



REPORT

CLINICAL TRIAL TRANSPARENCY IN THE NETHERLANDS

Mapping Unreported Drug Trials

TranspariMED

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REPORT

CLINICAL TRIAL TRANSPARENCY IN THE NETHERLANDS

Mapping Unreported Drug Trials

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1. INTRODUCTION

Failure to report clinical trial results is not a victimless crime. A 2017 [report](#) by Transparency International and Cochrane documents that a failure to fully report trial results has substantial negative consequences:

- Patients are harmed
- Public health agencies cannot make informed decisions
- Public health funds are wasted
- Medical progress is slowed down

Unreported trials contribute little to progress in science and public health and are therefore costly [research waste](#). In the past, unreported clinical trial results have caused public health [losses amounting to billions of Euros](#) and have led to the deaths of countless patients. For this reason, the Declaration of Helsinki has made reporting the results of every clinical trial a [universal ethical obligation](#) for all medical researchers worldwide.

We advocate full transparency of which clinical trials are ongoing and ensuring all results are disclosed in a timely manner.

Dr Tedros Adhanom Ghebreyesus
World Health Organization

In 2014, the European Union (EU) adopted rules that require the sponsors of all clinical trials registered on the EU Clinical Trials Registry to post summary results to the registry within 12 months of trial completion (six months for paediatric trials). These rules also apply to trials completed before 2014 and apply irrespective of whether a trial's outcomes have been published in the academic literature.

Lack of transparency in clinical trials harms patients. The timely posting of summary results is an ethical and scientific obligation.

Transparency International and Cochrane

This report aims to document the gaps in clinical trial transparency in the Netherlands by assessing the performance of the 23 Dutch companies, universities, hospitals and research institutions most active in conducting drug trials. Our research showed that only one of the largest 23 clinical trial sponsors in the Netherlands is adequately managing its data on the European registry and systematically uploading trial results. Shockingly, only 3% of trials assumed to be completed had results shared in the registry.

2. METHODOLOGY

Data Extraction

The EU Clinical Trial Register (EUCTR) was scraped and processed using EU TrialsTracker code and the standard methodology to determine the reporting status of each trial. As part of the process, free-text sponsor names are normalised for display on the website. Alongside the standard EUCTR scraper, a second scraper was run to obtain detailed sponsor info from section B of each EUCTR country level protocol (specifically the sponsor name, country, and sponsor status). This detailed sponsor information was then combined with the processed EU TrialsTracker data and normalisation data, to extract all trials with a Dutch sponsor.

The codes used are available on Github:

- EU Trials Tracker code and data
- EUCTR Sponsor section scraper
- The code for generating the dataset

Cohort Selection

The main cohort for this study consists of all clinical trial sponsors located in the Netherlands that had sponsored 10 or more clinical trials on EUCTR as of 1 June 2020. The full data set listed 28 sponsors with 10 or more trials listed. Based on a manual search of sponsor websites, five sponsors were excluded because they are companies headquartered outside the Netherlands.¹ This process yielded 23 clinical trial sponsors located in the Netherlands that have sponsored 10 or more trials listed on EUCTR.

Measuring and Estimating Sponsor Performance

Data on the clinical trial performance of each of the 23 included sponsors were manually extracted from the EU Trials Tracker on 27 June 2020. Due to delays by the European Medicines Agency (EMA) in making public trial results submitted by sponsors, the tracker data might not include all trial results that were uploaded by sponsors during May 2019. Thus, the data in this report reflect sponsors' trial reporting performance as of early May 2020.

The EU Trials Tracker was built by the EBM Data Lab, University of Oxford. The tracker is based exclusively on data that are publicly available on the EU Clinical Trial Register; the tracker is updated on a monthly basis. To the best of the author's knowledge, to date no instances of a trial incorrectly flagged as being due and missing results by the EU Trials Tracker based on registry records have been detected. The EU Trials 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 this report is externally replicable.

Because the national regulator and trial sponsors in the Netherlands have failed to ensure that data on the European trial register is accurate and up to date, many completed trials are falsely marked as 'ongoing' or lack a completion date. This makes it impossible to precisely determine the real number of trials missing results.

1. Astellas, Johnson & Johnson, Merck Sharp & Dohme (MSD), Boehringer Ingelheim and Sanofi were excluded for this reason. Acerta Pharma was not excluded; AstraZeneca holds 55% of the company, but Acerta itself remains based in the Netherlands.

Estimates on the number of trials missing results were calculated based on the assumption that 50% of each institution's trials were completed more than a year ago and are therefore currently due to upload their results. TranspáriMED divided the total number of trials per institution in half to arrive at an estimate of these due trials, and then subtracted the number of trials listed as both 'due' and 'reported' by the EU Trials Tracker. The resulting numbers were rounded down to the next integer if applicable.

The 50% assumption is based on the fact that the European register captures trials that began as early as 2004, and trials usually only run for a few years. Therefore, the register contains many trials that have been completed.

In the trial portfolios of major sponsors in other European countries for which more reliable data are available, around half of all trials are marked as being due to report results.²

A different methodology was applied to the trial portfolio of HAL Allergy. The company only has one trial that is marked as 'ongoing', and a further two trials have 'inconsistent data'. These three trials—whose status would usually have to be considered ambiguous—all have results available on the register.³ The remaining nine trials are marked as due; only one of them is missing results. Thus, HAL Allergy has only one trial without results overall, and the results for that trial are unambiguously (over)due. Hence, the report provides that precise figure rather than an estimate.



2. For example, data on Imperial College London's trial portfolio can be considered reasonably reliable because the university has reported over 97% of its verifiably due trials, has nearly no trials with inconsistent completion data, and has few very old trials that are still marked as 'ongoing'. Out of Imperial's 139 trials total, 76 trials (55%) are marked as being due to report results.

3. However, it is not clear whether the results for those trials are 'verifiably due', and hence they are not factored into the separate chart on sponsors' reporting performance.

3. RESULTS

Table 1 provides the data used to compile this report. Sponsors are listed in order of portfolio size. Radboud University has the largest clinical research portfolio among Dutch sponsors, with 212 drug trials listed on the European registry. With 195 trials listed, Erasmus University is the second largest sponsor. University of Amsterdam comes third, with 181 trials.

The column “No results” indicates the number of trials that are verifiably missing results in violation of European transparency rules. Note that out of the 23 largest sponsors of drug trials in the Netherlands, only four are private companies. Public sponsors account for 1,536 out of the 1,609 drug trials in this cohort.

Table 1. Data

| Sponsor | Trials | Results due | With results | No results |
|-----------------------------|-------------|-------------|--------------|------------|
| Radboud Universiteit | 212 | 9 | 2 | 7 |
| Erasmus Universiteit | 195 | 4 | 1 | 3 |
| Universiteit van Amsterdam | 181 | 8 | 0 | 8 |
| VU medisch centrum | 155 | 11 | 0 | 11 |
| Universiteit Leiden | 150 | 6 | 1 | 5 |
| Universiteit Utrecht | 143 | 9 | 1 | 8 |
| Rijksuniversiteit Groningen | 138 | 3 | 0 | 3 |
| Antoni van Leeuwenhoek | 75 | 2 | 0 | 2 |
| Universiteit Maastricht | 72 | 3 | 0 | 3 |
| Stichting HOVON | 57 | 2 | 0 | 2 |
| Solvay* | 36 | 18 | 8 | 10 |
| St. Antonius Ziekenhuis | 28 | 1 | 0 | 1 |
| CHDR | 24 | 2 | 0 | 2 |
| Isala | 19 | 0 | 0 | 0 |
| RIVM | 18 | 1 | 0 | 1 |
| Rijnstate | 15 | 0 | 0 | 0 |
| Sint Maartenskliniek | 15 | 2 | 0 | 2 |
| ZonMw | 15 | 0 | 0 | 0 |
| HAL Allergy* | 13 | 9 | 8 | 1 |
| Oogziekenhuis Rotterdam | 13 | 0 | 0 | 0 |
| AstraZeneca* | 13 | 1 | 0 | 1 |
| Emotional Brain* | 11 | 1 | 0 | 1 |
| SLO | 11 | 1 | 0 | 1 |
| TOTAL | 1609 | 93 | 21 | 72 |

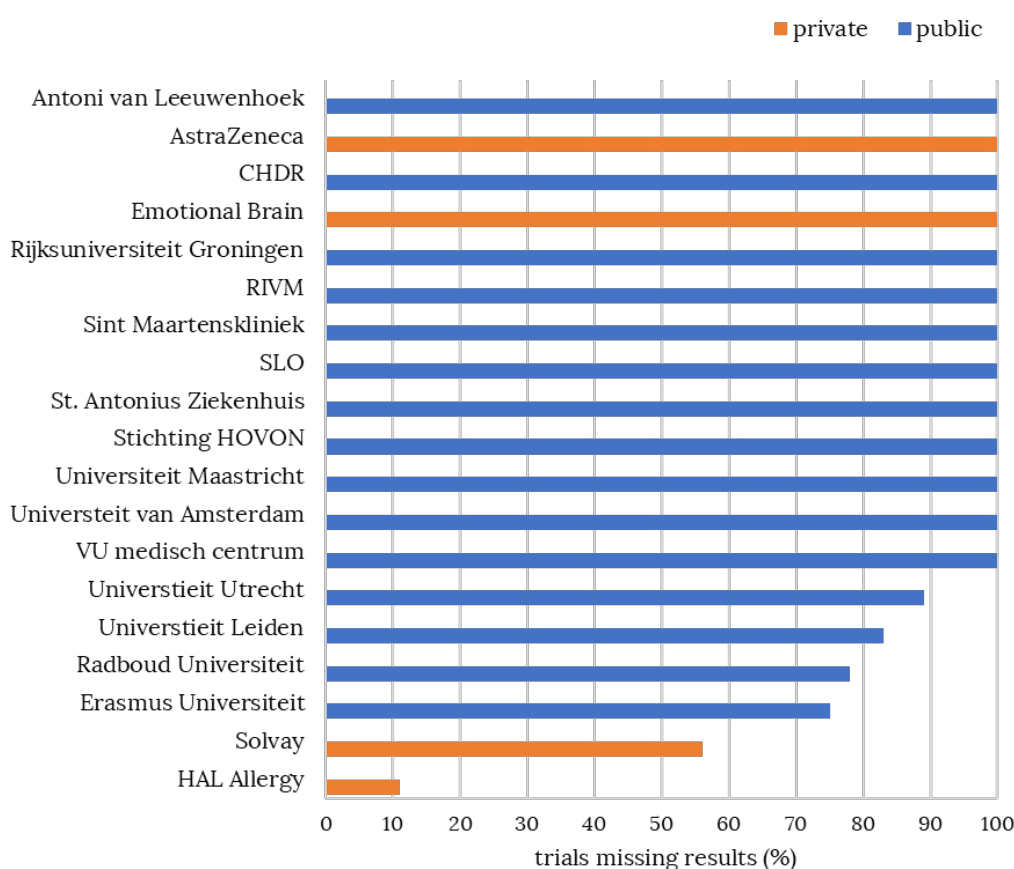
* Sponsors marked with an asterisk are commercial sponsors.

** **Abbreviations:** CHDR, Centre for Human Drug Research; HOVON, Hemato-Oncologie voor Volwassenen; RIVM, Rijksinstituut voor Volksgezondheid en Milieu; SLO, Stichting voor Lever- en Maag-Darm Onderzoek

The figure below presents the percentage of completed trials with missing results. Strikingly, only one of the largest 23 clinical trial sponsors in the Netherlands is adequately managing its data on the European registry and systematically uploading trial results.

- [HAL Allergy](#) has a near-perfect record of compliance with European transparency rules. Only one of the trials completed by the company is missing results.
- [Solvay Pharmaceuticals](#) has reported results for many of its trials, but 10 of the company's due trials remain verifiably in breach of transparency rules.
- The remaining 21 sponsors have a weak clinical trial transparency record, with 75% or more of clinical trial results missing. This group includes universities, hospitals, public bodies and pharmaceutical companies.

Completed trials with missing results



* Isala, Oogziekenhuis Rotterdam, Rijnstate and ZonMw are not listed as none of their trials were marked completed and due to report results.

Estimating the True Number of Missing Clinical Trial Results

In our cohort, the results of 93 trials are verifiably due, so sponsors are obliged to make them public on the register. Nonetheless, sponsors have only uploaded 21 of those verifiably due results; results for the other 72 verifiably due trials are missing, in clear violation of European transparency rules.

Interesting to note in the data table is that the number of trials reported to be completed is fairly low. Less than 6% (93 out of the 1,609 trials) run by the Dutch sponsors in our cohort are currently marked as having been completed a year or more ago. This is in contrast with the trial portfolios of [major sponsors](#) in other European countries, where around half of all trials are marked as being due to report results.⁴ Note that results are due regardless of whether the trial has actually ended or was stopped for safety, efficacy or other grounds. Given that clinical trials usually only run for a few years, a significant proportion of trials marked as ongoing in the Dutch cohort are due to report results as well (indeed, ‘ongoing’ trials are shown that began as early as 2004).

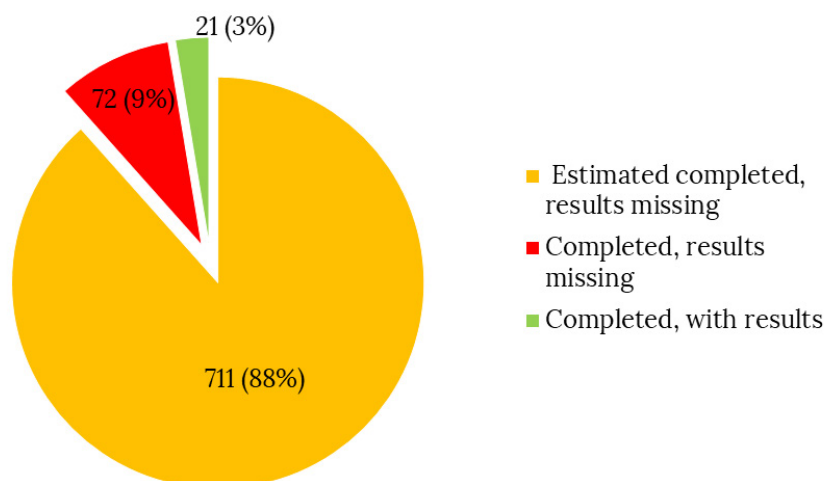
This means that the actual percentage of reported results is most likely even lower than presented in the figure above.

Assuming that Dutch trials follow similar timelines as trials in other European countries, around half of all Dutch trials should currently be due to report results. As the chart below shows, in addition to the 72 trials that are verifiably in violation of European transparency rules, results are missing for an estimated 711 additional completed trials. Thus, the total estimated number of trials missing results is 783 (=72+711). This brings the true percentage of reported results to a mere 3%.

Estimating Missing Results per Sponsor

The chart below shows the estimated number of trials missing results for each major sponsor. These figures are estimates; the precise number for each sponsor may differ (see the methodology section for details). Note that universities appear to be responsible for most of the missing clinical trial results in the Netherlands.

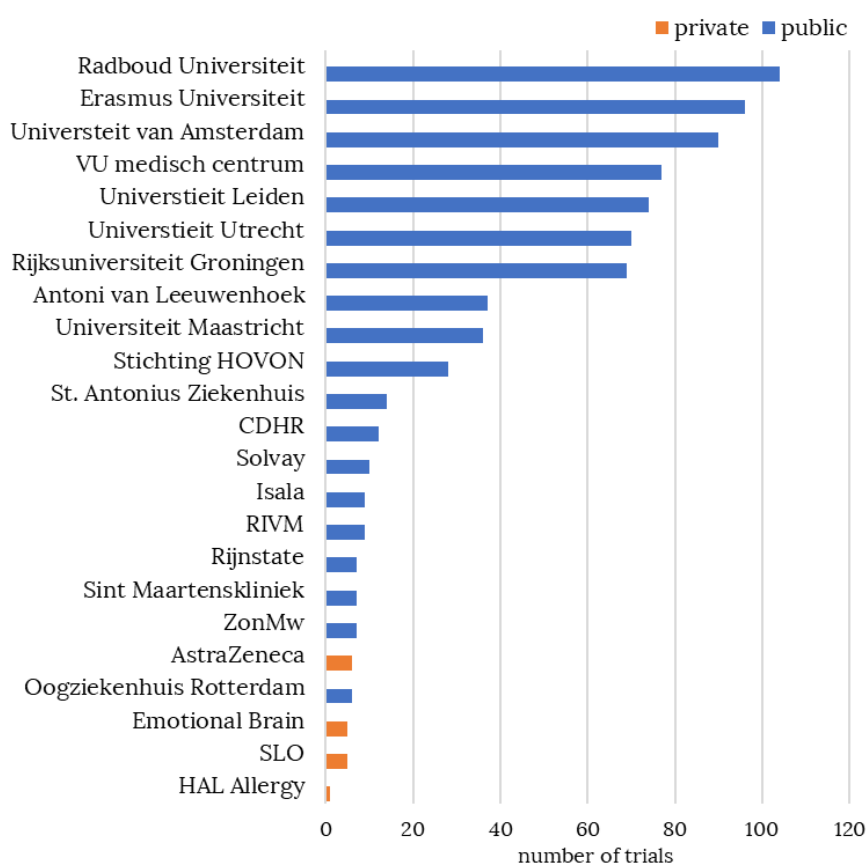
True estimate of missing results



4. For example, data on Imperial College London’s trial portfolio can be considered reasonably reliable because the university has reported over 97% of its verifiably due trials, has nearly no trials with inconsistent completion data, and has few very old trials that are still marked as ‘ongoing’. Out of Imperial’s 139 trials total, 76 trials (55%) are marked as being due to report results.

5. The estimates in this chart add up to only 779 trials missing results, rather than the 783 trials given as an estimate earlier in this report, because fractions were rounded down to the nearest integer. Also, HAL Allergy’s single missing trial was not estimated using the formula for other sponsors, but is a precise figure based on registry records. See the methodology section for details.

Estimated number of trials with missing results



4. DISCUSSION

The aim of this report was to identify the gap in clinical trial transparency of the major Dutch sponsors of clinical trials. We found that 93 of the 1609 studies in our cohort were filed to be completed over a year ago. Seventy-two of those completed studies did not upload the results to the EU trial clinical trial registry. Furthermore, we believe that the low number of completed studies is not realistic. We estimate that 711 of the studies that are marked as ‘ongoing’ are most likely finished. As such, only 21 of the 804 completed studies have uploaded their results.

All of the clinical trials identified in this report as missing summary results are in violation of EU transparency rules that were designed to protect the interests of patients and taxpayers.

Once the EU Clinical Trial Regulation comes into force, probably in late 2020 or 2021, national regulators will have the power to fine institutions for not uploading trial results to the European trial registry.

While not all trials lacking results on the European trial registry are completely unreported, the best available evidence suggests that around [half of all trials missing results](#) on the registry have also not reported their results in academic journals. Thus, dozens of trials run by the universities covered in this report are in acute danger of becoming research waste unless their results are made public soon.

Most of the missing results appear to stem from universities. As such, they should review their clinical trial portfolios across the EU registry, the US registry Clinicaltrials.gov, and other World Health Organization (WHO) primary trial registries, identify those trials that have remained completely unreported, and ensure that their results are made public as soon as possible.

Uploading Results to Trial Registries Does Not Harm Chances of Publication

A concern in academia might be that a manuscript will be rejected by a journal because the trial results are already uploaded to a trial registry. It seems that this concern can be rebutted, as there is [no recorded case](#) of this type of rejection occurring. Academic journals will accept articles reporting a trial's outcomes even if that trial's outcomes have already been made public in a trial registry. The International Committee of Medical Journal Editors has explicitly stated that the posting of summary results to trial registries is not considered prior publication by academic journals. Thus, because results reporting on registries is typically faster than academic publication, making trial results public on registries before they are published in an academic journal is the new norm in scientific communications.

Roles and Responsibilities for the Uploading of Data

Dutch trial sponsors can directly upload results onto the European register, but only the appropriate authority in the Netherlands can change the status of a trial from 'ongoing' to 'completed'. An earlier version of this report incorrectly identified the Medicines Evaluation Board (CBG) as the institution responsible for keeping track of clinical trials being conducted in the Netherlands. This is not the case - it is not

part of the CBG mandate to record or follow up on clinical trials. This is the responsibility of the Central Committee on Research Involving Human Subjects (CCMO). The fact that identifying what Dutch body is responsible has proven to be such a challenge is damning indictment of the opacity of the system, and may be one of the reasons for low reporting rates.

Ultimately, the body responsible should engage in a dialogue with Dutch trial sponsors and work with them to improve data quality and ensure that data on the register are consistent and accurate.

Global Best Practice

[WHO standards](#) require every sponsor of an interventional trial to post its results on every public registry where it was registered within 12 months of its primary completion date. Importantly, the WHO has explicitly stated that publishing trial results in the academic literature is not an acceptable substitute for posting trial results to public registries.

Best practices [jointly set out](#) by Cochrane and Transparency International also state that 'summary results for all clinical trials should be posted on the registries where they were originally registered within 12 months of study completion'. The two health integrity groups note that retrospectively posting the results of all past trials to registries 'would improve healthcare delivery and government agencies' decision-making on resource allocations, as well as saving billions of dollars' worth of medical research from being lost forever'.

Similarly, the trial reporting benchmark set out by the AllTrials campaign states that '[a] summary of results (...) should be posted where a trial was registered within one year of completion of a trial'.

Why is posting trial results to registries important?

First of all, completed trials that are falsely marked as still ‘ongoing’ negatively impact patients and undermine medical progress:

- Health technology assessment agencies, horizon scanners, systematic reviewers and medical researchers cannot find relevant trials, and/or cannot reliably determine whether a trial is still ongoing or has been prematurely ended, terminated, or completed. This makes it difficult to gain an overview of the complete scientific evidence base on a medicine.
- Clinicians, patient groups and patients cannot reliably determine which trials may currently be recruiting patients, making enrolment more difficult for patients and recruitment more difficult for sponsors. This drives up the cost and slows down the pace of medical research.
- Compliance with EU reporting rules is undermined because it is often impossible to determine whether or not a trial is due to report results.

Secondly, global best practices require posting the results of all trials to registries, as there are a several benefits to doing so:

- Posting results to registries accelerates medical progress because the 12-month timeline permits far more rapid results sharing than the slow academic publication process allows.
- Posting results to registries minimises the risk of a trial never having its results reported and becoming research waste, which can happen when a principal investigator dies or leaves their post during the prolonged process of submitting an academic paper to a succession of medical journals. Research shows that trial results posted on registries typically give a

more comprehensive and accurate picture of patient-relevant trial outcomes than corresponding journal articles do.

- Results posted on registries are easier to locate and are open access.
- Registry reporting facilitates the comparison of trial outcomes with a trial’s originally stated aims and, thus, discourages harmful research malpractices such as HARKing, p-hacking and the ‘silent’ suppression, addition or switching of the selected outcomes.

Please see the report by Cochrane and Transparency International for further details and links to the relevant literature.

Limitations

Undercounting of Due Trials

The EU Trials Tracker significantly undercounts the number of trials due to post results because many trials are falsely marked as “ongoing” in the registry even though they were in fact completed long ago. The proportion of false “ongoing” trials in the Netherlands is unknown, and is impossible to determine based on registry data.

Rather than present deeply flawed data at face value, TranspariMED generated an estimate of the numbers of trials that are likely to be due (see above). The heuristic used is not precise and is not firmly grounded empirically, but almost certainly provides a far more accurate picture than taking the data on the register at face value would do.

Undercounting of Results Posted

Due to delays by the EMA in making public trial results submitted by sponsors, trial results that were uploaded during late May 2020 may not have been captured by the EU Trials Tracker. As a result, some trials whose results were only recently made public on EUCTR may have been counted as unreported. In TranspariMED’s experience, the number of such trials—if any—is likely to be very low in a cohort this size.

In a few cases, sponsors had uploaded the results for trials marked as “ongoing” or having “inconsistent data”. These do not show up as “due and reported” in the EU Trials Tracker and were therefore not counted as such. These trials are a very small minority of all trials.

Trials not listed on the EU Clinical Trial Register

The data in this report exclusively covers clinical trials that were registered on the EU Clinical Trial Register. Under EU rules, all clinical trials of investigative medicinal products (CTIMPs) conducted in the EU must be registered on the

EU Clinical Trial Register, and must post their results there within 12 months of trial completion. Non-drug trials, including trials of medical devices (e.g., pacemakers) and non-drug treatments (e.g., surgery or physiotherapy), cannot be registered on the EU Clinical Trial Register and are thus registered on other trial registries. Such trials can be of even greater medical importance than drug trials, and sponsors are required to make their results public under global ethics rules. However, assessing sponsors’ reporting performance for these non-drug trials is beyond the scope of this report.

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