REPORT

CLINICAL TRIALS IN THE **EUROPEAN UNION**

A Roadmap to Greater Transparency

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A Roadmap to Greater Transparency

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INTRODUCTION

Clinical trials are at the core of the pharmaceutical research and development (R&D) process. The results of these studies inform decision-making on market approval, medicines pricing and reimbursement, and clinical practice. Clinical trial transparency is therefore extremely important for policy makers, public health bodies, the research community, healthcare professionals and patients.

Nevertheless, important information on clinical trials remains hidden from public and scientific scrutiny, even where research is publicly funded. This report discusses transparency concerns related to the current European Union (EU) trial registry, the forthcoming clinical trials portal and database, and barriers to the effective utilisation of clinical study reports (CSRs).

It concludes with nine actionable policy recommendations for the European Commission, the European Medicines Agency (EMA), and national competent authorities (NCAs) in EU Member States. The table below summarises these policy recommendations.

Why does clinical trial transparency matter?[a]

- Improves the allocation of public health resources
- Curbs the waste of medical research funds and avoids the unnecessary repetition of trials
- Accelerates medical progress and the discovery of new treatments and cures
- Improves decision-making by healthcare professionals and patients
- Improves patient safety by ensuring that all harms are reported

Policy Recommendations on Trial registration and Summary Results	
1	Email the sponsors of trials missing summary results
2	Ask NCAs to draw up strategies for achieving national compliance
3	Ensure that all trial registry entries are complete
4	Ensure that the status of all trials is accurate
5	Make the clinical trials portal and database user friendly to support compliance
6	Support trial sponsors via guidance, a helpdesk and networking
7	Set clear criteria for approving deferrals and protect Phase I participant
Policy Recommendations on Access to CSRs	
8	Improve the process for providing access to CSRs
9	Keep redactions to an absolute minimum and ensure disclosed CSRs preserve their scientific utility

[a] For more information see this 2017 publication from Transparency International, TranspariMED, Cochrane, and CRIT https://docs.wixstatic.com/ugd/01f35d_def0082121a648529220e1d56df4b50a.pdf

THE EU CLINICAL TRIAL REGISTRY

Scope of the Registry

The European clinical trials database (EudraCT), managed by the EMA, is a database containing information on clinical drug trials conducted in Europe.[b] It was set up in 2004 as a confidential database with a public-facing registry, the EU Clinical Trials Register, launched in 2011. Its data is fed into the World Health Organization's (WHO) global network of trial registries. Each trial is given a unique identification number.

What clinical trials does the public EU Clinical Trials Register include?

- Clinical trials of medicines in adults with investigator sites in the EU or the European Economic Area (EEA) that started after 1 May, 2004 (Phase II, III and IV only)
- All paediatric trials of medicines, including some conducted outside the EU/European Economic Area, some begun before 2004, and planned trials that failed to gain ethics approval (all phases: I–IV)
- Phase I clinical trials in the adult population are not displayed on the public registry unless they are part of a paediatric investigation plan (PIP)
- Clinical trials of medical devices and other non-drug treatments are not captured by the registry

Content of the Registry

The registry is publicly accessible, free of charge, and provides condensed information on the basic features of each listed trial.

What information does the EU Clinical Trials Register contain?

- Main characteristics on the trial: Trial phase, trial design, drug(s) used, therapeutic area, primary and secondary endpoint(s)
- Patients: Number and characteristics of patients enrolled, principal exclusion and inclusion criteria
- Key players: Institution (sponsor)
- Status: Whether a trial is still ongoing, has prematurely ended, been suspended or been completed
- Summary results: Information about the effects of the drug(s) on the participating patients

Summary Results Posted on the EU Clinical Trials Register

In theory, the registry should contain the summary results of every single clinical trial completed more than a year ago.[c] Summaries contain the positive and negative health effects that patients experienced during the trial, and include a listing of adverse events. Summary results provide valuable information on the efficacy and safety of the drug(s) used in the trial. If a trial compared more than one treatment, summary results indicate which treatment was more beneficial to patients' health.

[b] EudraCT is accessible to national competent authorities, the EMA, and the European Commission.
[c] Trials completed prior to 21 July, 2013, have the option to submit results in either tabular format, or submit a document (i.e., a journal article or CSR synopsis).

Research shows that summary results posted onto registries in tabular form are often more accurate and complete than trial results published in academic journals.[1, 2] In addition, it is far easier for researchers, doctors, and patients to locate trial results for a drug when these are all available on a searchable, open access registry, rather than dispersed between multiple, and often paywalled academic journals.

A 2012 European Commission guideline[3] specifies that summary results of each clinical trial must be submitted within 12 months of the end of the trial (six months in the case of paediatric trials).[d] The posting of all summary results in EudraCT became mandatory for trial sponsors as of July, 2014.[4] Sponsors had to complete the process of submitting summary results for all past trials by December, 2016. An EU regulation that requires summary results to be posted will formally come into force in late 2019 or early 2020 (see below).

What is a trial sponsor?

A 'trial sponsor' is usually the institution running the trial, not necessarily the organisation funding it. Thus, trial sponsors include universities and non-profits, as well as pharmaceutical companies.

Over Half of All Due Summary Results are Missing from the Registry

The EU Trials Tracker provides a useful overview of the reporting performance of trial sponsors across Europe. The tracker is updated on a monthly basis.

Despite clear EU requirements, over half of due summary results are missing from the EU Clinical Trials Register.
As of late January 2019, for trials verifiably completed more than 12 months ago, 46 percent were missing summary results. In addition, a very large but unknown number of long-completed trials are incorrectly listed as still ongoing in the registry. Thus, the real proportion of completed trials missing results is almost certainly significantly higher than the 46 percent identified by the tracker.

In total, at least 3,500 due clinical trials are currently missing results on the registry. A search of a sample of trials missing results on the registry showed that half have not published their results anywhere else, meaning that their outcomes are completely unknown.[5]

Perhaps surprisingly, universities and non-profits have a far weaker track record of publishing trial results in the EU Clinical Trial Register than industry. Data shows that 89 percent of trials sponsored by universities across Europe are missing results. With the exception of some academic institutions in the United Kingdom (UK), all major university trial sponsors in Europe have an extremely weak trial transparency record.[6]

[d] In line with Commission Guideline 2009/C28/01 on information concerning pediatric clinical trials. The six month deadline may be extended to 12 months for certain paediatric trials if justified on scientific grounds.

ACCESS TO CLINICAL STUDY REPORTS

What are Clinical Study Reports?

A CSR is a key component of the dossier that pharmaceutical companies submit to the EMA when they apply for a marketing authorisation allowing them to sell a medicine in Europe. CSRs can be thousands of pages in length, and provide comprehensive information on each relevant clinical trial of the new drug. Access to CSRs is essential to enable independent review of clinical trials and a better understanding of drugs' benefits and harms because they contain much more information than can be found in trial registry entries, journal articles, or other sources.

Independent researchers can now access CSRs held by the EMA through two mechanisms:

- Access-on-demand to older CSRs through requests addressed to the EMA (Policy 0043)
- Proactive disclosure of new CSRs by the EMA (Policy 0070)

These mechanisms are further discussed below, followed by a discussion of redactions and other limitations on access to CSRs under both policies.

Access-on-demand to Older CSRs (Policy 0043)

Access to Older CSRs in Theory

Like other regulators worldwide, the EMA long denied independent scientists and the public to access CSRs on the grounds of commercial confidentiality. This changed in November, 2010, when the EMA adopted its ´Policy on Access to Documents' (Policy 0043) and began sharing CSRs on request.[7] The European Ombudsman arguably played an important role in the EMA's landmark shift towards greater transparency.[8] Under Policy 0043, the EMA has already released millions of pages of CSRs and other information on request.

The EMA has sought to strike a "balance between private and public interests"[9] by adopting the general principle that documents are only released once the relevant regulatory procedure has been finalised. Disclosed documents might contain redactions on the grounds of commercial confidentiality and personal data protection; however, commercially confidential information may be released if the EMA considers there to be an overriding public interest in disclosure.[e]

Access to Older CSRs in Practice

Independent reviewers seeking access to regulatory documents held by the EMA have repeatedly flagged long delays and occasionally time-consuming procedures as key barriers to accessing CSRs.[10, 11, 12]

In late 2018, one research team reported that a number of obtained CSRs lacked important sections, including protocols, serious harm narratives, and/or completed case report forms. The team also warned that the EMA had been releasing documents in multiple tranches and unsuitable formats, making independent analysis of clinical trial outcomes exceedingly difficult.[13] In contrast, in 2011, the EMA reportedly granted a full request for CSRs of trials for the controversial drug, Tamiflu (oseltamivir).[14]

Recent Developments in Access to Older CSRs

In October, 2018, the EMA implemented a reviewed version of Policy 0043 that provides greater clarity about the types of releasable documents held by the Agency, at which point they can be shared, and whether they will be subject to redactions prior to disclosure. The extent to which this revision helps to facilitate access to CSRs and other documents in practice remains to be seen.

[e] In line with Regulation (EC) No 1049/2001 which regulates access to documents from EU institutions and agencies.

Regrettably, the revised policy limits CSR access to requesters who are EU citizens or based within the EU. Non-EU requesters, who had previously been able to access these documents, are now denied access. This move has drawn strong criticism from transparency advocates.[15]

Proactive Disclosure of New CSRs (Policy 0070)

Proactive Disclosure: A Huge Step Forward for Transparency

In October, 2016, the EMA began proactively publishing CSRs submitted by pharmaceutical companies on a dedicated website. The framework of disclosure is regulated by Policy 0070,[16] which entered into force in January, 2015.

The EMA's proactive disclosure policy only applies to CSRs received by the EMA from January, 2015, onwards as part of marketing authorisation applications, and from July, 2015, as part of new indication or line extension applications relating to existing authorised products. Older CSRs can still only be accessed on request (see above).

The EMA is the first and, so far, only regulator worldwide that routinely releases CSRs. Transparency advocates at the time lauded the EMA's move as a huge step forward.[17]

Unfortunately, the EMA has temporarily placed the proactive release of CSRs under Policy 0070 on hold due to capacity constraints related to its current relocation to Amsterdam.

Proactive Disclosure in Practice

In July, 2018, the EMA published its first report on the implementation of Policy 0070.[18] During the first year of implementation, it published over 3,000 documents, including CSRs[f], totaling 1.3 million pages. The documents released covered 54 procedures and 50 medicines, including orphan, biosimilar and generic drugs.

During the first year, more than 3,600 users registered on the EMA's website, generating over 22,000 document views and more than 80,000 document downloads for non-commercial research purposes. A 2017 EMA survey (with only 131 respondents) revealed that the vast majority of respondents reported that clinical reports were presented in an understandable format, and a majority found them useful. Respondents flagged data anonymisation, the absence of individual patient line listings, and difficulties in navigating the documents as key factors limiting their utility.

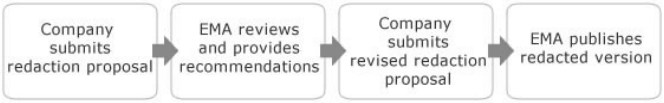
Limitations on Access to CSRs Under Policy 0070

EMA's Redaction Policy

CSRs are redacted before publication in order to remove information considered commercially confidential and data that might allow patients to be re-identified.

In principle, the EMA's understanding of what constitutes commercially confidential information is the same under Policies 0043 and 0070. Over the years, the EMA's approach to redactions seems to have been inconsistent. This may reflect the EMA's constant re-assessment of its position on what constitutes commercially confidential information. In early 2018, the European Ombudsman lauded this re-assessment process as a good practice in itself.[19]

The publication process under Policy 0070 works as follows: First, companies submit a redacted version of the CSR together with a table explaining which redactions were made on the grounds of commercial confidentiality, and a document explaining the patient data anonymisation techniques used. The EMA then decides whether or not to accept the redactions.



[f] Documents published under Policy 0070: Module 2.5 (clinical overview), module 2.7 (clinical summary), module 5 (CSRs) and appendices 16.1.1 (protocol and protocol amendments), 16.1.2 (sample case report form) and 16.1.9 (documentation of statistical methods).

[g] www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication. Accessed 4 January, 2019.

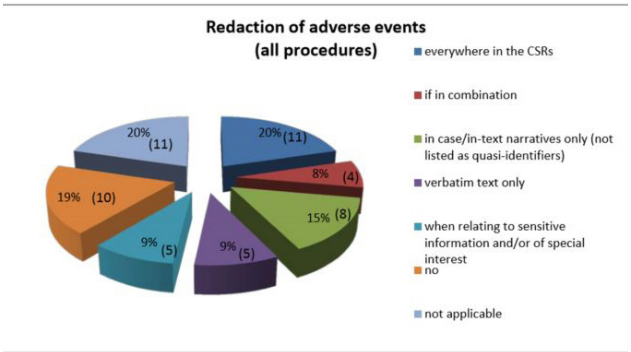
The EMA has developed specific guidelines for companies on the redaction of commercially confidential information and data anonymisation that accompany the implementation of Policy 0070.[20] The EMA's view is that information in the public domain, information that does not bear any innovative features (i.e., is common knowledge), and information whose disclosure would be in the public interest cannot be considered commercially confidential. The EMA lists specific administrative, quality-related, non-clinical, and clinical information that is of public interest. At the same time, it identifies some information that may be considered commercially confidential.[21]

EMA Redactions in Practice

In July, 2018, the EMA released a report on its implementation of Policy 0070 over its first one-year period. It had accepted redactions based on commercial confidentiality in 19 of the 54 procedures covered. However, only 1.5 percent of individual documents and only 0.01 percent of all pages released contained redactions due to commercial confidentiality. The EMA reported rejecting redaction requests by companies on numerous occasions.[22]

In addition to commercial confidentiality redactions, many redactions were reportedly made to protect personal data. For example, case narratives were redacted in full in half of all the procedures published, and partially redacted in a further fifth of procedures. The problem with using redactions as an anonymisation technique is that they might compromise the scientific utility of the reports more than would alternative techniques.[23] For this reason, in its guideline, the EMA encourages companies to transition as soon as possible to better anonymisation techniques. In 2017, the EMA established a multi-stakeholder Technical Anonymisation Group to further explore this issue.[h]

The EMA has published the chart below to summarise redactions of data on adverse events contained within CSRs for reason of anonymisation.



Source: EMA's Clinical Data Publication (Policy 0070) report (October 2016–October 2017, page 11).

According to the EMA, the approaches taken to the adverse reactions listed in the CSRs were: 11 procedures redacted them in their entirety; in four they were redacted where they were presented in combination (e.g., with age and gender); in eight procedures they were redacted in case/in-text narratives only (not listed as quasi-identifiers); in five procedures they were redacted when present in verbatim text; in a further five procedures they were redacted when relating to sensitive information and/or of special interest; for ten procedures there was no redaction and for 11 procedures with no patient identifiers there were no adverse reactions listed. A variety of approaches to redaction of adverse reactions has been followed to date.[24]

Access to CSRs: On-screen Viewing Versus Document Downloads

While drafting Policy 0070, the EMA considered permitting independent researchers to view the published reports on-screen only. Critics argued that it would be very difficult to do an in-depth review of these documents if they could only be viewed on-screen.[25, 26]

In the end, the EMA agreed to allow external parties wishing to review CSRs for academic and non-commercial research purposes to download CSRs provided that they give an address within the EU. For those wishing to access CSRs for general information purposes, access remains limited to on-screen viewing only.[27]

[h] For more information, see www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication/technical-anonymisation-group.

Intellectual Property Provisions

Under Policy 0070, the EMA states that CSRs and published reports are protected by copyright or other intellectual property held by the companies submitting them. It has been argued that risk of litigation for violating the terms of use may have a chilling effect on independent scientific reviewers.[28]

TRANSPARENCY PROVISIONS IN THE EU CLINICAL TRIAL REGULATION

Background and Scope of the Regulation

In April, 2014, the EU adopted a new Clinical Trial Regulation that introduces a greater level of harmonisation of the rules for conducting clinical trials in Europe and expands the scope of information to be published. [29]

The Clinical Trial Regulation applies only to drug trials—called CTIMPs (i.e., clinical trials of investigative medicinal products). It does not apply to many other kinds of trials, such as those for medical devices or non-drug treatments. The Regulation will replace the current EU Directive[i] six months after the new EU clinical trial portal is set up.[j] The current target for this is late 2019 or early 2020, but past experience suggests further delays are likely.[30]

New Timelines for Making Information on Clinical Trials Public

Under the Regulation, the EMA will set up and maintain a new EU clinical trial portal through which sponsors will apply for clinical trial authorisation and submit information on clinical trials. The portal will include a public interface. In 2015, the EMA outlined how the new system will operate, laying down specific disclosure rules and timelines for three different categories of clinical trials.[31, 32]

The information on clinical trials listed in the table below will be made public automatically as soon as the relevant point in time has been reached.[k]

> In April, 2014, the EU adopted a new Clinical Trial Regulation that introduces a greater level of transparency on clinical trials in Europe

[i] Directive 2001/20/EC on medicinal products for human use.

[j] This portal was previously known as the "Clinical Trials Portal and Database" (EUPD). Its name has recently been changed to "Clinical Trials Information System". See: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation.

[k] According to the EMA, deferrals on the timing for publication of documents will be set by the sponsor at the time of submission on the initial application, within the possibilities foreseen in the adopted disclosure rules. During the initial clinical trial authorisation assessment phase, the national competent authority will be able to question the sponsor's decision on deferrals and require further information. Amendment to the deferral may then be done by the sponsor at the request of the Member States.

	Category 1 (Phase I trials[l])	Category 2 (Phase II+III trials)	Category 3 (Phase IV trials[m])
Main trial characteristics[n]	Time of decision on the trial. Sponsor may opt to have a restricted number of fields made public and defer publication of the remaining information.[o]	Time of decision on the trial.	
Protocol[p]	Time of decision on trial. Sponsor may opt to defer publication up to the time of marketing authorisation or up to seven years after trial end (whichever is earlier).	Time of decision on trial. Sponsor may opt to defer this up to the time of marketing authorisation or up to five years after trial end (whichever is earlier).	Time of decision on trial. Sponsor may opt to delay publication until 12 months after trial end.[q]
Summary results (and a summary for laypersons)	Twelve months after trial end (unless later for scientific reasons). Publication can be deferred up to 18 months after due date, or until marketing authorisation, if earlier.[r]	Twelve months after trial end[s] (six months for paediatric trials).	
Clinical Study Reports	Only if submitted to medicines agencies in the EU as part of an application for marketing authorisation. Made public 30 days after decision by the corresponding medicines agency on marketing authorisation (whether positive or negative), or 30 days after withdrawal of the application.		

Full details about the timing of publication of this and other information on clinical trials are laid out in an EMA document.[33]

[l] Category 1 includes Phase I, bioequivalence and bioavailability trials and bio-similarity trials. These trials are considered to be more commercially sensitive than other trials.
[m] Category 3 also includes "low-intervention clinical trials". See Article 2 of the Clinical Trial Regulation for the definition.
[n] These include trial design, drug(s) used, endpoints, information on participants, in line with WHO Primary Registry requirements (https://www.who.int/ictrp/network/trds/en/). In addition, the summary curriculum vitaes of principal investigators will also be published, together with a statement regarding economic interests and institutional affiliations that might influence the impartiality of the investigators.
[o] The trial sponsor may apply for a deferral to keep some information from public view initially, but this information will be made public when the summary results for the trial become due. A short version of the justification for the deferral will be immediately published and a more detailed justification sometime after. Pediatric trials or trials listed in a PIP cannot delay publication.
[p] Including modifications to the protocol.
[q] According to the disclosure rules, the protocol would not normally be considered commercially confidential and the public interest is of overriding importance as these investigational medicinal products are already in routine use in medical practice; however, a deferral can be requested. The rationale for the request will be published at the time of decision on the trial.
[r] The deferral option does not apply to trials including paediatric subjects, or trials listed in a PIP, for which there is usually a six month deadline.
[s] Article 37.4 of the Regulation permits one exception to this rule: "Scientific reasons". See discussion below.

New Limits on Commercial Confidentiality

Importantly, in its recital, the EU Clinical Trials Regulation sends a strong pro-transparency message. It emphasises that in general information on clinical trials should not be considered commercially confidential. This includes data in CSRs and other information, such as the reasons for temporarily halting a trial or terminating it early, information on the authorisation of a trial, and clinical trial results.

In addition, the Regulation explicitly states that, even if information on clinical trials was commercially confidential, it must be disclosed if there is an "overriding public interest in disclosure" (Article 81).

The concept of an overriding public interest in disclosure is important and has already been invoked in the context of CSR disclosure by the EMA. In 2016, the European Ombudsman asked the EMA to consider that there is an overriding public interest for documents to be disclosed if the information that they hold has clinical value to healthcare providers and researchers. This includes information on the safety and efficacy of a medicine, including for its off-label use.[34]

The extent to which the letter and spirit of the EU Clinical Trial Regulation will be upheld, and CSRs will be redacted, is, as yet, unclear.

POLICY RECOMMENDATIONS

Policy Recommendations on Trial Registration and Summary Results

Note: Many of the recommendations below are fully aligned with the new International Standards for Clinical Trial Registries adopted by the WHO in 2018.[35] These require the EU Clinical Trial Register and its successor portal to meet key benchmarks, including:

- Registration before recruitment of the first participant
- Complete, accurate, and meaningful data provided during registration
- Clinical trials report results within 12 months of their primary completion date
- Registered records are updated at least once each year

Key Issue: Missing Summary Results

European trial sponsors have failed to post summary results for over half of clinical trials onto the EU trial registry. According to best estimates currently available, around half of the trials missing results on the public EU Clinical Trial Register have not reported their results elsewhere. This violation of EU guidelines leads to the misallocation of public health resources, wastes scarce medical research funds, slows the development of new treatments and cures, and is not in the best interest of patients.

Lack of Prompting of Trial Sponsors by the EMA

Despite recent improvements, the EMA has failed to regularly notify trial sponsors when their summary results are due to be posted, even though European Commission guidelines that say such trials should be flagged. Research shows that sending out simple reminder emails can significantly boost reporting rates.[36]

POLICY RECOMMENDATION 1:

The EMA should routinely contact all sponsors of due trials missing summary results by email to notify them of their (ethical and scientific, as well as regulatory) obligation to upload overdue results. EudraCT already contains the email addresses of trial sponsors, so this process is simple to implement in an automated fashion. In addition, the EMA should publicly flag all clinical trials whose results are overdue on the registry. Going forward, to support timely compliance, the EMA should set up a system that automatically reminds sponsors of their obligation to post results by email several months before, and after, a trial's results become due. The EMA should use this notification system to also ensure that sponsors regularly update their registry entries in line with existing registry requirements.

Lack of Effective Monitoring and Enforcement

When the EU Clinical Trial Regulation comes into force, probably during 2020, it will formally require trial sponsors to post the summary results of every applicable trial within a fixed time frame. However, enforcement of this provision will rest with individual Member States. Currently, to the best of our knowledge, no Member State has adopted/published plans to actively monitor compliance, impose fines, or otherwise meaningfully enforce this crucially important rule once the Regulation is in force.

POLICY RECOMMENDATION 2:
As the controller of the forthcoming public portal, the EMA should set, and regularly report against, public targets for achieving progressively more ambitious reporting rates over time, with 100 percent compliance by all trials as the final target. As part of this work, the EMA should encourage and support each NCA in drawing up and publishing a strategy for achieving national compliance, with clear timelines, targets and milestones.

Note: Non-commercial trial sponsors in the UK have recently begun uploading their missing summary results, with one major sponsor improving its compliance from 50 to 96 percent within a two-month time period, illustrating the large scope for rapid improvement.[t] The enquiry into clinical trials transparency made by the UK Parliament's Science and Technology Committee in 2018 significantly contributed to this process by raising the public and political profile of the issue. The Committee's excellent recommendations provide a useful point of reference for the EMA, NCAs, and Member State governments.[37]

Incorrect and Incomplete Registry Data

NCAs in several, if not all, Member States often fail to update the status of clinical trials to "completed" after trial sponsors have notified them that a trial has ended. This has led to a proliferation of trials falsely listed as "ongoing" on the registry. For example, a third of all trials at one university in the UK were, until recently, incorrectly listed as "ongoing"; after being contacted by the university, the country's NCA is now updating those registry entries.[u] In addition, crucially important data for some trials is missing. For example, 190 clinical trials currently listed on the EU Clinical Trial Register are lacking the name of their sponsor.[v]

As a result, it is currently impossible to determine whether many trials are due to post results or not, and/or who is responsible for posting these results. If these problems are not fixed, it will be impossible to effectively monitor and consistently enforce compliance with the Regulation's summary results reporting requirements.

POLICY RECOMMENDATION 3:
The EMA should urgently adjust the clinical trials registry interface to ensure that clinical trial registration can only be completed once sponsors have entered all 24 items specified by the WHO Trial Registration Data Set.[w] In addition, the EMA should routinely audit existing registry entries, publicly flag those trials that are missing any of the 24 items, and contact sponsors to notify them of the need to supply the missing data. In addition, the EMA should ensure that all changes to registry entries made by sponsors after the initial registration are tracked and made publicly visible.[x]

POLICY RECOMMENDATION 4:
The European Commission, with the EMA and NCAs, should work on an effective strategy that ensures the status of all clinical trials is updated promptly , and work on the retrospective updating of completed trials falsely listed as "ongoing" on the registry. Ongoing work by the UK's Medicines and Health Care products Regulatory Agency (MHRA) proves that this issue can easily be resolved by NCAs. The EMA itself should set, and regularly report against, public targets for progressively rectifying all incorrect trial status data. The EMA should consider following the example of the United States registry, which marks an uncompleted trial's status as "unknown" if the sponsor has not updated the registry entry for more than two years.

[t] See the forthcoming study by TranspariMED and Universities Allied for Essential Medicines, to be published on the TranspariMED website before the end of January 2019 (www.TranspariMED.org). See also the comparatively strong performance of UK versus other European trial sponsors as documented by the EU Trial Tracker.
[u] Source: TranspariMED interview with university staff member managing trial registry entries, January 2018.
[v] EU Trials Tracker. No Sponsor Name Given, Accessed 10 January 2019.
[w] For more information, see https://www.who.int/ictrp/network/trds/en/.
[x] Note that the American trial registry, Clinicaltrials.gov, already does this.

Lack of Support for Compliance

European non-commercial clinical trial sponsors, such as universities, consistently report that navigating the user interface of the current EU trial registry is unnecessarily complicated and excessively time consuming. In the words of one university administrator, uploading summary results via the current system is a "nightmare". In addition, universities have flagged a lack of effective how-to guidance as a barrier to improving compliance.[y] Unless and until the EMA (which manages the EU Clinical Trial Register and will soon manage the future portal) actively facilitates compliance, the problem of missing summary results will not be overcome.

POLICY RECOMMENDATION 5:
The planned EU clinical trials portal will only meet expectations if trial sponsors can use it in practice. The EMA, in tandem with NCAs, should conduct a formal review of the current system to identify and remove barriers to effective use of the EU Clinical Trial Register, design the user interface of the new portal so small and non-commercial trial sponsors with limited capacity can effectively and efficiently upload and update information. EMA should pre-test the portal with future users.[z]

POLICY RECOMMENDATION 6:
The EMA should develop easily understandable guidance on using the new portal for small and non-commercial trial sponsors, pre-test it with future users, and ensure that sponsors are made aware of this guidance material when they register trials.[aa] In addition, the EMA should set up a helpdesk to support trial registration through the new portal and reporting by sponsors, and catalyse the setup of a peer-to-peer support network.[ab]

Deferrals Policy and Practice

The implementation rules of the EU Clinical Trial Regulation allow trial sponsors to defer the publication of certain types of information on clinical trials on the public registry. This is problematic and, in the absence of clear criteria—notably those for "scientific reasons"—open to abuse. Delaying public access to Phase I clinical trial registrations and their summary results is ethically problematic as these trials can entail safety risks for participants.

POLICY RECOMMENDATION 7:
Deferrals to making information on clinical trials public must only be granted in exceptional cases. The EMA must develop and publish clear criteria for approving deferrals. Where a deferral is approved, the justification for that deferral must be made public immediately on the registry. The public interest should be put ahead of commercial considerations.

[y] TranspariMED interviews with several registry managers at UK universities, 2018-2019.
[z] EMA is reportedly working on such testing. EMA should ensure that pre-testing focuses on non-commercial and small sponsors, in particular. The public interface should also be pre-tested.
[aa] The three transparency tools published by TranspariMED may provide a useful starting point. See: www.transparimed.org/resources.
[ab] The US Clinical Trials Registration and Results Reporting Taskforce provides an effective and ultra-low-cost model for setting up an effective peer-to-peer trial reporting support network. See: www.transparimed.org/single-post/2018/08/22/Taskforce-launches-website-to-help-universities-to-register-and-report-clinical-trials.

Policy Recommendations on Access to Clinical Study Reports

Key issue: Limited scientific utility of access to CSRs

The EMA has justly been praised for its groundbreaking transparency policies regarding CSRs. However, the release process and approach to redactions currently limit the extent to which these laudable policies translate into greater uptake by, and utility to, the medical research community.

Clinical Study Report Accessibility and Utility

Independent clinical trial reviewers have complained about the duration and complexity of the processes for accessing regulatory documents held by the EMA, notably CSRs. This discourages the use of CSRs by external researchers including systematic reviewers, and undermines evidence-based decision-making by public bodies, healthcare practitioners and patients.

POLICY RECOMMENDATION 8:
The EMA should make access to CSRs more user-friendly and ensure that documents are released in formats that maximise their practical utility for the scientific community. Specifically, the EMA should allocate more resources to handling requests for access to documents, streamline and accelerate the process, and restore access to older CSRs under Policy 0043 to requesters based outside the EU. To simplify access to documents processes, EMA should publicly list all relevant documents it holds.

The EMA should also resume the publication of CSRs under Policy 0070 by July, 2019, at the latest, and ensure that its backlog of unpublished CSRs is cleared by the end of 2019.

Redaction Policy and Practice

A 2018 ruling by the General Court (Court of Justice of the EU) confirmed the EMA's approach that CSRs do not benefit from a general presumption of confidentiality. In addition, the European Ombudsman has supported the view that clinical trial data is information in the public interest and the new EU Clinical Trials Regulation sends a strong signal in this direction. However, disclosure of CSRs by the EMA has been somewhat inconsistent over the years, with various kinds of redactions being performed on different occasions. Redactions can compromise the scientific utility of CSRs.

POLICY RECOMMENDATION 9:
The EMA should ensure that redactions of any kind to CSRs are kept to an absolute minimum. In particular, information must be disclosed if there is an overriding public interest, even if it is considered commercially sensitive, and any anonymisation techniques used to protect personal data should safeguard the scientific utility of disclosed CSRs.

Keeping in mind the implementation of transparency requirements under the EU Clinical Trial Regulation, and in the context of marketing authorisation applications that go through the national, decentralised, or mutual recognition procedures, NCAs should have the final word on redactions proposed by marketing authorisation holders to submitted CSRs before publication.

ANNEX 1

LEGAL STRUGGLES OVER ACCESS TO INFORMATION ON MEDICINES IN EUROPE

The EMA's journey towards greater clinical trial transparency has not been plain sailing. Some pharmaceutical companies consider the data they submit to the EMA to have commercial value, and have taken the EMA to court over its decisions to grant third parties access to information. Landmark cases are listed below.

- In 2013, AbbVie sued the EMA to prevent third party access to CSRs for the drug, Humira (adalimumab). Both parties reached an out-of-court settlement agreement, and the EMA announced that it had accepted making certain redactions proposed by the company before releasing the CSRs.[38] This was followed by an inquiry from the European Ombudsman, who found redactions made to protect commercial interests unjustified.[39]

- In 2013, InterMune sued the EMA over its decision to share reports submitted as part of the marketing authorisation application for Esbriet (pirfenidone). InterMune ended up dropping the charges against the EMA.[40]

- In 2015, Pari Pharma brought a lawsuit against the EMA in relation to the disclosure to a competitor of similarity and superiority reports on Vantobra (tobramycin). In February, 2018, the General Court ruled in favour of the EMA.[41]

- In 2015, PTC Therapeutics initiated proceedings against the EMA in relation to the disclosure of a CSR for Translarna (ataluren). The General Court ruled that the CSR did not benefit from a general presumption of confidentiality.[42]

- In 2015, MSD Animal Health Innovation and Intervet International BV sued the EMA regarding the sharing of toxicology study reports for Bravecto (fluralaner). The General Court ruled in favour of the EMA.[43]

In February, 2018, the EMA issued a press release welcoming rulings by the General Court that backed the EMA's approach to transparency. "We are very pleased that the General Court affirmed that the information contained in these documents cannot be considered commercially confidential in its entirety," explained Stefano Marino, the EMA's Head of Legal.[44]

ANNEX 2

EMA CLINICAL DATA PUBLICATION POLICY VERSUS EU CLINICAL TRIAL REGULATION

The following overview was published by the EMA:

	Clinical Data Publication Policy	Clinical Trial Regulation
Medicinal Products covered	Centrally authorised products only	Investigational medicinal products regardless of whether they have a marketing authorisation
Clinical Studies Covered	Clinical studies submitted to the Agency in the context of an MAA, Art 58 procedure, line extension or new indication, regardless of where the study was conducted	Clinical trials conducted in the EU and paediatric trials conducted outside the EU that are part of paediatric investigation plans
Documents Published	Clinical data (clinical overview, clinical summaries and clinical study reports) and the anonymisation report	All clinical trial-related information generated during the life cycle of a clinical trial (e.g. protocol, assessment and decision on trial conduct, summary of trial results including a lay summary, study reports, inspections, etc)
Publication Channel	EMA clinical data publication website	Future EU portal and database
Date It Applies	1 January, 2015 (MAA or Art 58 procedure) or 1 July (line extension or new indication)	Expected in 2019
Publication From	October 2016	Expected in 2019

Source: EMA website, accessed December 2018 (www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication).

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