Clinical Trial Transparency in Austria

Progress update 2020-2021

March 29 2021
Vienna, Austria and Bristol, UK

"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

Conducted by:

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TranspariMED
Working to end evidence distortion in medicine

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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 (EU) rules adopted in July 2014 require the sponsors (organisations that conduct a trial) of each clinical trial registered in 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 violate European Union transparency rules that were designed to protect the interests of patients and taxpayers.

Scope

The data presented in this report reflect EU Trials Tracker data from 08 February 2021, covering the largest (by volume of drug trials launched) 14 clinical trial sponsors headquartered in Austria. The report does not include trials of international pharmaceutical companies that are not headquartered in Austria but might have had study sites in Austria.

Key findings

- **The 14 largest Austrian sponsors are jointly responsible for 722 clinical trials of investigational medicinal products** that are listed on the EU Clinical Trial Register. Sponsors have verifiably completed 367 of those trials more than a year ago, and they are obliged to make the results of those trials public on the registry.
- **Austrian sponsors have reported the results of 134 due trials (37%).** Results are still missing for 233 long-completed trials (63%). This is not yet ideal, but shows progress compared to 2020, when 82% of due trials were missing results.
- **The overall trend is positive.** Sponsors uploaded 73 missing trial results during 2020, more than in all previous years combined. The four largest sponsors account for 69 of the 73 results uploaded during 2020. Two sponsors have already achieved a reporting rate of 100%.
- **However, half of all major Austrian sponsors have made no visible progress.** They have not uploaded a single trial result during the past year.
- **Austrian medicines regulator, the Austrian Federal Office for Safety in Healthcare (BASG)** appears not to have been systematically contacting trial sponsors whose results are overdue.

Recommendations in brief

- **BASG should immediately contact all Austrian trial sponsors** with overdue drug trial results in their portfolios and provide them with a list of their overdue trials. In addition, BASG should regularly publish line-by-line data on missing trial results for all Austrian sponsors on its website, as per European Commission guidelines (2012/C 302/03, Art. 4.7).
- **BASG** should consider refusing or deferring regulatory approval for new trials launched by sponsors that are not making tangible progress on clearing their legacy portfolios of unreported trials.
- **BASG** should develop a mechanism for routinely and automatically imposing sanctions as soon as the EU Clinical Trials Regulation becomes Austrian national law. Despite BASG's efforts to improve trial reporting in Austria over the past year, half of all major sponsors have not uploaded a single missing trial result, illustrating that voluntary compliance efforts alone cannot guarantee that all trial results are rapidly made public.
- **The Austrian Ministry of Health** should review the UK's national clinical trial transparency strategy and conduct a feasibility study to determine how ethics approval documentation could be used to monitor registration and reporting of all clinical trials (not only drug trials).

2 PROGRESS IN TRIAL REPORTING 2020-2021

The four largest trial sponsors in Austria have made significant progress in their trial reporting.

Medical University Vienna has made significant and rapid progress by uploading 33 trial results during 2020**.** With a total of 401 drug trials in its portfolio, the university is the largest non-commercial trial sponsor in Europe. Its strong commitment to transparency sets a positive example for major sponsors across Europe.

The universities of ***Graz*** and ***Innsbruck*** have also made excellent progress. Because their portfolio sizes are smaller, they are likely to achieve full compliance earlier than their colleagues in Vienna. ***Arbeitsgemeinschaft Medikamentöse Tumortherapie (AGMT)*** has already succeeded in achieving full compliance; it has finished uploading all missing trial results.

However, while the overall trend is positive, progress is uneven. Seven sponsors have not uploaded a single trial result during the last year.[1] For Details see figure 1.

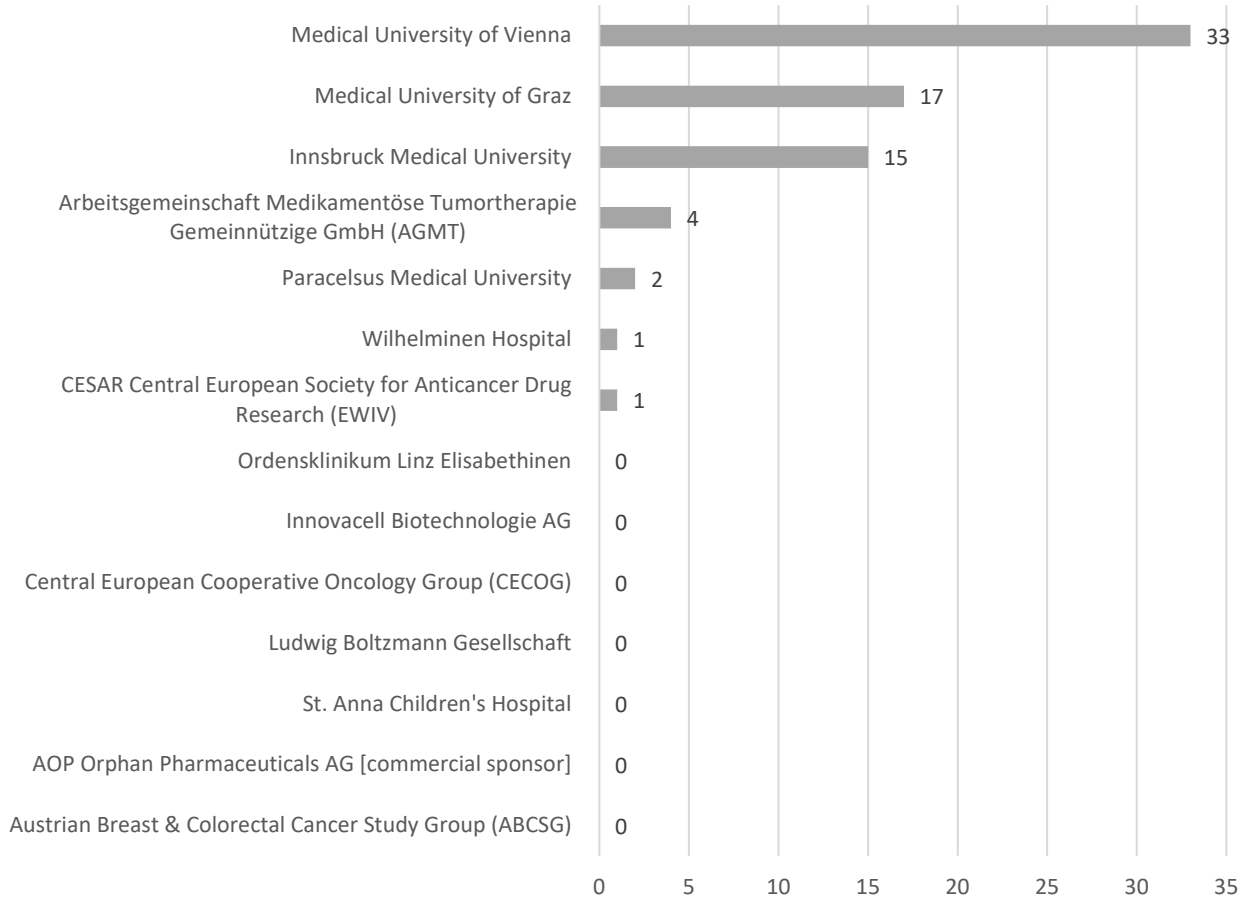

Figure 1: Trial results uploaded between 1.2.2020 – 31.1.2021

[1] The EU Trials Tracker consolidates trials linked to "St. Anna Children's Hospital" into one portfolio. On the European registry itself, the sponsor of these trials is sometimes identified as "St. Anna Kinderspital" and sometimes as "St. Anna Kinderkrebsforschung". TranspariMED's reports reflect the sponsor data displayed by the Tracker. Sponsors who believe that trials have been mistakenly allocated to them should contact the EU Trials Tracker team at the University of Oxford.

3 CURRENT TRIAL REPORTING PERFORMANCE

Only two out of Austria's 14 largest sponsors have made all of their due trial results public as required by European transparency rules.

Arbeitsgemeinschaft Medikamentöse Tumortherapie (AGMT) and the ***Central European Society for Anticancer Drug Research (CESAR)*** have a perfect reporting score of 100%. ***Innsbruck Medical University*** too is rapidly approaching a 100% reporting rate. Despite its strong efforts, ***Medical University Vienna*** has so far only reached a 27% reporting rate, partly because of the large size of its portfolio, partly because it prioritised uploading the results of more recent trials, which is a time-consuming process. Once the university moves on to older trials, the pace at which it uploads results is likely to significantly accelerate.

At the bottom of the league are four sponsors that have so far not made a single verifiably due trial result public: ***Ordensklinikum Linz***, ***Innovacell Biotechnologie***, **Arbeitsgemeinschaft für Medikamentöse Tumortherapie Gemeinnützige GmbH (*ABCSG)*** and **Central European Cooperative Oncology Group (*CEGOG)*** *(see figure 2)*. After being contacted by Cochrane Austria, ***ABCSG*** provided a detailed breakdown of its trial portfolio and pledged to upload all missing results by the end of July 2021. According to ABCSG, Austrian regulator ***BASG*** had never contacted them about the missing results. ABCSG suggested that "it would be extremely helpful to establish an automatic reminder system from the regulators". The episode illustrates that many results are missing from the registry because regulators did not actively reach out to the institutions they are supposed to regulate. ABCSG's statement can be found in Annex 2.

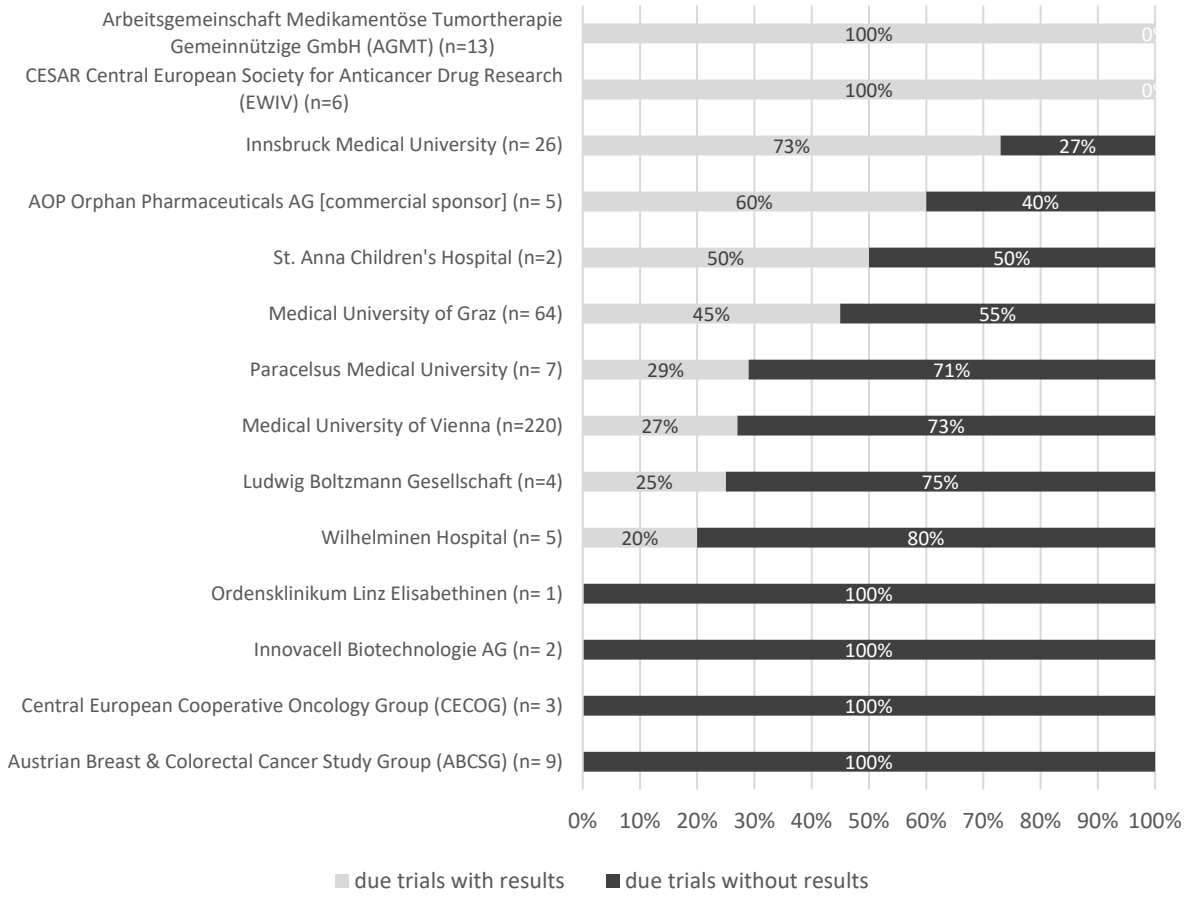

Figure 2: Percentage of trial results reported

Note: Data reflects publicly visible registry data as end of January 2021, based on Tracker data

4 NUMBER OF CLINICAL TRIALS STILL MISSING RESULTS

Austria's largest trial sponsors have yet to make public the results of 233 drug trials that are subject to European transparency requirements.

Because its overall trial portfolio is so large, ***Medical University Vienna*** still accounts for nearly two-thirds of all missing trial results, but the university is making rapid progress. ***ABCSG*** has committed to reporting all due results by summer 2020. If ***Graz***, ***Innsbruck*** and ***Paracelsus Medical University*** maintain their current pace of uploading results, they may also be able to achieve full compliance before the end of 2021. ***AGMT*** and ***CESAR*** are already fully compliant with transparency rules.

While Austria's largest trial sponsors are making strong progress, the performance of some ***smaller sponsors*** remains a concern. Some of these sponsors may not even be aware that they are breaking the rules, and civil society groups like TranspariMED and Cochrane Austria do not have the capacity to contact all of them individually. Unless Austrian regulator ***BASG*** contacts these sponsors and actively monitors their compliance, the results of some Austrian trials may never be made public and end up as costly medical research waste.

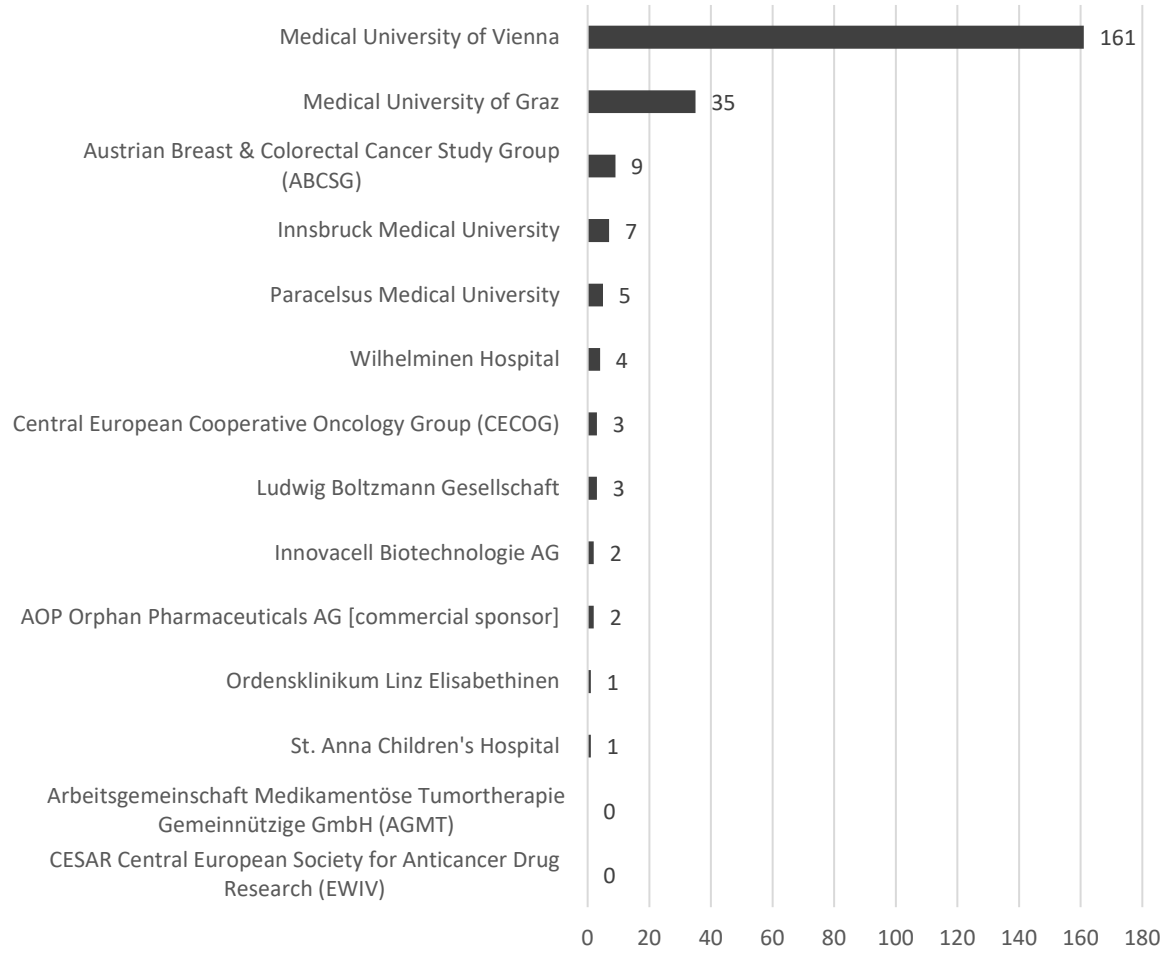

Figure 3: Number of due trials missing results for 14 major Austrian trial sponsoring organisations

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

European Union rules adopted in July 2014 require 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 violate EU transparency rules that were designed to protect the interests of patients and taxpayers. Once the EU Clinical Trial Regulation comes into force in late 2021, national medicines regulators will have the power to fine institutions for not uploading trial results to the 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, many trials run by the sponsors covered in this report are in acute danger of becoming research waste unless their results are made public soon.

Pharmaceutical companies, universities and hospitals should review their clinical trial portfolios across the European registry, the American 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 uploading 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 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 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 to registries typically give a more comprehensive and accurate picture of patient-relevant trial outcomes than corresponding journal articles do.
- Results posted to 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 1: DATA TABLE

The table below displays the data for Austrian trial sponsors discussed in this report.
All data were extracted from the the EU Trials Tracker on 08 February 2021, and reflect publicly visible registry data as of 31 January 2021.

Sponsor name	Total trials	Due trials	With results	Results missing	% reported
Medical University of Vienna	**401**	220	59	161	27
Medical University of Graz	**122**	64	29	35	45
Innsbruck Medical University	**70**	26	19	7	73
AG Medikamentöse Tumortherapie (AGMT)	**29**	13	13	0	100
Austrian Breast & Colorectal Cancer SG (ABCSG)	**17**	9	0	9	0
Paracelsus Medical University	**17**	7	2	5	29
AOP Orphan Pharmaceuticals AG	**14**	5	3	2	60
CESAR Anticancer Drug Research	**11**	6	6	0	100
St. Anna Kinderspital	**10**	2	1	1	50
Ludwig Boltzmann Gesellschaft	**8**	4	1	3	25
C.E. Cooperative Oncology Group (CECOG)	**6**	3	0	3	0
Innovacell Biotechnologie AG	**6**	2	0	2	0
Wilhelminen Hospital	**6**	5	1	4	20
Ordensklinikum Linz Elisabethinen	**5**	1	0	1	0
TOTAL	**722**	**367**	**134**	**233**	**average 37%**

ANNEX 2: STATEMENTS BY BASG AND MAJOR TRIAL SPONSORS

TranspariMED and Cochrane Austria invited the four largest Austrian sponsors to provide a statement on their current practices in reporting results and future plans. We also invited Arbeitsgemeinschaft für Medikamentöse Tumortherapie Gemeinnützige GmbH (ABCSG) to give a statement, because they were missing results from 9 out of 9 due trials. In addition, we also asked the regulator BASG to provide a statement on their activities and future plans. Their responses – in some case slightly edited for clarity – are below.

Statement by Austria medicines regulator BASG (19.3.2021)

The progress made by Austrian sponsors with the help of EMA and the BASG has to be acknowledged. During 2020 resources had to be directed towards the preparation for the Clinical Trial Regulation and Medical Devices Regulation and of course the pandemic situation. We agree that the efforts to achieve transparency now need to be taken up again.

However, from the point of view of the BASG it is unlikely that a publication rate of 100% will be reached. Publication requirements were introduced by the European Commission retrospectively, when many trials in question were already completed for years. Considering the speed of innovation in medicinal product development, results from trials dating back more than a decade might have to be considered outdated. Investing public resources towards such a goal has therefore to be considered carefully.

Sponsors should always be aware of their legal obligations and follow them on their own. The public information campaign by the BASG has been ongoing since the requirement for publication was introduced in 2012. Also EMA initiated their own campaign to inform all sponsors. It is quite worrying that a major sponsor still claims to have been unaware of their legal obligation and was expecting to be reminded by the BASG.

The following actions are therefore planned:

- The BASG will include a reminder in the confirmation of receipt for the End-of-Trial notification that a clinical trial summary report needs to be posted together with information on timelines and modalities.
- Sponsors of completed trials for which results are overdue will be contacted by the BASG based on a EudraCT DWH report. This report has to be produced by EMA as the host of the EudraCT database and EU Clinical Trials Register.
- No proportionate legal measures are available in the context of the current legislation. The possibilities for proportionate legal action will be explored in the context of the practical application of the Clinical Trials Regulation (EU) 536/2014. Please note that legal sanctions cannot be "automatically imposed", but require due legal process.
- Regarding the posting of line-by-line data on missing trial results (2012/C 302/03, Art. 4.7), this refers to the EU Public Registry and also lies within the responsibility of the European Medicines Agency. We agree that flagging overdue trials in the EU Public Registry would be a beneficial measure, as its visibility surpasses that of any NCA website.
- It is legally not possible to refuse or defer regulatory approval to a sponsor for one trial based on an administrative violation (“Verwaltungsübertretung”) for another trial. Approval can only be refused or deferred for concerns of patient safety or validity and reproducibility of results for the trial in question.
- Proposals for the Austrian Ministry of Health are outside of our remit to comment.

Statement by Medical University Vienna (22.3.2021)

„Das EU Clinical Trial Register stellt für universitäre Einrichtungen eine große administrative Herausforderung dar, um den gesetzlichen und den eigenen Ansprüchen an Transparenz gerecht zu werden. 2020 gab es von Seiten des europäischen Registers eine Vereinfachung betreffend nicht durchgeführter bzw. vorzeitig beendeter Studien. Durch die enge Zusammenarbeit zwischen Behörde, Ethikkommission, dem Koordinationszentrum für Klinische Studien, den StudienkoordinatorInnen der MedUni Wien und dem Klinikbetreiber ist es gelungen, die Datenlage entscheidend zu verbessern. Support und Schulungen durch das Koordinationszentrum für Klinische Studien der MedUni Wien werden daher weitergeführt."

Michael Wolzt, Leiter des Koordinationszentrums für Klinische Studien der Medizinischen Universität Wien

Statement by Medical University Graz (20.3.2021)

The Medical University of Graz has made significant progress towards completing trial results due to be reported in the *EU Clinical Trials Register*. The rate of trials for which investigators failed to report in time has decreased considerably over the past year.

As a service unit within the University, the Coordination Center for Clinical Trials has regularly contacted principal investigators to remind them of reporting duties. The Coordination Center has provided information material on the reporting process and offers advice and hands-on support where needed.

In addition to this effort to clear the "burden of the past", the Medical University of Graz plans to implement the completion of records in the *EU Clinical Trials Register* as a new criterion for approving of the start of new clinical trials. When principal investigators wish to start a trial under the sponsorship of the Medical University of Graz, this new trial will only be approved after checking the *EU Clinical Trials Register* and ensuring that either no reporting is due or that there is a legitimate reason for any delay in reporting. Additional measures to make sure that reporting requirements are met in a timelier manner are currently under consideration.
Training and communication activities to raise and sustain awareness of the importance of the issue will support these endeavors.

The Medical University of Graz targets a 100% completion rate, and efforts will continue until this target is reached.

Statement by Medical University Innsbruck

We did not receive a statement by Medical University Innsbruck until 25.3.2021.

Statement by Arbeitsgemeinschaft Medikamentöse Tumortherapie (AGMT) (10.3.2021)

AGMT puts patients first and fully believes that scientific excellence and accuracy, as well as adherence to scientific reporting rules is of utmost interest for transparency, reliability of data, and acceptance of medicine and science by the public. We make every effort to fulfil these criteria and are proud that these efforts are recognized.

Statement by Austrian Breast and Colorectal Cancer Group (ABCSG) (24.2.2021)

ABCSG acknowledges that we have failed to comply with the EU Guidance 2012/c302/03, which stipulates that study results must be made public via the EUCTR within a defined period after study end. The main reason is the loss of knowledge for older ABCSG trials in the course of staff turnover and focus on publishing study results for the scientific community. In order to not miss upcoming timelines, it would be extremely helpful to establish an automatic reminder system from the regulators. Also, we would like to stress, that ABCSG as a privately funded nonprofit organization did not waste any government funding and that no cancer patient would have received another treatment in case of timely reporting via EUCTR.

Please note that

- 7 of 9 studies listed in the EU Trial Tracker have already been published in scientific journals (EU 2012/c302/03 Section 4.3): 2007-006750-26, 2004-002030-19, 2005-003740-62, 2010-024354-11, 2011-004822-85, 2004-002358-72, 2013-000639-29
- in addition, for all 9 studies, an ICH compliant Clinical Study Report has been filed

2 studies listed as 'terminated' under 'Due Trials' in the EU Trials Tracker have been cancelled before study activation, without any patient recruitment:

- 2009-009874-28
- 2013-001028-21

CAPA: A 'Cancelled before Active Statement' will be filed under 'Summary attachment' until 30March2021 in the EudraCT Result Database.

The following corrections of wrong/missing data in the EudraCT Database, to which only BASG has access rights, have been submitted to BASG in the calendar weeks 7 and 8:

- For study 2007-006750-26, listed under 'Inconsistent Data' in the EU Trials Tracker, the completion of the yet missing 'End of Trial Date' has been requested from BASG. After correction by BASG this study should be listed as 'Due Trials'.
- For study 2010-024216-34, listed as 'ongoing' under 'not due trials' in the EU Trials Tracker, the correction of the study status (Prematurely Ended) has been requested from BASG. This study was cancelled before study initiation.

CAPA: the 'Cancelled before Active Statement' will be filed under 'Summary attachment' until 30March2021 in the EudraCT Database.

The following studies will be worked up in line with the modalities of '*Trial results: modalities and timing of posting as per EU Guidance 2012/c302/03 [Version 28 Sep 2020]*':

- For following studies, which have been terminated/cancelled (with randomised patients) before 21July2013, the mandatory 'Summary' will be uploaded until 31May2021:
  - 2007-006750-26
  - 2004-002030-19
  - 2005-003740-62

- For following studies, which have been terminated/cancelled after 21July2013 a mandatory 'full-data-set' will be uploaded until 31July2021.
  - 2011-001010-34
  - 2010-024354-11

- 2010-023324-25
- 2013-000639-29

We trust that our reply and Capa Plan will provide an appropriate perspective to resolve the outstanding database filings.

ANNEX 3: METHODOLOGY

This report assesses the progress made by Austrian sponsors in the year since the report "Clinical Trial Transparency in Austria: Mapping unreported drug trials" was published in February 2020. It re-assesses the same cohort of 14 Austrian sponsors using publicly available EU Trials Tracker data. The report's scope is limited to clinical trials of investigational medicinal products (CTIMPs) and excludes trials of medical devices and non-drug treatments. All data cited in this report are externally reproducible. Please see the original report for details on the methodology used.

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