Missing clinical trial results in America

Violations of federal law and FDA response

24 January 2022
Bristol (United Kingdom)

> "Legislation or supporting regulations [should include] sanctions if a clinical trial is not registered and/or results are not reported."
>
> - WHO Pharmaceutical System Transparency & Accountability Assessment Tool

> *"We advocate full transparency of which clinical trials are ongoing and ensuring all results are disclosed in a timely manner in accordance with the WHO Joint Statement on disclosure of results from clinical trials.*
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> -
> - Dr Tedros Adhanom Ghebreyesus, Director-General, World Health Organisation

> *"Lack of transparency in clinical trials harms patients. The timely posting of summary results is an ethical and scientific obligation."*
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> -
> - Transparency International and Cochrane: Guide for Policy Makers

TransparIMED
working to end evidence distortion in medicine

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BACKGROUND

Failure to report clinical trial results is not a victimless crime. It has substantial negative consequences for patients, taxpayers and public health. Pharmaceutical companies, medical device companies, universities and hospitals are obliged to make public the results of some – but by far not all – clinical trials under U.S. law. The 2007 Food and Drug Administration Amendments Act (FDAAA) requires the results of such trials to be made public on the ClinicalTrials.gov registry within 12 months of trial completion.

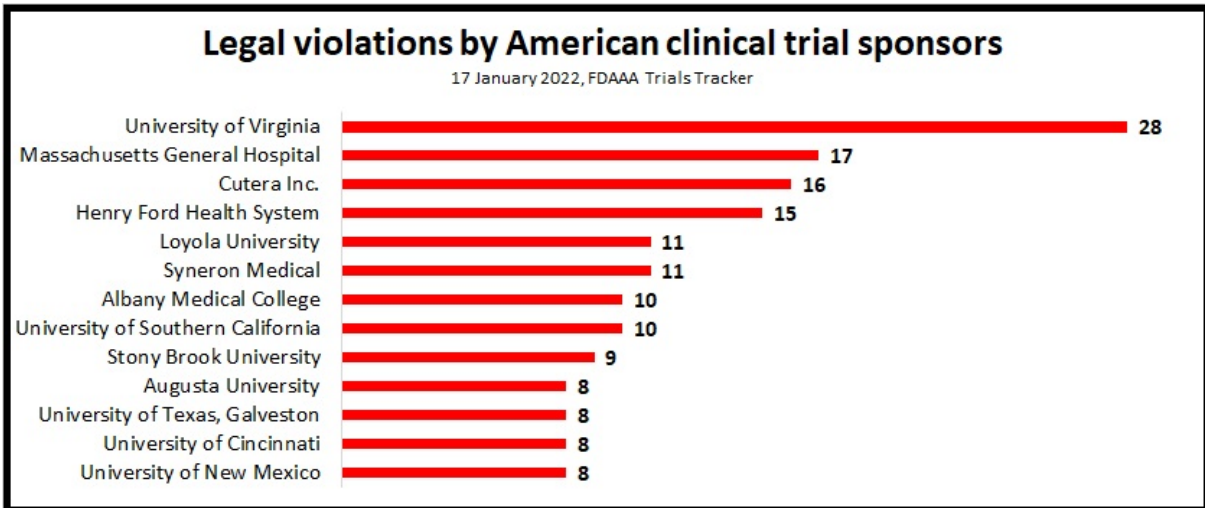
After more than a decade of inaction, the FDA recently started enforcing FDAAA, threatening companies and academic researchers that are breaking the law with fines. Between July 2020 and the end of April 2021, the FDA sent a total of 54 "Pre-Notices of Noncompliance" that flagged missing trial results and instructed sponsors to upload them as required by law, triggering compliance in over 90% of cases. On three occasions so far, FDA has escalated its warning to the stage of sending out a "Notice of Noncompliance," giving the responsible party a deadline of 30 days to make the results public. In each case, the recipients of the letter rapidly made public the missing trial result, and the sponsoring organisation started uploading other missing results – not just the single result flagged by FDA. However, to date the FDA has not made any use of its legal powers to impose fines.

While many leading sponsors have made substantial efforts to achieve compliance in recent years, over 3,000 clinical trial results that have become due since February 2018 are still missing, in violation of the law. Experience strongly suggests that more robust enforcement action by the FDA, as opposed to the agency's current piecemeal approach, would ensure that most of those missing results are rapidly made public. This would significantly benefit patients, save substantial amounts of public money, and improve public health.

WORST FDAAA VIOLATORS IN ABSOLUTE TERMS

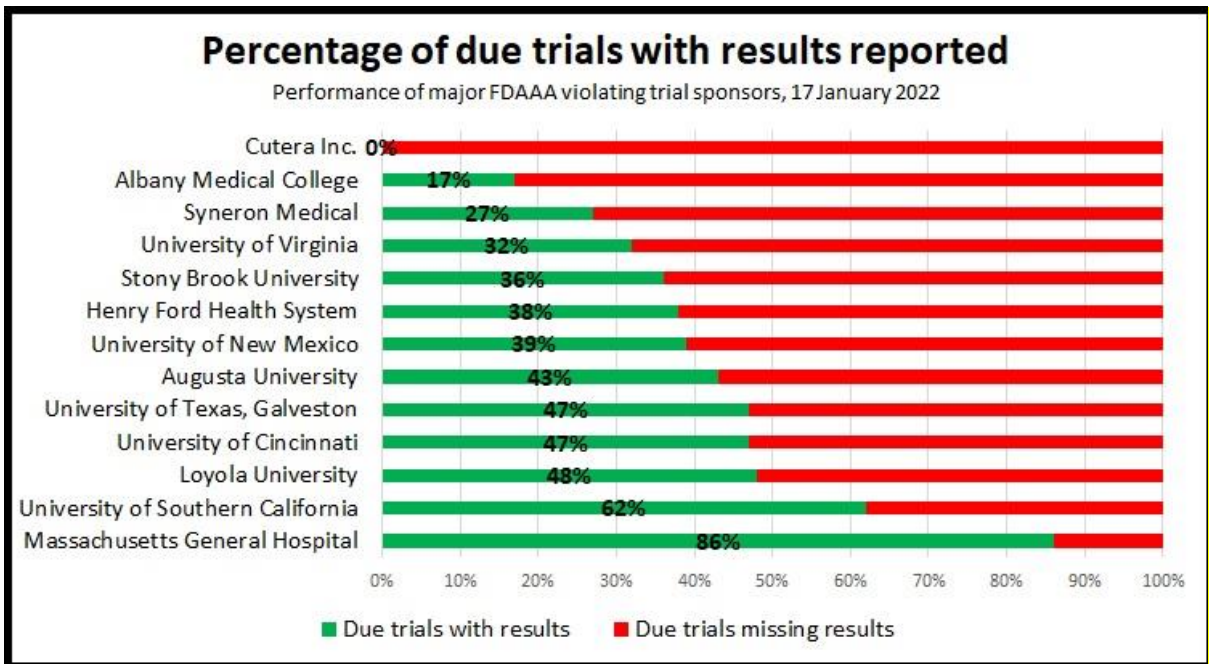
The thirteen worst offenders between them account for 159 missing results, or 5.2% of all 3,039 clinical trials that have become due since February 2018 and that are missing results in violation of the law.

The ***University of Virginia*** is responsible for the largest number of clinical trials missing results (28 results missing), followed by ***Massachusetts General Hospital*** (17) and the company ***Cutera*** (16).



RELATIVE REPORTING PERFORMANCE OF SPONSORS

In relative terms, the worst sponsor in the cohort is the company ***Cutera***, which has a rock bottom reporting rate of 0%, leaving all of its 16 due trial results unreported. ***Albany Medical College*** (17%) and the company ***Syneron Medical***[1] (27%) have also uploaded results for only a small percentage of their due clinical trials.



RECENT IMPROVEMENTS IN TRIAL REPORTING

TranspariMED contacted major violators of FDAAA in early November 2021 to inform them that they were breaking the law and encourage them to upload missing results.[2] Ten weeks later, some sponsors have significantly improved their performance, while others have not.

Several sponsors have made no visible progress. This includes the worst offender in absolute terms, the ***University of Virginia***, and both commercial companies contacted by TranspariMED in November 2021, ***Cutera*** and ***Syneron Medical***.

Cutera stands out as an exceptionally weak performer, with all of its 16 due trials missing results. TranspariMED has reached out to Cutera repeatedly during 2020-2021 to inform it that it was breaking the law, but the company has so far not addressed the issue. According to the FDAAA Trials Tracker, the FDA could by now have collected over $155 million in fines from Cutera for its legal violations.

The sponsor in the cohort with the largest overall trial portfolio, ***Massachusetts General Hospital***, has also not made visible progress. The hospital is one of America's top five trial sponsors by size, with a total of 118 due FDAAA trials in its portfolio, of which 17 are currently missing results. Its reporting rate of 86% is significantly below that of other American sponsors of comparable size, all of which have reporting rates of between 97% and 100%.

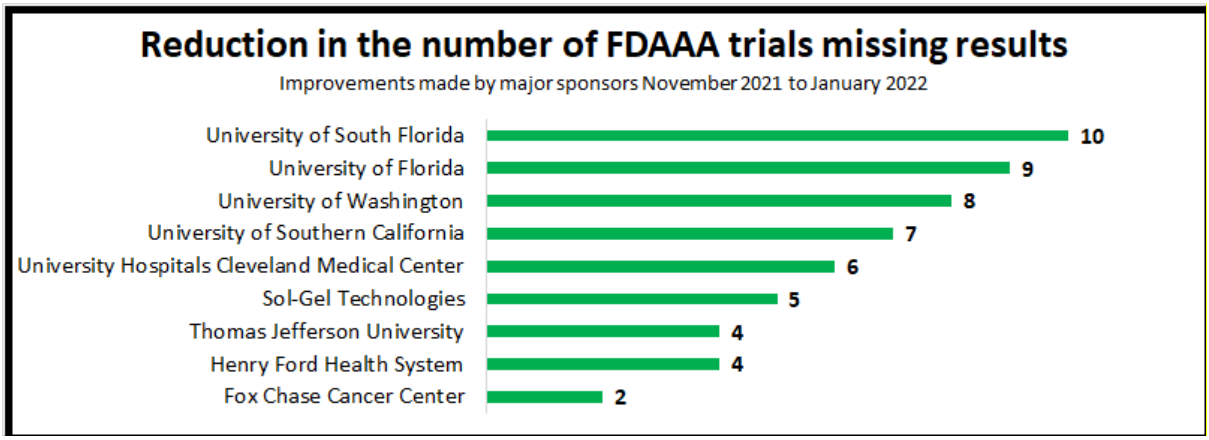
[1] Syneron Medical is now part of Candela Medical.

[2] TranspariMED was unable to contact Albany Medical College by email because the college's website was blocked by the UK-based Internet Services Provider (ISP) used by TranspariMED. Albany Medical College did not respond to Tweets asking the College's media team to contact TranspariMED by email.

In November 2021, Massachusetts General Hospital explained that:

> *"The MGH is committed to the timely reporting of clinical trial results and has a robust process in place to notify investigators when results are overdue. This includes the use of an automated program that reminds investigators of upcoming reporting deadlines and alerts them of issues on their records. Additionally, we audit the status of studies listed as late in order to identify challenges and support investigators in ensuring results are reported."*
>
> *"Organizational trial data on ClinicalTrials.gov changes frequently, and presently there are 2,148 records listed on the MGH account, with 13 flagged as late. Of those, some are in process or are under review. Delays in reporting can be caused by many factors, including the peer review process, administrative requirements and employment or affiliation changes."*

Nine sponsors have significantly improved their performance since November 2021, reducing their collective compliance gap by 55 trial results. The ***University of South Florida*** reduced by 10 the number of its outstanding FDAAA trial results, the ***University of Florida*** now has 9 fewer results missing (and has achieved a 100% reporting rate), and the ***University of Washington*** 8 fewer missing results.



FDA ENFORCEMENT ACTION

Records obtained through Freedom of Information requests by researchers connected to the advocacy group ***Universities Allied for Essential Medicines*** show that between July 2020 and April 2021, the FDA had sent out only 47 Pre-Notices of Noncompliance related to missing trial results, an average of less than two such communications per week.

In its November 2021 report, TranspariMED found that only one of the 51 US-based sponsors with the largest numbers of missing results at the time, ***University Hospitals Cleveland Medical Center***, had received an FDA "Notice of Noncompliance." Only three of the 51 largest violators (UH Cleveland, University of Arizona and University of Florida) had received a "Pre-Notice of Noncompliance," the early-stage FDA warning.

The ***FDA*** has previously explained that it follows a "risk-based approach" to selecting violators for enforcement action. However, the FDA so far appears not to have contacted most of the sponsors responsible for the largest numbers of missing trial results. For example, Cutera's 16 missing results have not attracted a single FDA Notice of Noncompliance to date. Available evidence strongly suggests that more robust and better targeted FDA enforcement could significantly boost clinical trial reporting, benefiting both patients and taxpayers.

Recent improvements in the trial reporting performance of ***University Hospitals Cleveland Medical Center*** illustrate the potential wider impact of stepping up FDA enforcement actions. In August 2021, an academic investigator who had run a UH Cleveland-sponsored trial that remained unreported on the American trial registry received a Notice of Noncompliance from the FDA.

Even though the FDA notice had been addressed and sent to the individual investigator rather than to UH Cleveland, and that researcher at that point no longer worked at the institution, UH Cleveland subsequently improved its trial reporting performance across its entire portfolio. In August 2021, the hospital had a reporting rate of only 21%. By November 2021, its performance had improved to 54%. Today, UH Cleveland has a reporting rate of 85%, with only two of its due trials still missing results.

RECOMMENDATIONS

- **The FDA should significantly step up its enforcement efforts.** Since February 2018 alone, 3,039 clinical trial results have remained unreported, in violation of federal law. The human and financial cost of such unreported trial results for U.S. patients and taxpayers is well documented. Nonetheless, the FDA appears to be sending out less than an average two Pre-Notices of Noncompliance per week. The FDA should aim to send a Pre-Notice of Noncompliance to the responsible party for each of the 3,039 missing results as soon as possible. The cost of doing this would be marginal and could be recouped through fines; the FDA could by now have collected fines exceeding $155 million from the company Cutera alone.

- **Clinical trial sponsors should upload the results of all their due FDAAA trials** onto ClinicalTrials.gov as rapidly as possible. Such efforts should extend to all FDAAA trials, not only those flagged by the FDAAA Trials Tracker (whose cut-off date of February 2018 fails to include older trials also subject to FDAAA). Going forward, sponsors should upload the results of ***all future interventional trials*** onto ClinicalTrials.gov within 12 months of trial completion irrespective of whether they are subject to FDAAA or not, as recommended by the World Health Organisation. Useful guidance can be found here and here.

METHODOLOGY AND LIMITATIONS

Authorship

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No conflicts of interest to declare.

Methodology

TranspariMED published its first report on major FDAAA violators in November 2021, based on trial reporting data as of 02 November 2021. This follow-up report provides an update on the reporting performance of the most salient clinical trial sponsors based in the United States, based on data manually extracted from the FDAAA Trials Tracker on 17 January 2022. Please see the first report for details on cohort selection.

The FDAAA Trials Tracker was built by EBM Data Lab, University of Oxford. The Tracker periodically scrapes data that is publicly available on ClinicalTrials.gov. The Tracker individually lists every trial flagged as overdue, and includes a link back to the original registry entry for every trial. Thus, all data in both reports are externally replicable.

FDA Notices of Noncompliance are publicly listed and were accessed through the FDA website. Data on FDA Pre-Notices of Noncompliance issued from 2020 onwards were obtained from the FDA through Freedom of Information requests by Reshma Ramachandran, Christopher J. Morten, and Joseph S. Ross (see also their study based on these data). TranspariMED would like to thank these researchers for sharing their data.

Limitations

- Undercounting of FDAAA violations

The FDAAA Trials Tracker only covers clinical trials whose results became due from February 2018 onwards, when the FDAAA Final Rule came into force. However, a court case since then has clarified that the law covers trials stretching as far back as 2007. No aggregate data is available for reporting violations involving these older trials. In addition, this report only assesses *whether* results have been made public on ClinicalTrials.gov, but not *when* they were made public. Thus, it does not capture FDAAA violations incurred by reporting trial results late, after expiry of the one-year deadline set by FDAAA. Overall, this report significantly undercounts the true extent of FDAAA violations by sponsors.

- Reporting on ClinicalTrials.gov of non-FDAAA trials

FDAAA only covers some types of clinical trials. Many other clinical trials are not obliged by law to make their results public on ClinicalTrials.gov. According to WHO best practices, the summary results of all interventional clinical trials should be made public on trial registries within 12 months of trial completion, regardless of national laws. However, this report focuses narrowly on legal compliance, so sponsors' reporting performance for non-FDAAA trials on ClinicalTrials.gov was not assessed.

- Extent of complete non-reporting of FDAAA trials

This report only assesses whether sponsors complied with the legal requirement to make applicable clinical trial results public on ClinicalTrials.gov. Some of trials that are in violation of FDAAA reporting requirements may have made their results public in other formats, for example in the peer-reviewed literature.