0.54	0	1.62	0.1	-			
	2.1-Sub	F	Y	0.82	0.72	0.92	N/A	6.48	6	0.37	7	3.3	0.00096	44.1	0.06	1	0.82
			N	0.84	0.71	0.98	N/A	6.25	5	0.28	20	2.2	0.03	-			
	2.1-Total	F	Y	0.81	0.72	0.91	N/A	6.91	7	0.44	0	3.5	0.00046	42.2	0.49	1	0.52
			N	0.82	0.7	0.96	N/A	6.78	6	0.34	12	2.47	0.01	-			
	2.2-Sub	F	Y	0.84	0.76	0.92	N/A	21.12	8	0.0003	65	3.56	0.00037	51.5	2.86	1	0.17
			N	0.99	0.86	1.13	N/A	11.12	7	0.13	37	0.01	0.85	-			
	2.2-Total	F	Y	0.89	0.81	0.98	N/A	48.42	9	<0.00001	81	2.35	0.019	49.9	4.62	1	0.10
			N	1.09	0.96	1.24	N	28.8	8	0.0003	72	1.3	0.19	-			

								6									
25	Fig-2-AF	R	Y	1.08	0.85	1.37	0.05	18.52	4	0.001	78	0.62	0.54	21.3	0.09	1	0.78
			N	1.14	0.87	1.5	0.05	14.43	3	0.002	79	0.94	0.35	-			
	Fig-2-Total	R	Y	0.97	0.78	1.21	0.07	32.38	11	0.0007	66	0.27	0.79	14.8	0.01	1	0.95
			N	0.98	0.77	1.25	0.07	29.19	10	0.001	66	0.17	0.87	-			
26	Fig-2-Sub	R	Y	0.91	0.56	1.49	0.06	6.77	6	0.32	11	0.37	0.71	51.2	0.02	1	0.89
			N	0.86	0.38	1.95	0.26	6.69	5	0.24	25	0.37	0.71	-			
	Fig-2	R	Y	0.9	0.72	1.13	0	15.16	22	0.86	0	0.88	0.38	20.2	0.02	1	0.89
			N	0.89	0.69	1.14	0	15.09	21	0.82	0	0.92	0.36	-			
	Fig-3-Sub	R	Y	0.85	0.67	1.08	0.04	10.48	6	0.11	43	1.3	0.19	23.1	0.18	1	0.69
			N	0.78	0.61	1	0.02	6.53	5	0.26	23	1.95	0.05	-			
	Fig-3	R	Y	0.78	0.69	0.89	0.04	42.8	24	0.01	44	3.66	0.0002	8.2	0.06	1	0.82
			N	0.76	0.67	0.87	0.03	36.88	23	0.03	38	4.11	<0.0001				

27	Fig-1-All	R	Y	0.95	0.91	1.01	0	4.26	6	0.64	0	1.76	0.08	74.2	0	1	0.96
			N	0.95	0.86	1.05	0	4.22	5	0.52	0	1.05	0.29	-			
	Fig-1-Urinary	R	Y	0.91	0.84	0.98	0	2.82	3	0.42	0	2.47	0.01	39.5	0.26	1	0.64
			N	0.87	0.79	0.97	0	1.62	2	0.33	0	2.61	0.009	-			
28	Fig-1	R	Y	0.71	0.6	0.84	0.05	48.34	11	<0.00001	77	3.99	<0.0001	13.6	0	1	0.98
			N	0.71	0.59	0.86	0.06	46.46	19	<0.00001	78	3.47	0.0005	-			
	Fig-2	R	Y	0.52	0.43	0.64	0	5.24	11	0.92	0	6.31	<0.00001	22	0	1	0.98
			N	0.5	0.4	0.63	0	4.57	10	0.92	0	5.96	<0.00001	-			
	Fig-3	R	Y	0.43	0.37	0.5	0	11.28	11	0.42	2	10.9	<0.00001	20.3	0	1	0.96
			N	0.43	0.35	0.53	0.01	11.27	10	0.34	11	8.26	<0.00001	-			
	Fig-4	R	Y	0.76	0.65	0.89	0.06	89.92	10	<0.00001	89	3.39	0.0007	10.3	0.02	1	0.90
			N	0.77	0.65	0.92	0.06	83.9	9	<0.00001	89	2.97	0.003	-			
	Fig-5	R	Y	0.7	0.64	0.76	0.01	40.11	7	<0.00001	83	8.13	<0.00001	15.6	0	1	0.96
			N	0.7	0.63	0.78	0.01	36.2	6	<0.00001	83	6.73	<0.00001	-			

	Fig-6	R	Y	0.94	0.74	1.19	0.07	31.18	9	0.0003	71	0.5	0.62	16.2	0	1	0.96
			N	0.94	0.72	1.24	0.08	28.08	8	0.0005	72	0.42	0.67	-			
29	Fig-2	R	Y	0.87	0.81	0.94	0	9.65	11	0.56	0	3.67	0.0002	7	0	1	1.0
			N	0.87	0.81	0.94	0	9.65	10	0.47	0	3.53	0.0004	-			
	Fig-3	R	Y	0.91	0.86	0.95	0	4.72	12	0.97	0	3.8	0.0001	19.6	0.01	1	0.94
			N	0.91	0.86	0.96	0	4.59	11	0.95	0	3.25	0.001	-			
30	Fig	R	Y	0.49	0.36	0.65	0.05	9.13	5	0.1	45	4.87	<0.00001	28	0.12	1	0.75
			N	0.52	0.35	0.79	0.09	8.48	4	0.08	53	3.12	0.002	-			
31	Fig-2B	R	Y	1.01	0.83	1.22	0.04	79.88	6	<0.00001	92	0.09	0.93	20.8	0.04	1	0.86
			N	1.04	0.83	1.29	0.05	47.92	5	<0.00001	90	0.35	0.73	-			
	Fig-3B	R	Y	1.24	0.87	1.76	0.13	72.45	5	<0.00001	93	1.21	0.23	24.2	0.13	1	0.7377
			N	1.37	0.99	1.91	0.08	23.79	4	<0.00001	83	1.9	0.06	-			
32	Fig-1A	F	Y	0.88	0.82	0.95	N/A	1.86	6	0.92	0	3.24	0.001	42.2	0	1	1
			N	0.88	0.8	0.97	N/A	1.84	5	0.87	0	2.55	0.01	-			
	Fig-1B	F	Y	0.89	0.81	0.97	N/A	2.35	5	0.8	0	2.51	0.01	35.8	0	1	0.9672

			N	0.89	0.79	1	N/A	2.35	4	0.67	0	2.02	0.04	-			
	Fig-2A	F	Y	0.77	0.69	0.85	N/A	4.93	6	0.55	0	4.94	<0.00001	32.9	0.02	1	0.8989
			N	0.76	0.66	0.86	N/A	4.8	5	0.44	0	4.28	<0.0001	-			
	Fig-2B	F	Y	0.92	0.81	1.04	N/A	6.44	5	0.27	22	1.35	0.18	30.1	0.03	1	0.8812
			N	0.9	0.77	1.05	N/A	6.29	4	0.18	36	1.37	0.17	-			
	Fig-3A	F	Y	0.85	0.79	0.92	N/A	18.45	8	0.002	57	4.03	<0.0001	32.4	1.67	1	0.2653
			N	0.93	0.85	1.02	N/A	7.38	7	0.39	5	1.57	0.12	-			
	Fig-3B	F	Y	0.46	0.38	0.55	N/A	9.16	6	0.16	35	8.17	<0.00001	36	0.14	1	0.73
			N	0.48	0.39	0.61	N/A	8.81	5	0.12	43	6.3	<0.00001	-			
	Fig-4	F	Y	0.99	0.85	1.15	N/A	8.9	4	0.06	55	0.13	0.89	31.1	0.16	1	0.71
			N	1.04	0.87	1.25	N/A	8.05	3	0.04	63	0.42	0.67	-			
	Sup-Fig-2-Sub	F	Y	0.79	0.6	0.8	N/A	0.72	1	0.4	0	5	<0.00001	99.6	0.29	1	0.62
			N	0.17	0.01	4.3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	Sup-Fig-2-Total	F	Y	0.85	0.79	0.92	N/A	18.45	8	0.02	57	4.03	<0.0001	32.4	1.67	1	0.27
			N	0.93	0.85	1.02	N/A	7.38	7	0.39	5	1.57	0.12	-			
	Sup-Fig-3-	F	Y	0.88	0.66	1.17	N/A	N/A	N/A	N/A	N/A	0.9	0.37	100	N/A	N/	N/A

	Sub		N	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-		A	
	Sup-Fig-3-Total	F	Y	0.99	0.85	1.15	N/A	8.9	4	0.06	55	0.13	0.89	31.1	0.16	1	0.71
			N	1.04	0.87	1.25	N/A	8.05	3	0.04	63	0.42	0.67	-			
33	Fig-2	R	Y	0.82	0.68	0.99	0.02	13.22	7	0.07	47	2.08	0.04	29.2	0	1	1.0
			N	0.81	0.62	1.06	0.04	11.69	6	0.07	49	1.55	0.12	-			
	Fig-3-1.1.1	R	Y	0.83	0.69	1	0.02	12.62	7	0.08	45	1.95	0.05	29.3	0	1	0.95
			N	0.83	0.65	1.07	0.03	10.55	6	0.1	43	1.43	0.15	-			
	Fig-3-1.1.3	R	Y	0.74	0.58	0.96	0.06	38.17	10	<0.0001	74	2.31	0.02	24.6	0	1	0.95
			N	0.74	0.52	1.06	0.11	37.12	9	<0.0001	76	1.63	0.1	-			
	Fig-3-1.1.4	R	Y	0.84	0.68	1.04	0.05	68.15	10	<0.00001	85	1.64	0.1	19.7	0.10	1	0.77
			N	0.89	0.69	1.14	0.06	53.02	9	<0.00001	83	0.95	0.34	-			
	Fig-3-Total	R	Y	0.81	0.74	0.9	0.03	142	41	<0.00001	71	4.25	<0.0001	27	0.05	1	0.83
			N	0.83	0.74	0.93	0.04	118.8	36	<0.00001	70	3.09	0.002	-			

34	Fig-2A-Sub	R	Y	1.21	0.91	1.61	0.06	13.77	5	0.02	64	1.29	0.2	28	0.89	1	0.40
			N	1.46	1.25	1.7	0	3.11	4	0.54	0	4.86	<0.00001	-			
	Fig-2A-Total	R	Y	1.45	1.06	1.97	0.13	40.76	16	0.0006	61	2.36	0.02	16.7	0.14	1	0.73
			N	1.59	1.17	2.16	0.1	27.68	15	0.02	46	2.97	0.003	-			
	Fig-2B-Sub	R	Y	1.23	0.56	2.73	0.68	23.71	7	0.001	70	0.51	0.61	23.7	0.15	1	0.72
			N	1.35	0.42	4.31	1.49	20.82	6	0.002	71	0.5	0.62	-			
	Fig-2B-Total	R	Y	1.45	1.06	1.97	0.13	40.76	16	0.0006	61	2.36	0.02	16.7	0.14	1	0.73
			N	1.59	1.17	2.16	0.1	27.68	15	0.02	46	2.97	0.003	-			
	Fig-3-Total	R	Y	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			N	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
35	Fig-2	R	Y	0.46	0.36	0.57	0.04	10.78	6	0.1	44	6.71	<0.00001	21.4	0.59	1	0.49
			N	0.4	0.32	0.49	0	4.23	4	0.38	5	8.67	<0.00001	-			
36	Fig-1A	R	Ys	0.72	0.55	0.94	0.08	20.1	6	0.003	70	2.39	0.02	19.3	0.56	1	0.50

			N	0.84	0.68	1.03	0.02	7.81	5	0.17	36	1.68	0.09	-			
	Fig-2A	R	Y	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			N	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
37	Fig-2-1.1.3	F	Y	0.87	0.68	1.12	N/A	0.01	1	0.92	0	1.07	0.29	78.4	0.02	1	0.89
			N	0.85	0.49	1.47	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	Fig-2-Total	F	Y	0.89	0.78	1.03	N/A	3.81	8	0.87	0	1.58	0.11	23.7	0	1	0.95
			N	0.9	0.77	1.05	N/A	3.78	7	0.81	0	1.31	0.19	-			
38	Fig-2	R	Y	0.98	0.79	1.22	0.06	40.83	23	0.01	44	0.16	0.87	15.5	0.62	1	0.48
			N	0.06	0.78	1.27	0.07	37.78	22	0.02	42	0.03	0.97	-			
	Fig-4A	F	Y	0.81	0.64	1.02	N/A	8.09	6	0.23	26	1.77	0.08	73.9	0.48	1	0.53
			N	0.62	0.38	1.02	N/A	6.5	5	0.26	23	1.89	0.06	-			
39	Fig-3	R	Y	1.13	0.96	1.34	0	1.37	3	0.71	0	1.47	0.14	35.3	0.01	1	0.92
			N	1.15	0.93	1.41	0	1.32	2	0.52	0	1.31	0.19	-			
	Fig-5	R	Y	0.84	0.75	0.96	0	1.7	3	0.64	0	2.68	0.007	27.2	0.01	1	0.92
			N	0.85	0.74	0.99	0	1.62	2	0.45	0	2.14	0.03	-			
40	Fig-2	F	Y	0.79	0.65	0.96	N/A	4.62	4	0.33	13	2.36	0.02	82.7	0.38	1	0.57

			N	0.9	0.57	1.41	N/A	4.3	3	0.23	30	0.47	0.64	-			
	Fig-3	R	Y	1.02	0.47	2.2	0.46	14.73	4	0.005	73	0.05	0.96	31.7	0.31	1	0.61
			N	1.39	0.58	3.33	0.37	5.84	3	0.12	49	0.75	0.45	-			
41	Fig-2-1.1.2	R	Y	0.79	0.64	0.97	0	0.58	1	0.45	0	2.27	0.02	90.9	0.71	1	0.45
			N	1.01	0.52	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	Fig-2-Total	R	Y	0.81	0.72	0.9	0	1.55	5	0.91	0	3.84	0.0001	26.5	0.03	1	0.88
			N	0.82	0.72	0.93	0	1.31	4	0.86	0	3.04	0.002	-			
	Fig-3A-1.2.2	R	Y	0.54	0.27	1.06	0.2	5.73	1	0.02	83	1.8	0.07	54.5	0.78	1	0.43
			N	0.37	0.22	0.6	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	Fig-3A-Total	R	Y	0.7	0.54	0.92	0.05	9.54	3	0.02	69	2.59	0.01	26.6	0	1	0.96
			N	0.68	0.46	0.99	0.09	9.5	2	0.009	79	1.99	0.05	-			
	Fig-4-2.1.2	R	Y	0.74	0.31	1.78	0.34	5.92	1	0.01	83	0.68	0.5	55.7	0.48	1	0.53
			N	1.22	0.63	2.38	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	Fig-4-Total	R	Y	0.82	0.59	1.14	0.11	17.91	5	0.003	72	1.17	0.24	21.5	0.32	1	0.60
			N	0.95	0.79	1.13	0	3.95	4	0.41	0	0.62	0.54	-			
	Fig-5A-	R	Y	0.6	0.32	1.1	0.14	3.12	1	0.08	68	1.65	0.1	57.4	0.54	1	0.50

	2.2.2		N	0.42	0.23	0.76	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	Fig-5A-Total	R	Y	0.72	0.57	0.92	0.02	4.72	3	0.19	36	2.65	0.008	26.7	0.02	1	0.89
			N	0.68	0.48	0.97	0.05	4.61	2	0.1	57	2.13	0.03	-			
42	Fig-2-1.2	R	Y	0.8	0.43	1.51	0.17	4.54	1	0.03	78	0.68	0.5	58.2	0.57	1	0.49
			N	1.18	0.67	2.06	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	Fig-2-Total	R	Y	1.02	0.73	1.43	0.17	50.25	7	<0.00001	86	0.13	0.89	15.8	0.14	1	0.73
			N	1.13	0.78	1.62	0.17	33.73	6	<0.00001	82	0.64	0.52	-			
	Fig-3-1.2	R	Y	0.49	0.22	1.1	0.3	7.75	1	0.005	87	1.73	0.08	53.2	0.90	1	0.40
			N	0.31	0.19	0.52	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	Fig-3-Total	R	Y	0.65	0.48	0.87	0.06	11.19	3	0.01	73	2.87	0.004	26.2	0.01	1	0.93
			N	0.61	0.4	0.93	0.11	11.19	2	0.004	82	2.27	0.02	-			
43	Fig-3-1.1.4	F	Y	0.69	0.52	0.93	N/A	1.64	1	0.2	39	2.46	0.01	97	0	1	1.0
			N	0.09	0	2.06	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	Fig-3-2.1.4	F	Y	0.78	0.65	0.94	N/A	1.33	1	0.25	25	2.63	0.009	98.7	0.03	1	0.86
			N	0.14	0.01	2.7	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			

	Fig-5-1.3.4	F	Y	0.59	0.48	0.73	N/A	3.16	1	0.08	68	4.89	<0.00001	93	1.97	1	0.23
			N	0.22	0.07	0.68	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	Fig-5-2.3.4	F	Y	0.66	0.57	0.76	N/A	8.33	3	0.04	64	5.9	<0.00001	89.8	5.87	1	0.07
			N	0.33	0.19	0.57	N/A	1.88	2	0.39	0	3.93	<0.0001	-			
44	Fig-1-Sub	R	Y	0.92	0.71	1.2	0	4.13	5	0.53	0	0.59	0.55	87.5	0.92	1	0.39
			N	1.31	0.62	2.79	0	3.17	4	0.53	0	0.7	0.48	-			
	Fig-1-Total	R	Y	0.9	0.77	1.05	0	5.68	9	0.77	0	1.37	0.17	28.5	0.01	1	0.92
			N	0.91	0.76	1.09	0	5.64	8	0.69	0	1.05	0.29	-			
	Fig-2-Sub	R	Y	0.89	0.79	0.99	0	3.63	5	0.6	0	2.17	0.03	91.6	0	1	0.97
			N	0.84	0.58	1.23	0	3.56	4	0.47	0	0.88	0.38	-			
	Fig-2-Total	R	Y	0.89	0.77	1.03	0.01	12.59	10	0.25	21	1.59	0.11	39.6	0	1	1.0
			N	0.88	0.7	1.11	0.03	12.57	9	0.18	28	1.07	0.28	-			
	Fig-3-Sub	R	Y	0.66	0.51	0.87	0.08	30.06	6	<0.0001	80	2.93	0.003	23.1	0.02	1	0.89
			N	0.67	0.44	1.02	0.18	29.6	5	<0.0001	83	1.85	0.06	-			
	Fig-3-Total	R	Y	0.84	0.62	1.12	0.17	82.31	11	<0.00001	87	1.19	0.23	13.1	0.03	1	0.87

			No	0.86	0.58	1.27	0.29	78.27	10	<0.00001	87	0.75	0.45	-			
45	Fig-2-Sub	R	Yes	0.73	0.54	0.97	0.02	1.35	1	0.25	26	2.15	0.03	86.6	0.99	1	0.38
			No	1.06	0.51	2.21	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	Fig-2-Total	R	Yes	0.65	0.52	0.83	0.03	14.33	3	0.002	79	3.52	0.0004	44.9	0.27	1	0.63
			No	0.73	0.43	1.23	0.14	5.16	2	0.08	61	1.19	0.23	-			
	Fig-3-Sub	R	Yes	0.61	0.34	1.1	0.1	1.25	1	0.26	20	1.65	0.1	89.6	0.06	1	0.82
			No	0.25	0.05	1.41	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	Fig-3-Total	R	Yes	0.57	0.38	0.86	0.1	16.63	3	0.0008	82	2.65	0.008	42.2	0	1	0.96
			No	0.52	0.26	1.07	0.22	4.57	2	0.1	56	1.77	0.08	-			
	Fig-4-Sub	R	Y	0.89	0.79	1	N/A	N/A	N/A	N/A	N/A	2	0.05	100	N/A	N/A	N/A
			N	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
	Fig-4-Total	R	Y	0.89	0.79	0.99	0	2.29	3	0.51	0	2.17	0.03	92.7	0.27	1	0.63
			N	0.94	0.43	2.04	0.13	2.21	2	0.33	9	0.15	0.88	-			

Abbreviations: AM – Analysis Method; Est. – Estimate; F – Fixed; FD – Falsified Data; LCI – Lower 95% Confidence Interval; N – No; N/A – Not Available; R – Random; SW – Study Weight; UCI – Upper 95% Confidence Interval; Y - Yes

Table 4: Meta-Analysis Sensitivity Analysis (Apixaban & Rivaroxaban)																	
Meta-Analysis Details				**Sensitivity Analysis**											**ANOVA**		
Citation	**Table**	**AM**	**FD**	**Est.**	**LCI**	**UCI**	**Heterogeneity**					**Overall Effect**		**SW**	**F-test**	**df**	**p-value**
							τ	**χ^2**	**df**	**p-value**	**I^2**	**z-value**	**p-value**				
26	Fig-2-Sub	R	Y	0.96	0.69	1.35	0	2.82	8	0.95	0	0.21	0.83	4.9	0	1	0.98
			N	0.97	0.68	1.37	0	0.82	5	0.98	0	0.19	0.85	-			
	Fig-2	R	Y	0.9	0.72	1.13	0	15.16	22	0.86	0	0.88	0.38	22.5	0.02	1	0.90
			N	0.87	0.67	1.14	0	6.98	18	0.94	0	1.02	0.31	-			
	Fig-3-Sub	R	Y	0.74	0.53	1.02	0.12	18.25	7	0.01	62	1.86	0.06	50.9	0.40	1	0.56
			N	0.88	0.45	1.72	0.34	14.79	3	0.002	80	0.37	0.71	-			
	Fig-3	R	Y	0.78	0.69	0.89	0.04	42.8	24	0.01	44	3.66	0.0002	25.5	0.01	1	0.95
			N	0.79	0.67	0.92	0.04	25.81	15	0.04	42	2.91	0.004	-			
27	Fig-1-All	R	Y	0.95	0.91	1.01	0	4.26	6	0.64	0	1.76	0.08	84.2	0.06	1	0.82
			N	0.91	0.73	1.14	0.02	3.66	2	0.16	45	0.79	0.43	-			
34	Fig-2A-Sub	R	Y	0.87	0.25	3.03	0.92	8.16	5	0.15	39	0.23	0.82	11.4	0	1	0.96
			N	0.75	0.18	3.01	1.13	7.39	4	0.12	46	0.41	0.68	-			
	Fig-2A-	R	Y	1.45	1.06	1.97	0.13	40.76	16	0.000	61	2.36	0.02	17.6	0.13	1	0.73

	Total									6							
			N	1.58	1.16	2.17	0.10	27.51	14	0.02	49	2.87	0.004	-			
	Fig-2A-Sub	R	Y	1.48	1.21	1.82	0	2.58	4	0.63	0	3.74	0.0002	0.4	0	1	0.99
			N	1.48	1.2	1.82	0	2.39	3	0.49	0	3.71	0.0002	-			
	Fig-2A-Total	R	Y	1.45	1.06	1.97	0.13	40.76	16	0.0006	61	2.36	0.02	17.6	0.14	1	0.73
			N	1.58	1.16	2.17	0.10	27.51	14	2	49	2.87	0.004	-			
	Fig-3-Total	R	Y	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
			N	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-			
38	Fig-2	R	Y	0.98	0.79	1.22	0.06	40.83	23	0.01	44	0.16	0.87	17.3	0	1	0.97
			N	0.97	0.75	1.25	0.08	36.84	19	0.008	48	0.27	0.79	-			

Abbreviations: AM – Analysis Method; Est. – Estimate; F – Fixed; FD – Falsified Data; LCI – Lower 95% Confidence Interval; N – No; N/A – Not Available; R – Random; SW – Study Weight; UCI – Upper 95% Confidence Interval; Y - Yes

V. CONCLUSION

Over 20 years ago, Chalmers and Altman argued that the consolidation of medical knowledge through meta-analyses of randomized clinical trials provided the most compelling evidence for the efficacy of medical interventions; since then, systematic reviews and meta-analyses have proliferated (1-2). Clinical trials of the highest quality, which are routinely published in the most prestigious medical journals and thus more likely to be included in meta-analyses, are those conducted in support of marketing applications to the U.S. Food and Drug Administration (FDA). However, although Seife has shown that the FDA has called some data into question and rejected the data for consideration, these questionable data had made it into the medical literature (3). Two cross-sectional studies were conducted to uncover the patterns of protocol non-compliance observed by the FDA in regard to the clinical trials under its purview. Subsequently, a systematic review was then performed to determine meta-analyses that used studies known to include data called into question by the FDA, through its identification of protocol non-compliance, and a sensitivity analysis of the studies included in the identified meta-analyses.

To the author's knowledge, the cross-sectional study in Manuscript 1 is the first analysis of FDA citations for any FDA program area. It was shown that from Fiscal Years 2007 to 2015, FDA inspections under its Bioresearch Monitoring program have steadily increased, but the issuance of FDA Form 483, Inspectional Observations, has decreased. However, one-third of the violations cited by FDA Investigators were related to the adherence to the investigational procedures, i.e. protocol non-compliance. Violations of the informed consent process and the generation and maintenance of adequate study records were the next most common violations. Thus, even though

compliance with FDA regulations has improved, there is still room for improvement, particularly with ensuring that data collected are collected following the established protocol and that participant rights are protected through adequate consent procedures.

The violations cited in FDA Form 483s, Inspectional Observations, do not constitute the agencies final decision on violations of FDA's regulations; thus, the purpose of Manuscript 2 was to analyze the violations of FDA regulations that constituted research misconduct through the agency's final determination as indicated in regulatory actions (4). To the author's knowledge, this cross-sectional study was the first analysis of both Warning Letters (WL) and Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) letters. The study was able to analyze 194 of the most significant regulatory actions published by the FDA. While medical device researchers received Warning Letters at higher rates than biologic researchers, biologic and pharmaceutical researchers were more likely to receive the more egregious NIDPOE letter than medical device researchers. In addition, it was shown that NIDPOE letters were disproportionately issued to researchers who failed to provide proper supervision over the clinical trial and/or submitted false information to the sponsor, and subsequently to the FDA. Similar to the trend in FDA citations, researcher compliance improved from Fiscal Years 2007 to 2015, but improvements are still needed among researchers of all three study test article classifications (biologic, medical device, pharmaceutical) to reduce research misconduct, including the submission of false information.

Manuscript 3, which to the author's knowledge is a first of its kind, examined the effect of including studies that used falsified data in a meta-analysis. The systematic review of apixaban studies found 22 meta-analyses. Among these, there were 99

statistical analyses available for sensitivity analyses of the effect of including published studies that had falsified data. Nearly one-third of the results of analyses showed considerable changes from the published analyses that would have affected the conclusions derived from the original meta-analysis publication. Changes included the odds ratio point estimate crossing of the 1.0 threshold, loss of statistical significance, gain of statistical significance, or both the loss of statistical significance and the change of the odds ratio point estimate (crossing of the 1.0 threshold). Model analysis showed that random effects models were more robust against the effects of falsified data. This novel study underscores the need for a robust sensitivity analysis for meta-analyses.

Clinical trials regulated by the FDA are considered to be of the highest quality, and this quality appears to be improving over time based on the decreasing trend in FDA citations and issued regulatory actions. However, the use of clinical trial data identified by the FDA as having suffered from research misconduct, namely falsification of data, in meta-analyses can provide biased results. A robust sensitivity analysis that considers data quality from available sources can help ensure calculation of the best estimates. Furthermore, stronger methods are needed to prevent the publication of data that have been identified as unreliable; the questionable data affects not only the original publication, but also any subsequent meta-analysis that uses the published results.

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