Compliance With Legal Requirement To Report Clinical Trial Results On ClinicalTrials.gov: A Cohort Study

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Background

Non-reporting of clinical trials can distort the evidence-base for clinical practice, breaches researchers' ethical obligations to participants, and represents an important source of research waste.[1] The imperative to report all clinical trial results is widely recognised, for example by the World Health Organisation and the Declaration of Helsinki.[2,3] Cohort studies have historically shown that the results of clinical trials are routinely left unpublished.[4,5] However, new laws in the United States and European Union now require the results of certain trials to be reported rapidly in tabular form onto a clinical trial registry, in addition to any other potentially slower forms of dissemination such as journal publication.[6–8]

The FDA Amendments Act of 2007 (FDAAA 2007) is a US law that requires certain interventional clinical trials to report their results directly to ClinicalTrials.gov, the US trial registry, within one year of the "primary completion date" (the date of the last subject's final follow-up visit for measurement of the final primary outcome). The US research community generates a large proportion of global trials, ClinicalTrials.gov is the largest registry in the world, and as of November 2019, half of the largest pharmaceutical companies in the world are US-based: this legislation therefore has potential to substantially improve trial reporting.[9,10] Since its passage in 2007, competing interpretations of the law have created confusion over which trials are required to report, and undermined independent assessment of FDAAA compliance.[11–13]

US legislation typically requires "rulemaking" by relevant executive agencies to fully clarify and implement all or parts of a law. This process involves the proposal of a draft rule, an open public comment period, and finally the publication of a "Final Rule" in the US Federal Register. "Clinical Trials Registration and Results Information Submission" (The Final Rule) was proposed by the US Department of Health and Human Services in 2015, and published in the Federal Register in late 2016 for implementation in 2017, a full decade after passage of the FDAAA 2007.[14] This Final Rule specifically clarified which trials are covered by the FDAAA 2007, when and how they should register and report, and which trials can request delays.[15,16] The characteristics of trials covered by the legislation were robustly described using unambiguous inclusion criteria with direct links to data fields on ClinicalTrials.gov. The FDA was also empowered to enforce the law by levying fines greater than $10,000 per day on the sponsor of each trial for non-compliance.[14]

The first trials covered by this new and improved legal regime became due in January 2018. We therefore set out to describe the extent of compliance with the FDAAA trial reporting rules; describe compliance at the level of individual sponsors; and explore factors associated with compliance.

Methods

Data Sources

We downloaded raw data for the entire registry in XML format from ClinicalTrials.gov (https://clinicaltrials.gov/ct2/resources/download) at least 15 times each month from March 2018 to September 2019. All cross-sectional analyses in this manuscript were performed on data extracted from ClinicalTrials.gov on 16 September 2019; monthly trends analysis used archived data closest to the 15th day of each month from March 2018 to September 2019.

Inclusion Criteria

Our cohort was "all trials due to report results under the Final Rule of the FDAAA 2007". Full detailed methodology are available in Supplementary Materials and a preprint methods paper.[17] In short, each trial on ClinicalTrials.gov was assessed against the "Applicable Clinical Trials" (ACT) and "probable ACT" (pACT) standards in the Final Rule following the logic in Table 1: the term "probable ACT" is an official designation with concrete criteria that

identify the cohort of ACTs starting before January 2017.[14,18,19] As per FDAAA legislation, each trial was considered due to report results if it was more than one year since the primary completion date (or study completion date if primary completion date was unavailable). We excluded trials where ClinicalTrials.gov granted a time-limited "certificate of delay": these are available for interventions or new clinical indications that have not yet received a marketing authorisation by the FDA, or under exceptional circumstances. Where missing or inconsistent registry data obstructed our ascertainment of whether a trial was due to report, we conservatively excluded it from our set of due applicable trials; where perfect ascertainment of due date was obstructed by a missing "day of the month" field, we conservatively assumed the trial was due to report at the latest possible date.

Table 1: ACT and pACT Identification Logic

Outcome Ascertainment

A trial was considered "reported" if results had been submitted ever, including late submission, and were either publicly available, or undergoing quality control (QC) review at ClinicalTrials.gov. A trial was considered "compliant" if these results were submitted within one year of the primary completion date, as required by the legislation.

Descriptive Statistics and Trends

We calculated the number and proportion of trials "reported", and "compliant", for the most current data (16 September 2019). We calculated the number of trials due, the proportion reported, and the proportion compliant, for each individual sponsor with more than 30 due trials on the registry. ClinicalTrials.gov defines a "sponsor" as "The organization or person who initiates the study and who has authority and control over the study." The sponsor may or may not also be the funder: however, the sponsor is legally responsible under FDAAA 2007 for the accuracy of registry data, and for reporting the results of the trial; the funder has no such responsibilities. Each trial has only a single lead sponsor. For each month from March 2018 to September 2019 we calculated the number of trials overdue and unreported, the proportion reported, and the proportion compliant, at mid-month, and plotted these on a graph.

Regression Analysis

To examine trial characteristics associated with reporting we a priori selected explanatory variables, based on clinical and methodological interest, which could be robustly derived from registry data; all variables were included in the final regression model. The following variables were generated: sponsor class (industry, non-industry, US government); presence of an industry collaborator; presence of a US government collaborator; phase (1/2, 2, 2/3, 3, 4, or "not applicable [usually early stage device trials]"); whether the trial was terminated; the trial's start year; separate indicator variables for the inclusion of each covered intervention type (drug, device, biologic/vaccine, diagnostic test, radiation treatment, combination treatment, and genetic treatment); trial location (US only, US + other countries, no US location, no location data); the total number of trials the sponsor had registered on ClinicalTrials.gov (as an indicator for the extent of a sponsor's experience with conducting trials, divided into quarters for analysis); and whether the trial had reached its "study completion date", meaning that the follow up time for all registered outcomes has been reached (rather than only the "primary outcomes", as per the "primary completion date" which triggers reporting under the legislation). A data dictionary providing further detail on each of these variables is available in Supplementary Materials. We generated crude descriptive statistics, broken down by each of these exposure variables, for proportion "reported" and "compliant"; we additionally conducted two logistic regressions using "reported" and "compliant" as outcome variables in order to identify trial characteristics associated with reporting.

Survival Analysis

We used the Kaplan-Meier method to model time from the date of primary completion to results submission for all due trials, and separately for industry and non-industry sponsored trials.

Software

We used Python 3·7 (Python Software Foundation) to download and process the raw ClinicalTrials.gov XML data, prepare data for analysis, and to generate summary statistics, figures on trends, and Kaplan-Meier plots (using the Lifelines module).[20] Logistic regression was conducted using STATA 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.). All data and software for downloading, processing and analysing raw data are shared online and referenced in Supplementary Materials for review and re-use (https://osf.io/x8nbv/ & https://github.com/ebmdatalab/fdaaa_trends).

Role of the Funding Source

This work was funded under a grant from the Laura and John Arnold Foundation. No specific funding was sought for this project. The funder had no role in: the study design; the collection, analysis, nor interpretation of the data; the writing of this report; nor the decision to submit for publication. All authors had access to all study data and all authors were responsible for the decision to submit the manuscript.

Results

Characteristics of Included Trials

The ClinicalTrials.gov database contained 316,342 trials in total at 16 September 2019. We excluded 294,817 trials as they were neither an ACT nor a pACT under the Final Rule. We excluded a further 16,650 trials as they were not yet due to report results. 666 trials were excluded as they were due, but had received a Certificate Of Delay. 4209 trials were therefore identified as due to report results onto ClinicalTrial.gov under the Final Rule of FDAAA 2007. A flow diagram for all trials on ClinicalTrials.gov is available in Supplementary Materials. 3,326 (79%) were identified as pACTs and 883 (21%) as ACTs. The median number of participants in these trials was 57 (IQR: 24-150). Table 2 includes characteristics of the due cohort: approximately half had non-industry sponsors (51·8%); most included a drug intervention (70·5%); and most were conducted solely in the US (71·3%). 63·1% of included trials had a start date of 2015 or later. Cohort details for start year are available in Supplementary Materials due to space restrictions.

Descriptive Statistics

1722 out of 4209 due trials had submitted results on time and in compliance with the law (40·9%, 95% CI: 39.4% to 42·2%) meaning 2487 trials have breached the law. 2686 out of 4209 trials had results submitted at any time (63·8%, 95% CI: 62·4% to 65·3%). Table 2 details the proportion of trials reported, and compliant, for each level of each variable. As above, detailed information on start year is available in Supplementary Materials.

Table 2: Proportion of Applicable Trials that are Reported, and Compliant, by Trial Category

Regression Analysis

Crude univariable and adjusted multivariable odds ratios for reporting and compliance across all explanatory variables are presented in Table 3. In the adjusted analyses, industry sponsors were significantly more likely to report results (OR 1·62, 95% CI: 1·35 to 1·96) and be compliant (3·08, 2·52 to 3·77) than non-industry, non-US government sponsors. Similarly, the presence of an industry collaborator regardless of sponsor class increased the adjusted odds of reporting (1·29, 1·06 to 1·58) and compliance (1·30: 1·08 to 1·58). Trials that had reached full completion date for all trial outcomes were more likely to report results (1·67, 1·29 to 2·17) and be in compliance (1·28, 1 to 1·65). Sponsors who have a large number of

trials registered on ClinicalTrials.gov were substantially more likely to report results (17·11, 13 to 22·54) and report in compliance (11·84, 9·36 to 14·99) when compared with the smallest sponsors. Trials with sites both inside the US and in other countries were more likely to report results than trials with only US sites (Any Reporting OR: 1·85, 95% CI: 1·48 to 2·32, Compliant OR: 1·93, 1·57 to 2·38). Trials wholly outside of the US (0·44, 95% CI: 0·32 to 0·60) and with no location data at all (0·42, 0·26 to 0·70) were less likely to report results than trials with only US sites. Based on reviewer feedback we conducted two post-hoc sensitivity analyses: one examining only the ACT population of trials (n=883); and one in which ACT/pACT status was included as an additional explanatory variable in the original regression. In the adjusted models ACTs are less likely to report at all (·66, ·54 to ·81) but no more likely to be compliant than pACTs (·84, ·69 to 1·03); only one finding described above changed substantially in the ACT-only model ("presence of an industry collaborator" was no longer significant); full results tables for these analyses are available in Supplementary Materials.

Table 3: Crude and Adjusted Odds Ratios for Factors Associated with Reporting under FDAAA 2007

Sponsor Ranking

Reporting and compliance performance is given in Table 4 for the 13 sponsors with more than 30 trials due; performance for all sponsors with at least ten due trials (n=78) is given in Supplementary Materials. An updated list giving current data for the performance of all sponsors will be maintained at fdaaa.trialstracker.net/rankings.

Table 4: Reporting Performance of Large Sponsors (≥30 due trials)

Time to Reporting

Figure 1a shows the delay in days from primary completion to results submission, generated with the Kaplan-Meier method; trials with results first submitted prior to the provided primary completion date (n=27, ·6%) were counted as reporting at time 0. The median delay from primary completion date to submission date was 424 days, 59 days higher than the legal reporting requirement of one year. The survival curves for industry sponsored and non-industry sponsored trials show the different overall reporting behaviours for each group (Figure 1b; for this analysis non-industry and "US gov" were combined since only 194 government sponsored trials were due). While both groups dramatically increase their trial reporting as they approach their due date, this phenomenon is more apparent among industry-sponsored trials; however, after trials become overdue, an industry trial is more likely to remain unreported (Figure 1c). 95% confidence intervals are provided for Figures 1b & 1c.

Figure 1: Kaplan-Meier Curves Showing Time to Reporting for All Trials and Industry/Non-Industry Sponsors

Trends in FDAAA 2007 Compliance

Figure 2 shows the proportion of trials that reported at all, the proportion of compliant trials, and the cumulative number of overdue trials, at the midpoint of each month from March 2018 to September 2019.

Figure 2: Percent Reported, Percent Compliant, and Number of Overdue Trials by Month

Discussion

Summary

The long-awaited Final Rule on FDAAA 2007 reporting requirements has been largely ignored by sponsors: only 63·8% of due trials have submitted results; and only 40·9% have

submitted results within the legal one year deadline. There is currently no sign of improvement: the proportion of compliant trials has plateaued since July 2018. Industry sponsors, and sponsors with extensive experience of running large numbers of trials, are more likely to report results, while US Government sponsored trials have the lowest compliance rate of any sponsor class (31·4%): the fact that the US government cannot comply with its own laws is especially concerning. The total number of unreported trials as of September 2019 is 1523, out of 4209 due to report.

Strengths and Limitations

This is the first study to assess compliance with the Final Rule of the FDA Amendments Act 2007, a long-awaited piece of legislation that covers thousands of clinical trials on the largest registry in the world. Our analysis includes all publicly identifiable trials covered by the legislation, and reports longitudinal data in addition to cross-sectional analysis. All data and software for downloading, processing, and analysing raw data are shared openly for independent critical review consistent with the principles of open science; our method for identifying applicable trials has been available for open public review since February 2018.[17] (https://github.com/ebmdatalab/clinicaltrials-act-tracker & https://github.com/ebmdatalab/clinicaltrials-act-converter)

We rely on the accuracy of source data at ClinicalTrials.gov. Usefully however FDAAA makes sponsors legally responsible for ensuring that their own registry data is accurate, and holds each sponsor liable for breaches of the law using the information provided by them on the registry, even if that information is out of date or inaccurate. A sponsor is therefore in breach of the law if they have failed to report on time, or if they appear to have failed to report on time, due to their own failure to provide correct registry information. This is a positive feature of the law: incomplete and inaccurate data on a registry would otherwise compromise its utility as a tool for enforcement and public accountability.

In only one situation, legally withheld data on ClinicalTrials.gov can block ascertainment of whether a trial is "applicable": specifically, ClinicalTrials.gov declines to make public whether a trial is part of a "New Drug Application" or "Investigational Device Exemption" due to issues of commercial confidentiality. In cases where this field would be the deciding factor for inclusion, we conservatively excluded the trial from our analysis, in order to avoid ever incorrectly asserting that a trial is in breach of the law.

This study only examines the availability of results directly on ClinicalTrials.gov as required by law, not the quality of reported results, nor their availability elsewhere. However, prior research has established that results reporting to ClinicalTrials.gov is generally of high quality and in many aspects more complete than journal publication.[21–23] Previous studies have established that ClinicalTrials.gov is often the sole repository for the results associated with registered trials: this underscores the importance of sponsors complying with FDAAA.[24,25]

Findings in Context:

These findings substantially expand and improve on prior research. Past assessments of the FDAAA 2007 prior to the implementation of the Final Rule reported low rates of compliance. In 2012, Prayle and colleagues found that just 22% of trials with a primary completion date greater than 12 months prior had reported results.[12] A 2015 study by Anderson and colleagues reported that 13.4% of "Highly Likely ACTs" had reported within 12 months, while 38.3% had reported results ever.[11] However, due to the absence of data fields on ClinicalTrials.gov which are now required by law, and the absence of clarification by the Final Rule, both studies understandably but incorrectly included trials that are in fact not applicable. Other research on FDAAA 2007 pre-dates the clarity of the Final Rule and manually assessed only very small subsets of applicable trials rather than the entire population.[13,26,27]

Our findings on compliance with FDAAA are consistent with our previous findings on compliance with European Union rules which require all trials on medicinal products conducted in Europe since 2004 to report results directly onto the European Clinical Trials Register within 12 months of completion.[8] For European trials we similarly found that industry sponsors, and sponsors with a large number of trials in progress, were more likely to report results. High levels of non-compliance with the FDAAA 2007 Final Rule among non-industry sponsors is consistent with prior survey research showing variable preparedness for the Final Rule among US academic organisations.[28]

Policy Implications

Clinical trials are not abstract research projects: they are large, expensive, practical evaluations that aim to directly inform clinical practice. Efforts to synthesize evidence into systematic reviews or inform guidelines are compromised by missing trial data. Patients and clinicians cannot make informed choices when the results of clinical trials are routinely withheld.[29] The importance of addressing the bias from non-publication of clinical trials has been emphasised since at least 1980.[30] It is therefore disappointing to note that forty years later the community has only progressed to legislation being passed and then largely ignored. One explanation for the high observed rates of non-compliance may be the apparent absence of any enforcement action by regulators. The Final Rule established explicit sanctions, including fines of up to $10,000 a day (now $12,103 inflation adjusted).[14,31] We estimate that with strict enforcement of the compliance actions described in the Final Rule, over $4 billion in fines could have been collected as of September 2019.[17] To our knowledge there have been no fines imposed by the FDA to date; indeed we are unable to find any public record of any enforcement action by the FDA on any aspect of the Final Rule.

Following outreach from the authors to the FDA about compliance with the FDAAA 2007 reporting requirements an FDA Senior Health Policy Analyst responded in May 2018 stating that “the agency’s goal is to achieve voluntary compliance with the law without having to resort to legal action” and they monitor non-compliance using a “risk-based approach” centered on “higher risk [ACTs], or [ACTs] of significant public health importance; responsible parties for which there is a pattern of previous non-compliance...and [ACTs] for which noncompliance...may exist in conjunction with noncompliance with other laws and regulations concerning the conduct of the trial” (full letter available in Supplementary Materials). The FDA reiterated this general enforcement in draft enforcement guidance: trial reporting was to be checked as part of Bioresearch Monitoring Program (BIMO) inspections and multiple levels of notice would be issued prior to any civil monetary penalties.[32] Despite public comment on this guidance closing in November 2018, and more than 1500 unreported applicable trials to date, no formal response or plan for enforcement has been issued by the FDA as of writing.

In our view compliance with both European and US legislation on trial reporting will only improve when regulators routinely impose fines, and other sanctions, on sponsors who breach their ethical and legal obligation to report trial results appropriately. In the absence of statutory enforcement, open public audit is widely recognised as a valuable tool to increase accountability and improve quality in a policy setting.[33,34] Even a fraction of the fines we estimate the FDA could have collected to date would fund a robust audit and feedback infrastructure with the aim of improving trial reporting under the FDAAA 2007. Absent this, we have established an openly accessible public website at fdaaa.trialstracker.net where updated data on compliance with FDAAA will be posted on a daily basis, providing compliance statistics for each individual sponsor, and identifying each individual overdue trial for every sponsor. We hope that sponsors who aim to comply fully with the law will find this service helpful.

Conclusion

Compliance with important US rules on clinical trial reporting has been poor, and is not improving. Effective enforcement and action from sponsors is needed; until then, open public audit of compliance for each individual sponsor may help.

Contributors: The project was conceived by BG. BG obtained the funding for the project. SB wrote the code for processing and storing data from ClinicalTrials.gov and maintains the FDAAA TrialsTracker code-base. NJD wrote the code to identify applicable trials, conduct the analyses, and adapted prior code from BG for the analysis in STATA. NJD conducted all analyses with input from BG. NJD wrote the first draft of the manuscript. All authors contributed to the interpretation of the results and final manuscript. BG is guarantor.

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Data Sharing: All code for this study, along with code for the entire TrialsTracker project, is available via open source licensing on GitHub (https://github.com/ebmdatalab/fdaaa_trends). All underlying datasets for this study are available for download from the Open Science Foundation (https://osf.io/x8nbv/). Archived ClinicalTrials.gov data for any other dates held by the authors is freely available upon request.

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Research in Context

Evidence before this study:

Non-reporting of clinical trial results has been well-documented for several decades, and represents a substantial threat to the integrity of the evidence-base for all of clinical medicine. The FDA Amendments Act 2007 aimed to address this issue. Prior studies examining compliance were hindered by ambiguities in the legislation, and incomplete data that blocked identification of applicable trials; most only included small subsets of trials. The Final Rule clarifying the Act was implemented in 2017. A search of PubMed and Google Scholar for “FDA Amendments Act” finds no assessment of compliance with the Final Rule. Compliance with similar new EU rules on trial reporting was assessed in 2018 and found to be poor (49.5%).

Added value of this study

This is the first study to assess compliance with the Final Rule of the FDA Amendments Act 2007: this law was widely celebrated as a solution to the problems of publication bias and clinical trial reporting. Our findings raise important questions around lack of enforcement and the need for public accountability. All our data and software for downloading, processing and analysing raw data are shared openly for independent review and re-use; this is the gold standard for reproducibility and facilitates other researchers in the field. We will maintain updated compliance data for each individual sponsor and trial at fdaaa.trialstracker.net as an open public service to help sponsors who aim to comply fully with the law.

Implications of the available evidence

The FDAAA 2007 was reasonably expected to ensure results reporting for the large number of trials conducted under the regulatory authority of the US. Our findings definitively demonstrate, with the most current data possible, that compliance has been poor. It is encouraging to note that results reporting is more common among trials with an industry sponsor, and those conducted by an experienced sponsor with a large number of registered trials: this suggests that research experience and robust internal governance processes can contribute to improved performance. However with 2487 trials conservatively identified as breaching the law it is very concerning to note that there has been no enforcement by the FDA to date. It is likely that enforcement would improve compliance; until then, public accountability through tools such as fdaaa.trialstracker.net may help.