Missing clinical trial data in Europe

Assessing and comparing the performance of national medicines agencies

Paris (France), Amsterdam (NL), and Bristol (UK)
05 July 2021

"We advocate full transparency of which clinical trials are ongoing and ensuring all results are disclosed in a timely manner… [F]ull 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

"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

EXECUTIVE SUMMARY

About this report

This report, based on data collected by researchers at the University of Oxford, shows that national medicines regulators in 14 key European countries[1] are failing to ensure that potentially life-saving data on new medicines and vaccines is rapidly and consistently made public as required by long-standing European Union transparency rules.

While numerous previous TranspariMED reports have assessed the extent to which companies and institutions follow European transparency rules, this is the first-ever report to assess to what degree national medicines regulators themselves follow and enforce the rules that they are responsible for upholding.

Key findings

This report documents that many national medicines regulators in Europe fail to:

- **Make clinical trial registrations visible.** The protocols for 1,207 drug trials approved by the regulator in ***France*** and 831 drug trials overseen by the regulator in ***Poland*** remain invisible on the European trial registry.

- **Ensure that results of trials are rapidly made public:**
    - 90% of older single-country trials approved by the regulator in the ***Netherlands*** do not have results available on the registry. Regulators in ***France, Italy, Finland, Sweden,*** and ***Spain*** also frequently fail to ensure that results are made public in line with European transparency rules.
    - At least 5,976 clinical trial results are missing across the 14 countries. The largest gaps are in ***Italy*** (1,221 results missing), followed by ***Spain*** (884), the ***Netherlands*** (839), ***France*** (698) and ***Germany*** (554).

- **Keep data on trials up to date.** Weak data management by regulators has left the European registry riddled with inaccurate and missing data. National regulators in the ***Netherlands, Belgium, Italy*** and ***Spain*** are exceptionally negligent in this regard; only the UK and ***Poland*** perform well.

Policy recommendations

Each national medicines regulator in Europe can and should immediately and unilaterally initiate three simple, low-cost steps to improve the medical evidence base and safeguard patients' and taxpayers' interests, as recommended by 18 health and patient groups from across Europe:

1. Contact all sponsors of completed trials for which results are overdue
2. Review sponsors' results disclosure compliance during pharmacovigilance inspections
3. Systematically update the completion status of all clinical trials

[1] The UK left the European Union in January 2021, after the data underlying this report had been collected. This report nonetheless includes UK data because it sometimes provides a useful benchmark against which other regulators' performance can be measured.

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 – only clinical trials can provide reliable data on whether potential new treatments and vaccines are safe and effective, or not.

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 39,700 clinical trials, including over 6,500 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.

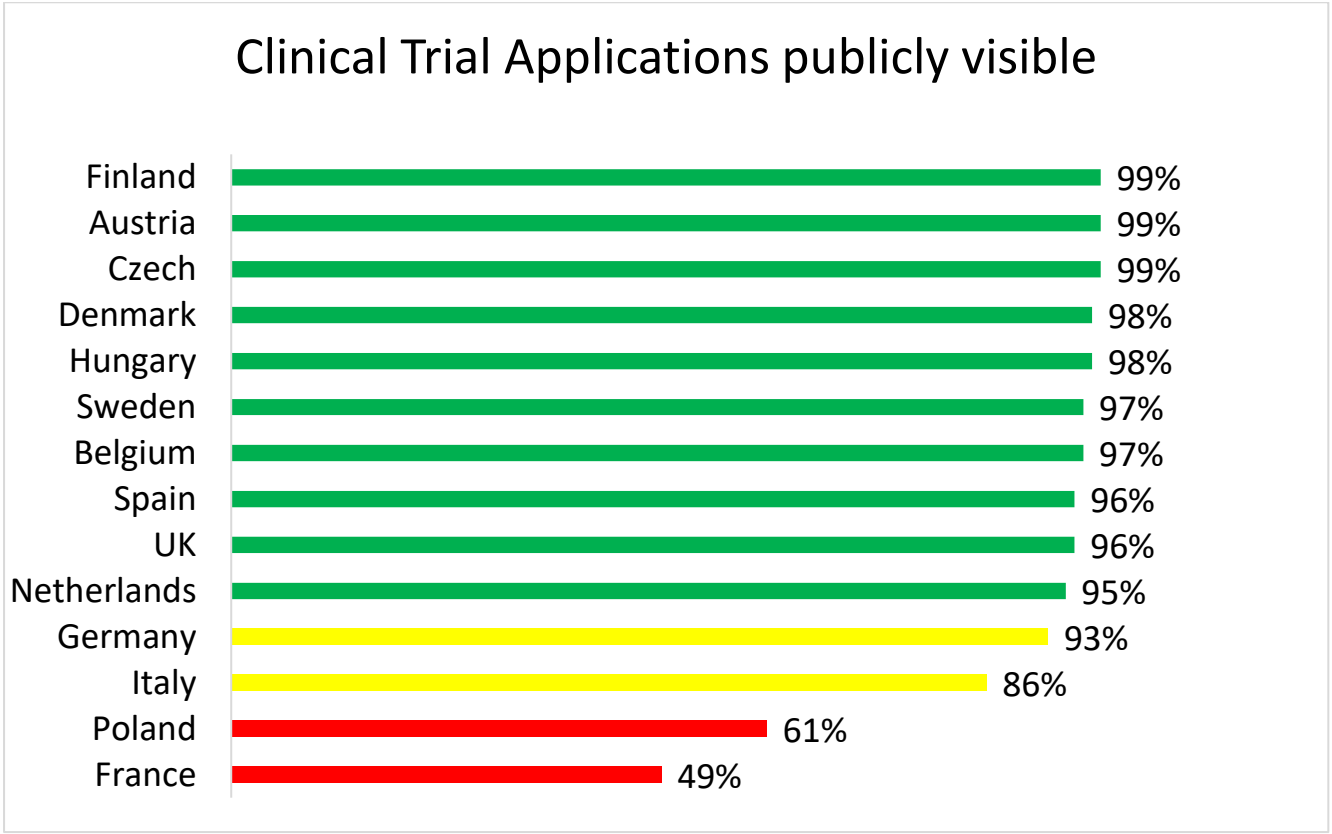
Responsibility lies with national medicines regulators

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 ongoing discussions between various European Union bodies about a possible Europe-wide approach to fixing these problems are highly welcome, this process does not preclude national regulators from taking action now.

TRIAL REGISTRATION

Key findings: 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.[2] The regulator in ***Poland*** also performs weakly, with only 61% of protocols of approved national Clinical Trial Applications publicly available on the registry, leaving 831 protocols invisible. ***Italy*** and ***Germany*** also disappoint on this metric, though to a lesser degree. 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.

Why this matters: Clinical trial registration provides crucial information about who is researching which medicines for what diseases. 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. After approving new drug trials, some national regulators fail to consistently ensure that these registrations then become publicly visible. The very weak performance of some regulators on this metric is a surprise finding of this study.

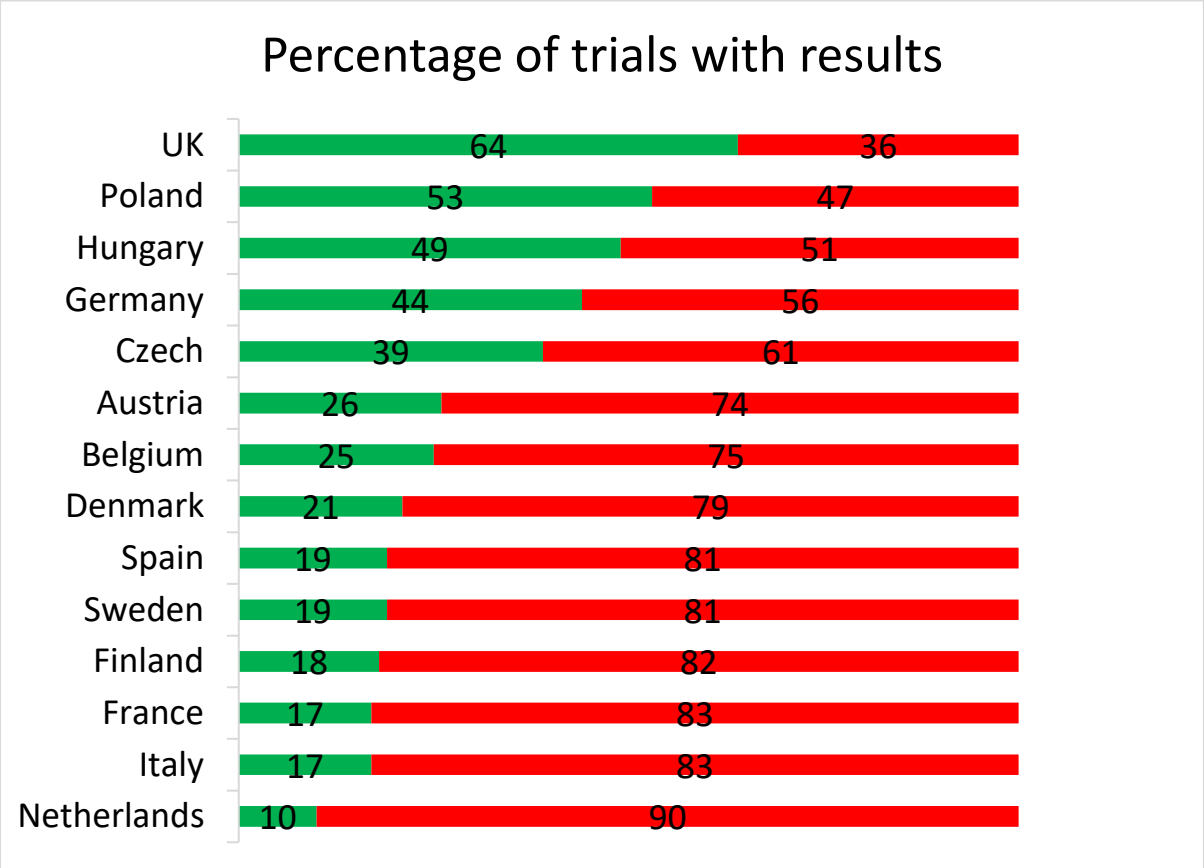


[2] The performance of Romania is even worse in this regard. Please see the data table in the Annex for more details.

RESULTS REPORTING

Key findings: Results reporting is strongest in the ***UK***, where a parliamentary enquiry and subsequent follow-up by the national regulator led to a surge in trial reporting. While compliance with reporting rules remains far from perfect in the UK, its 64% reporting rate for trials authorised up to 2015 with only a UK location sets a useful benchmark against which other regulators can be measured. No other regulator has achieved a comparable reporting rate.[3] The ***Netherlands, France, Italy, Finland, Sweden, Spain*** and ***Denmark*** perform especially badly, with reporting rates of less than a third of the UK's. The data in the chart below is limited to single-country trials approved up to 2015; as the example of the UK shows, a significant majority of those trials should by now have results available on the registry.

Why this matters: Many trial results are published partially or not at all in scientific journals, and the journal publication process often takes several years. In order to prevent valuable medical discoveries from being lost forever, and to accelerate the speed of medical progress, companies and institutions running drug trials in Europe are obliged to make the results of all drug trials public within 12 months of trial completion. However, many national medicines regulators still fail to follow up with companies and institutions whose trial results are overdue, leading to low reporting rates.

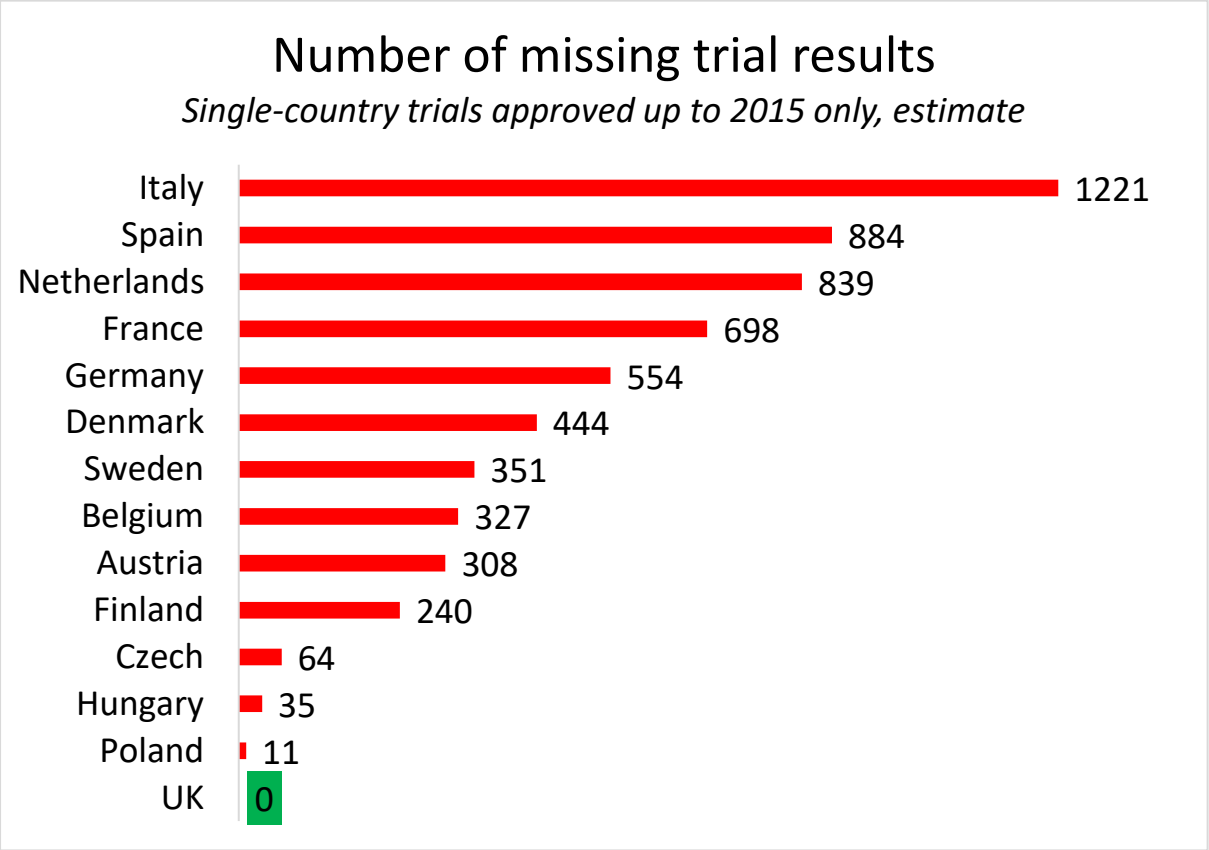


[3] Poland, Hungary and Czech probably perform comparatively well because many trials in those countries are run by large pharma companies that tend to have high reporting rates irrespective of which country they run a trial in.

NUMBER OF MISSING TRIAL RESULTS

Key findings: Based on very conservative assumptions, the 14 most important national regulators in Europe have failed to ensure the publication of at least 5,976 clinical trial results for which they are unambiguously responsible. ***Italy*** performs worst on this metric, with an estimated 1,221 trials missing results, followed by ***Spain*** (884 results missing), the ***Netherlands*** (839), ***France*** (698) and ***Germany*** (554).[4] As the UK was used as a benchmark for estimating other regulators' performance, the UK is shown as having no missing results in the chart below.

Why this matters: Missing clinical trial results harm patients, undermine public health, waste public funding, and slow down the development of new treatments and vaccines. 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 Union 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.



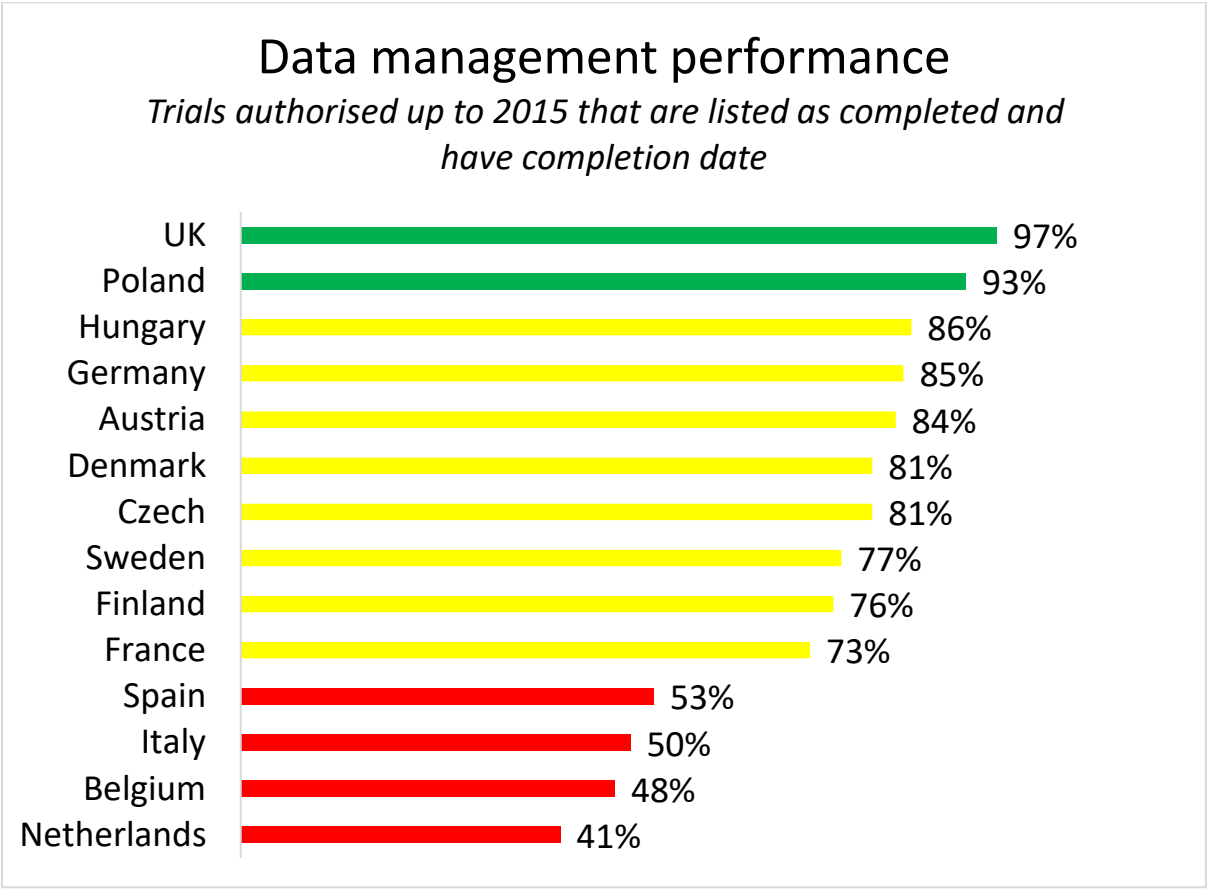
Note: Actual figures for all regulators are almost certainly significantly higher *as the estimates here only take into account single-country trials approved up to 2015; multi-country and shorter more recent trials are not included. Also, estimates are based on the very conservative assumption that only 64% of all single-country trials approved up to 2015 were due to report results as of December 2020.*

[4] Poland, Hungary and Czech may perform comparatively well because many trials in those countries are run by large pharma companies that tend to have high reporting rates irrespective of which country they run a trial in.

DATA QUALITY

Key findings: The vast majority of clinical trials authorised in 2015 or earlier are now completed, but most national regulators have failed to ensure that related records are up to date. Because the ***UK***'s national regulator has systematically updated its records, it provides a useful benchmark: 97% of such trials in the UK have now been completed. Apart from the UK, only ***Poland*** appears to consistently keep its records up to date.[5] National regulators in the ***Netherlands, Belgium, Italy*** and ***Spain*** perform especially badly, leaving the European trial registry riddled with inaccurate and unreliable data about which trials are still ongoing and which have been completed and when.

Why this matters: Trial registries are the only way for the medical research community to see who is currently researching what. For example, without trial registries, nobody would know which Covid treatments and vaccines are currently being tested in trials, and how far individual trials have progressed. Public health bodies rely on this information to predict when results from important trials will become available, and to inform evidence syntheses that attempt to fully summarise all trials conducted in a specific treatment area. Therefore, the European trial registry should tell us whether trials are still ongoing, or whether they have been completed. National medicines regulators are responsible for keeping this information up to date – but often they fail to do so.



[5] Note however that many Polish trials do not appear on the registry in the first place; see further above.

DATA TABLE

The table below presents data for all 31 countries participating in the European clinical trial registry system as of 1 December 2020.

- The **top three performers** within a category are highlighted in green
- The **three worst performers** within a category are highlighted in red

Country	Total CTAs (#)	Registration (%)	Results rep. (%)	Results missing (#)	Data quality (%)
Austria	4146	99	26	308	84
Belgium	5946	97	25	327	48
Bulgaria	2007	92	63	1	86
Croatia	401	100	50	1	92
Cyprus	5	0	N/A	N/A	N/A
Czech Republic	4304	99	39	64	81
Denmark	4069	98	21	444	81
Estonia	1020	93	44	9	80
Finland	2533	99	18	240	76
France	5852	49	17	698	73
Germany	11517	93	44	554	85
Greece	1791	98	30	38	86
Hungary	4473	98	49	35	86
Iceland	133	97	19	17	81
Ireland	1169	94	25	61	75
Italy	7559	86	17	1221	50
Latvia	1079	99	73	0	74
Liechtenstein	0	N/A	N/A	N/A	N/A
Lithuania	1237	98	48	8	86
Luxembourg	8	33	N/A	N/A	N/A
Malta	18	71	N/A	N/A	N/A
Netherlands	5692	95	10	839	41
Norway	683	45	6	76	85
Poland	3242	61	53	11	93
Portugal	1591	98	38	13	88
Romania	239	17	68	0	82
Slovakia	1791	97	58	4	79
Slovenia	388	96	33	12	78
Spain	9566	96	19	884	53
Sweden	3893	97	19	351	77
UK	10975	96	64	0	97

Notes: CTAs = Clinical Trial Applications. The main report only presents data for the 14 countries (marked in bold font above) that had more than 2,500 Clinical Trial Applications each. The United Kingdom left the European registry system at the end of 2020, after the data presented above had been collected.

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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Data sources. The data in this report is based on publicly available data that was scraped from the EU Clinical Trials Register on 1 December 2020, and that is explored in more detail in the academic preprint "Trends and Variation in Data Quality and Availability on the EU Clinical Trials Register: A Cross-Sectional Study" by Nicholas DeVito and Ben Goldacre, both from the University of Oxford. For a more detailed methodology, please refer to the original preprint. In some instances, a further data analysis was performed specifically for this report, as described below.

Trial registration. 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.

Results reporting. The cohort consists of all single-country trials whose Clinical Trial Applications were approved up to and including 2015. Because these trials were performed in a single country, there is no ambiguity about which national regulator is responsible for ensuring that results are reported. (The trial sponsor, i.e. the company or university running a trial, is responsible for uploading results; the national regulator is responsible for regulating sponsors, i.e. ensuring that they consistently follow the rules.) While all trials in the cohort were approved in 2015 or earlier, a small percentage of those trials are expected to still be ongoing today. The exact percentage of ongoing trials is unknown due to regulators' weak data management performance.

- ***Percentage of trials with results.*** Percentage of all single-country trials approved up to 2015 within the country that had summary results available on the European trial registry as of 1 December 2020. Because a minority of trials had still not been completed by that date, no regulator can be expected to achieve 100% on this metric. However, national regulators effective at ensuring sponsors' compliance with the rules should at the very least have a reporting rate of 64%, the benchmark set by the UK. (This benchmark is very conservative because even in the UK, many long-completed trials are still missing results: as the section on data management performance shows, 97% of all trials authorised in the UK up to 2015 were completed by 1 December 2020; results only become due one year after trial completion.)

- ***Number of missing trial results.*** The estimates are based on the assumption that 64% of all single-country trials approved up to 2015 within any given country should have had summary results available on the European trial registry as of 1 December 2020 (UK baseline, see above). The estimate was calculated by subtracting the number of available trial results from 64% of the number of total trials. Actual figures for all regulators are almost certainly significantly higher as the estimates here (a) only take into account single-country trials (b) that were approved up to 2015, and (c) assumes a low due rate of only 64%. Multi-country and more recent trials are not included in the estimate.

Data management performance. The cohort consists of all Clinical Trial Applications approved up to 2015. The vast majority of those trials have by now been completed, as the UK benchmark metric of 97% illustrates. When a trial is completed, the sponsor has to notify the national regulator ('End of Trial Notification'), and the regulator should then change the trial's status from 'ongoing' to 'completed' on the European registry and insert the completion date in the protocol. While some sponsors do not always submit 'End of Trial Notifications' as required, the UK's example shows that regulators can – and should be expected to – follow up with sponsors to obtain reliable trial status information, and make that information publicly available on the registry. 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. For disaggregated figures for status and dates, please see the preprint publication.

Note on data for Germany. Germany has two National Competent Authorities, 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. Please see the preprint for disaggregated performance figures for BfArM and PEI.

Scope of this report.

- The data in this report exclusively cover drug trials that were registered on the EU Clinical Trial Register. Under EU rules, all ***clinical trials of investigational medicinal products*** (CTIMPs) conducted in the European Union ***must*** be registered on the EU Clinical Trial Register, and sponsors ***must*** post the results of those trials onto the register within 12 months of trial completion.
- ***Non-drug trials***, including trials of medical devices (e.g. pacemakers or artificial hips) and non-drug treatments (e.g. surgery or physiotherapy), ***cannot*** be registered on the EU Clinical Trial Register and must thus be registered on other trial registries. Data for non-drug trials is ***beyond the scope of this report***. However, non-drugs trials can be of even greater medical importance than drug trials. Sponsors are required to make their results public (in some form) under global ethics rules, and according to WHO best practices, sponsors should make their results public on a trial registry within 12 months of trial completion. However, regulatory oversight of non-drug trials is currently weak across Europe.

The lack of European transparency rules for non-drug trials makes it important for all EU Member States to develop **national clinical trial transparency strategies** to ensure that *all* clinical trials involving patients in their country are registered and their results made public.