Clinical Trial Transparency at European Universities

Mapping unreported drug trials

06 October 2021
Bristol (UK) & Amsterdam (NL) & Vienna (Austria)

"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

"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

"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

www.TranspariMED.org https://haiweb.org/ www.austria.cochrane.org

1 KEY FINDINGS AND RECOMMENDATIONS

Obligation to report the results of all drug trials

Failure to report clinical trial results is not a victimless crime. It has substantial negative consequences for patients and public health.

Under European Union guidelines adopted in July 2014, institutions running drug trials have the obligation to make the results of those trials public on the European trial registry within one year of trial completion (6 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.

This European guideline will become national law in every EU member state from 31 January 2022. From then on, national medicines regulators will have the power to impose sanctions on institutions that fail to make results public on the registry.

Key findings

The 26 largest research institutions in mainland Europe have between them run 4,588 drug trials. Most institutions are now uploading trial results, with 641 results available to date. Overall, 28% of due trial results have by now been reported. That reporting rate represents a dramatic improvement over past years, and seems likely to significantly increase over the coming months.

- ***Out of 26 institutions, 21 are now clearly working to clear their backlogs of missing results.***
- There is a clear and accelerating trend towards greater transparency across the sector as a whole. While some institutions started the process years ago and have already made significant progress, most are still at an early stage, with large backlogs of unreported trials left to clear.
- With 198 results uploaded, Europe's largest non-commercial trial sponsor, the ***Medical University Vienna***, leads in terms of absolute reporting performance, followed by KU Leuven (85 results) and the Charite (82 results).
- In terms of relative performance, ***Medical University Vienna*** is also far ahead, with an estimated reporting rate of 96%, followed by ***EORTC***.
- Only 5 trial sponsors show no clear signs of progress. These sponsors are all located in ***Italy*** and the ***Netherlands***.

Recommendations

- **Research institutions** should upload all missing summary results onto the European trial registry as rapidly as possible. Going forward, they should ensure that the results of all future clinical trials – including non-drug trials – are uploaded onto trial registries within one year of trial completion, as set out in the WHO Joint Statement. Useful resources here.

- **National medicines regulators** should contact all clinical trial sponsors with missing results and remind them of their obligation to make those public on the EU registry.

- **National research funders** should sign up to and fully implement the WHO Joint Statement to protect patients and prevent medical research financed by taxpayers from going to waste.

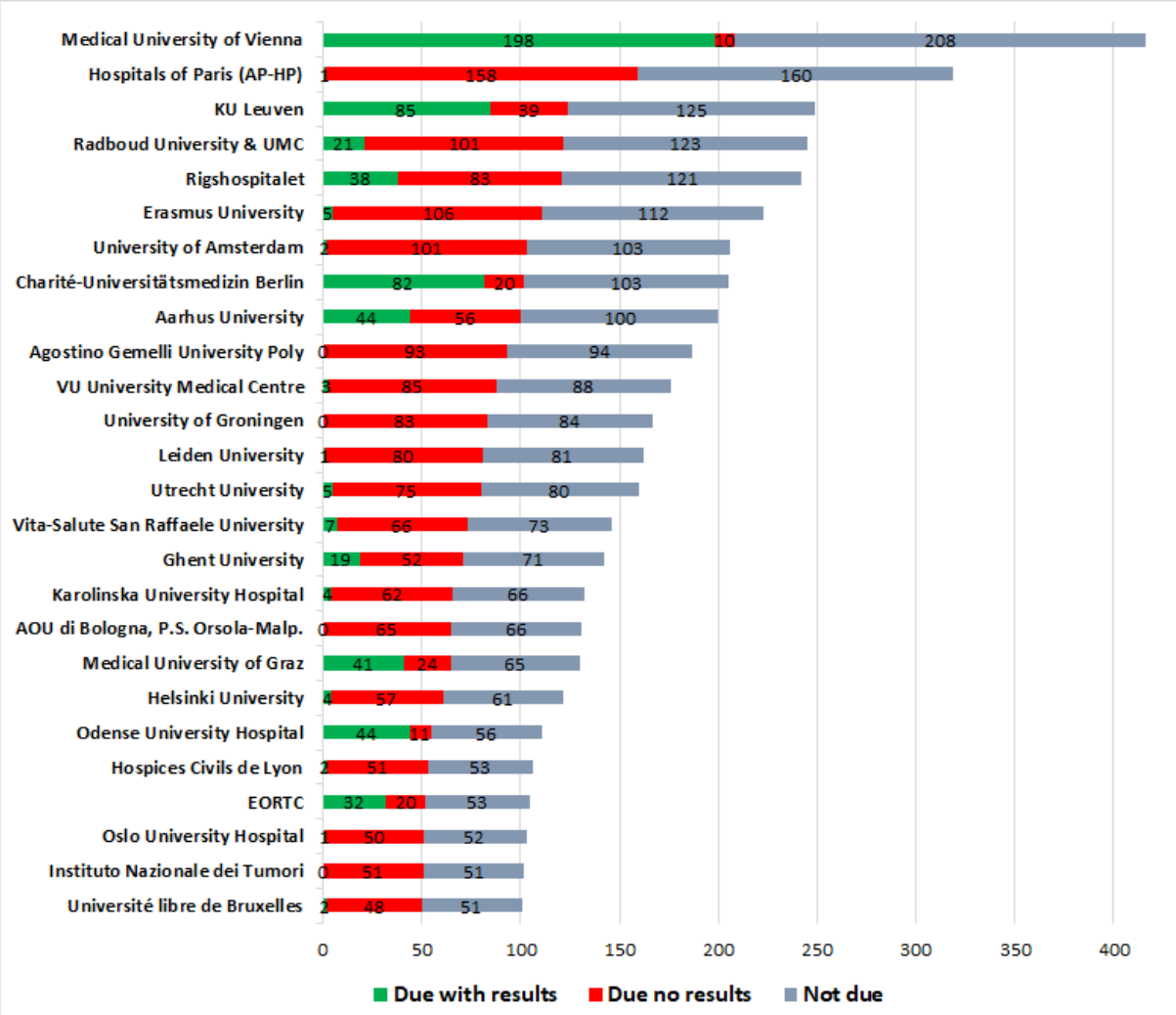
- **National governments** should put into place systems to ***monitor*** whether clinical trials are registered and reported, and adopt ***sanctions*** for non-compliance.

2 REPORTING PERFORMANCE BY INSTITUTION

The 26 largest research institutions in mainland Europe have between them run 4,588 drug trials. Most institutions are now uploading trial results, with 641 results available to date. Overall, 28% of their estimated 2,288 due trials now have results on the registry – a dramatic improvement over the past year.

The chart below lists institutions by the total number of trials they have run. For each institution, it shows the number of due trials with results (green), and the estimated numbers of due trials still missing results (red) and trials that are not yet due to report results (grey). For example, Europe's largest non-commercial trial sponsor, Medical University Vienna, has uploaded 198 due results, leaving an estimated 10 due results still unreported, while its remaining 208 trials do not yet have to report results.

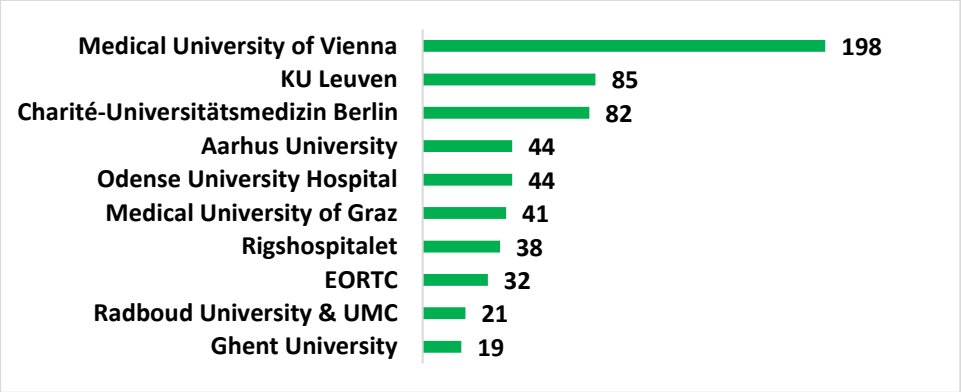
Current reporting trends are far more positive than the chart suggests because many institutions have only very recently started uploading results. For example, the second largest sponsor, AP-HP, appears to be making no progress, but registry data shows that it is now uploading missing results. In total, 21 of the 26 institutions listed below are now working to fix the problem.



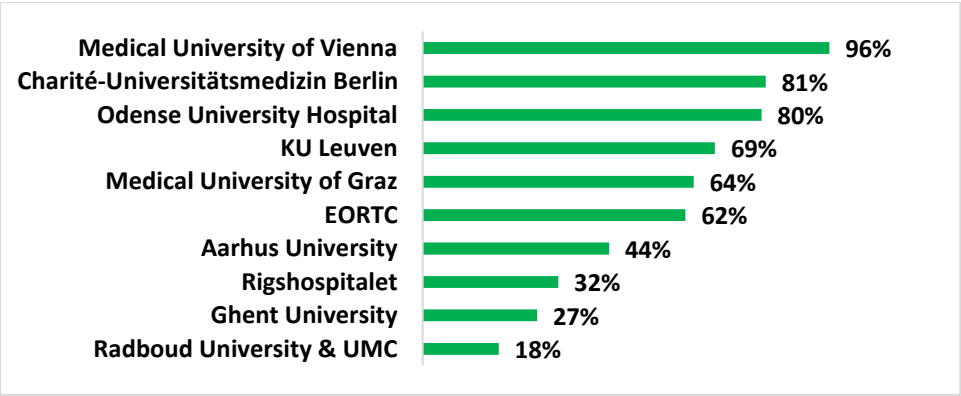
Notes: ***EORTC***'s actual performance is almost certainly far better than the estimate-based figures above suggest. ***Radboud UMC*** believes it should be listed separately from the university; this report is based on the current allocation of trials by the Tracker. The methodology section explains in detail how the figures above were generated.

3 STAR PERFORMERS AND LAGGING INSITUTIONS

The chart below shows the top 10 performers in terms of absolute numbers of due results uploaded. This metric favours large sponsors that started the process early. ***Medical University Vienna*** is the clear leader with 198 due results uploaded onto the registry.



The chart below shows the top 10 performers in terms of estimated percentage of due trials with results. Again, ***Medical University Vienna*** is the clear leader, having already uploaded an estimated 96% of its due trial results. ***EORTC***'s performance is probably comparable, but is underestimated here due to the methodology used. ***Charite***, ***Odense***, ***Leuven*** and ***Graz*** have also already cleared more than half of their estimated backlogs.



Only five institutions show no clear signs of progress. These negative outliers are all located in Italy and the Netherlands:

- ***Agostino Gemelli University Poly***
- ***AOU di Bologna, P.S. Orsola-Malpini***
- ***Instituto Nazionale dei Tumori***
- ***University of Groningen***
- ***Leiden University***

A manual search of registry data shows that ***Leiden*** only uploaded a single trial result during the period May-August 2021. The other four institutions did not upload any results during that period. It appears that these institutions have yet to start the process of systematically uploading missing results.

The 21 other institutions covered by this report are all working to upload their missing trial results. While the performance of some of these institutions does not yet look impressive, they are all on the right track.[1] Future reports will follow their progress and 'name and fame' the most rapid improvers.

[1] Please see the methodology section for more details.

4 DATA TABLE

The table below presents the figures used in this report. The five institutions highlighted red still show no clear signs of progress. All other institutions are currently working on clearing their backlogs of unreported clinical trials.

Institutions are listed by the total size of their drug trial portfolios, with the largest sponsors on top.

Data was extracted manually from the University of Oxford's EU Trials Tracker, and reflects data available on the European trial registry as of 01 September 2021.

Institution	Country	Total trials	Due with results	Due no results*	Not due*
Medical University of Vienna	Austria	416	198	10	208
Hospitals of Paris (AP-HP)	France	319	1	158	160
KU Leuven	Belgium	249	85	39	125
Radboud University & UMC	Netherlands	245	21	101	123
Rigshospitalet	Denmark	242	38	83	121
Erasmus University	Netherlands	223	5	106	112
University of Amsterdam	Netherlands	206	2	101	103
Charité-Universitätsmedizin Berlin	Germany	205	82	20	103
Aarhus University	Denmark	200	44	56	100
Agostino Gemelli University Poly	Italy	187	0	93	94
VU University Medical Centre	Netherlands	176	3	85	88
University of Groningen	Netherlands	167	0	83	84
Leiden University	Netherlands	162	1	80	81
Utrecht University	Netherlands	160	5	75	80
Vita-Salute San Raffaele University	Italy	146	7	66	73
Ghent University	Belgium	142	19	52	71
Karolinska University Hospital	Sweden	132	4	62	66
AOU di Bologna, P.S. Orsola-Malp.	Italy	131	0	65	66
Medical University of Graz	Austria	130	41	24	65
Helsinki University	Finland	122	4	57	61
Odense University Hospital	Denmark	111	44	11	56
Hospices Civils de Lyon	France	106	2	51	53
EORTC**	Netherlands	105	32	20	53
Oslo University Hospital	Norway	103	1	50	52
Instituto Nazionale dei Tumori	Italy	102	0	51	51
Université libre de Bruxelles	Belgium	101	2	48	51
TOTAL		**4588**	**641**	**1647**	**2300**

** Estimated, please see the methodology section for details.*

*** EORTC's actual performance is almost certainly far better than the estimate-based figures above suggest.*

5 WHY THIS MATTERS

Relevance to public health and clinical practice

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

Legal and regulatory framework

Since July 2014, European Union guidelines have required sponsors to upload the summary results of each and every clinical trial registered on the European trial registry EudraCT onto the registry within 12 months of trial completion (6 months for paediatric trials). These rules also apply to trials concluded before 2014.

> ***From 31 January 2022, when the EU Clinical Trial Regulation fully comes into force, making drug trial (CTIMP) results public will be a legal requirement in every European Union member state.***

The Danish regulator has already announced that it intends to make full use of its new powers. It remains unclear how national medicines regulators (NCAs) in other European countries plan to enforce the law in 2022. In the United States, the FDA recently started enforcing a similar law, threatening sponsors with a fine of $10,000 per day if they do not make results public.

Concerns about research waste

Unreported trials contribute nothing 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 led to the death 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.

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, hundreds of trials run by European universities are likely to be in acute danger of becoming research waste unless their results are made public soon.

We urge sponsors to review their clinical trial portfolios across the EU registry, the US registry Clinicaltrials.gov, and other WHO primary trial registries, identify those trials that have remained completely unreported, and ensure that their results are made public as soon as possible.

Global best practices

WHO standards require every 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 onto 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 onto 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."

There are good reasons for this emphasis on posting all trial results onto registries:

- Posting results onto registries accelerates medical progress because the 12-month timeline permits far more rapid results sharing than the slow academic publication process allows.
- Posting results onto registries minimises the risk of a trial never reporting its results 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 comparison of trial outcomes with a trial's originally stated aims, and thus discourages harmful research malpractices such as the 'silent' suppression, addition, or switching of selected outcomes, HARKing, and p-hacking.

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

No barriers to subsequent publication in academic journals

The International Committee of Medical Journal Editors has explicitly stated that the posting of summary results onto trial registries is not considered prior publication by academic journals. Thus, 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. 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 now the norm in best practice scientific communications.

ANNEX: METHODOLOGY AND LIMITATIONS

Authorship

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Methodology

- Cohort selection

The cohort includes all non-commercial clinical trial sponsors in the European Union and the European Economic Area (i.e. Norway) that have run more than 100 Clinical Trials of Investigative Medicinal Products (CTIMPs) listed on the European trial registry, the EU Clinical Trial Register (EUCTR). The cohort was selected using data from the EU Trials Tracker.

- Sponsor performance data

Data on sponsors' trial reporting performance was manually extracted using the EU Trials Tracker built by EBM Data Lab, University of Oxford. The EU Trials Tracker periodically collates and curates data that is publicly available on the EU Clinical Trial Register. 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 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.

The data was extracted from the EU Trials Tracker on 22 September 2021. At that point, the EU Trials Tracker had last been updated by scraping EUCTR data on 01 September 2021. Thus, the data in this report is accurate as of 01 September 2021.

- Identifying lagging institutions

Many institutions have started systematically uploading missing trial results only in recent months, and this does not always translate into immediate improvements on the Tracker.

Typically, institutions upload the results of a trial first, and only then contact their national regulator asking it to update the trial's status to 'completed' and insert a completion date into the protocol, which can take several weeks. In these cases, the uploaded results do not immediately translate into visible progress on the charts and in the data table of this report because the Tracker identifies them as still "ongoing" or having "inconsistent data", rather than as being "due with results" (see also below). Institutions typically make very slow visible progress during the initial stage of cleaning up their registry records, but then accelerate rapidly over the subsequent months.

To distinguish between institutions that have recently started uploading results but do not show visible improvements on the Tracker yet, and institutions that show no evidence whatsoever of systematically uploading missing results, a manual search of the registry data of all sponsors with less than five "due with results" trials on the Tracker was performed. Institutions that had not ***uploaded at least two missing trial results during May-August 2021*** were classed as laggards. All other institutions appear to be systematically tackling the problem.

Example: As of September 2021, the Tracker listed only one trial sponsored by Hospitals of Paris (AP-HP) as "due with results,", suggesting no meaningful activity by AP-HP. However, an additional 5 AP-

HP trials listed as "ongoing" or having "inconsistent data" by the Tracker also have results. Registry records show that AP-HP uploaded two of those results in May 2021 (see here and here), and one further result in June 2021 (see here). It is extremely unlikely that three individual investigators suddenly and spontaneously decided to upload their results in this narrow time window, and therefore indicates that AP-HP as an institution is now starting to take action.

Leiden is a borderline case, with only one result uploaded during May-August 2021 (leaving open the possibility that this was only due to an individual researcher's actions); the other four 'laggard' institutions identified in the report did not upload a single trial result during this time period.

Future reports will continue to track the progress of all sponsors over time.

Limitations

- Estimate of the number of actually due trials per sponsor

Data in this report is based on the conservative assumption that in a typical sponsor's trial portfolio, half of all trials will have been completed over a year ago, and will thus be due to report results. This heuristic is based on reviews of sponsors' trial portfolios in countries where national regulators perform well at keeping registry data up to date, and has been used in multiple previous TranspariMED national reports.

The resulting estimates of due trials are inevitably imprecise, and individual sponsors may have a slightly lower or (more frequently) higher number of due trials in practice. However, for the purpose of comparing sponsor performance across multiple countries that have different levels of regulatory performance, assuming that 50% of each sponsor's trials are due provides far more accurate picture than taking registry status information at face value.

Example: The Austrian regulator performs well at data management, and 224 of Vienna University's 416 trials are identifiable as due on the registry. In contrast, Agostino Gemelli University Polyclinic has run 187 trials, but only 11 are identifiable as due. By using the assumption that 50% of all trials are due, this report generates the estimate that 208 Vienna trials are due (a slight undercount) and the estimate that 93 Agostino Gemelli trials are due (which is far more realistic than the figure of 11 trials based on taking registry data at face value).

- Trials that have results but other data inconsistencies and gaps

The EU Trials Tracker draws on registry data and only marks trials as "due with results" if it meets the following three conditions: (1) trial is marked as completed or terminated, (2) trial protocol has a completion date, (3) trial results have been uploaded onto the registry. The Tracker does not count trials that have results available but do not meet both conditions (1)+(2) above as "due with results".

This report follows the same methodology. As a result, it slightly undercounts the number of results uploaded by some sponsors.

Sponsors can ensure that such trials are counted as reported during the next monthly update of the Tracker by contacting their national medicines regulator and asking it to update the trial status and/or insert a completion date into the protocol. (In practice, sponsors often wait until a result has been uploaded before they contact their regulator requesting these changes, as this creates a better headline figure for their reporting performance on the Tracker. This practice does not harm patients.)

- Results reported in other formats

This report does not take into account whether trial results have been made public in other formats, for example in academic journals. Sponsors have the obligation to report results specifically on the European trial registry, and this report measures their compliance with this rule. Registry reporting is not an arbitrary bureaucratic requirement, but serves the interests of European patients and public health.

- 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 European Union must be registered on the EU Clinical Trial Register.

However, trials not covered by these rules, including trials of medical devices (e.g. pacemakers) and non-drug treatments (e.g. physiotherapy), cannot be registered on the EU Clinical Trial Register. Sponsors usually register such trials on other registries, notably the U.S. registry ClinicalTrials.gov. While reporting the results of such trials is also important, and WHO best practices clearly state that all trials should post results onto all registries where they are listed, such non-CTIMP trials are beyond the scope of this report.