Clinical Trial Transparency at German Universities

Mapping unreported drug trials

30 December 2019
Bielefeld, Germany and Bristol, UK

> *"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. This is consistent with the principal goal of medical research: to serve the betterment of humanity. In the case of clinical trials, full transparency on results advances both scientific understanding and timelines for product development and ultimately enables access to essential medicines."*
>
> - Dr Tedros Adhanom Ghebreyesus, Director-General, 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

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1 KEY FINDINGS AND RECOMMENDATIONS

Obligation to report the results of all trials

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

European Union rules adopted in July 2014 require the sponsors of each and every clinical trial registered on the EU clinical trials registry to post those trials' summary results onto 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

Overall, the 35 university medical centres in Germany have registered 1,312 clinical trials of investigative medicinal products on the European trial registry. Of these, 477 trials have verifiably been completed more than a year ago, and should thus have results available.
However, results are only available on the registry for 32 of those trials (6.7%). Results are missing for the other 445 trials (93.3%).

- ***Münster university is Germany's top performer, with 61% of its due clinical trial results available***. All other universities have uploaded less than a third of their due results.
- With 68 due trials missing results, the ***Charité in Berlin*** has by far the largest backlog of unreported trials. Other universities with large gaps in their trial portfolios are ***LMU München*** (29 trials), ***Mainz*** (28 trials), ***TU München*** (27 trials), and ***Hannover*** (26).
- Out of the 32 German university trial results available on the registry, 11 have been posted by ***Münster university*** alone. ***Leipzig*** has uploaded 4 results. No other university has posted more than 2 results. 17 of the universities with due trials have not posted a single result.
- German universities' results posting rate of 6.7% is far below the average European trial reporting rate of 62.5%.

The strong performance by Münster and other leading European universities demonstrates that university medical centres in Germany can – and can be expected to – do far better.

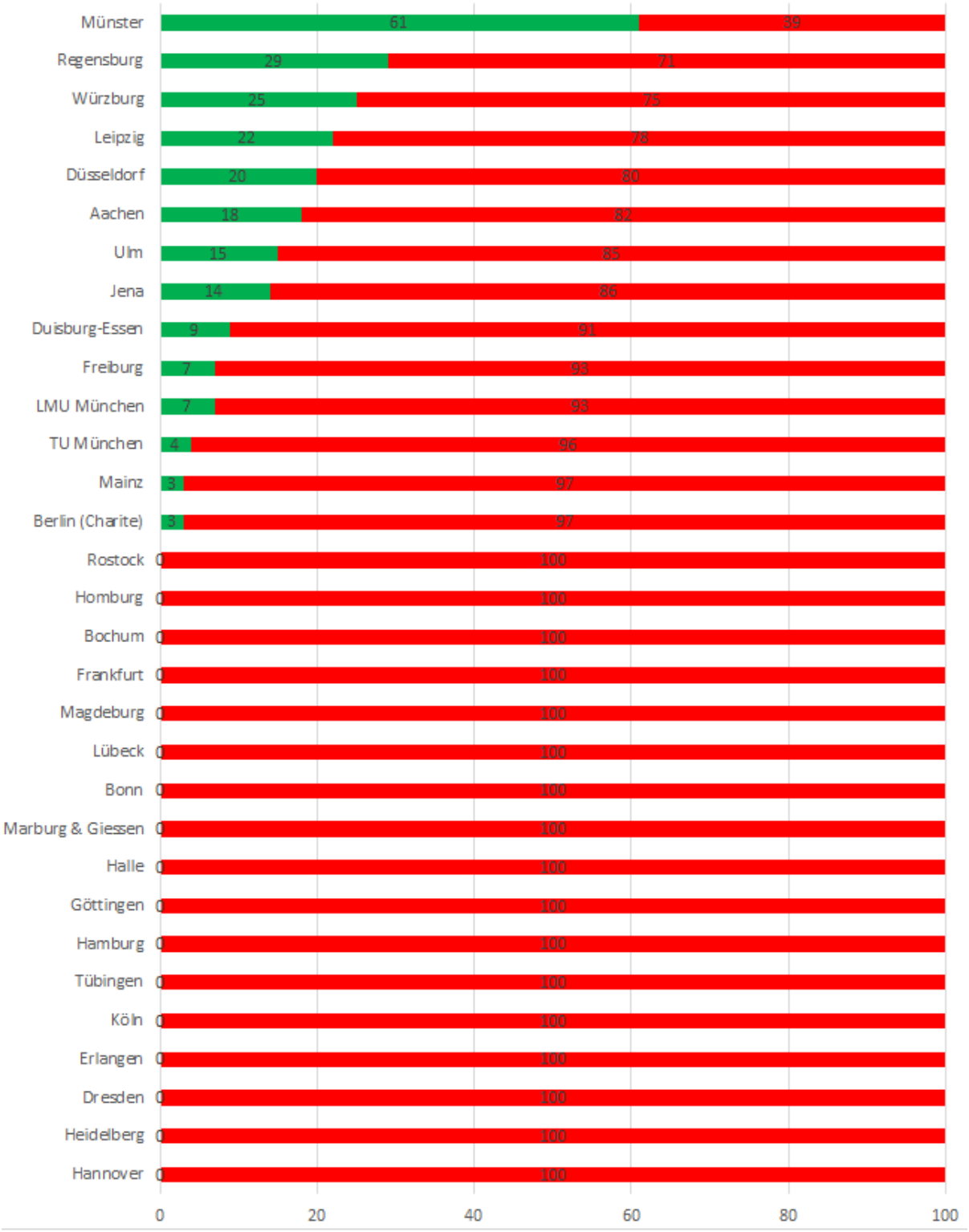
Recommendations in brief

- **Universities** 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.
- **Bundesministerium für Bildung und Forschung and Deutsche Forschungsgemeinschaft** should commit to World Health Organisation best practices for avoiding research waste.
- **BfArM and Paul Ehrlich Institut** should monitor compliance, directly contact trial sponsors whose results are overdue, update the status of existing registry entries, and draw up plans to impose fines after the EU Clinical Trials Regulation comes into force.
- **The German government** should use Research Ethics Committee records to monitor whether clinical trials are prospectively registered and upload their results onto registries on time.

Detailed recommendations are listed further below.

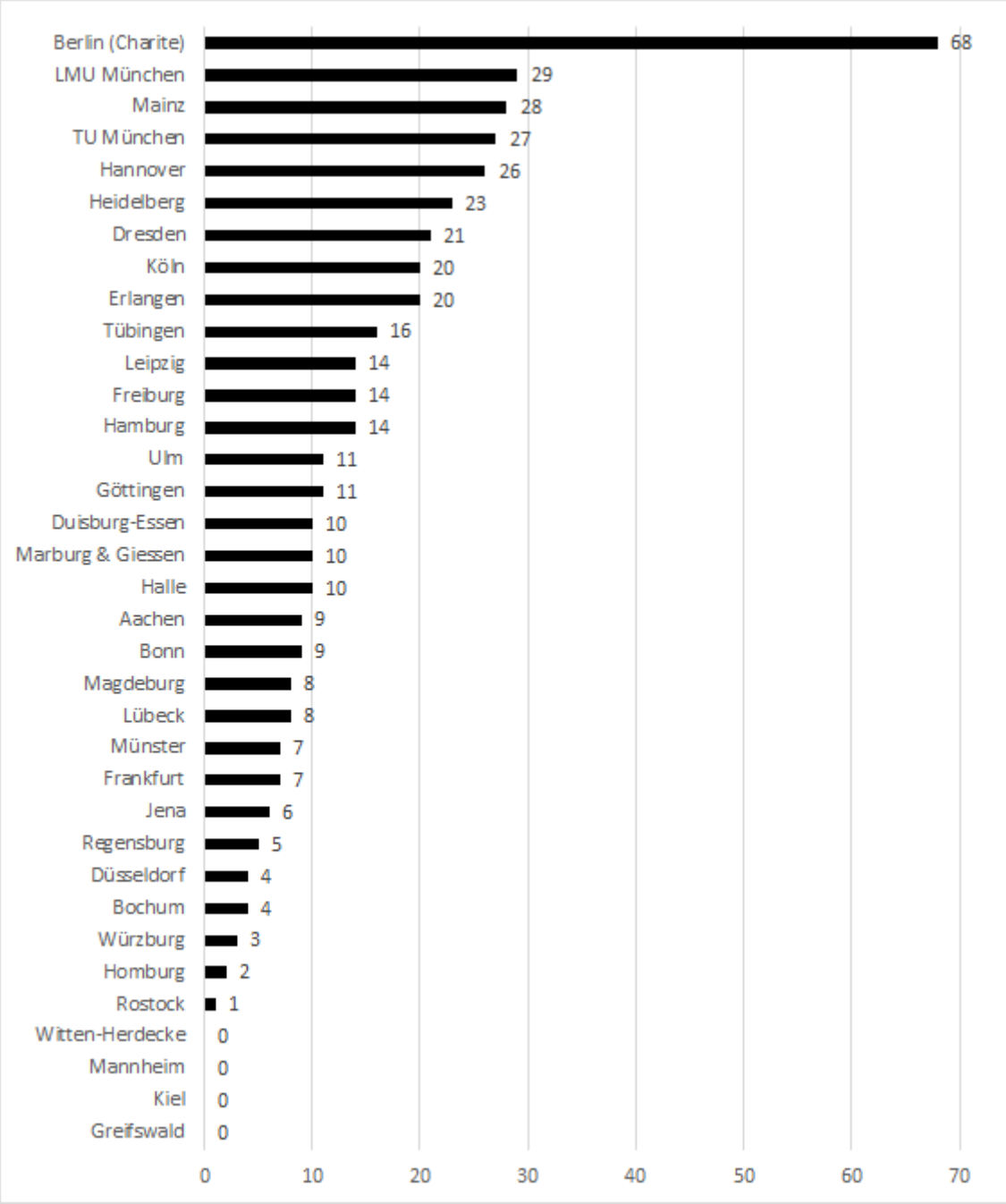
2 REPORTING PERFORMANCE BY UNIVERSITY

On average, German universities have only uploaded 6.7% of their due clinical trial results. Performance varies strongly by university. Münster is the clear leader, with 61% of trial results available. At the bottom of the table are 17 universities that have not uploaded a single result.



3 CLINICAL TRIALS MISSING RESULTS BY UNIVERSITY

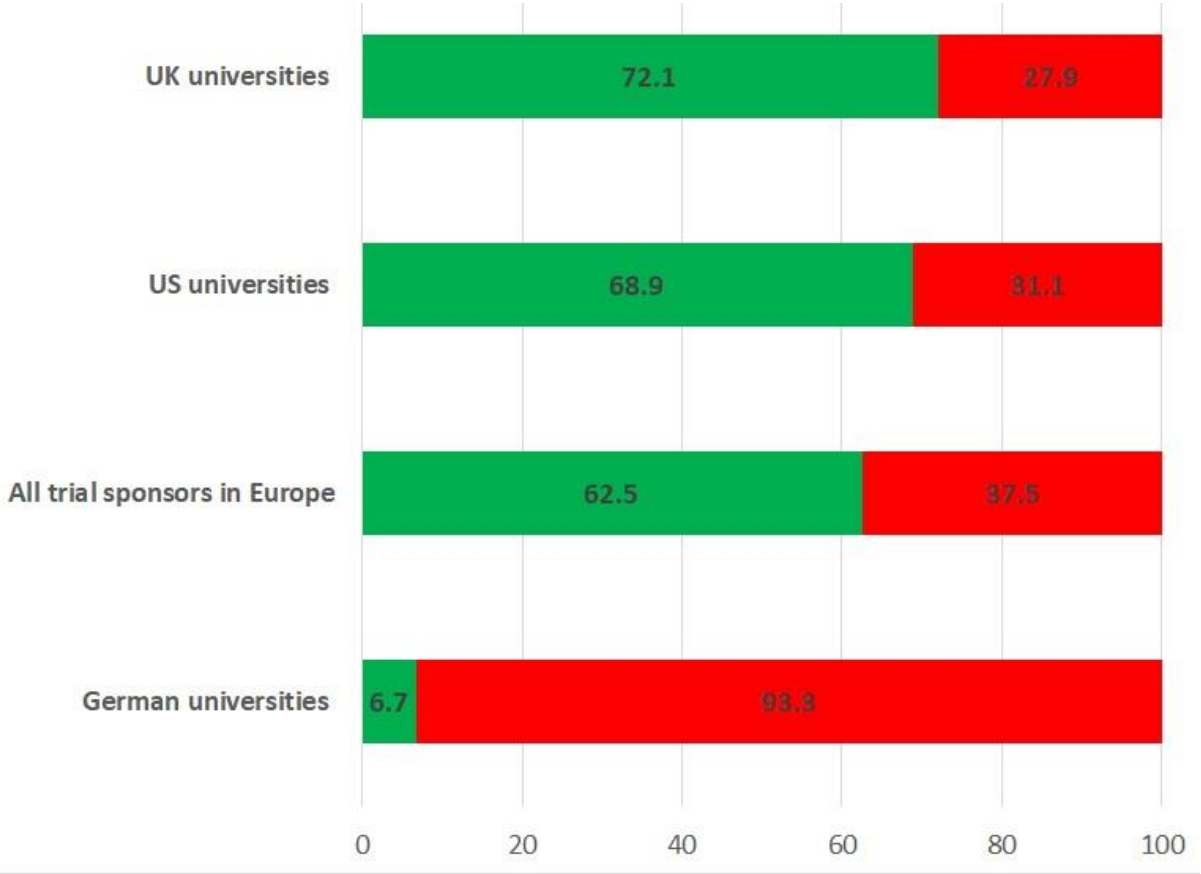
German universities have failed to make the results of 445 of their trial public on the European trial registry, in violation of European Union transparency rules. With 68 due trials missing results, the Charité in Berlin has by far the largest backlog of unreported trials. Seven universities between them account for half of all trials that are still missing results: Charité, LMU München, Mainz, TU München, Hannover, Heidelberg and Dresden.



Witten-Herdecke, Mannheim, Kiel and Greifswald have trials listed on the European registry, but none of those trials are verifiably due to post results yet.

4 GERMAN UNIVERSITIES IN GLOBAL COMPARISON

German universities perform significantly worse than their counterparts in other countries. German universities' results posting rate of 6.7% is far worse than the reporting performance of British and American universities, and well below the average European trial reporting rate of 62.5%.



Data sources: UK universities: CEBM report, October 2019; US universities: TranspariMED & UAEM report, March 2019 [measures FDAAA compliance]; All trial sponsors in Europe: EU Trials Tracker, November 2019 [includes industry sponsors]

5 EXAMPLES OF TRIALS MISSING RESULTS ON THE EUROPEAN REGISTRY

This section takes a closer look at some trials run by German universities that are missing results on the European registry. It briefly outlines the purpose of each trial, and explains how posting its results onto the registry in line with existing rules would have benefited patients.

Limiting neurological damage in people suffering from multiple sclerosis (Charite)

- *Violation of European Union transparency rules*
- *Medical progress slowed down*

Trial 2008-005213-22 was sponsored by the Charite. It set out to discover whether a drug could help to limit neurological damage and improve cognitive functioning in people suffering from multiple sclerosis by enrolling 60 German patients and giving them either the drug or a placebo. The trial was completed in February 2016, but no results have been posted on the European registry yet.
The same trial was (probably unnecessarily) double registered on the American registry, where no results have been posted either.
Contacted by email, a member of the research team explained that: "We are currently finalizing the statistical evaluation. A publication in a scientific journal and the entries in the corresponding databases are in preparation." It is highly encouraging that the researchers plan to post the results onto these registries. However, if Charite had ensured that European Union disclosure timelines are adhered to, the trial's results would have become publicly available in early 2017, thus accelerating the development of more effective treatments for multiple sclerosis.

Fingolimod for patients with multiple sclerosis (Charité)

- *Violation of European Union transparency rules*
- *Medical progress slowed down*

Trial 2012-000411-91 was sponsored by the Charité. The trial set out to discover how fingolimod (brand name Gilenya), a drug used by German patients since 2011, affects natural killer cells in people with multiple sclerosis. The study aimed to enrol 40 German patients suffering from relapsing-remitting multiple sclerosis, the most frequent form of the disease.
The study was completed in early August 2018, and thus should have uploaded its results onto the European trial registry by August 2019. However, the results have been made public neither on the trial registry nor in an academic journal. Contacted by email, a member of the research team explained that "preliminary results have been presented on academic meetings and congresses. A full paper is about to be prepared."
While it is laudable that Charite investigators have used scientific meetings to rapidly present their results, and are now preparing to publish the trial's outcomes in a journal, academic publication timelines are slow. Therefore, it seems likely that most of the research community – and doctors treating patients with multiple sclerosis – will only get to see the results of the trial in 2020 or 2021 at the earliest.
This trial illustrates how consistent posting of results onto the trial registry within the 12 month time frame required by the European Union could accelerate progress in medical research and clinical practice.

Gabapentin for patients with co-ordination, balance and speech problems (Charité)

- *Violation of European Union transparency rules*
- *Weak registry management undermines trial recruitment efforts*
- *Risk of public funds being wasted*

Trial 2008-005167-33 was sponsored by the Charité. It set out to discover whether the drug gabapentin (brand name Neurontin) could help patients with ataxia, a group of disorders that affect co-ordination, balance and speech. The trial aimed to enrol a total of 72 patients suffering from ataxia: 36 people with neurodegenerative cerebellar disease, and 36 people with multiple sclerosis.
The trial was completed in March 2016, and thus its results should have been uploaded onto the European registry by March 2017. However, no results are available there.
The same trial was (probably unnecessarily) additionally registered on the German trial registry DRKS, where it is also missing results and is falsely listed as still recruiting patients. The Charité's and other universities' failure to keep registry entries up to date has resulted in the proliferation of trials incorrectly marked as still recruiting, which makes it hard for patients to find trials they can enrol in.
Furthermore, the WHO recommends registering each trial on only one trial registry if possible.
A search for the trial registry numbers and keywords in PubMed and Google Scholar did not return any journal articles discussing the trial's results, suggesting that even today – over a year after a BMJ blog first drew attention to the Charité's failure to make the gabapentin trial's results public – the outcomes have not been made publicly available in any form.
According to registry data, the trial was funded by the Deutsche Forschungsgemeinschaft (DFG). Unless the Charité acts quickly to make the results of this trial public, the benefits and harms of gabapentin detected during this taxpayer-funded trial could be lost to medical knowledge forever.

Improving treatment for patients with kidney transplants (LMU München)

- *Violation of European Union transparency rules*
- *Risk of research waste*

Trial 2013-004956-39 was sponsored by LMU München. It set out to discover better ways to treat patients who had received a kidney transplant. The trial was completed in May 2016 and thus its results should have been made public on the European registry by the end of May 2017 latest. According to registry data, the trial was supported by Pfizer, but European Union transparency rules clearly state that the trial sponsor – LMU München – is responsible for posting results onto the registry.
A search for the trial registry number and keywords in PubMed and Google Scholar did not return any journal articles discussing the trial's results, suggesting that the trial's outcomes have not been made publicly available in any form, and have thus not made any contribution to furthering medical research or improving clinical practice.
Unless LMU München acts quickly to make the results of this trial public, the time and effort volunteered by kidney transplant patients participating in the trial will have been in vain, and the potential benefits and harms of the new treatment could be lost to medical knowledge forever.[1]

[1] University comment (see Annex II): *"The study SMART-DAS, EudraCT-NR 2013-004956-39 was submitted to the responsible higher federal authority in accordance with the legal requirements; we could not figure out whether it had already been published."*

Improving the lives of patients with schizophrenia (LMU München)

- *Probable violation of European Union transparency rules*
- *Apparent failure to keep registry entry up to date*
- *Only partial reporting of trial outcomes*
- *Risk of research waste*

Trial 2005-004501-28 was sponsored by LMU München. The trial set out to compare the impact of two different drugs on cognitive functioning and quality of sleep in 60 German patients with schizophrenia. The trial started over ten years ago and has almost certainly been completed, but is still marked as 'ongoing', making it hard for patients to find genuinely ongoing trials that they can enrol in.
A search for the trial registry number and keywords in PubMed and Google Scholar only returned one 2007 article, which presented interim results for the drugs' impact on patients' driving skills only. The final results for all patients, on all pre-specified outcome measures including quality of life, appear not to have been made public, raising the spectre of research waste.[2]

Improving the lives of patients with coronary artery disease (Mainz university)

- *Violation of European Union transparency rules*
- *Failure of university and BfArM to ensure that trial status is up to date*
- *Incomplete, inconsistent and out of date registry data indicates lack of oversight*
- *Evidence base for coronary heart disease treatments hard to navigate*

Trial 2006-004533-15 was sponsored by Mainz university. It examined a potential new approach to treating endothelial dysfunction in 80 German patients with coronary artery disease.
The trial started over ten years ago. In the European registry – where no results have been posted – the trial is still listed as ongoing, even though its outcomes were reported in a journal in 2008. According to registry data, BfArM is the German 'National Competent Authority' for this trial. Thus, BfArM is responsible for updating the status of registry entries after receiving an end of trial notification by the trial sponsor. It is unclear whether Mainz university failed to notify BfArM that the trial had ended, or whether BfArM received a notification but failed to then update the status of the trial. Either way, Mainz university seems to lack the central oversight required to detect such problems and follow up to get them resolved.
The university (probably unnecessarily) double registered the industry-funded trial in another WHO primary trial registry, ISRCTN, where the trial is listed as having been completed in May 2008. The ISRCTN registry entry omits the trial's European registry number, and fails to link to the journal article reporting the trial's outcomes, making it more difficult for systematic reviewers to navigate the evidence base for coronary artery disease treatments.

[2] University comment (see Annex II): "*For the AriZip study, EurdaCT no. 2005-004501-28, we found, thanks to the enquiry, that the study had apparently not yet been reported as completed. So far, the results of this study have only been made available to the specialist public as part of a lecture, but have not been published. We will make the publication as soon as possible.*"

Improving progression-free survival in cancer patients (Mainz university)

- *Violation of European Union transparency rules*
- *Inconsistencies between different registry entries*
- *Three-year delay in sharing results with the scientific community*

Trial 2009-014336-38 was sponsored by Mainz university. The trial set out to find new ways to improve progression-free survival in patients with advanced stomach cancer.
The trial ended in July 2013, but still has not posted summary results onto the European trial registry. It was also (probably unnecessarily) registered on the American trial registry Clinicaltrials.gov. The university attempted to upload the results to Clinicaltrials.gov results in August 2018, but has not responded to subsequent quality review feedback provided by that registry, so no tabular results are publicly visible there either. (Clinicaltrials.gov reviews the quality and consistency of results submitted, and frequently requests changes to be made.)
The university has failed to ensure that registry data is consistent, with the European registry entry listing more secondary outcome measures than the American entry does. This makes it hard for other researchers to distinguish between exploratory and confirmatory trial outcomes.
Trial outcomes were reported in an academic journal only in August 2016, more than three years after the trial had ended – a not atypically slow academic publication timeline. The paper references only the trial's Clinicaltrials.gov number, but not its European registry number, which makes it harder to find.

Helping young children who are at high risk of diabetes (TU München)

- *Violation of European Union transparency rules for paediatric trials*
- *Risk of research waste*

Trial 2014-005287-15 was sponsored by TU München. It aimed to find out whether providing a daily dose of insulin to young children aged six months to two years with high genetic risk for diabetes induces immune responses to proinsulin. A total of 44 German infants and toddlers participated in the trial.
According to European Union rules, trials involving children must post their results onto the registry within 6 months of completion (for trials involving adults, the time frame is 12 months). TU München's trial was completed in December 2017, but nearly two years later, the university has still not uploaded its results onto the registry.
A search for the trial registry number and keywords in PubMed and Google Scholar did not return any journal articles reporting the trial's outcomes. Unless and until TU München makes the results of this trial public, its findings will not contribute to doctors' understanding of how to best treat infants and toddlers with a high risk of developing diabetes.
The trial, which was funded (presumably with public money) by the Deutsches Zentrum für Diabetesforschung, appears to be at acute risk of becoming research waste.[3]

[3] University comment (see Annex II): "*2014-005287-15: does not fall under §42b (2) since IMP has not been approved yet; a peer reviewed publication of the results is planned*"

Improving the life expectancy of cancer patients (TU München)

- *Failure of university and Paul Ehrlich Institute ensure that trial status is up to date*

Trial 2004-004024-12 was sponsored by TU München. It aimed to discover whether a new treatment combination could help patients with advanced adenocarcinoma of the esophagus and stomach. Among other things, the trial set out to determine the toxicity of the new treatment, and its impact on the survival rates of 46 German cancer patients.
The trial was launched in 2005, and was projected to last only one year. Its outcomes were published in a journal in 2010. However, the trial is still listed as 'ongoing' on the European registry.
According to registry data, Paul Ehrlich Institut is the German 'National Competent Authority' for this trial. Thus, Paul Ehrlich Institut is responsible for updating the status of registry entries after receiving an end of trial notification by the trial sponsor. It is unclear whether TU München failed to notify Paul Ehrlich Institute that the trial had ended, or whether Paul Ehrlich Institute received a notification but failed to then update the status of the trial. Either way, TU München seems to lack the central oversight required to detect such problems and follow up to get them resolved.

Treating elderly patients with cancers that cannot be surgically removed (Hannover university)

- *Violation of European Union transparency rules*
- *Medical progress slowed down*

Trial 2011-004168-30 was sponsored by Hannover university. The trial investigated the possibility of using a novel agent to improve progression-free survival, quality of life and overall survival for elderly cancer patients undergoing chemotherapy. Hannover university enrolled 120 German patient volunteers with cancer in the trial. The trial was completed in March 2017 and thus its results should have been made publicly available on the registry by end of March 2018 latest.
However, in violation of European Union rules, the university did not upload the trial results onto the registry. Some outcomes of the trial were only made public in October 2018 in a journal article. If the university had followed European Union rules, all outcomes of the trial would have been available to cancer researchers and oncologists months earlier.
Hannover university (unnecessarily) also registered the same trial on the American registry Clinicaltrials.gov. While the university has not posted the trial's results there either, it has updated the American registry entry to note that the trial has been completed.

Improving the treatment of patients with depression (Hannover university)

- *Violation of European Union transparency rules*
- *Evidence gap on depression treatment options*
- *Risk of research waste*

Trial 2009-015125-36 was sponsored by Hannover university. It aimed to determine whether botulinum toxin (Botox) was an effective treatment for mild or moderate treatment of depression by giving 15 German patients either the treatment or a placebo and then monitoring their depression levels. The trial was completed in December 2011 but the university has still not uploaded its results to the European registry.
A search for the trial registry number and keywords in PubMed and Google Scholar did not return any journal articles reporting the trial's outcomes, suggesting that they have never been made public, despite continuing medical uncertainty about Botox' potential as a treatment for depression. Unless and until Hannover university makes the results of this trial public, its findings will not contribute to doctors' understanding of how to best treat depression.

6 GERMAN UNIVERSITY DATA AT A GLANCE

The data below can also be downloaded as an Excel file.

University	# total	# due	# results	# missing	% results	Hyperlink (link to the university's EU Trials Tracker data)
Aachen	40	11	2	9	18	http://eu.trialstracker.net/sponsor/rwth-aachen-university
Berlin (Charite)	190	70	2	68	3	http://eu.trialstracker.net/sponsor/charite-universitatsmedizin-berlin
Bochum	15	4	0	4	0	http://eu.trialstracker.net/sponsor/ruhr-university-bochum
Bonn	26	9	0	9	0	http://eu.trialstracker.net/sponsor/university-of-bonn
Dresden	45	21	0	21	0	http://eu.trialstracker.net/sponsor/dresden-university-of-technology
Duisburg-Essen	30	11	1	10	9	http://eu.trialstracker.net/sponsor/university-duisburg-essen
Düsseldorf	11	5	1	4	20	http://eu.trialstracker.net/sponsor/heinrich-heine-university-dusseldorf
Erlangen	56	20	0	20	0	http://eu.trialstracker.net/sponsor/university-erlangen-nuremberg
Frankfurt	43	7	0	7	0	http://eu.trialstracker.net/sponsor/goethe-university
Freiburg	43	15	1	14	7	http://eu.trialstracker.net/sponsor/university-of-freiburg
Göttingen	21	11	0	11	0	http://eu.trialstracker.net/sponsor/university-of-gottingen
Greifswald	7	0	0	0	n/a	http://eu.trialstracker.net/sponsor/medical-university-greifswald
Halle	28	10	0	10	0	http://eu.trialstracker.net/sponsor/martin-luther-university-halle-wittenberg
Hamburg	47	14	0	14	0	http://eu.trialstracker.net/sponsor/university-of-hamburg
Hannover	53	26	0	26	0	http://eu.trialstracker.net/sponsor/hannover-medical-school
Heidelberg	77	23	0	23	0	Two links - see methodology section of this report
Homburg	11	2	0	2	0	http://eu.trialstracker.net/sponsor/saarland-university
Jena	17	7	1	6	14	http://eu.trialstracker.net/sponsor/friedrich-schiller-university-jena
Kiel	3	0	0	0	n/a	http://eu.trialstracker.net/sponsor/university-of-kiel
Köln	63	20	0	20	0	http://eu.trialstracker.net/sponsor/university-of-cologne
Leipzig	36	18	4	14	22	http://eu.trialstracker.net/sponsor/leipzig-university
LMU München	76	31	2	29	7	http://eu.trialstracker.net/sponsor/university-of-munich-ludwig-maximilians
Lübeck	27	8	0	8	0	http://eu.trialstracker.net/sponsor/schleswig-holstein-university-hospital
Magdeburg	23	8	0	8	0	http://eu.trialstracker.net/sponsor/otto-von-guericke-university-magdeburg
Mainz	46	29	1	28	3	http://eu.trialstracker.net/sponsor/johannes-gutenberg-university-of-mainz
Mannheim	8	0	0	0	n/a	http://eu.trialstracker.net/sponsor/central-institute-of-mental-health-in-mannheim
Marburg & Giessen	26	10	0	10	0	Two links - see methodology section of this report
Münster	32	18	11	7	61	http://eu.trialstracker.net/sponsor/university-of-munster
Regensburg	26	7	2	5	29	http://eu.trialstracker.net/sponsor/university-of-regensburg
Rostock	3	1	0	1	0	http://eu.trialstracker.net/sponsor/universitat-rostock
TU München	65	28	1	27	4	http://eu.trialstracker.net/sponsor/technical-university-of-munich
Tübingen	59	16	0	16	0	Two links - see methodology section of this report
Ulm	43	13	2	11	15	http://eu.trialstracker.net/sponsor/university-of-ulm
Witten-Herdecke	5	0	0	0	n/a	http://eu.trialstracker.net/sponsor/university-of-wittenherdecke
Würzburg	11	4	1	3	25	http://eu.trialstracker.net/sponsor/university-of-wurzburg
TOTAL	**1312**	**477**	**32**	**445**	**avg 6.7%**	

7 RECOMMENDATIONS FOR GERMAN UNIVERSITIES

Recommendations for universities

- **Excellence in reporting results is an integral part of overall research excellence.** As trial sponsors, universities – not individuals – are responsible for ensuring that their data on trial registries are complete and kept up to date, and that results are posted on time. Universities should **establish central oversight** over their clinical trial registry entries, across all trial registries, and track all past and future trials. This presentation by TranspariMED provides some guidance.

- Looking forward, universities should adopt **policies** that ensure that the summary results of all their interventional clinical trials are routinely and consistently uploaded onto all registries where these trials are listed within 12 months of trial completion, as per WHO best practices. This policy checklist may be helpful.

- Looking back, universities should **audit** their existing trials across all WHO primary registries and Clinicaltrials.gov, to identify trials whose data are incomplete or out of date, or that are missing results on the registry. Universities should then draw up a plan for addressing the problem.

- For trials listed on the ***European registry***, all missing results should be uploaded. These can easily be identified using the EU Trials Tracker. Guidance on how to upload results can be found in TranspariMED's collection of transparency tools and in these presentations.

- The university should compile a spreadsheet listing all trials on the ***European registry*** with their correct completion dates, and ask the responsible authority (BfArM or Paul Ehrlich Institut) to update their status. (Only regulators can update the of trials listed on the European registry. On other trial registries, universities can update the status of trials themselves.)

- During the audit of ***other WHO primary registries and Clinicaltrials.gov***, the university will have identified trials that are missing summary results on these registries. The university should then check for each of these trials whether it has reported outcomes in an academic journal. (German universities can use the IntoValue data set to identify which of their trials on Clinicaltrials.gov and the German DRKS registry have not published outcomes in journals.) Trials that have not made their results public anywhere are in acute danger of becoming research waste. Universities should upload the summary results of these trials onto the registry where they are listed, before the data is lost forever.

Need additional guidance or support?

The TranspariMED website hosts a collection of useful transparency tools and case studies of universities that have successfully fixed the problem.

TranspariMED is keen to hear from universities what additional resources and support would be helpful to support their trial reporting efforts. Please email tillbruckner@gmail.com and share your experiences and suggestions.

8 POLICY RECOMMENDATIONS

> ***"WHO calls for ethics committees, regulatory authorities, professional bodies, sponsors, investigators, and funding agencies to act in their jurisdictions to ensure results from all interventional clinical trials are reported and publicly disclosed."***
>
> World Health Organisation statement, 2015

> ***"Legislation or supporting regulations… [should] require all clinical trials to be registered… prior to commencing the trial, public disclosure of results of any newly conducted clinical trial, public disclosure of unreported results for clinical trials conducted in the past, [and] sanctions if a clinical trial is not registered and / or results are not reported."***
>
> WHO, Pharmaceutical System Transparency and Accountability Assessment Tool, 2018

Recommendations for the German government

- **The German government** should put into place systems to monitor whether clinical trials conducted within its jurisdiction are posting their summary results onto public registries within 12 months, as per WHO best practices, and impose sanctions on trial sponsors who fail to make results public within that deadline. This involves centrally following up on ethics approvals made by Research Ethics Committees to check whether trials were prospectively registered and uploaded their results on time. (The UK is currently preparing to do this.)

Recommendations for BMBF and Deutsche Forschungsgemeinschaft

- **Bundesministerium für Bildung und Forschung (BMBF) and Deutsche Forschungsgemeinschaft** should sign up to the **WHO Joint Statement** and fully implement its provisions to protect patients, accelerate medical progress, and prevent medical research financed by taxpayers from going to waste. A 2018 study indicates that BMBF in particular is not doing enough to prevent research waste. Many major medical research funders from other countries have already signed up to the WHO Joint Statement, and two of these funders – Wellcome Trust and MRC – have already published their first audit results.)

Recommendations for BfArM and Paul Ehrlich Institut

- BfArM and Paul Ehrlich Institut share the role of German **national competent authority** for EU-regulated drug trials. Depending on the type of trial, either BfArM or Paul Ehrlich Institut act as the national competent authority. Entries on the European trial registry clearly identify the German authority responsible for overseeing any given trial.

- BfArM and Paul Ehrlich Institut should review all trials on the European registry that they are responsible for, and that are currently listed as "ongoing" and **update their status** to "completed" if applicable. This will make it easier for patients to find trials to participate in, and for public health agencies and researchers to gain an overview of the complete scientific evidence base on a medicine. (The British regulator MHRA is already doing this.)

- Failure to report clinical trial results is not a victimless crime. BfArM and Paul Ehrlich Institut should formulate and clearly communicate plans to **impose fines** for violating reporting requirements after the EU Clinical Trials Regulation comes into force.

9 WHY THIS MATTERS

A recently published study of 1,509 clinical trials run by German universities found that 433 of these trials (over 28%) had become research waste due to universities' failure to ensure that their results are made public. Between them, these trials aimed to recruit 56,730 patients.

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

European Union rules adopted in July 2014 require each and every clinical trial registered on the EU clinical trials registry to post summary results onto 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. 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 onto 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 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, dozens of trials run by the universities covered by 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 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."

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 onto registries so important?

There are good reasons why global best practices require posting the results of all trials 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.

Uploading results onto trial registries typically precedes publication in academic journals

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

ANNEX I: IMPROVING TRIAL REPORTING – LESSONS FROM UK UNIVERSITIES

On average, UK universities perform far better than their peers in Germany. On average, they have already posted the results for over 72% of their clinical trials onto the European registry, and some individual UK universities have attained reporting rates of 100% Why do UK universities perform so strongly?

UK universities have become European leaders in transparency due to pressure from parliament, research funders, and the public.

- **Parliamentary pressure:** The Science and Technology Committee of UK parliament held an enquiry into research integrity during 2018-2019. Committee members were shocked to discover that many universities were routinely violating transparency rules. In early 2019, the Chairman of the Committee wrote to all UK universities warning them that if they did not rapidly upload the missing trial results, they would be called before the Committee to explain themselves. This set off a race to fix the problem.

- **Pressure from research funders:** Britain's two public medical research funding bodies, the NIHR and the MRC, as well as the non-profit Wellcome Trust, in 2017 all signed the WHO Joint Statement on Public Disclosure of Results from Clinical Trials. By signing up, these funders committed themselves to adopting policies on trial registration and trial reporting that are in line with WHO best practices, and monitoring their grantees' compliance with these rules. Two funders, Wellcome Trust and MRC, have already published their first audit results. In coming years, UK universities that fail to post the results of trials onto registries on time may no longer be able to access public medical research funds.

- **Public pressure:** A loose coalition of health integrity groups convened by TranspariMED that included Universities Allied for Essential Medicines (UAEM-UK), HealthWatch UK, Transparency International Health, and STOPAIDS engaged with parliament, the media and directly with universities to press for better trial reporting. TranspariMED and UAEM-UK also published several reports documenting the performance of individual UK universities. In parallel, the AllTrials campaign, which focuses mainly on the UK, strongly campaigned on the issue, including by regularly emailing its over 90,000 supporters. The EBM Data Lab at the University of Oxford, which is linked to the AllTrials campaign (and which built the EU Trials Tracker this report's data is drawn from), directly supplied the parliamentary Committee with data on individual universities' performance.

This pressure has had a huge impact on UK universities' trial reporting performance. For example, King's College London improved its reporting rate from 18% to 100% within less than a year. The University of Nottingham, starting from an even lower baseline, has by now posted the results for over 94% of its trials. (See their respective case studies for details on how they fixed the problem.) Many medical universities in the UK are also reviewing their data on other registries such as the US registry Clinicaltrials.gov and ISRCTN. This demonstrates that where there is a will, there is a way – universities in Germany too can solve this problem if they decide to do so.

The UK government is now working to put into place a comprehensive national clinical trial monitoring system that will use Research Ethics Committee records to track every single clinical trial conducted on UK soil – including commercial trials and multi-country trials – to ensure that it is registered and reports its results.

ANNEX II: UNIVERSITY RESPONSES

The press offices of the five universities with the largest number of unreported trials were contacted twice by email to give them the opportunity to flag and correct errors in the section discussing individual trials, and were at the same time invited to "provide a formal response or a statement on [their] clinical trial registry management efforts" should they wish to do so.

- Three universities did not respond to repeated enquiries: Charite, Mainz and Hannover.
- LMU Munich and TU Munich did respond; their responses are reproduced below.

Response by LMU Munich

"The study SMART-DAS, EudraCT-NR 2013-004956-39 was submitted to the responsible higher federal authority in accordance with the legal requirements; we could not figure out whether it had already been published.

For the AriZip study, EurdaCT no. 2005-004501-28, we found, thanks to the enquiry, that the study had apparently not yet been reported as completed. So far, the results of this study have only been made available to the specialist public as part of a lecture, but have not been published. We will make the publication as soon as possible.

The Medical Faculty and the University Hospital of the LMU Munich regularly draw the attention of the researchers to the obligation to publish the study results within 12 months. A central review of the publication of studies has not yet taken place, but is conceptually in preparation with an appropriate IT study platform and central quality management including instructions."

Response by TU Munich

"The basic idea of a requirement for publication is to inform the public about the conduct of clinical trials, its sponsors, themes, medicines and results. In Germany this has been an obligation for many years and TUM is compliant with this requirement, both through publication of the contents of clinical trials on medicinal products in EudraCT (https://eudract.ema.europa.eu) as well as publication of results with the national competent authorities (BfArM and PEI).

For this purpose TUM is uploading summary clinical trial reports (according to the German Medicinal Products Act, Arzneimittelgesetz, AMG, §42b and §67) to the national portal (Pharmnet.Bund) for publication by and through the national competent authorities. The competent authority PEI has confirmed that (according to GCP Ordinance - GCP-V § 13 (9)) there is currently no legal basis in Germany for Clinical Trial Result Reporting in EudraCT. Thus, clinical trial reports of national clinical trials of TUM are accessible to the public through public access to the German database once review of and upload by the competent authorities is finalized.

Indeed, for multinational clinical trials, the EU-portal would be decisive. However, TUM has not finalized respective multinational clinical trials. As soon as the new clinical trials regulation (536/2014) comes into effect (upon set up of the EU portal and database, in 2020/21) all national as well as multinational clinical trials, including clinical trials of TUM, will be registered, approved, followed and reported through one single EU Portal.

Within the above mentioned context:
2004.004024-12: see open access publication in BJCancer attached
2014-005287-15: does not fall under §42b (2) since IMP has not been approved yet; a peer reviewed publication of the results is planned"

ANNEX III: RESPONSES BY GERMAN REGULATORS

TranspariMED contacted the two responsible German regulators ("National Competent Authorities" in European Union parlance), BfArM and Paul Ehrlich Institut, by email on three occasions over a two-week period to clarify their position on summary results posting onto the European trial registry by German universities.

Note: With regard to the EMA letter referenced below, BfArM at the time stated on its website that *"BfArM explicitly supports this demand"*:

Despite repeated reminders, neither of the two regulators provided a formal statement.

Text of TranspariMED email

"I recently received a response by a German university stating the following:

> *"The competent authority PEI has confirmed that (according to GCP Ordinance - GCP-V § 13 (9)) there is currently no legal basis in Germany for Clinical Trial Result Reporting in EudraCT. Thus, clinical trial reports of national clinical trials of [university] are accessible to the public through public access to the German database [presumably Pharmnet.Bund] once review of and upload by the competent authorities is finalized."*

The university response then argues that uploading results onto EudraCT would be "decisive" only in the case of multinational clinical trials. In a nutshell, the university seems to believe that there is no obligation to upload the results of CTIMPs conducted exclusively in Germany to EudraCT post completion.

While it may (or may not) be true in a narrow sense that there is "currently no legal basis in Germany" for enforcing EudraCT reporting requirements, the June 2019 "Letter to stakeholders regarding the requirements to provide results for authorised clinical trials in EudraCT" by the European Commission, EMA and HMA reminded sponsors of their:

> *"OBLIGATION for the reporting of clinical trial summaries in the EU Clinical Trials Database". [capitalisation added]*

This letter was co-signed by the Chair of HMA Management Group, and thus presumably endorsed by both PEI and BfArM.

Can you please by COB Friday 29 Nov 2019 provide me with a formal statement for inclusion in the report that clarifies [regulator's] position on whether or not there is currently an "obligation" for German trial sponsors to upload the results of their past and future clinical trials onto EudraCT within 12 months of trial completion? Please provide the statement in English language and ensure that it includes the word "obligation" (or "no obligation")."

ANNEX IV: METHODOLOGY AND LIMITATIONS

Authorship

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Methodology

- **Cohort selection**

The cohort for this study consists of all 36 German university medical centers, as listed in Table 2 by Wieschowski et al 2019. The EU Trials Tracker was subsequently searched for each city name, relevant university sponsors were identified, and their performance data extracted.

In some cases, Tracker data for more than one listed sponsor were combined:

- Data for ***Marburg and Giessen*** were combined as these universities jointly run the University Hospital of Giessen and Marburg. Their joint performance data thus combine Tracker data for trials run by the joint university hospital (12 trials total) and by Philipps-Universität Marburg (14 trials total).
- Performance data for ***Heidelberg*** university combine EU Trials Tracker data for trials run by the university (24 trials total) and by the university hospital (53 trials total).
- Performance data for ***Tübingen*** university combine EU Trials Tracker data for trials run by the university (5 trials total) and by the university hospital (54 trials total).

In three cases, the sponsor name did not include the city name. This report thus uses performance data for Goethe University for ***Frankfurt*** university, for the Universitätsklinikum Schleswig-Holstein for ***Lübeck*** university, and for the Universität des Saarlandes for ***Homburg*** university.

The only "***Mannheim***" trials listed on the EU Trials Tracker are trials sponsored by the Zentralinstitut für Seelische Gesundheit in Mannheim (8 trials total), so these are listed as Mannheim university trials in the report.

Ghost trials not included. The data in this report does not include several clinical trials that were apparently run by German universities, but where the sponsor's identity is marked as "unclear" by the EU Trials Tracker.[4] For example, trial 2005-002822-78 appears on a different registry as having been sponsored by University Hospital Freiburg, but the EU Trials Trackers marks it as "Unclear Sponsor Name Given - Klinik Neuropädiatrie Und Muskelkrankheiten". This is because on the European registry, the trial sponsor is listed only as "Klinik Neuropädiatrie und Muskelkrankheiten," and no point of contact is provided. This particular trial has results available on the registry.

According to registry data, no trials by Greifswald, Kiel, Mannheim and Witten-Herdecke are (yet) due to post results.

- **University performance data**

Data on universites' trial reporting performance was manually extracted using the EU Trials Tracker built by EBM Data Lab, University of Oxford. The EU Trials 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

[4] A number of examples of what appear to be German and Austrian university 'ghost trials' can be found by typing the term "klinik" into the sponsor search window of the EU Trials Tracker.

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 data was extracted from the EU Trials Tracker on 08 November 2019. At that point, the EU Trials Tracker has last been updated in early November 2019. Thus, the data in this report accurately reflects European trial registry entries as of early November 2019. Due to delays by the European Medicines Agency in making trial results received public, trial results that were uploaded during October 2019 may not have been captured by the Tracker.

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.

Data validation for individual trials and university responses

The report discusses some individual trials missing results on the European registry. Trials were chosen by browsing the trial portfolios of the five universities with the largest number of unreported trials, and identifying trials that illustrate frequent registry management issues and their consequences for patients.

Publication status was determined through a search of Google Scholar for (1) the registry number, and (2) a combination of key words, including the name of the lead investigator where available. Because such a search can miss salient publications, wherever the trial registry identified the lead investigator's email, that person was contacted by email to verify publication status.

In addition, the press offices of all five universities were contacted twice by email to give them the opportunity to flag and correct errors.

- Three universities did not respond to repeated enquiries: Charite, Mainz and Hannover.
- LMU Munich and TU Munich did respond; their responses are provided in Annex II.

Responses by national regulators BfArM and Paul Ehrlich Institut

TranspariMED contacted the two responsible German regulators ("National Competent Authorities in EU parlance), BfArM and Paul Ehrlich Institut, by email on three occasions over a two-week period to clarify their position on summary results posting onto the European trial registry by German universities. Despite repeated reminders, neither of the regulators provided a formal statement.

Limitations

- **Undercounting of due trials**

The EU Trials Tracker significantly undercounts the number and proportion 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.

Under the current European reporting system, universities directly upload their summary results onto the EU registry – as trial sponsors, they are legally obliged to do this and the process is fully within their own control. However, universities cannot directly update the status (ongoing/completed) of their trials. Instead, they must notify the national medicines regulator when a trial is completed, and the regulator then updates the trial's status on the registry to "completed". As the example above shows, the regulator appears to have failed to consistently update registry entries after trials were completed.

BfArM and Paul Ehrlich Institut should follow the positive example of the UK's regulator, the MHRA, and systematically review and update the status of all clinical trials that have been conducted in the country. This will not only allow the identification of more trials whose results are overdue, but also make it easier for German patients to identify trials that they can enrol in.

- **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. Universities are required to make their results public under global ethics rules. However, assessing universities' trial reporting performance for these non-drug trials is beyond the scope of this report.