How many clinical trials completed by ten major UK non-commercial sponsors in 2017 remain completely unpublished? – Protocol for a mixed methods study

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Background

Worldwide, a significant proportion of clinical trials end up as costly research waste because their results are never made public. The resulting gaps in the medical evidence base harm patients and undermine public health.

In the wake of a 2018 UK parliamentary enquiry and sustained engagement by advocacy groups and UK public bodies, non-commercial clinical trial sponsors in the UK substantially improved outcome reporting for CTIMPs by uploading the summary results of many CTIMPs onto EudraCT, including for older legacy trials. However, previous research indicates that many institutions' efforts to improve trial reporting did not extend to other trial registries. The UK's national #MakeItPublic strategy now aims to ensure that going forward, all clinical trials involving UK patients will make their results public, but the strategy's scope does not extend retrospectively to older legacy trials.

Previous studies have found that in the absence of any external intervention, the results of very few trials that remain unpublished after 5 years will ever be made public. However, a recent TranspariMED project in Germany indicated that outreach to institutions that sponsored trials that have remained unreported in the past can spur non-commercial sponsors to tackle legacy research waste, notably by reaching out to the principal investigators of older unreported trials.

The current project was originally funded by HealthSense (formerly Health Watch UK), a UK charity, in late 2019. Start-up of the original project was delayed by the pandemic. The protocol below significantly deviates from the original research proposal due to new developments (political, regulatory and scientific) in the intervening years.

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.

The secondary objective of this study is to create a public database of a cohort of currently unreported non-CTIMP clinical trials that other researchers can later use to assess the impact of this study's outreach to sponsors on subsequent outcome reporting for those trials.

Hypothesis

The study hypothesis is that the results of some clinical trials in the cohort were never made public.

Methodology

1. Cohort selection

The lead researcher (TB) first identified the ten most prolific non-commercial sponsors of clinical trials in the UK by accessing the EU Trials Tracker on 27 October 2022, employing the number of CTIMPs run by each sponsor as a proxy indictor of overall trial volume.

Table 1: Selection of UK sponsors according to total number of CTIMPs sponsored

Sponsor	CTIMPs	With results*
University College London	163	97%
University of Oxford	146	99%
Imperial College London	145	97%
University of Birmingham	118	100%
King's College London	107	99%
Guy's and St Thomas' NHS Foundation Trust	82	94%
University of Dundee	74	100%
University of Leeds	72	98%
NHS Greater Glasgow and Clyde	71	100%
Newcastle upon Tyne Hospitals NHS [Foundation] Trust	69	93%

** Due trial results posted on EUCTR, as per EU Trials Tracker data*

The lead researcher then used the advanced search functions of the ClinicalTrials.gov and ISRCTN registries on 28 October 2022 to identify all clinical trials run by these ten sponsors that were completed or terminated in 2017. Inclusion criteria:

1. The (lead) sponsor is one of the ten UK non-commercial sponsors listed above[1]
2. Interventional clinical trial completed or terminated 01 January 2017 and 31 December 2017[2]

The lead researcher applied these search criteria to both registries and extracted the trial ID numbers, patient enrolment numbers[3], and registry reporting status[4] of all available trials that matched these criteria. No duplicate registrations were detected.[5]

Table 2: Overview of study population prior to publication searches

Sponsor name	CT-GOV	ISRCTN	Total trials
University College London	12	2	14
University of Oxford	31	0	31
Imperial College London	24	1	25
University of Birmingham	9	0	9
King's College London	18	2	20
Guy's and St Thomas' NHS Foundation Trust	8	0	8
University of Dundee	7	0	7
University of Leeds	15	0	15
NHS Greater Glasgow and Clyde	7	2	9

[1] CT-GOV search field: "Sponsor (lead)"; ISRCTN: "sponsor organisation"
[2] CT-GOV: "primary completion date"; ISRCTN: "overall trial end date"
[3] Final (actual) enrolment numbers were extracted where available; else target enrolment numbers were extracted.
[4] CT-GOV: availability of tabulated summary results; ISRCTN: availability of (any) results as per registry flag
[5] No duplicate registrations were detected during manual review of the EUCTR and CT-GOV number fields on ISRCTN-registered trials. CT-GOV registered trials were not systematically screened for duplicates.

Newcastle upon Tyne Hospitals NHS Foundation Trust	6	1	7
All sponsors	**137**	**8**	**145**

The final cohort consists of 145 interventional clinical trials run by ten major non-commercial UK sponsors that are registered on ClinicalTrials.gov or ISRCTN and that were completed or terminated during 2017. These trials had a combined (actual or planned) enrolment of 34,102 patients.

The Declaration of Helsinki, which stipulates that all clinical trial results must be made public (albeit without specifying the reporting format or timeframe), is applicable to all trials in the study cohort.

The study cohort excludes CTIMPs because all sponsors included in this study already have reporting rates of at least 93% for those trials on EUCTR (see above). After years of systematic efforts by such UK sponsors to improve their EUCTR reporting performance, any CTIMP results still missing from EUCTR are very probably not recoverable. The study cohort also excludes trials exclusively registered on other ICTRP contributing registries; the number of such trials (if any) is likely to be tiny.

2. First literature search

Trials identified during cohort selection as having posted tabular summary results on ClinicalTrials.gov (25 trials total) were marked as "reported" prior to the literature search.

For each of the remaining 120 trials, a team member will search for results using a 3 step process:

1. Scanning of the "results" section of the registry entry for publications
2. The clinical trial identifier (NCT or ISRCTN number) will be entered on Google Scholar. The first 2 pages will be searched for potential matches.
3. 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 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 tabular summary results posted onto clinical trial registries, 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 search steps 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 as a full outcome publication.*

3. Validation of findings

All outreach to 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. The team will not reach out to principal investigators as the ultimate responsibility for safeguarding adherence to Declaration of Helsinki ethical imperatives lies with the institution that sponsored a trial.

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 (based on a dataset shared with sponsors), and to (b) provide a short on-the-record statement on their clinical trial reporting policies and plans.

We will remove any trials identified by sponsors as having been "withdrawn" (= never enrolled patients) from the cohort. Trials that were terminated early will be retained in the cohort.

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 the sponsor did not provide information on the publication status of the trial.

We will search for results using a 3-step process:

1. PubMed will be searched for the clinical trial identifier (NCT or ISRCTN number)
2. 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.
3. 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 the (a) number and (b) percentage of trials in the cohort that have not made their results public in the form of tabular summary results posted onto clinical trial registries and/or articles published in peer-reviewed journals and/or PhD theses.

There are three secondary outcome measures:

- The number of persons who participated in unreported clinical trials in the cohort.
- The estimated financial research waste (in GBP) caused by unreported clinical trials in the cohort, based on a cost-per-trial estimate previously published by TranspariMED.
- Number and percentage of sponsors whose responses indicated that they were following up on, or planned to follow up on, unreported clinical trials in the cohort.

Summary Statistics

Primary outcomes

Table 1: Number and percentage of trials in the cohort that have not fully reported results

	Number	Percentage
Results reported		
Results not reported		
Total trials		100%

We will additionally provide a breakdown of the outcome measures above by trial sponsor.

Secondary outcomes

The number of persons who participated in completely unreported clinical trials in the cohort, and the estimated financial research waste (in GBP) will be reported in narrative form. The number and percentage of sponsors whose responses indicated that they were following up on, or planning to follow up on, unreported clinical trials in the cohort will be presented in narrative form; this narrative may include a qualitative analysis of sponsor responses.

We may also include a narrative discussion of several trials to highlight the scientific, clinical and/or fiduciary implications of late and/or non-reporting of clinical trial results.

Data sharing

The complete study dataset and all sponsor responses will be permanently archived on a public repository, which will be linked to in the published manuscript.

Sponsors' statements provided to the research team will be included in full in a supplementary annex of the final manuscript.

[PROTOCOL ENDS]