

Compliance with legal requirement to report clinical trial results on ClinicalTrials.gov: a cohort study



Nicholas J DeVito, Seb Bacon, Ben Goldacre

Summary

Background Failure to report the results of a clinical trial can distort the evidence base for clinical practice, breaches researchers' ethical obligations to participants, and represents an important source of research waste. The Food and Drug Administration Amendments Act (FDAAA) of 2007 now requires sponsors of applicable trials to report their results directly onto ClinicalTrials.gov within 1 year of completion. The first trials covered by the Final Rule of this act became due to report results in January, 2018. In this cohort study, we set out to assess compliance.

Methods We downloaded data for all registered trials on ClinicalTrials.gov each month from March, 2018, to September, 2019. All cross-sectional analyses in this manuscript were performed on data extracted from ClinicalTrials.gov on Sept 16, 2019; monthly trends analysis used archived data closest to the 15th day of each month from March, 2018, to September, 2019. Our study cohort included all applicable trials due to report results under FDAAA. We excluded all non-applicable trials, those not yet due to report, and those given a certificate allowing for delayed reporting. A trial was considered reported if results had been submitted and were either publicly available, or undergoing quality control review at ClinicalTrials.gov. A trial was considered compliant if these results were submitted within 1 year of the primary completion date, as required by the legislation. We described compliance with the FDAAA 2007 Final Rule, assessed trial characteristics associated with results reporting using logistic regression models, described sponsor-level reporting, examined trends in reporting, and described time-to-report using the Kaplan-Meier method.

Findings 4209 trials were due to report results; 1722 (40.9%; 95% CI 39.4–42.2) did so within the 1-year deadline. 2686 (63.8%; 62.4–65.3) trials had results submitted at any time. Compliance has not improved since July, 2018. Industry sponsors were significantly more likely to be compliant than non-industry, non-US Government sponsors (odds ratio [OR] 3.08 [95% CI 2.52–3.77]), and sponsors running large numbers of trials were significantly more likely to be compliant than smaller sponsors (OR 11.84 [9.36–14.99]). The median delay from primary completion date to submission date was 424 days (95% CI 412–435), 59 days higher than the legal reporting requirement of 1 year.

Interpretation Compliance with the FDAAA 2007 is poor, and not improving. To our knowledge, this is the first study to fully assess compliance with the Final Rule of the FDAAA 2007. Poor compliance is likely to reflect lack of enforcement by regulators. Effective enforcement and action from sponsors is needed; until then, open public audit of compliance for each individual sponsor may help. We will maintain updated compliance data for each individual sponsor and trial at fdaaa.trialstracker.net.

Funding Laura and John Arnold Foundation.

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Introduction

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 WHO 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 USA and EU now require 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 Food and Drug Administration Amendments Act (FDAAA) of 2007 is a US law that requires certain

interventional clinical trials to report their results directly to the US trial registry ClinicalTrials.gov, within 1 year of the primary completion date (the date of the last participant's final follow-up visit for measurement of the final primary outcome). The US research community generates a large proportion of global trials, and ClinicalTrials.gov is the largest registry in the world; additionally, as of November, 2019, half of the ten largest pharmaceutical companies in the world are based in the USA. This legislation therefore has the potential to substantially improve trial reporting.^{9,10} Since its passage in 2007, competing interpretations of the FDAAA have created confusion over which trials are required to report, and undermined independent assessment of FDAAA compliance.^{11–13}

Published Online
January 17, 2020
[https://doi.org/10.1016/S0140-6736\(19\)33220-9](https://doi.org/10.1016/S0140-6736(19)33220-9)
See Online/Comment
[https://doi.org/10.1016/S0140-6736\(20\)30105-7](https://doi.org/10.1016/S0140-6736(20)30105-7)

The DataLab, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
(N J DeVito MPH, S Bacon BA, B Goldacre MBBS)

Correspondence to:
Dr Ben Goldacre, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford OX2 6GG, UK
ben.goldacre@phc.ox.ac.uk

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 Food and Drug Administration Amendments Act (FDAAA) of 2007 aimed to address this issue. Previous studies examining compliance were hindered by ambiguities in the legislation and incomplete data that blocked identification of applicable trials; most studies 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 complete assessment of compliance with the Final Rule. Compliance with similar new EU rules on trial reporting was assessed in 2018 and was found to be poor, with only 3601 (49.5%) of 7274 trials reporting results.

Added value of this study

To our knowledge, this is the first study to assess compliance with the Final Rule of the FDAAA of 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 all 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 USA. Using data extracted from ClinicalTrials.gov up to Sept 16, 2019, our findings show that compliance has been poor and is not improving. It is encouraging to note that results reporting is more common among trials with an industry sponsor, and among those conducted by a 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 in our study, it is concerning to note there has been no enforcement by the FDA to date. Action by regulators would improve compliance; until then, public accountability through tools such as fdaaa.trialstracker.net could help.

Panel: ACT and probable ACT identification logic**ACT logic (trials started on or after Jan 18, 2017)**

“Study Type” is Interventional AND (“FDA Regulated Drug” OR “FDA Regulated Device”) is Yes AND “Phase” is (1/2, 2, 2/3, 3, 4 OR N/A) AND “Primary Purpose” is NOT Device Feasibility AND “Study Status” is NOT Withdrawn.

Probable ACT logic (trials started before, but completed on or after Jan 18, 2017)

“Study Type” is Interventional AND “Phase” is (1/2, 2, 2/3, 3, 4 OR N/A) AND “Primary Purpose” is NOT Device Feasibility AND “Study Status” is NOT Withdrawn.

IF (“FDA Regulated Drug” OR “FDA Regulated Device”) field is available: (“FDA Regulated Drug” OR “FDA Regulated Device”) is Yes.

IF (“FDA Regulated Drug” OR “FDA Regulated Device”) field is NOT available: “Intervention Type” is (Biological OR Drug OR Device OR Genetic OR Radiation OR Combination Product OR Diagnostic Test) AND “Study Location” includes (United States OR US Territories) AND “Is FDA Regulated” is (True OR Null).

ACT=applicable clinical trial.

Information Submission 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 January, 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 US\$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. In this cohort study, we set out to describe the extent of compliance with the FDAAA 2007 trial reporting rules, describe compliance at the level of individual sponsors, and explore factors associated with compliance.

Methods**Data collection**

We downloaded raw data for the entire registry in XML format from ClinicalTrials.gov 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 Sept 16, 2019; monthly trends analysis used archived data closest to the 15th day of each month from March, 2018, to September, 2019.

US legislation typically requires rule-making 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. The Final Rule of *Clinical Trials Registration and Results*

For instructions on downloading ClinicalTrials.gov content for analysis see <https://clinicaltrials.gov/ct2/resources/download>

All trials due to report results under the Final Rule of the FDAAA 2007 were included in our cohort. Full detailed methods are available in the appendix (pp 1–5) and online.¹⁷

Data analysis

Each trial on ClinicalTrials.gov was assessed against applicable clinical trial (ACT) and probable ACT standards in the Final Rule following the logic in the panel; the term “probable ACT” is an official designation with concrete criteria that identify the cohort of ACTs starting before January, 2017.^{14,18,19} Our logic for trial identification uses the field “Is FDA Regulated”, which was available before the Final Rule and is now depreciated on ClinicalTrials.gov. We used an archived version of the field as a conservative check on probable ACTs per the described logic. These data were retrieved from a Jan 5, 2017, archive of ClinicalTrials.gov available from the Clinical Trials Transformation Initiative (the field was removed on Jan 11, 2017).

As per FDAAA legislation, each trial was considered due to report results if more than 1 year had passed since the primary completion date (or study completion date if primary completion date was unavailable). We excluded trials which had been granted a time-limited certificate of delay by ClinicalTrials.gov; these certificates can be obtained for trials of new interventions or clinical indications that have not yet received a marketing authorisation by the FDA, or for trials under exceptional circumstances. When 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. When 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.

A trial was considered reported if results had been submitted (at any point, including late submission) and were either publicly available, or undergoing quality control review at ClinicalTrials.gov. A trial was considered compliant if these results were submitted within 1 year of the primary completion date, as required by the legislation.

We calculated the number and proportion of trials reported and compliant for the most recent date (Sept 16, 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

	Trials due to report (%)	Trials with any results (%; 95% CI)	Compliant trials (%; 95% CI)
Total	4209 (100%)	2686 (63.8%; 62.4–65.3)	1722 (40.9%; 39.4–42.4)
Sponsor class			
Non-industry	2178 (51.8%)	1358 (62.4%; 60.3–64.4)	737 (33.8%; 31.9–35.9)
Industry	1837 (43.6%)	1184 (64.5%; 62.2–66.6)	924 (50.3%; 48.0–52.6)
US Government	194 (4.6%)	144 (74.2%; 67.6–79.9)	61 (31.4%; 25.3–38.3)
Industry collaborator	715 (17.0%)	482 (67.4%; 63.9–70.8)	310 (43.4%; 39.8–47.0)
US Government collaborator	461 (11.0%)	330 (71.6%; 67.3–75.5)	180 (39.0%; 34.7–43.6)
Phase			
1/2	327 (7.8%)	191 (58.4%; 53.0–63.6)	117 (35.8%; 30.8–41.1)
2	1329 (31.6%)	916 (68.9%; 66.4–71.4)	575 (43.3%; 40.6–45.9)
2/3	99 (2.4%)	56 (56.6%; 46.6–66.0)	40 (40.4%; 31.2–50.4)
3	750 (17.8%)	557 (74.3%; 71.0–77.3)	415 (55.3%; 51.8–58.9)
4	600 (14.3%)	392 (65.3%; 61.4–69.0)	242 (40.3%; 36.5–44.3)
NA	1104 (26.2%)	574 (52.0%; 49.0–54.9)	333 (30.2%; 27.5–32.9)
Terminated	663 (15.8%)	475 (71.6%; 68.1–74.9)	301 (45.4%; 41.6–49.2)
Reached full completion	3811 (90.5%)	2434 (63.9%; 62.3–65.4)	1547 (40.6%; 39.0–42.2)
Trial contains a drug	2968 (70.5%)	2025 (68.2%; 66.5–69.9)	1320 (44.5%; 42.7–46.3)
Trial contains a biological or vaccine	369 (8.8%)	265 (71.8%; 67.0–76.2)	180 (48.8%; 43.7–53.9)
Trial contains a device	1020 (24.2%)	533 (52.3%; 49.2–55.3)	314 (30.8%; 28.0–33.7)
Trial contains a diagnostic test	25 (0.6%)	14 (56.0%; 36.2–74.0)	7 (28.0%; 13.8–48.7)
Trial contains radiation treatment	103 (2.5%)	64 (62.1%; 52.4–71.0)	34 (33.0%; 24.6–42.7)
Trial contains a combination product	13 (0.3%)	7 (53.8%; 27.3–78.4)	2 (15.4%; 3.6–46.6)
Trial contains a genetic treatment	11 (0.3%)	5 (45.5%; 19.4–74.3)	4 (36.4%; 13.6–67.5)
Trial location			
US only	3000 (71.3%)	1843 (61.4%; 59.7–63.2)	1046 (34.9%; 33.2–36.6)
US and other country	876 (20.8%)	700 (79.9%; 77.1–82.4)	565 (64.5%; 61.3–67.6)
No US location	242 (5.8%)	99 (40.9%; 34.9–47.2)	79 (32.6%; 27.0–38.8)
No location data available	91 (2.2%)	44 (48.4%; 38.2–58.6)	32 (35.2%; 26.0–45.5)
Total number of trials registered per trial sponsor			
First quarter (1–12)	1128 (26.8%)	451 (40.0%; 37.2–42.9)	241 (21.4%; 19.1–23.9)
Second quarter (13–219)	1119 (26.6%)	601 (53.7%; 50.8–56.6)	362 (32.4%; 29.7–35.2)
Third quarter (221–910)	1004 (23.9%)	766 (76.3%; 73.6–78.8)	491 (48.9%; 45.8–52.0)
Fourth quarter (925–3276)	958 (22.8%)	868 (90.6%; 88.6–92.3)	628 (65.6%; 62.5–68.5)

Table 1: Reported and compliant applicable clinical trials by trial category

number of trials overdue and unreported, the proportion reported, and the proportion compliant, at mid-month, and plotted these on a graph.

To examine trial characteristics associated with reporting we a priori selected explanatory variables on the basis of 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

See Online for appendix
For the Clinical Trials
Transformation Initiative see
<https://aact/ctti-clinicaltrials.org/snapshots>

	Any results crude OR (95% CI; p value)	Any results adjusted OR (95% CI; p value)	Compliant crude OR (95% CI; p value)	Compliant adjusted OR (95% CI; p value)
Sponsor class				
Non-industry	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Industry	1.09 (0.96–1.25; 0.17)	1.62 (1.35–1.96; <0.0001)	1.98 (1.74–2.25; <0.0001)	3.08 (2.52–3.77; <0.0001)
US Government	1.74 (1.25–2.43; 0.0011)	0.82 (0.54–1.23; 0.34)	0.90 (0.65–1.23; 0.50)	0.48 (0.33–0.69; <0.0001)
Industry collaborator	1.21 (1.02–1.44; 0.028)	1.29 (1.06–1.58; 0.013)	1.13 (0.96–1.33; 0.14)	1.30 (1.08–1.58; 0.0065)
US Government collaborator	1.49 (1.20–1.84; 0.00025)	1.45 (1.12–1.87; 0.0049)	0.92 (0.75–1.12; 0.39)	1.19 (0.94–1.51; 0.15)
Phase				
1/2	0.49 (0.37–0.64; <0.0001)	0.65 (0.47–0.90; 0.0086)	0.45 (0.34–0.59; <0.0001)	0.91 (0.66–1.24; 0.55)
2	0.77 (0.63–0.94; 0.010)	0.99 (0.78–1.25; 0.90)	0.62 (0.51–0.74; <0.0001)	1.05 (0.84–1.30; 0.69)
2/3	0.45 (0.29–0.69; 0.00028)	0.52 (0.32–0.86; 0.0097)	0.55 (0.36–0.84; 0.0056)	0.94 (0.58–1.51; 0.78)
3	1 (ref)	1 (ref)	1 (ref)	1 (ref)
4	0.65 (0.52–0.83; 0.00037)	1.01 (0.75–1.34; 0.97)	0.55 (0.44–0.68; <0.0001)	1.15 (0.88–1.52; 0.31)
NA	0.38 (0.31–0.46; <0.0001)	0.65 (0.46–0.92; 0.014)	0.35 (0.29–0.42; <0.0001)	0.87 (0.62–1.21; 0.40)
Terminated	1.53 (1.27–1.83; <0.0001)	1.42 (1.16–1.74; 0.00078)	1.24 (1.05–1.47; 0.011)	1.16 (0.96–1.41; 0.11)
Reached full completion	1.02 (0.83–1.27; 0.83)	1.67 (1.29–2.17; 0.00011)	0.87 (0.71–1.07; 0.19)	1.28 (1.00–1.65; 0.050)
Trial contains a drug	1.88 (1.65–2.16; <0.0001)	1.71 (1.20–2.44; 0.0030)	1.67 (1.45–1.92; <0.0001)	1.45 (1.05–2.01; 0.024)
Trial contains a biological or vaccine	1.49 (1.18–1.89; 0.00087)	1.64 (1.14–2.35; 0.0074)	1.42 (1.15–1.76; 0.0013)	1.51 (1.11–2.08; 0.0098)
Trial contains a device	0.53 (0.46–0.61; <0.0001)	1.90 (1.30–2.77; 0.00093)	0.56 (0.48–0.65; <0.0001)	1.35 (0.95–1.92; 0.099)
Trial contains a diagnostic test	0.72 (0.33–1.59; 0.42)	1.51 (0.60–3.79; 0.38)	0.56 (0.23–1.34; 0.19)	1.14 (0.43–3.01; 0.80)
Trial contains radiation treatment	0.93 (0.62–1.39; 0.72)	0.81 (0.50–1.32; 0.40)	0.71 (0.47–1.07; 0.10)	1.00 (0.63–1.59; 0.99)
Trial contains a combination product	0.66 (0.22–1.97; 0.46)	1.48 (0.44–5.00; 0.53)	0.26 (0.06–1.18; 0.081)	0.48 (0.10–2.30; 0.36)
Trial contains a genetic treatment	0.47 (0.14–1.55; 0.22)	0.94 (0.25–3.54; 0.93)	0.82 (0.24–2.82; 0.76)	1.73 (0.46–6.41; 0.41)
Trial location				
US only	1 (ref)	1 (ref)	1 (ref)	1 (ref)
US and other country	2.50 (2.08–2.99; <0.0001)	1.85 (1.48–2.32; <0.0001)	3.39 (2.90–3.97; <0.0001)	1.93 (1.57–2.38; <0.0001)
No US location	0.43 (0.33–0.57; <0.0001)	0.44 (0.32–0.60; <0.0001)	0.91 (0.68–1.20; 0.49)	0.77 (0.55–1.06; 0.11)
No location data available	0.59 (0.39–0.89; 0.013)	0.42 (0.26–0.70; 0.0074)	1.01 (0.65–1.57; 0.95)	0.67 (0.4–1.13; 0.13)
Total number of trials registered per trial sponsor				
First quarter (1–12)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Second quarter (13–219)	1.74 (1.47–2.06; <0.0001)	1.72 (1.44–2.06; <0.0001)	1.76 (1.46–2.13; <0.0001)	1.76 (1.44–2.16; <0.0001)
Third quarter (221–910)	4.83 (4.00–5.83; <0.0001)	6.09 (4.93–7.53; <0.0001)	3.52 (2.92–4.25; <0.0001)	6.18 (4.94–7.73; <0.0001)
Fourth quarter (925–3276)	14.48 (11.30–18.54; <0.0001)	17.11 (13.00–22.54; <0.0001)	7.00 (5.76–8.51; <0.0001)	11.84 (9.36–14.99; <0.0001)
Start year (increase of 1 year)	0.91 (0.90–0.94; <0.0001)	1.00 (0.97–1.04; 0.82)	1.00 (0.97–1.02; 0.75)	1.05 (1.02–1.08; 0.00090)

OR=odds ratio.

Table 2: Crude and adjusted ORs for factors associated with reporting under the Food and Drug Administration Amendments Act 2007

[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, biological or vaccine, diagnostic test, radiation treatment, combination treatment, and genetic treatment); trial location (US only, US and 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 had 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 the appendix (pp 7–9). 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 to identify trial characteristics associated with reporting.

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 3.75 (Python Software Foundation, Wilmington, DE, USA) to download and process the raw ClinicalTrials.gov XML data, prepare data for analysis,

and generate summary statistics, figures on trends, and Kaplan-Meier plots (using the Lifelines module).²⁰ Logistic regression was conducted using STATA 14.1 (StataCorp, College Station, TX USA.). All software for downloading, processing, and analysing raw data are shared online on GitHub²¹ and referenced in the appendix (pp 1–5) for review and re-use.

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 of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. All authors had full access to all the data in the study and all authors were responsible for the decision to submit the manuscript for publication.

Results

On Sept 16, 2019, the ClinicalTrials.gov database contained 316 342 trials in total. We excluded 294 817 trials as they were neither an ACT nor a probable ACT 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 from ClinicalTrials.gov. 4209 trials were therefore identified as due to report results onto ClinicalTrials.gov under the Final Rule of FDAAA 2007. A flow diagram for all trials on ClinicalTrials.gov is available in the appendix (p 6).

3326 (79.0%) of 4209 due trials were probable ACTs and 883 (21.0%) were ACTs. The median number of participants in these trials was 57 (IQR 24–150). Table 1 includes characteristics of the due cohort: approximately half had non-industry, non-US Government sponsors (2178 [51.8%]), and most included a drug intervention (2968 [70.5%]) and were conducted solely in the USA (3000 [71.3%]). 2657 (63.1%) of included trials had a start date of 2015 or later. Cohort details for start year are available in the appendix (p 10).

1722 (40.9%; 95% CI 39.4–42.2) trials had submitted results on time and in compliance with the law, meaning 2487 trials breached the law. 2686 (63.8%; 62.4–65.3) trials had results submitted at any time. Table 1 details the proportion of trials reported, and compliant, for each level of each variable. Detailed information on start year is available in the appendix (p 10).

Crude univariable and adjusted multivariable odds ratios (ORs) for reporting and compliance across all explanatory variables are presented in table 2. In the adjusted analyses, industry sponsors were significantly more likely to report results (OR 1.62 [95% CI 1.35–1.96]) and be compliant (OR 3.08 [2.52–3.77]) than non-industry, non-US Government sponsors. Similarly, the presence of an industry collaborator regardless of sponsor class increased the adjusted odds of reporting (OR 1.29 [1.06–1.58]) and compliance (OR 1.30 [1.08–1.58]). Trials

	Trials due	Trials with any results (%)	Compliant trials (%)
MD Anderson Cancer Center	85	71 (83.5%)	29 (34.1%)
National Cancer Institute	79	65 (82.3%)	24 (30.4%)
Massachusetts General Hospital	58	46 (79.3%)	32 (55.2%)
Mayo Clinic	47	45 (95.7%)	10 (21.3%)
Novartis Pharmaceuticals	46	46 (100%)	46 (100%)
Gilead Sciences	45	45 (100%)	43 (95.6%)
GlaxoSmithKline	43	43 (100%)	42 (97.7%)
Pfizer	42	42 (100%)	39 (92.9%)
Hoffmann-La Roche	38	38 (100%)	36 (94.7%)
University of California, San Francisco	38	26 (68.4%)	6 (15.8%)
AstraZeneca	37	37 (100%)	37 (100%)
Memorial Sloan Kettering Cancer Center	36	34 (94.4%)	33 (91.7%)
University of North Carolina, Chapel Hill	32	32 (100%)	26 (81.3%)

Table 3: Reporting performance of large sponsors with more than 30 due trials

For the GitHub repository of all the code for this study see https://github.com/ebmdatalab/fdaaa_trends

that had reached full completion date for all trial outcomes were more likely to report results (OR 1.67 [1.29–2.17]) and be in compliance with the Final Rule (OR 1.28 [1.00–1.65]). Sponsors who have a large number of trials (887–3254) registered on ClinicalTrials.gov were significantly more likely to report results (OR 17.11 [13.00–22.54]) and report in compliance (OR 11.84 [9.36–14.99]) than sponsors with a small number of trials (1–12). Trials with sites both inside the US and in other countries were more likely to report results than trials with only US sites (any results OR 1.85 [1.48–2.32]; compliant OR 1.93 [1.57–2.38]). Trials outside of the US (OR 0.44 [0.32–0.60]) and with no location data available (OR 0.42 [0.26–0.70]) were less likely to report results than trials located in the USA only. Based on reviewer feedback we conducted two post-hoc sensitivity analyses: one examining only the ACT population of 883 trials, and one in which ACT or probable ACT status was included as an additional explanatory variable in the original regression. In the adjusted model, ACTs are less likely to report at all (OR 0.66 [0.54–0.81]) but no less likely to be compliant than probable ACTs (OR 0.84 [0.69–1.03]); only one finding from our primary analyses 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 the appendix (pp 11–16).

Reporting and compliance performance for the 13 sponsors with more than 30 trials due is given in table 3; performance for all 78 sponsors with at least ten due trials is given in the appendix (pp 17–19). We will maintain an updated list of current data for the performance of all sponsors at fdaaa.trialstracker.net/rankings.

Figure 1A shows the delay from primary completion date to results submission for all trials, generated with the Kaplan-Meier method. 27 (0.6%) of 4209 due trials

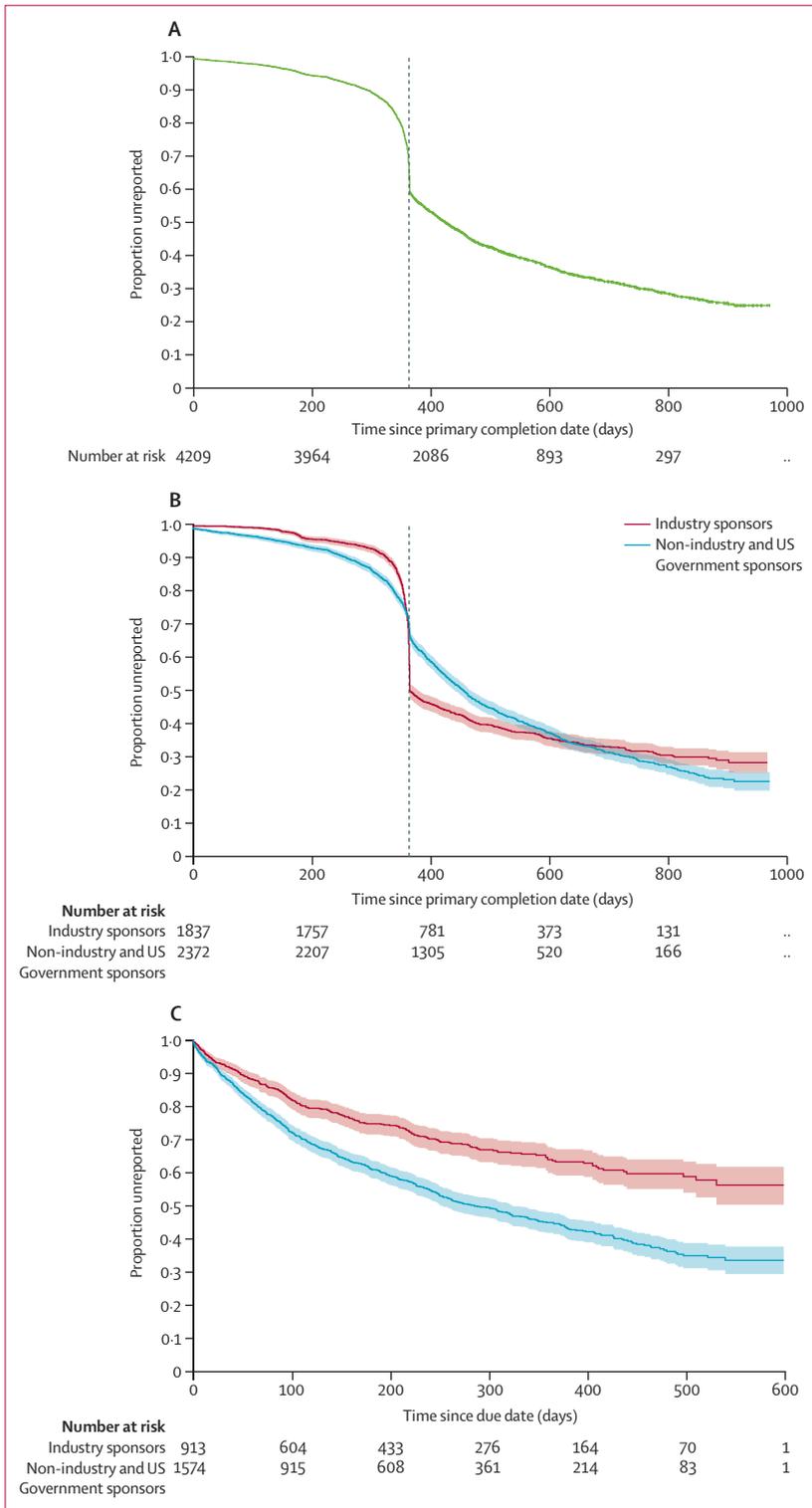


Figure 1: Kaplan-Meier curves showing time to reporting from primary completion date for all trials (A), trials by industry and non-industry sponsors (B), and overdue trials by industry and non-industry sponsors (C). The dotted line indicates the 1-year deadline by which trials should report their results according to the Food and Drug Administration Amendments Act of 2007. 95% CIs are provided for panels B and C.

that had submitted results before the primary completion date were counted as reporting at time 0. The median delay from primary completion date to submission date was 424 days (95% CI 412–435), 59 days longer than the legal reporting requirement of 1 year. Figure 1B shows the delay in results submission for trials by industry sponsors and non-industry sponsors. For this analysis non-industry sponsors and US Government sponsors were combined since only 194 government-sponsored trials were due. Although both groups substantially increase their trial reporting as they approach their due date, this increase is more apparent among industry-sponsored trials. Figure 1C shows reporting over time for overdue non-compliant trials that did not have results reported 1 year after their primary completion date. Our findings show that after trials become overdue, an industry-sponsored trial is more likely to remain unreported.

Figure 2 shows the proportion of trials that reported at all, the proportion of compliant trials, and the cumulative number of overdue, unreported trials, at the midpoint of each month from March, 2018, to September, 2019. Our findings show that although overall reporting has increased gradually over time, compliance has remained stable at approximately 40% since July, 2018. Copies of all raw and processed data used for this analysis are available via the Open Science Framework.²²

Discussion

The long-awaited Final Rule on FDAAA 2007 reporting requirements has been widely ignored by sponsors; by Sept 16, 2019, only 2686 (63.8%) of 4209 due trials had submitted results and only 1722 (40.9%) had submitted results in compliance with the 1-year deadline; the total number of unreported trials is 1523 (36.1%). Currently, there is no sign of improvement—the proportion of compliant trials has plateaued at around 40% since July, 2018. Industry sponsors and sponsors running large numbers of trials were more likely to report results, while trials sponsored by the US Government had the lowest compliance of any sponsor class with only 61 (31.4%) trials reporting results within 1 year of primary completion. The fact that the US Government cannot comply with its own laws is especially concerning.

To our knowledge, this is the first study to assess compliance with the Final Rule of the FDAAA 2007, a 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 a 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.^{17,21}

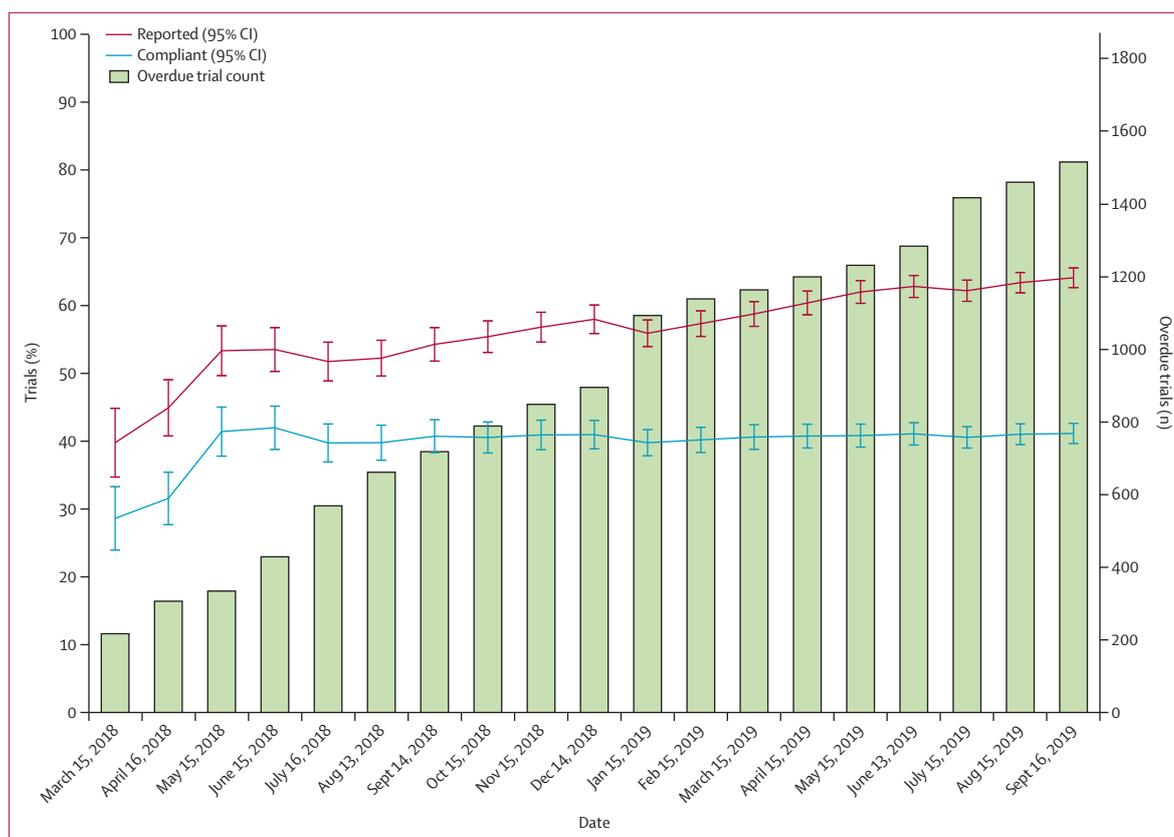


Figure 2: Reported, compliant, and overdue trials by month

We rely on the accuracy of source data at ClinicalTrials.gov. Usefully, FDAAA makes sponsors legally responsible for ensuring that their own registry data are 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 not reported on time, or if they appear to have not reported 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 based on public ACT identification criteria provided by ClinicalTrials.gov. 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 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, previous research has established that results reporting to ClinicalTrials.gov is generally of high quality and in many aspects more complete than journal publication.^{23–25} ClinicalTrials.gov is often the sole repository for the results associated with registered trials; this underscores the importance of sponsors complying with FDAAA.^{26,27}

Our findings substantially expand and improve on previous research studying compliance with FDAAA. Past assessments of the FDAAA 2007 before implementation of the Final Rule reported low compliance. In 2012, Prayle and colleagues¹² found that just 163 (22%) of 738 trials with a primary completion date of more than 12 months prior had reported results. A 2015 study by Anderson and colleagues¹¹ reported that 1790 (13·4%) of 13 327 highly likely ACTs had reported within 12 months, while 5110 (38·3%) had reported results at any time. 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 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.^{13,28,29}

For the method used to identify applicable trials see <https://github.com/ebmdatalab/clinicaltrials-act-tracker> and <https://github.com/ebmdatalab/clinicaltrials-act-converter>

Our findings on compliance with FDAAA are consistent with our previous findings on compliance with EU rules, which require all trials on medicinal products conducted in EU countries 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 registered trials, were more likely to report results. High levels of non-compliance with the FDAAA 2007 Final Rule among non-industry sponsors is consistent with previous survey research showing variable preparedness for the Final Rule among US academic organisations.³⁰

Clinical trials are not abstract research projects; they are large, expensive, practical evaluations that aim to directly inform clinical practice. Efforts to synthesise 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.³¹ The importance of addressing the bias from non-publication of clinical trials has been emphasised since at least the 1980s.³² It is therefore disappointing to note that 40 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 could be the apparent absence of any enforcement action by regulators. The Final Rule established explicit sanctions, including fines of up to \$10000 a day (now \$12 103 inflation adjusted).^{34,33} 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 that they monitor non-compliance using a risk-based approach, centred 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 the appendix pp 20–22). The FDA reiterated this general enforcement strategy in draft enforcement guidance: trial reporting was to be checked as part of Bioresearch Monitoring Program inspections and multiple levels of notice would be issued before any civil monetary penalties.³⁴ Despite public comment on this guidance closing in November, 2018, and more than 1500 unreported applicable trials as of

Sept 16, 2019, no formal response or final plan for enforcement has been issued by the FDA at the time of writing.

In our view, compliance with both EU 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.^{35,36} 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 as part of our overarching TrialsTracker project, 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.

In 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 could help.

Contributors

BG conceived and obtained the funding for the project. SB wrote the code for processing and storing data from ClinicalTrials.gov and maintains the FDAAA TrialsTracker codebase. NJD wrote the code to identify applicable trials, conduct the analyses, and adapt 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.

Declaration of interests

BG has received research funding from the Laura and John Arnold Foundation, Wellcome Trust, Oxford Biomedical Research Centre, NHS National Institute for Health Research School of Primary Care Research, Health Foundation, and WHO. He also receives personal income from speaking and writing for lay audiences on the misuse of science. As of 2020 the TrialsTracker is funded by the Good Thinking Society. NJD is employed under BGs grant from the Laura and John Arnold Foundation and is supported in his doctoral studies through a Naji Foundation Scholarship. He has previously been employed on grants from the Open Society Foundation and the State Attorney General Consumer and Prescriber Education Grant Program. SB is employed under BG’s grants related to research integrity and the Open Prescribing project.

Data sharing

All the code for this study, along with code for the entire TrialsTracker project, is available via open source licensing on GitHub.²¹ All underlying raw and processed datasets for this study are available for download from the Open Science Framework.²² Archived ClinicalTrials.gov data for any other dates held by the authors are freely available upon request.

Acknowledgments

The TrialsTracker is funded by the Good Thinking Society. BG is funded by the Laura and John Arnold Foundation to conduct work on research integrity. No specific funding was sought for this project. The authors would like to thank the DataLab team for their ongoing support of the TrialsTracker project.

For the GitHub repository of all the code for this study see https://github.com/ebmdatalab/fdaaa_trends

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