What is the outcome reporting performance of paediatric clinical trials involving American children that are in violation of FDAAA reporting requirements? - Protocol for a Mixed Methods Study

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Background

Delays in making clinical trial results public can slow down the development and adoption of new, improved treatments. Non-publication of trial results leaves gaps in the medical evidence base, as does incomplete publication of trial results. Excessive delays, non-publication and incomplete publication of trial outcomes all generate research waste.

Section 801 of the 2007 Food and Drug Administration Amendments Act (FDAAA) requires entities sponsoring certain clinical trials to make the tabular summary results of those clinical trials publicly available on the public ClinicalTrials.gov trial registry within 12 months of a trial's primary completion date.

Previous research has shown that while sponsor compliance with FDAAA has improved over time, not all sponsors consistently meet their legal obligations, and thousands of results for such trials remain missing from the registry. However, there is no comprehensive overview of whether and how rapidly the results of such trials are made public in the academic literature.

Objectives

The primary objective of this study is to assess how many clinical trials in the cohort have never made their results public in the academic literature, and the number of participants in these trials.

The secondary objective of this study is to assess the time to publication for the trials in the cohort that have made their results public in the academic literature, and the number of participants in these trials.

Hypothesis

The study hypothesis is that the results of some clinical trials in the cohort are not made public at all, and that the results of the remaining trials are sometimes only made public in the academic literature more than 12 months post primary completion date.

Methodology

1. Cohort selection

The lead author (TB) selected the study cohort based on a dataset supplied by Nicholas DeVito (ND).

The dataset consisted of all studies registered on ClinicalTrials.gov as of 08 September 2022, supplemented by columns identifying whether trials were subject to FDAAA reporting requirements, i.e. Applicable Clinical Trials (ACTs) or probably Applicable Clinical Trials (pACTs) according to the original FDAAA Final Rule definitions. ACTs and pACTs were identified using the FDAAA Trials Tracker methodology, which has previously been described elsewhere.

The dataset was then narrowed down as follows:

Step 1: Delete all trials that are neither ACTs nor pACTs -> 34,649 trials (edit01)
Step 2: Delete all trials with maximum age of 18 or above -> 21,272 trials (edit02)
Step 3: Delete all trials with no maximum age stated -> 1,464 trials (edit03)

= cohort of all pACTs and ACTs involving only children

Step 4: Delete all trials whose results are not due (column D) -> 663 trials (edit04)
Step 5: Delete all trials with summary results (column E) -> 180 trials (edit05)
Step 6: Delete all trials with results pending (column F) -> 141 trials (edit06)
Step 7: Delete all trials with delay certificate (column H) -> 133 trials (edit07)

= cohort of all overdue pACTs and ACTs involving only children = 133 trials

Step 8: Delete all trials with location data that excludes United States -> 97 trials (edit08)

- 81 trials with confirmed US location, 16 trials with no location data

Step 9: Manually search 16 trials with no location data in the dataset and exclude those whose sponsor is an entity located outside the United States -> 84 trials (edit09)

= cohort of all overdue pACTs and ACTs involving U.S. children = 84 trials = 5,967 enrolled globally

Thus, the final cohort consists of 84 clinical trials that exclusively involved children, and that included children located in the United States, that were in violation of FDAAA reporting requirements as of 08 September 2022.

The cohort is deliberately based on very restrictive inclusion criteria, in order to ensure that each trial included verifiably (as per data entered into ClinicalTrials.gov) meets the criteria stated above.

Thus, we excluded trials that are not subject to legal reporting requirements under the original Final Rule, which excludes many older trials stretching back to 2007, which a post Final Rule court ruling also required to report results; The FDAAA Trials Tracker is unable to identify those trials. We also excluded trials that involved adults as well as children, and trials that did not provide relevant age data on the registry. We also excluded paediatric trials that, while subject to FDAAA, did not involve U.S. children.

2. First literature search

For each of the 84 included trials, a team member (SY) will search for results using a 4-step process:

1) Scanning of the "results" section of ClinicalTrials.gov for summary results submitted after 08 September 2022.
2) Scanning of the "results" section of ClinicalTrials.gov for publications that have either been uploaded by sponsor/investigator or automatically indexed by the registry.
3) The clinical trial identifier (NCT ID) will be entered on Google Scholar. The first 2 pages will be searched for potential matches.
4) Google Scholar will be searched by entering the following search terms: title and principal investigator name. In the search, the name will be put into "quotation marks", but not the title. The first 2 pages will be searched for potential matches.

For all steps, if a publication is found it will be verified that it is indeed a results publication for the study and not only a mention of the registry ID in a different context (for example a review of multiple trials, or a trial protocol). This verification is performed based on title and abstract of the publication and if needed by referring to the full text. In case we identify publications, the hyperlink to the publication and the publication date[1] will be extracted.

If the publication is not a final results publication reporting on a trial's primary outcome measure, the publication search will be continued. If a results publication is found, we stop the publication search for this trial at that step. If no hit occurs, we will proceed to the next step.

In line with common practice in this field, we will only classify articles published in peer-reviewed journals and PhD theses as publications. We will not count conference abstracts, posters, presentation slides, or other grey literature as publications, but will capture those separately in the spreadsheet as 'grey literature'.

Only if all four searches stay without results, the study will be characterized as "no publication found".

> *Note: If any trial's putative outcome publication date precedes its primary completion date, we will review the publication and assess whether it qualifies a full outcome publication.*

3. Validation of findings

All outreach to FDA and trial sponsors will identify the study as being run by TranspariMED. All emails will disclose that TranspariMED plans to proactively share the results of this study with the media. In case of non-response, two reminder emails will be sent. The team will not reach out to principal investigators as the ultimate responsibility for complying with FDA reporting requirements lies with the company or institution that sponsored a trial.

- **Validation of findings with FDA**

The team will reach out by email to the press office of FDA with the dataset of trials missing results and related publications. The team will request FDA to review the list and (a) identify any trials that have been inappropriately included, and (b) flag any relevant publications that have been overlooked,

[1] For studies providing only month/year, the first day of the month is used. The earliest date the article was published in any format will be recorded.

and (c) provide a short on-the-record statement for inclusion in a supplementary annex of the final manuscript.

- **Validation of findings with trial sponsors**

The team will reach out by email to the press offices (or where not available, other public contact emails stated on sponsors' websites) of sponsors of those trials for which no results could be located, and invite sponsors to (a) flag any relevant publications that the study team may have overlooked, and to (b) provide a short on-the-record statement on their clinical trial reporting policies and plans for inclusion in a supplementary annex of the final manuscript.

4. Second literature search

As an additional quality control measure, we will run a second search for publications for those clinical trials where the first search did not return publications, and where neither FDA nor the sponsor provided information on the publication status of the trial.

We will search for results using a 4-step process:

1) The "results" section of ClinicalTrials.gov will be scanned for (a) tabular summary results and (b) other publications [repeat of the earlier search in case results have been submitted or published in the meantime]
2) PubMed will be searched for the NCT number
3) PubMed will be searched for +"intervention name" and +"condition name" (both in "quotation marks" and preceded by a + sign). The first 2 pages will be searched for potential matches.
4) Google Scholar will be searched for +"intervention name" and +"condition name" (both in "quotation marks" and preceded by a + sign). The first 2 pages will be searched for potential matches.

Outcome Measures

The primary outcome measures are (a) the extent and (b) the speed of trial outcomes publication in a peer-reviewed journal or PhD thesis for trials missing tabular summary results on ClinicalTrials.gov.

We will calculate time to publication by calculating the time difference between a trial's primary completion date and the date the trial's outcomes were first made public in a peer-reviewed journal.

We anticipate including a narrative discussion of several trials in our manuscript to highlight the scientific, clinical and/or fiduciary implications of late and/or non-reporting of clinical trial results.

Summary Statistics

Table 1: Publication speed and research waste in paediatric trials missing CT-gov results, % of trials

	Timely publication	Delayed publication			Research waste	Publication speed (months, average)*
	Within 1 year	Within 1-2 years	Within 2-3 years	After 3 years	No results	
All trials	5%	11%	24%	27%	33%	27.4

** Calculated for reported trials only [Note: outcome numbers above are purely illustrative.]*

Table 2: Publication speed and research waste in paediatric trials missing CT-gov results, # of patients

	Patients total	Timely publication	Delayed publication			Research waste
		Within 1 year	Within 1-2 years	Within 2-3 years	After 3 years	No results
All trials	10,035	450	1,343	Etc		

Table 3: Publication speed and research waste in paediatric trials missing CT-gov results, # of trials

	Trials total	Timely publication	Delayed publication			Research waste
		Within 1 year	Within 1-2 years	Within 2-3 years	After 3 years	No results
All trials	488	23	Etc			

[PROTOCOL ENDS]