Missing clinical trial data in Europe

Assessing and comparing the performance and progress of national medicines agencies

Amsterdam, 03 October 2022

> *"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

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EXECUTIVE SUMMARY

About this report

This report assesses to what degree national medicines regulators themselves follow and enforce the rules that they are responsible for upholding.

The report is based on data scraped from the European clinical trial registry. It assesses the status quo of national regulator performance as of July 2022, and tracks their progress since December 2020. The report shows that national medicines regulators in several key European countries are failing to ensure that potentially life-saving data on new medicines and vaccines are rapidly and consistently made public as required by long-standing European Union transparency rules.

Why this matters

Unreported clinical trials leave gaps in the medical evidence base that harm patients, undermine public health, and lead to public funding being wasted. National medicines regulators are responsible for overseeing drug trials involving their own national citizens and ensuring that these adhere to existing laws, regulations and guidelines.

Key findings

- **Missing trial results.** National medicines regulators in Europe have failed to ensure the publication of at least 5,488 clinical trial results for which they are unambiguously responsible. The largest reporting gap by far is in ***Italy***, where an estimated 1,299 results are missing. Four countries – Italy, the ***Netherlands***, ***Spain*** and ***France*** between them account for over two thirds of missing clinical trial results.

- **Mixed progress in absolute terms.** National regulators in four countries – ***Germany, Austria, Denmark*** and ***Belgium*** – have succeeded in considerably reducing the number of missing trial results. In contrast, the number of missing results has further grown in ***Italy*** and ***France***.

- **Improvements in reporting rates.** Strong engagement by the ***European Medicines Agency*** at the central level has boosted trial reporting rates across all countries since 2020. Parallel engagement by national regulators has led to high reporting rates in ***Germany*** and ***Austria***, and substantial progress in ***Denmark*** and ***Belgium***. Progress in other countries is more limited, suggesting little or no engagement by their national regulators.

Recommendation

National regulators must act now. The remarkable progress made by some countries between 2020 and 2022 clearly shows that strong engagement by national regulators can drive substantial improvements in clinical trial reporting. For example, Austria improved its reporting rate from 26% to 65% within less than two years. National regulators whose countries are currently lagging behind should rapidly roll out successful approaches used by their peers before countless clinical trial results become lost forever. This is not only an ethical and scientific imperative, but also far more cost-effective than having to re-run the same trials again several years down the line.

WHY THIS MATTERS

Negative impact on European patients and taxpayers

National regulators' failures to follow and enforce the rules they are responsible for upholding makes it impossible to reliably determine who is currently researching which medicines in Europe, and what the benefits and harms of those medicines are. The resulting ***gaps in the medical evidence base harm patients, undermine public health, and lead to public funding being wasted*** – both directly, because the outcomes of many publicly funded clinical trials never see the light of day, and indirectly, because health bodies tasked with procuring the best medicines for any given disease often cannot access important research results.

Modern medicine depends on evidence generated by clinical trials

The pandemic has illustrated the crucial role that clinical trials play in enabling people worldwide to live long and healthy lives. Without clinical trials, we would still not know that hydroxychloroquine does not help Covid patients to recover, while corticosteroids can save patients' lives – and we would still have no ***vaccines against Covid***. No matter what the disease – cancer, AIDS, or malaria – clinical trials are essential for assessing whether potential new treatments and vaccines are safe and effective.

Clinical trial registries provide a unique overview of medical research

At any given moment, thousands of clinical trials are taking place around the world to answer urgent medical questions. A ***global network of clinical trial registries***, whose data is centrally pooled by the World Health Organisation, provides a continuously updated overview of who is researching what, and what discoveries have been made, allowing scientists to focus their efforts on the most promising potential treatments, and helps them to avoid duplicating each others' work.

The ***European trial registry*** EudraCT (together with its public interface EUCTR) forms part of that network. It currently contains data on over 42,500 clinical trials, including over 7,000 trials involving children. All drug trials conducted in Europe must be registered on EudraCT, and after they have been completed, their results must be uploaded there, ensuring that medical discoveries are rapidly and consistently made available to the global medical research community.

Negligence by national medicines regulators leaves gaps in the European registry

While the European registry is centrally managed by the European Medicines Agency, ***national medicines regulators in each EU Member State are responsible for overseeing drug trials*** run within their own country. Their regulatory responsibilities include finalising registrations on the EudraCT before they begin (which allows them to be made public on the EUCTR), ensuring that the results of trials are uploaded on time, and keeping data on the registry up to date.

Responsibility lies with national medicines regulators

National medicines regulators are responsible for ensuring that all clinical trials involving their own national citizens – and often paid for by national taxes – adhere to existing laws, regulations and guidelines. However, as this report shows, ***national regulators often fail to meet their responsibilities***, leaving the European trial registry riddled with incorrect information and data gaps. While the European Medicines Agency in recent years has successfully worked to improve data quality at the central level, some national regulators appear not to have matched this effort.

MISSING TRIAL RESULTS BY COUNTRY

Based on very conservative assumptions, national regulators in Europe have failed to ensure the publication of at least 5,488 clinical trial results for which they are unambiguously responsible.[1]

Italy performs worst on this metric, with an estimated 1,299 trials missing results, followed by the ***Netherlands*** (849 results missing), ***Spain*** (837), and ***France*** (736).

These four regulators now account for over two thirds of missing results for the trials in this cohort. With the exception of Spain, the number of unreported trials for which they are responsible has further grown since our last assessment in December 2020.

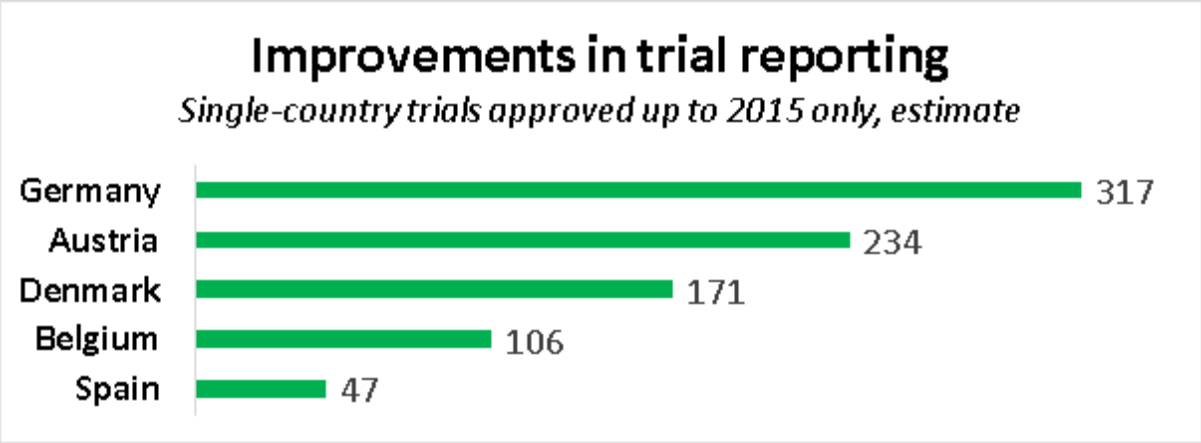
Note: Actual figures for all regulators are almost certainly significantly higher *as the estimates here only take into account single-country trials approved up to 2015; multi-country and shorter more recent trials are not included. Also, estimates are based on the very conservative assumption that only 74% of all single-country trials approved up to 2015 were due to report results as of July 2022.*

[1] The estimates below only cover drug trials that were run in a single country. Because only one country is involved, it is clear which national medicines regulator is responsible for ensuring that trial results are reported in line with European transparency rules. Thus, each missing result represents a failure of a national regulatory agency to protect the interests of patients and taxpayers in its own country by ensuring that the sponsor that ran the trial subsequently uploads the results

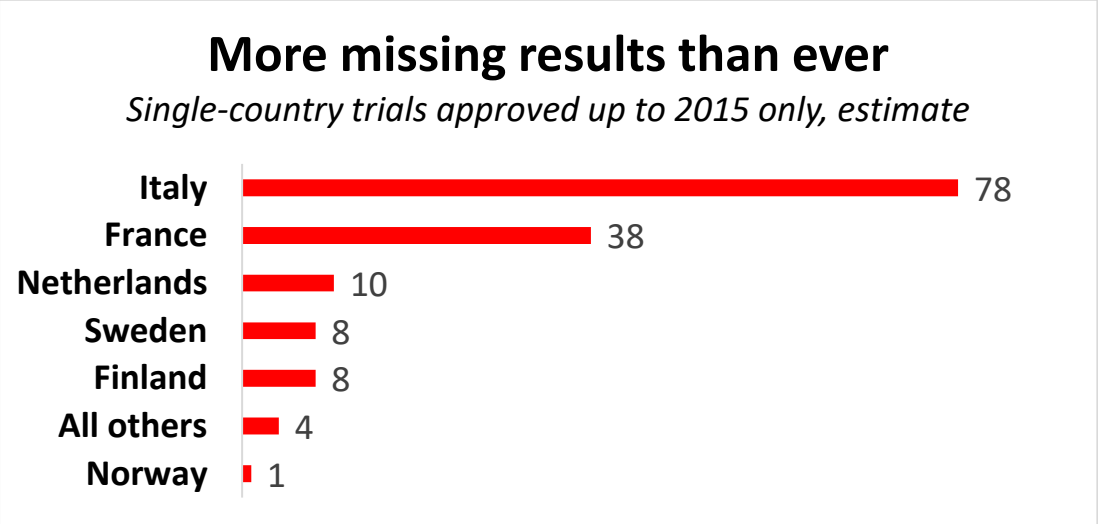
CHANGES IN THE NUMBER OF MISSING RESULTS

National regulators in five countries have made significant progress in reducing the number of missing results in this cohort of trials.

In absolute terms, ***Germany*** is the top performer. Between December 2020 and July 2022, engagement by its twin national regulators BfArM and Paul-Ehrlich-Institut succeeded in reducing the number of missing results by 317 trials. In relative terms, smaller ***Austria*** (234 trials) is even more impressive, while regulators in ***Denmark*** and ***Belgium*** also achieved substantial progress. Meanwhile, the reduction in ***Spain*** (47 trials) is small against the backdrop of 837 trials that still remain unreported there (see the previous page).



While the regulators in the five countries listed above have made significant progress in absolute terms, the number of missing results continues to grow in other key countries. Notably, for this cohort of trials, more results are now missing than two years ago in ***Italy*** (78 more results missing) and in ***France*** (38 more missing).



Note: Since our last assessment, many more trials that were approved up to 2015 have been completed and become due to report results (see next page). Therefore, the absolute number of missing results will keep increasing over time unless regulators significantly improve trial reporting within their jurisdictions.

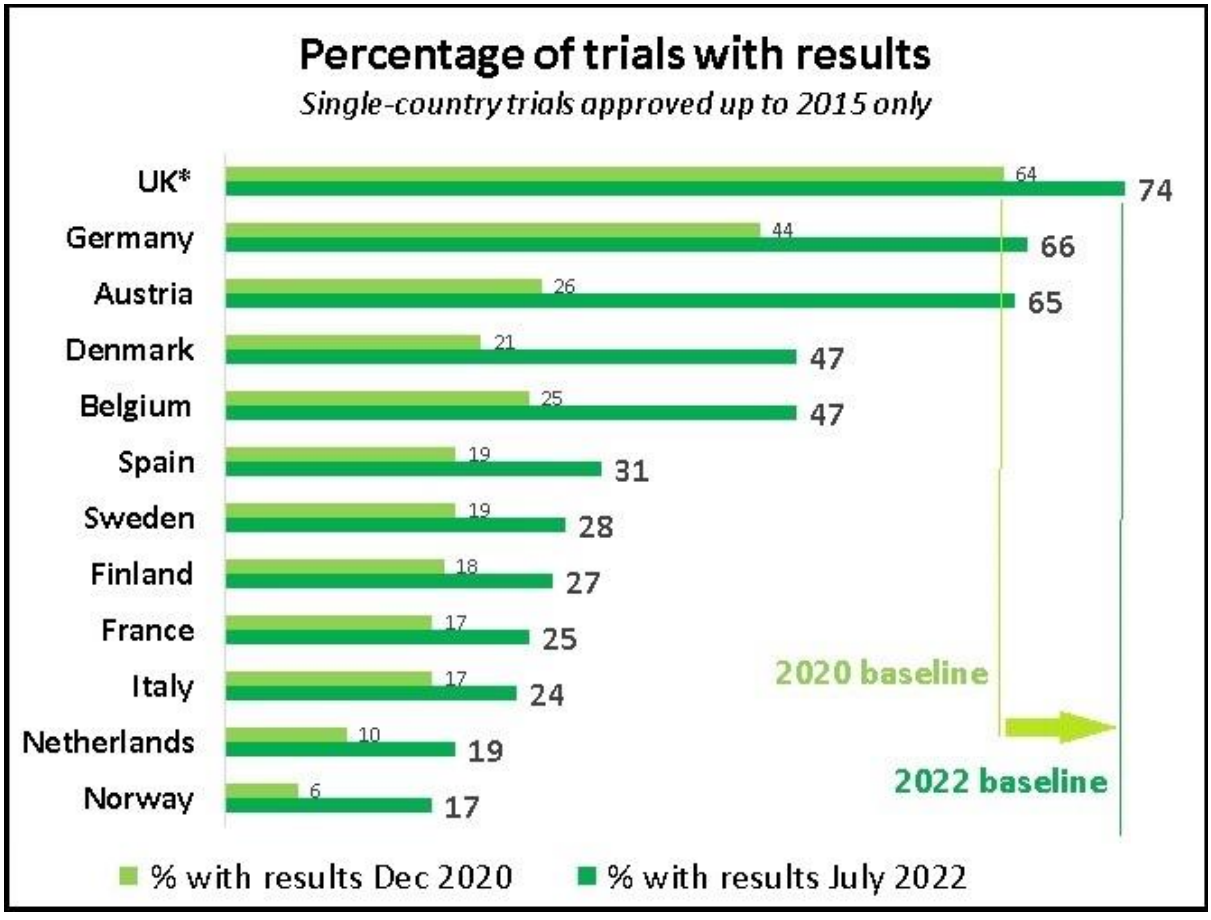
RELATIVE REPORTING PERFORMANCE BY COUNTRY

Multiple measures implemented centrally by the European Medicines Agency have improved trial reporting across the continent. However, reporting has improved far more in some countries, illustrating the large difference that proactive engagement by national regulators can make.

Thanks to long-standing and very strong regulatory engagement, trial reporting is exceptionally strong in the UK, which has now left the European Union: 74% of single-country trials authorised there up to 2015 now have results available on the registry. Note that not all such trials have yet been completed; we therefore use 74% as the benchmark for European reporting excellence throughout this report.

Germany (66%) is now rapidly approaching this benchmark for excellence, as is ***Austria*** (65%), whose dramatic improvement in reporting rates since 2020 illustrates the positive difference that strong engagement by a national regulator can make. ***Denmark*** (47%) and ***Belgium*** (47%) have also significantly boosted their performance since 2020.

The improvements in other countries are more modest. It is possible that they are exclusively driven by a combination of central European Medicines Agency initiatives and individual academic institutions' efforts to clean up their trial portfolios. However, it is equally plausible that recent engagement by some national regulators may also be a contributing factor, notably in the ***Netherlands*** and ***Norway***, which show strong increases in relative performance over their very low 2020 baselines.



ANNEX I: NOTE TO HEADS OF MEDICINES AGENCIES

In contrast to the 2020 report, this report does not discuss two issues in the main narrative section: (1) availability of trial protocols, and (2) accuracy of registry entries. While these issues are of little interest to non-expert readers and the media, they are highly important to health policy makers and patients, and therefore need to be addressed by the NCAs concerned.

The relevant metrics for both issues are presented on the following page (Annex II), with data points of particular concern highlighted in red.

1. Visibility of trial protocols

The 2020 report noted that in some countries, drug trials approved by the NCAs were often invisible on the registry. According to the 2020 report:

> *"When comparing information from trials with results to registered protocols on the EUCTR, half of all drug trials approved by the regulator in **France** were invisible on the European trial registry, affecting at least 1,207 trials... Prior experience from the UK suggests that sponsors probably did register the trials with the regulators, but that the protocols are stranded somewhere in the system and thus remain publicly invisible to researchers, doctors and patients."*
>
> ***"If trial protocols are not visible on registries, research funders cannot determine which areas of medical research are in greatest need of further investment, scientists may waste their time unnecessarily duplicating other teams' work, and patients cannot locate trials that they can enrol in."***

The 2022 data show that this problem remains completely unaddressed. Today, protocol visibility on the registry remains at less than 80% within the portfolios of seven different NCAs.

2. Accuracy of registry entries

In the UK, 97% of all protocols (both single-country and multi-country) approved up to 2015 are now listed as completed with a completion date in the protocol, suggesting that across Europe, virtually all such trials have by now come to an end. However, within the portfolios of eight NCAs, less than 80% of such trials are currently marked as completed, which does not seem plausible.

These apparent inaccuracies have negative consequences for science, taxpayers, and patients. They make it difficult for health technology assessment agencies, horizon scanners, systematic reviewers and researchers to gain an overview of the research landscape, undermining evidence synthesis and horizon scanning efforts. They also make enrolment more difficult for patients and therefore undermine sponsors' recruitment efforts.

ANNEX II: DATA TABLE

	Registered % 2020	Results % 2020	Missing # 2020	Data quality % 2020	Registered % 2022	Results % 2022	Missing # 2022	Data quality % 2022
Austria	99	26	308	84	98	65	74	86
Belgium	97	25	327	48	97	47	221	55
Bulgaria	92	63	1	86	93	71	3	87
Croatia	100	50	1	92	99	75	0	93
Cyprus	0	N/A	N/A	N/A	33	N/A	N/A	N/A
Czech Republic	99	39	64	81	99	47	69	83
Denmark	98	21	444	81	98	47	273	87
Estonia	93	44	9	80	90	60	6	81
Finland	99	18	240	76	99	27	248	78
France	49	17	698	73	54	25	736	85
Germany	93	44	554	85	93	66	237	86
Greece	98	30	38	86	97	47	30	87
Hungary	98	49	35	86	96	56	43	87
Iceland	97	19	17	81	97	27	17	82
Ireland	94	25	61	75	90	34	63	78
Italy	86	17	1221	50	94	24	1299	52
Latvia	99	73	0	74	98	78	0	74
Lithuania	98	48	8	86	98	54	8	86
Luxembourg	33	N/A	N/A	N/A	25	N/A	N/A	N/A
Malta	71	N/A	N/A	N/A	71	N/A	N/A	N/A
Netherlands	95	10	839	41	95	19	849	50
Norway	45	6	76	85	48	17	77	89
Poland	61	53	11	93	63	68	6	95
Portugal	98	38	13	88	98	68	16	95
Romania	17	68	0	82	23	68	1	92
Slovakia	97	58	4	79	96	66	5	81
Slovenia	96	33	12	78	97	46	11	81
Spain	96	19	884	53	96	31	837	66
Sweden	97	19	351	77	96	28	359	78
UK	96	64	0	97	95	74	0	97

ANNEX III: THE UK NATIONAL CLINICAL TRIAL TRANSPARENCY SYSTEM

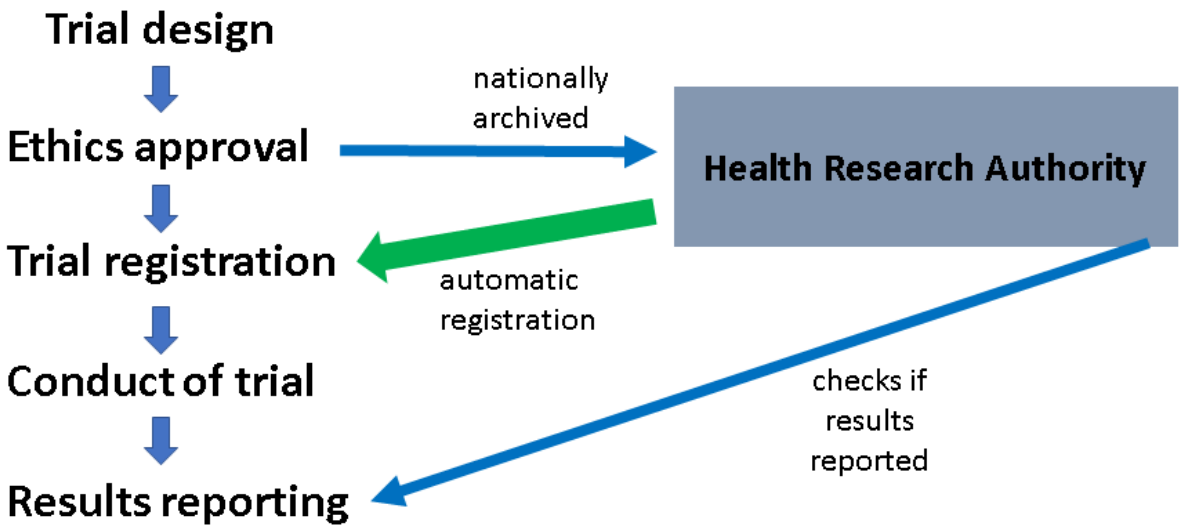
This annex provides an overview of the UK's innovative national trial transparency system. The system will ensure that in future all clinical trials conducted in the UK (drug trials, device trials, and all other interventional trials) are pre-registered and make their results public.

Fixing clinical trial registration

Ethics committees (around 60 countrywide) send the protocols of all studies that they approve to the Health Research Authority in London. Staff at the Health Research Authority (HRA) then ***directly register*** every clinical trial on the ISRCTN registry. After the trial has been registered, the principal investigator of the trial takes over registry management, and is responsible for keeping the registry entry updated and uploading the results.

Fixing clinical trial reporting

Because it directly registers all trials run in the country, the HRA has a comprehensive overview of all clinical research. One year after a trial has been completed, the HRA ***checks on the registry*** to see whether the results have been uploaded there. If not, it sends a reminder to the principal investigator. The HRA also publishes annual trial audits with line-by-line data that shows who has made their trial results public on time, and who has not.



Enforcing the rules

In 2023, the UK will probably adopt a national law requiring ***every*** interventional clinical trial result to be made public (probably within 12 months on a trial registry as recommended by the World Health Organization). It appears likely that ***trial sponsors***, and not individual investigators, will be the party legally responsible for ensuring that results are uploaded. The law will be enforced by the national medicines regulator MHRA. Because the regulator has access to HRA trial audit data (see above), it can easily identify all violations. In practice, the medicines regulator is very likely to effectively enforce the law.

How did this happen?

In 2018, UK parliament's Science and Technology Committee launched an ***enquiry*** into clinical trial transparency. After many heated debates, the Committee published a report recommending that the Health Research Authority (HRA) develop a ***national transparency strategy***.

The HRA set up and led a committee to develop the strategy. The committee included civil servants, industry, academia, transparency groups, and patient representatives. In parallel, the HRA launched a consultation process. After discussion with all stakeholders, the HRA adopted the model outlined above. See here for the strategy.

Throughout this process, a ***coalition of health groups*** including TranspariMED, Cochrane, UAEM and Transparency International kept up the pressure for reform. Discover how they did this here.

Making transparency easy

The motto of the national #MakeItPublic strategy is "make transparency easy, make transparency the norm". The focus is on ***supporting researchers and sponsors***, not on punishing them. The new approach creates a clinical trial workflow that is more streamlined and less bureaucratic than before. There is an ongoing process of integrating the systems of the various players and aligning their transparency requirements. In future, legislation, ethics committees, public research funders, and the ISRCTN registry will all have exactly the same transparency rules. Researchers and trial sponsors benefit from clear and simple rules and workflows, faster study approval, and less paperwork.

Key advantages

- All interventional trials involving UK patients covered
- 100% of trials registered
- 100% of trial results made public
- Faster sharing of results (probably within 12 months via the ISRCTN trial registry)
- Less bureaucracy for researchers and trial sponsors

Supporting measures

The two major public research funders (NIHR and MRC) already actively monitor the registration and reporting of all trials that they fund. The ISRCTN registry already sends out regular emails to remind researchers to update registry data and upload results. All stakeholders are continuously taking steps to improve transparency.

Cost and value for money

The exact cost of developing and implementing the strategy is unclear because it involves work by multiple players. However, the total cost to all players combined is certainly ***less than one million Euros***, a marginal amount compared to the immense costs of medical reseach waste.

ANNEX IV: METHODOLOGY

Authorship. The data in this report was generated by Nicholas DeVito, University of Oxford. Till Bruckner from TranspariMED generated the charts and wrote the report.
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Report scope. The data in this report exclusively cover drug trials that were registered on the EU Clinical Trial Register. Under EU rules, during the relevant time period, all clinical trials of investigational medicinal products (***CTIMPs***) had to be registered on that registry, and sponsors were obliged to post the results of those trials onto the registry within 12 months of trial completion. (Trials that are not CTIMPs, such as trials of medical devices and other non-drug treatments, fall outside the scope of this report.) The cohort was further narrowed down to ***single-country trials***, i.e. CTIMPs that were conducted within only one country, because for each of those trials it is unambiguous which national regulator is responsible for managing the data and ensuring that sponsors actually do upload the results as required. The cohort is limited to ***trials registered up to 2015***; a large majority of those trials have now been completed and should have results available on the register.

Data sources. The data in this report are based on publicly available data that was scraped from the EU Clinical Trial Register in early July 2022. The methodology is described in detail in the publication "Trends and variation in data quality and availability on the European Union Clinical Trials Register: A cross-sectional study" by Nicholas DeVito and Ben Goldacre, both from the University of Oxford.

Data analysis. For the 2022 report, the data were analysed using the same approach as in the earlier 2020 report. Please refer to the methodology section of the 2020 report for more details.

Baseline adjustment. For the calculation of the estimated number of missing results, the UK reporting rate was used as a baseline to set the minimum level of reporting that other national regulators should be expected to achieve. This is a very conservative baseline because even in the UK, despite long-standing efforts by its regulator, some trials are still missing results. That baseline was 64% as of December 2020, and 74% as of July 2022. For each report, the estimate of missing trials for each country was calculated by subtracting the number of publicly available trial results from 64% (in 2020) and 74% (in 2022) of the number of total trials.

Data table in the Annex. Please refer to the methodology section of the 2020 report for more details. Briefly:

- ***Registered %.*** For this metric, the cohort is limited to trials that have tabular summary results available on the European trial registry; those results list all countries in which the trials took place. On the registry, every single one of these trials (100%) should have a separate trial protocol publicly available for every country in which patients had been recruited. The metric used in this report is the percentage of such trial protocols that are actually publicly available.
- ***Data quality %.*** The performance metric used in this report is the percentage of Clinical Trial Applications approved up to 2015 that are both marked as 'completed' and have a completion date in the trial protocol. The data for UK trials suggest that around 97% is a realistic benchmark.

Note on data for Germany. Germany has two separate national regulators, BfArM and PEI. Each of the two regulators is responsible for a separate portfolio of trials, segmented by trial type. This report aggregates performance data for both regulators into a single national-level performance metric.