Clinical Trial Transparency in Belgium

Mapping unreported drug trials

Brussels (Belgium) and Bristol (UK), 06 May 2021

"We advocate full transparency of which clinical trials are ongoing and ensuring all results are disclosed in a timely manner… full transparency on results advances both scientific understanding and timelines for product development and ultimately enables access to essential medicines."

Dr Tedros Adhanom Ghebreyesus, World Health Organisation

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

Transparency International and Cochrane

"Legislation or supporting regulations [should include] sanctions if a clinical trial is not registered and/or results are not reported."

WHO Transparency and Accountability Assessment Tool

TEST aankoop TEST achats

Kom op tegen Kanker

Cochrane Belgium

TranspariMED

1 KEY FINDINGS AND RECOMMENDATIONS

Obligation to report the results of all trials

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

European Union (EU) rules adopted in July 2014 require the sponsors (organisations that conduct a trial) of each clinical trial registered on the EU Clinical Trials Register to post those trials' summary results to the registry within 12 months 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. Thus, all of the clinical trials identified in this report as missing summary results are in violation of European Union transparency rules that were designed to protect the interests of patients and taxpayers.

Key findings

The results presented in this report reflect EU Trials Tracker data on the 14 Belgian companies and institutions sponsoring the largest number of drug trials.

Overall, the 14 largest trial sponsors based in Belgium have registered 1,098 clinical trials of investigative medicinal products on the EU Clinical Trial Register. Of these, 292 trials have verifiably been completed more than a year ago and should thus have results available. Results are verifiably missing for 64 of these trials (22%).

The true number of missing trial results is substantially higher, but cannot be precisely determined due to weak data management by some sponsors and AFMPS.

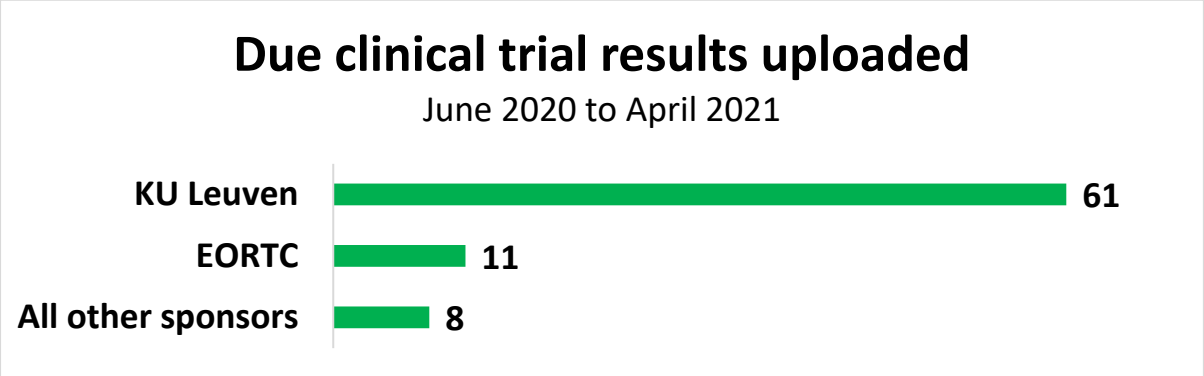
- **Overall, pharmaceutical companies perform well.** Three out of five companies assessed have a perfect compliance record. Only 4 industry trial results are verifiably missing.
- **Non-profit trial sponsors have a mixed performance**. Two sponsors, ***KU Leuven*** and ***EORTC***, have already achieved a strong reporting record. All other sponsors perform weakly.
- **Trends are also mixed.** While some universities and university hospitals now appear to be working to fix the problem, ***Université libre de Bruxelles***, ***University of Antwerp*** and ***CHU Brugmann*** do not seem to have taken action yet.
- **Belgian non-profit sponsors perform worse than their counterparts in Germany, Denmark, Austria and the UK.**

Recommendations

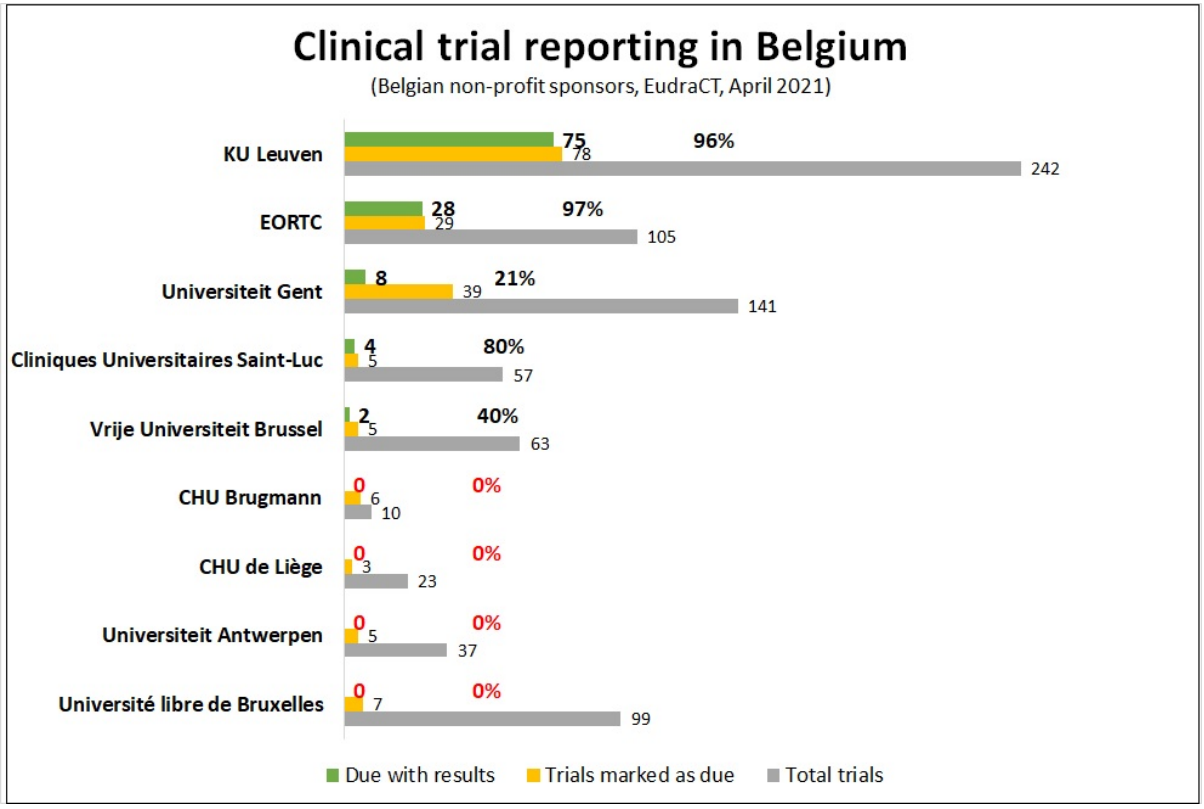
- **Belgian trial sponsors** should establish central oversight over their clinical trial registry entries, adopt policies that reflect WHO best practices, audit existing registry records, and upload missing clinical trial results as fast as possible. See here for useful tools.
- **The national medicines regulator AFMPS** should contact trial sponsors whose results are overdue, ensure that data on the register are consistent and accurate, monitor compliance, and develop a mechanism for routinely and automatically imposing sanctions.
- **Public and philanthropic research funders** in Belgium should sign up to the WHO Joint Statement and monitor whether the results of trials they fund are made public.

2 CLINICAL TRIAL REPORTING IN BELGIUM

This report focuses on the nine largest non-profit sponsors in Belgium because all industry sponsors already perform strongly. Since June 2020, ***KU Leuven*** has uploaded the results of 61 verifiably due trials, and the European Organisation for Research and Treatment of Cancer (***EORTC***) has uploaded 11 due trial results. The seven other non-profit sponsors combined have uploaded only 8 results.



The chart below illustrates the large gap in performance between front-runners *KU Leuven* and *EORTC*, and all other Belgian non-profit sponsors. KU Leuven's total portfolio includes 242 trials, of which 75 are marked as due and have results available. (Many trials have not been completed yet, so not all trials are due to report results.) In contrast, Ghent University's portfolio includes 141 trials, but only 8 are marked as due and have results. Even more extreme is Université libre de Bruxelles: out of its portfolio of 99 trials, not a single trial that is marked as due and has results.[1]



[1] The methodology used in this report only counts trials as "verifiably due and missing results" when a trial is verifiably due (i.e. is marked as completed, and has a completion date in the protocol). Many completed trials are falsely listed as still 'ongoing' on the database and/or have no completion date; these are not counted as overdue. Conversely, sponsors may have uploaded results for a small number of trials that are not "verifiably due"; these are also not counted in this report. See the next section and the methodology section for details.

3 DATA QUALITY PROBLEMS

The available figure of 64 *verifiably* due trials missing results in Belgium is far lower than the *true* number of due trials missing results because many trials are falsely listed as ongoing. With the exception of ***KU Leuven*** and ***EORTC***, all major non-profit sponsors have a very weak reporting performance, but the exact number of missing results per sponsor is impossible to determine because of data quality problems on the European Clinical Trial Register.

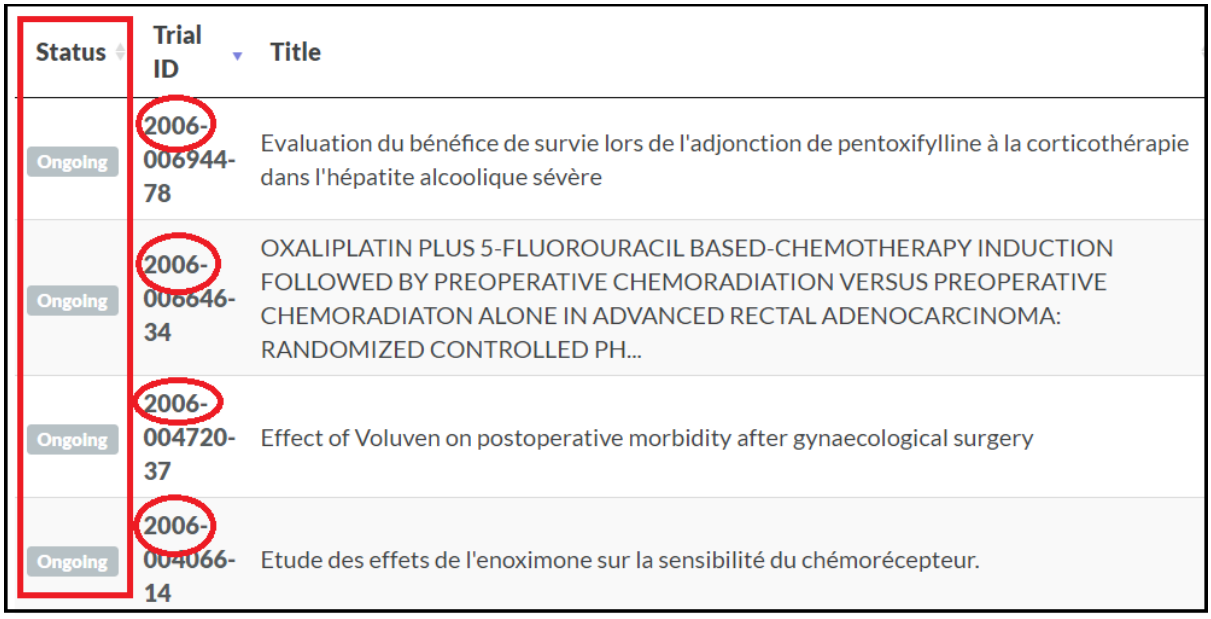
This section uses the portfolio of Université libre de Bruxelles to illustrate widespread data quality problems and the difficulty of precisely determining the true number of due trials currently missing results in Belgium. Please note that these problems are not unique to Université libre de Bruxelles; the same issues can be found in the portfolios of many other Belgian trial sponsors.

Drug trial portfolio of Université libre de Bruxelles

According to the EU Trials Tracker, which aggregates data from the European Trial Register, Université libre de Bruxelles has sponsored a total of 99 drug trials.

- Only 7 of these trials are marked as "completed" and have a completion date. All 7 trials are verifiably due, and all 7 trials are missing results.
- 13 trials have inconsistent data, including:
    - 10 trials are marked as "completed" but lack a completion date
    - 2 trials are marked as "ongoing" but also have a completion date
    - 1 trial lacks status information

  It is unknown how many of these trials were completed more than a year ago and thus should have results. Currently, only 2 of the 13 trials with inconsistent data have results.
- The remaining 79 trials are marked as "ongoing". However, many of these trials were almost certainly completed long ago. For example, 26 trials that were launched more than a decade ago still remain listed as "ongoing", as the screenshot below illustrates.



Status	Trial ID	Title
Ongoing	2006-006944-78	Evaluation du bénéfice de survie lors de l'adjonction de pentoxifylline à la corticothérapie dans l'hépatite alcoolique sévère
Ongoing	2006-006646-34	OXALIPLATIN PLUS 5-FLUOROURACIL BASED-CHEMOTHERAPY INDUCTION FOLLOWED BY PREOPERATIVE CHEMORADIATION VERSUS PREOPERATIVE CHEMORADIATON ALONE IN ADVANCED RECTAL ADENOCARCINOMA: RANDOMIZED CONTROLLED PH...
Ongoing	2006-004720-37	Effect of Voluven on postoperative morbidity after gynaecological surgery
Ongoing	2006-004066-14	Etude des effets de l'enoximone sur la sensibilité du chémorécepteur.

Image source: EU Trials Tracker screenshot, 05 April 2021

How many Université libre de Bruxelles drug trials are missing results?

According to long-standing European Union guidelines – which will become national law in all EU Member States in January 2022 – sponsors are obliged to make public on the registry the results of all drug trials that were completed more than a year ago.

Out of Université libre de Bruxelles' 99 drug trials, 7 trials were verifiably completed over a year ago and are missing results. Each of these trials is clearly and unambiguously in violation of transparency requirements.

However, it is extremely likely that far more of the university's trials were completed long ago, but remain falsely listed as ongoing (see above). Assuming that half of all its 99 trials were completed more than a year ago – a reasonable assumption based on data from other countries – around 49 of the university's trials are currently due, of which only 2 trials[2] have results.

Thus, Université libre de Bruxelles has probably failed to upload around 47 due trial results onto the registry – a far larger number than the 7 missing results clearly identifiable from registry data.

Impact on patients and medical progress

In addition to undermining efforts to monitor sponsors' compliance with transparency rules, data quality problems in Belgium 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.

AFMPS role and responsibility

The problems flagged above may originate with trial sponsors, with AFMPS, or with both. When a trial ends, the sponsor should inform AFMPS of the trial end, and AFMPS should then update the trial status on the registry and insert the completion date. If either party fails to meet its responsibilities, the trial will falsely remain listed as "ongoing".[3]

As the national regulator, AFMPS is ultimately responsible for safeguarding the quality of Belgian trial data on the European register. AFMPS should engage in a dialogue with Belgian trial sponsors and work together with them to improve data quality. Regulators in other European countries have successfully ensured that data on the register are consistent and accurate, showing that this is feasible.

[2] Both of these trials currently have inconsistent completion data, see further above.

[3] Sponsors cannot directly update the completion status of a trial on the European trial registry. In 2020, some Belgian trial sponsors reported that AFMPS had not consistently responded to their requests to update incorrect data.

4 FEEDBACK FROM AFMPS AND TRIAL SPONSORS

Prior to publication of this report, Test Aankoop/Test Achats and Kom op tegen Kanker reached out to national regulator AFMPS and all trial sponsors named in this report asking them to share their perspectives on trial reporting.

Future reports by Test Aankoop/Test Achats, Kom op tegen Kanker, Cochrane Belgium and TranspariMED will track Belgian sponsors' progress over time. Sponsors can use TranspariMED's collection of transparency tools to inform their efforts to improve performance.

Communication with AFMPS

We contacted the Agency for Medicines during the summer of 2020 to inform it about the poor compliance of non-commercial sponsors with EU trial reporting rules. In this context, we also asked the agency to clarify how its carries out its tasks and about its follow-up measures. We also asked the agency which sanctions it will be able to impose in case of non-compliance with EU reporting rules, once this legislation enters into force in January 2022.

Despite sending a reminder, ***we never received an answer from AFMPS to our questions***.

Communication with trial sponsors

We contacted all sponsors during the summer of 2020 to inform them about their individual compliance with EU transparency rules. In addition, we asked them which actions they plan to undertake to improve their results reporting, and asked for a concrete commitment to take action.

There seemed to be a weak understanding of rules and mechanisms among several non-commercial sponsors. One sponsor suggested that trials with a small number of participants did not have to post results; this is incorrect. Several sponsors claimed that it was impossible to report the results of trials that were terminated early; this is also incorrect. These responses suggest that AFMPS could improve its efforts to communicate existing regulations and actively support compliance. We clarified some misunderstanding with the help of TranspariMED to enable sponsors to better comply with their obligations.

Several sponsors noted that they had asked AFMPS to change incorrect data on the trial registry, but that AFMPS had not always consistently followed up. (While sponsors can directly upload results onto the database, only AFMPS can mark trials as "completed".) Thus, according to sponsors, some of their trials remain falsely listed as "ongoing" and lack a completion date in the protocol even after they had notified AFMPS that the trial had been completed.

Several sponsors noted that the EU database is not user friendly. While this is true, the European Medicines Agency has substantially improved the system over the past year, notably by creating a responsive helpdesk. Commercial sponsors, but also non-commercial sponsors KU Leuven and EORTC, illustrate that Belgian sponsors can achieve strong reporting rates using the current system.

In 2020, we gave sponsors a period of more than 6 months to improve their results reporting. Finally we informed sponsors about our plans to communicate our findings to the media.

The table below gives an overview of the results of our communication with sponsors. We scored them on different parameters:

- Did they respond to our emails;
- Did they mention concrete actions they had undertaken or planned to take, and did these actions result in concrete improvement in reporting due trials;
- Did they show that they were working to tackle reporting problems, or did they mention a concrete action plan to tackle existing reporting problems.

	Answered	Actions undertaken and effect on results reporting	Reported concrete work on reporting and/or action plan
EORTC	yes	yes, with visible concrete improvements	yes
KULeuven	yes	yes, with visible concrete improvements	in some measure
UGent	yes	yes, with visible concrete improvements	in some measure
VUBrussel	yes	yes, with visible concrete improvements	yes
UAntwerpen	yes	yes, but without concrete improvements (so far)	in some measure
ULB/Bordet	yes	yes, but without concrete improvements (so far)	yes
ULiege	yes	no	in some measure
CHU Brugmann[4]	no	no	no
Cliniques Universitaires Saint Luc	no	yes, with visible concrete improvements	no
Galapagos	yes	yes, with visible concrete improvements	yes
Ablynx (Sanofi)	no	no	no
Tibotec (Johnson & Johnson)	yes	not applicable	yes
SMB	yes	not applicable	yes
UCB	yes	no	in some measure

Kom op tegen Kanker and Test Aankoop/Test Achats would like to thank AFMPS and the sponsors who responded for sharing their perspectives.

[4] Due to technical problems, CHU Brugmann received only the mail we sent in July 2020 (with the communication of their results, our question about which actions they would undertake to improve reporting, and our announcement about plans for future media outreach. The CHU did not receive a later follow-up mail with technical explanations of EudraCT trial reporting and further concrete planning of media outreach.

5 WHY THIS MATTERS

Relevance to public health and clinical practice

Failure to report clinical trial results is not a harmless infringement. 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

European Union rules adopted in July 2014 require each and every clinical trial registered on the EU Clinical Trials Registry to post summary results to the registry within 12 months 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.

Thus, 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.

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 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.

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.

Universities should 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 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 so important?

There are good reasons why global best practices require posting the results of all trials to registries:

- 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.

Uploading results to trial registries typically precedes publication in academic journals

There is no recorded case, ever, in which a manuscript was rejected by a journal because the trial results had already been uploaded to a trial registry.

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 becoming the new norm in scientific communications.

ANNEX I: DATA TABLE

The table below contains the data used to compile this report. It is exclusively based on publicly available data from the European trial registry EUCTR that was aggregated by the EU Trials Tracker. Data for each institution can be accessed by searching the EU Trials Tracker.

Data on the percentage of due trials with results is not reliable for all sponsors and should therefore not be used to compare institutional performance. For example, Vrije Universiteit Brussel has a nominal reporting rate of 40%, but only (an implausibly low) 5 out of its 63 trials are marked as completed and due to report results, and 2 of those trials have results. In contrast, Ghent University with a portfolio of 141 trials has 39 trials that are marked as completed and due to report results, and has uploaded results for 8 of those trials, a nominal reporting rate of just 21%. In fact, Ghent's reporting performance is stronger than that of Brussels, but this difference remains hidden because of Brussels' weaker data quality management.

For this reason, the report displays due results reported in the context of institutions' overall trial portfolios: Vrije Universiteit Brussel has uploaded the results of 2 due trials against a total portfolio of 63 trials, while Ghent University has uploaded the results of 8 due trials against a total portfolio of 141 trials.

Sponsor name	Total trials	Due trials	Due with results	Due no results	% due with results	2020 Due with results	Change 2020-2021
KU Leuven	242	78	75	3	96	14	61
UCB	213	68	65	3	96	55	10
Ghent University	141	39	8	31	21	6	2
EORTC	105	29	28	1	97	17	11
Université libre de Bruxelles	99	7	0	7	0	0	0
Vrije Universiteit Brussel	63	5	2	3	40	0	2
Cliniques Universitaires Saint-Luc	57	5	4	1	80	0	4
Tibotec (Johnson & Johnson)	49	13	13	0	100	12	1
University of Antwerp	37	5	0	5	0	0	0
Galapagos	29	14	14	0	100	10	4
CHU de Liège	23	3	0	3	0	0	0
Laboratoires SMB	18	13	12	1	92	9	3
Ablynx (Sanofi)	12	7	7	0	100	7	0
CHU Brugmann	10	6	0	6	0	0	0
TOTAL	**1098**	**292**	**228**	**64**	**78**	**130**	**98**

Note: 2020 data were collected in June 2020. All other data were collected in April 2021.

ANNEX II: METHODOLOGY AND LIMITATIONS

Authorship

Report author: Dr Till Bruckner (Founder, TranspariMED) tillbruckner@gmail.com
Data extraction: Nicholas DeVito (EBM Data Lab, University of Oxford)

The author would like to thank Nicholas DeVito for volunteering his time and expertise for extracting the data used for cohort selection. EBM Data Lab as an institution was not involved in developing this report. Any errors in this report are exclusively the responsibility of TranspariMED. The author does not have any potential conflicts of interest.

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 an Austrian sponsor.

The data in this report reflects data publicly available on EUCTR as of 01 April 2020.

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 headquartered in Belgium that had sponsored 10 or more clinical trials on EUCTR as of 01 June 2020.

The full data set listed 18 sponsors with 10 or more trials listed. Based on a manual search of sponsor websites, 4 sponsors were excluded because they are companies headquartered outside Belgium.[5] In contrast, 2 Belgian companies that have been acquired by companies headquartered outside Belgium, but continue to operate from locations inside Belgium, were retained.[6]

This process yielded 14 clinical trial sponsors located in Belgium that had sponsored 10 or more trials listed on EUCTR as of 01 June 2020.

[5] These are GlaxoSmithKline, Bristol-Myers Squibb, Johnson & Johnson, and Boehringer Ingelheim
[6] These are Tibotec (Johnson & Johnson) and Ablynx (Sanofi).

Measuring sponsor performance

Data on the clinical trial performance of each of the 14 sponsors was manually extracted from the EU Trials Tracker on 05 April 2021.

The tracker data reflected trials results that were publicly available on EUCTR as of 01 April 2021. Due to delays by the European Medicines Agency in making public trial results submitted by sponsors, the tracker data might not include all trial results that were uploaded by sponsors during March 2021. Thus, the data in this report reflect sponsors' trial reporting performance as of early March 2021.

The EU Trials Tracker was built by the EBM Data Lab, University of Oxford, and its methodology published in a peer reviewed journal. 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.

Limitations

Undercounting of due trials

The EU Trials Tracker significantly undercounts the number of trials due to post results in Belgium 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 Belgium is unknown, and is impossible to determine based on registry data.

Undercounting of results posted

Due to delays by the European Medicines Agency in making public trial results submitted by sponsors, trial results that were uploaded during late March 2021 may not have been captured by the EU Trials Tracker. In consequence, 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 is likely to be very low in a cohort this size. In addition, the Tracker lists trials with results that are not marked as completed and/or have no completion date in the protocol as having "inconsistent data"; such trials are not counted as 'reported' by the Tracker or in this report. The number of such trials is low. Please see here for more details.

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, 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 Belgian sponsors' reporting performance for these non-drug trials is beyond the scope of this report.