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Ensuring that the results of all clinical trials are posted in France

Working Group on "Transparency and publicising of health research results"

May 2025

Ouvrir la science !

Ensuring that the results of all clinical trials in France are posted

Report submitted to the Open Science Steering Committee set up on 16 May 2024

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Working Group on "Transparency and the publicising of the results of health research"

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Mission statement of the Working Group

MINISTÈRE
DE L'ENSEIGNEMENT
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ET DE LA RECHERCHE
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MINISTÈRE
DE LA SANTÉ
ET DE LA PRÉVENTION
Liberté
Égalité
Fraternité

La Directrice générale de la recherche et de l'innovation
La Directrice générale de l'offre de soins

Paris, le 10 octobre 2023

Monsieur le Professeur,

Comme vous le savez, la France se distingue en Europe par le faible taux de publications des essais cliniques, même lorsque les promoteurs sont institutionnels (structures publiques).

Les biais de publication ainsi induits sont une perte de chance pour la connaissance basée sur les preuves (les résultats positifs étant plus volontiers publiés), pour la société (engagement non justifié de dépenses publiques) et *in fine* pour les patients dans la prise en charge ou la prévention des maladies.

Pour limiter ce biais de publication, différentes dispositions sont déjà mises en œuvre mais restent insuffisantes. Ainsi en France dans le cadre du Programme Hospitalier de Recherche Clinique (PHRC), une des tranches de versement est conditionnelle à la publication des résultats de l'étude. À l'étranger, des amendes peuvent être appliquées aux chercheurs/institutions qui ne publieraient pas les résultats.

Nous vous confions la mission de présider le groupe de travail du Comité pour la science ouverte ayant pour intitulé "*Transparence et publicité des résultats de la recherche en santé*". Les missions de ce groupe de travail seront de formuler des propositions afin de réduire le biais de publications en France. En particulier, des propositions d'actions à court, moyen et long terme pour les ministères et opérateurs concernés devront être formulées et un dispositif de suivi de la situation devra être proposé.

La composition de ce groupe permet de regrouper les expertises dans ce domaine, afin de proposer des conclusions opérationnelles applicables dans les établissements et dans la communauté scientifique. Vous auditionnerez également des experts français et étrangers. Vous vous appuierez sur les services de nos deux ministères pour mener à bien cette mission.

.../...

Professeur Philippe RAVAUD
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Nous souhaitons recevoir les conclusions du groupe de travail à la fin du mois d'avril 2024. Ces conclusions seront ensuite soumises au Comité de pilotage de la science ouverte, qui se tiendra sous notre présidence en mai 2024.

Sachant pouvoir compter sur votre expérience et votre engagement pour la réussite de cette mission, nous vous prions d'agréer, Monsieur le Professeur, l'expression de notre considération distinguée.

Claire Giry

Marie Daudé

Summary

It is our collective responsibility to post all clinical trial results in a timely fashion.

The Working Group on "Transparency and the publicising of the results of health research", was appointed by the French Ministry in charge of Research, in conjunction with the French Ministry in charge of Health. It seeks to address the problem of publication bias, which is the tendency to prioritise the publication of positive results. However, if they are based on an incomplete, skewed understanding of research results, this bias may result in erroneous health policy decisions.

This report makes recommendations towards all stakeholders involved in clinical research, and covers the entire scientific process and its funding. It places particular emphasis on the importance of posting clinical trial results in the registry used to declare them, within a maximum one-year delay after the trial ends. This sort of development is crucial in order to reduce publication bias. The posting of results involves the making public of aggregated data for the main results of a trial (i.e. descriptions of trial's participants and their characteristics, primary and secondary results, and adverse events). This posting is not considered to be a peer-reviewed scientific publication, and is independent of any potential publication in a scientific journal. The posting of results is an ethical obligation, as stated by the World Health Organisation (WHO), the International Committee of Medical Journal Editors (ICMJE) and the World Medical Association. It is also a legal obligation that is subject to precise European regulations (as in the United States of America).

Above all, the Working Group recommends that all stakeholders should communicate more effectively about the issues involved in posting clinical trial results and assist with the introduction of a clear means of organising these postings within reasonable timeframes. It underlines the benefit of having national indicators produced by the French Open Science Monitor, which should be applied to each sponsor, in order to encourage them to correct any potential shortcomings. Publishing guidelines should enable good practices to be implemented in the area.

The group recommends that the posting of results be integrated into clinical research training programmes, into the financial arrangements for clinical trials in France, into the collective and individual assessment procedures in clinical research, and that the issue should be considered in institutions' strategies relating to scientific integrity.

To facilitate posting and improve quality, the group suggests that an open-source tool should be developed to generate the template of results to be posted. This tool could be implemented taking inspiration from both European regulations and the procedure in place in the U.S. clinical trial registry, ClinicalTrials.gov, in order to avoid introducing unnecessary complexity and divergence in the sponsors' work.

The group suggests that sponsors should get involved and undertake educational work in three phases to ensure that the results are posted: raising awareness before launching the

trial, issuing a warning as soon as the trial ends, and, where necessary, issuing a reminder from twelve months after the trial ends.

The group also suggests that the National Research Coordination Committee (CNCR) should be assigned the task, for a transitional period of 12 to 24 months of supporting sponsors to implement the Working Group's recommendations.

Similarly, the working group proposes that the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) (French National Agency for the Safety of Medicines and Health Products) should issue a reminder of posting obligations during its inspection missions and when communicating about clinical trials.

The group also suggests expanding the national and European regulations to all clinical trials. Indeed, there is no ethical, scientific or public health rationale that justifies the current situation where nonpharmacological clinical trials are exempt from the obligation to post their results.

Lastly, the functionalities of the European CTIS registry need to evolve to meet the expectations of the international scientific and editorial communities regarding the posting of results. Furthermore, as CTIS does not cover all clinical trials, the question of where to post the trials concerned will arise.

Disclaimer

The indicators presented in this report correspond to the values of the Open Science Monitor in May 2024. Slight variations may therefore occur between this report and the Monitor's current indicators, as the Monitor is subject to a continuous improvement process and annual updates.

Introduction

The issue of publication bias in clinical trials affects science, public health and scientific integrity, and results in squandered funding.

The French Open Science Monitor[1] shows that between 2012-2022, only 57% of the results of French clinical trials have been made public in clinical trial registries (the American registry Clinicaltrials.gov and/or the European registry[2]). This percentage is even lower when restricted to trials that comply with the European regulations, i.e. results posted within twelve months of trial's end. Hence, in 2022, only 36% of trials' results were posted or published within expected deadline[3]. The situation is even more worrying when this indicator is calculated only for trials with public sponsors, as it reaches 15% of trials with results posted or published.

This low rate of posting of the results of clinical trials is a source of publication bias. Publication bias is the tendency to favour the publication of positive results, i.e. results favouring one treatment versus another or versus a placebo. This issue has been known for a long time and is widely documented in the scientific literature[4]. In the domain of health research, this bias can result in decisions being taken based on partial information. It also contributes to the phenomenon of "research waste", where allocated funds are wasted. This bias also constitutes an obstacle to the principles of research integrity, with researchers having a duty to publicly disclose the results of research involving human subjects[5]. However, a European regulation voted in 2014[6], which has since been progressively implemented, makes it compulsory to report, at least in summary form, the results of clinical trials on drugs. The French National Plan for Open Science[7] together with the French strategy to accelerate digital health have committed to support expanding the obligation for transparency in health research results to non-pharmalogical clinical trials.

The Working Group on "Transparency and publicising of health research research" was created at the request of the French Ministry in charge of Research and the French Ministry in charge of Health. It was assigned to recommend measures that are likely to improve the situation in France in terms of reporting of clinical trial results, in particular the posting of results in clinical trial registries.

[1] https://barometredelascienceouverte.esr.gouv.fr/

[2] EUDRACT: https://eudract.ema.europa.eu/. This registry has since been replaced by the Clinical Trials Information System – CTIS.

[3] This rate rises to 52% when we look at a three-year period after the trial has ended.

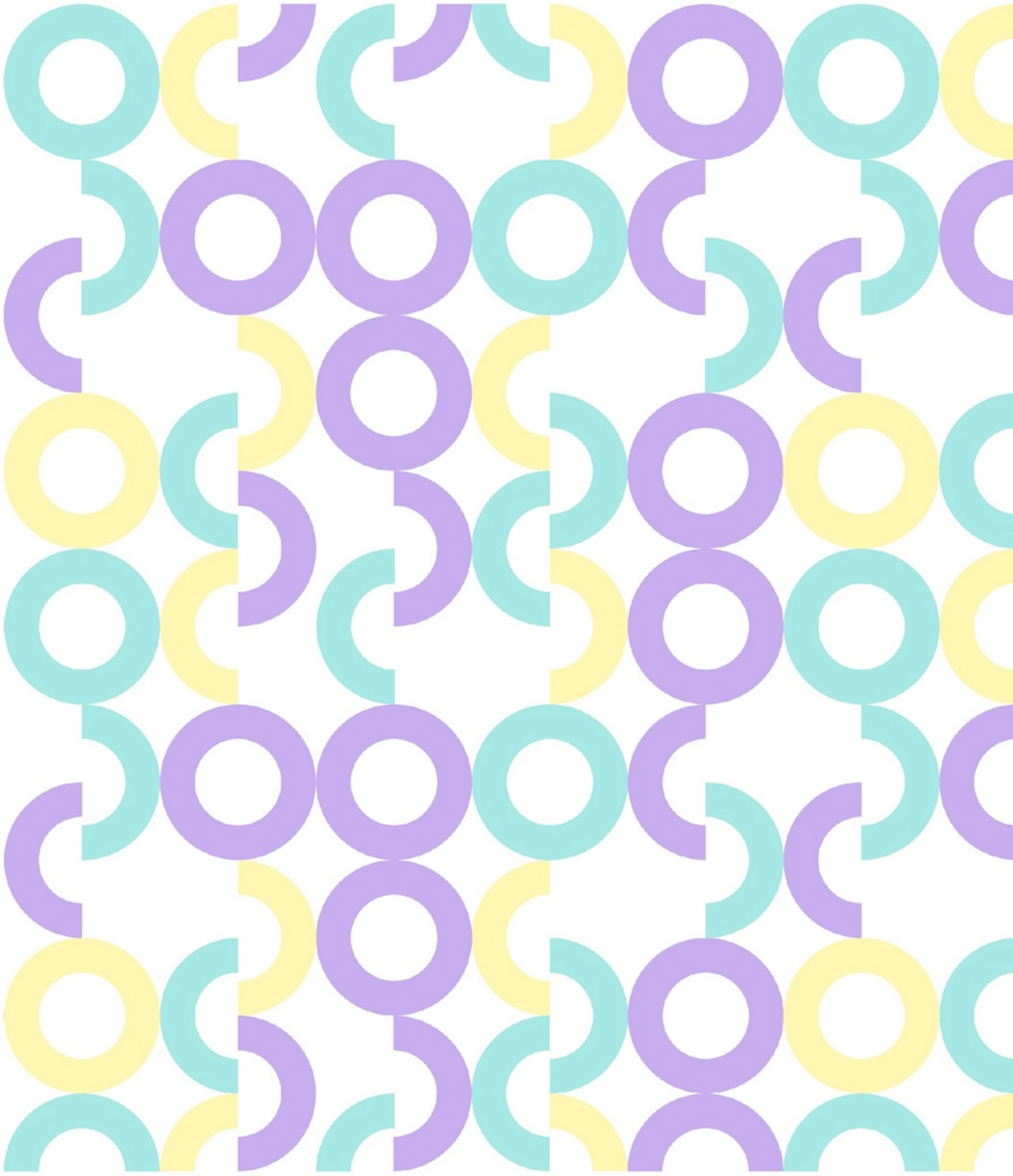
[4] Fanelli D. Negative results are disappearing from most disciplines and countries. Scientometrics. 2012;90(3):891-904. doi:10.1007/s11192-011-0494-7

[5] ALLEA, European Code of Conduct for research integrity, 2023. https://allea.org/wp-content/uploads/2023/06/European-Code-of-Conduct-Revised-Edition-2023.pdf

[6] Posting of clinical trial summary results in European Clinical Trials Database (EudraCT) to become mandatory for sponsors as of 21 July 2014. European Medicines Agency. https://www.ema.europa.eu/en/news/posting-clinical-trial-summary-results-european-clinical-trials-database-eudract-become-mandatory

[7] https://www.enseignementsup-recherche.gouv.fr/fr/le-plan-national-pour-la-science-ouverte-2021-2024-vers-une-generalisation-de-la-science-ouverte-en-48525

Table of contents



Current situation

Over time, it has become compulsory to register clinical trials in order to limit the impact of publication bias. This effort has been driven by many different stakeholders, including medical journal editors and the World Health Organisation.

Registering clinical trials, an old idea that has become compelling.

In the USA, starting in 1997, the Food and Drug Administration Modernization Act (FDAMA 113) set out federal requirements for the sponsors of clinical trials investigating serious diseases. It required them to register information from the clinical trial protocols before patients were recruited. Initially this law was poorly observed, and only a very limited number of trials were registered. Hence, in 2000, a clinical trial registry, ClinicalTrials.gov, was introduced in the USA to encourage implementation of the 1997 law. This registry is managed by the United States National Library of Medicine (NLM).

The International Committee of Medical Journal Editors (ICMJE) required the registration of clinical trials as a condition for publication (2004).

In 2004, several health scandals linked to failure to publish trials results suddenly made this old and hitherto neglected idea of registering clinical trials a compelling one[8]. The International Committee of Medical Journal Editors (ICMJE) has mandated that, for publications in their journals, clinical trial results must first be registered in a public trial registry. The ICMJE declared that for trials where recruitment starts after July 1, 2005, registration must occur no later than the beginning of the patient recruitment phase for all clinical trials. For trials where recruitment started before this date, ICMJE member journals required registration by September 2005 for the trial to be considered for publication[9] (DeAngelis JAMA 2004).

The Ottawa Statement: A group of researchers established key principles for clinical trial registration: all trials must be registered prior to participants recruitment and the results must be registered regardless of whether the studies are eventually published (2004)

Also in 2004, a group of Canadian researchers set out the following three key principles for registering clinical trials (Ottawa Statement):

[8] Dickersin K, Rennie D. Registering clinical trials. JAMA. 2003 Jul 23;290(4):516-23. doi: 10.1001/jama.290.4.516. PMID: 12876095 and Rennie D. Trial Registration: A Great Idea Switches From Ignored to Irresistible. JAMA. 2004;292(11):1359–1362.

[9] DeAngelis, Catherine D., Jeffrey M. Drazen, Frank A. Frizelle, Charlotte Haug, John Hoey, Richard Horton, Sheldon Kotzin, et al. "Clinical Trial Registration. A Statement From the International Committee of Medical Journal Editors." *JAMA* 292, nº 11 (15 September 2004): 1363-64. https://doi.org/10.1001/jama.292.11.1363.

1. Registration of all types of trials: "Protocol information and the results of all trials related to health or healthcare, regardless of the topic, design, outcomes or the market status of interventions assessed, should be registered and made publicly available."
2. Timing of public access to registered protocol information: "The public should have cost-free access to the Unique ID, minimum protocol items, and consent forms prior to participant enrolment. Registered amendments of the protocol should be made publicly available as they occur."
3. Registration of unpublished results: "As a minimum, results for outcomes and analysis specified in the protocol (as approved by the institutional review boards/independent ethics committees), as well as data on harm, must be registered, regardless of whether or not they are published."

The World Health Organisation (WHO) called for the registration of all trials (2005)

At the fifty-eighth World Health Assembly in 2005, the Clinical Trials Registry Platform was created by the international scientific community, international partners, the private sector, civil society and other concerned stakeholders, aiming to provide a single point of access and to guarantee unambiguous identification of trials in order to improve access to information for patients, families, patient groups and others.

The World Health Organisation (WHO) created the International Clinical Trials Registry Platform (ICTRP) (2007)

The only way of ensuring the availability of complete, accurate information on clinical trials is to register all trials before the first participant is recruited. WHO believes that clinical trial registration is a question of scientific, ethical and moral responsibility. It decided to create a platform that functions as a meta-registry, gathering data from WHO-approved registries. This platform provides a single point of access and ensures the unambiguous identification of trials with a Universal Trial Number (UTN). It is known as the International Clinical Trials Registry Platform (WHO-ICTRP), and was officially launched in 2007. It relies on primary registries that meet precise criteria: free public access, open to anyone wishing to register a prospective trial, managed by a non-profit organisation, and equipped with a system to ensure the validity of the registered data, which must be accessible electronically. These registries must include at least 24 essential items and be available in English.

Mandatory registration of clinical trials was established by law in the United States (2007)

In the United States in 2007, the Food and Drug Administration Amendments Act (FDAAA) section 801 required that all clinical trials be registered[10] (with the exception of phase I drug trials).

[10] https://www.govinfo.gov/content/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf#page=82

An obligation was included in the ethical principles for medical research involving humans - Helsinki Declaration (2008 then 2013)

In 2008, the World Medical Association introduced the Helsinki Declaration, formalising a statement of ethical guidelines for medical research involving humans. Principle 19 states: *"Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject".*

In 2013, this declaration was revised to include the section "Research Registration and Publication and Dissemination of Results", where principle 35 reads as follows:

> *"Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject involved in the research."*

Principle 36 is as follows:

> *"Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make available to the public the results of their research on human subjects. All parties are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive results, as well as positive results, must be published or otherwise made available to the public. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Research reports that are not in accordance with the principles of this Declaration should not be accepted for publication."*

Registration, a legal obligation in Europe (2014)

In 2014, the European parliament and council regulation no 536/2014 of 16 April 2014 on Clinical Trials on Medicines for Human Use and amending Directive 2001/20/EC made trial registration a legal obligation.

In addition to trial registration, the posting of results was made mandatory

The second important phase in the development of clinical trial registration concerned the posting of results both in the United States and in Europe. This initiative seeks to provide universal access to the aggregated results of all registered clinical trials (accessible to the general public, researchers and evidence synthesis experts) regardless of whether the results are published late or not at all in peer-reviewed journals.

In 2007 in the United States, the law required the posting of all clinical trials results

The "Food and Drug Administration Amendments Act of 2007" (FDAAA 801) introduced a new section that required the results of all clinical trials to be posted within a deadline of one year following completion, in accordance with a strictly defined template. Failure to post results could lead to financial penalties of up to 10,000 dollars per day of delay

and to the withdrawal of federal funding. The FDAAA also widened the scope of Clinicaltrials.gov by including a new section dedicated to results posting.

In 2012, the European Commission explicitly recommended the posting of results

In 2012, the European Commission published guidelines entitled "Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No. 1901/2006"[11]. This document covers the implementation of the European Union regulation designed to make clinical trial results accessible to the public. It outlines the procedures for posting emphasizing that the results must be made public via the "EU Database on clinical trials (EudraCT)," within 6 months after the completion of pediatric trials and 12 months after the completion of adult trials. Member states are also responsible for verifying that the results of the trials they have authorized have been posted as required.

In 2012, the AllTrials campaign had a major impact

AllTrials is an international initiative launched by scientific journals (BMJ, PLOS), the Oxford Centre for Evidence-Based Medicine, the Cochrane Collaboration, the James Lind Initiative and "Sense about Science" in the USA. It advocates for the registration of all past and present clinical trials, along with the reporting of their complete methodologies and results summaries. This petition was signed by 747 organisations. Cf. https://www.alltrials.net/

In 2014, a new European regulation on clinical trials made the posting of results mandatory

The European Parliament and Council Regulation (EU) no. 536/2014 dated 16 April 2014 on Clinical Trials on Medicines for Human Use amending Directive 2001/20/EC introduced an obligation to post results: *"Irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the EU database a summary of the results of the clinical trial. The content of that summary is set out in Annex IV".*

The regulation sets out the information to be posted, the posting schedule (time limit of 1 year after the end of the trial), its implementation date, the posting site (European clinical trials database, EudraCT) and provides guidance on how to deal with cases of non-compliance and factual inaccuracies. Annex IV sets out the content of the summary of the clinical trial results; it must include: basic characteristics of the participants, assessment criteria, adverse events, substantial amendments made to the protocol, and finally, a declaration from the sponsor confirming the accuracy of the information reported.

[11] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52012XC1006%2801%29

In 2017, there was a new WHO statement on public disclosure of the results of clinical trials

The "Joint Statement on the Public Disclosure of the Results of Clinical Trials[12]", signed in 2017 by the WHO and numerous research and non-governmental organisations, set out new standards for greater transparency in clinical trials.

It states that the characteristics of all trials should be recorded in a clinical trial registry that is accessible to the public, free to access and searchable, in compliance with the international standards approved by the WHO (www.who.int/ictrp). Clinical trials registrations should be completed before the first participant undergoes their initial first medical procedure, or as soon as possible afterwards. The registry entries must be updated as needed to reflect the final number of participants and the study's primary outcome completion date (defined as the last data collection point for the last participant concerning the primary endpoint).

The summarised results of the clinical trials should be made publicly available in timely manner once the primary study is complete. There are two main ways of doing so: by posting in the results section of the clinical trials registry and by publishing in a journal. A 12-month time limit from the end of the primary study (defined as the last data collection visit of the last participant for the primary outcome) should become an international standard for disclosing summarised results. Since the journal publication timelines are not entirely within the control of the sponsor or investigator, this joint declaration focuses on utilising registries - such as clinicaltrials.gov and EU-CTR - to fulfill the expectation for results disclosure. Although journal publication is also expected, a target timeline of 24 months after the study completion is suggested, in order to allow the peer review process occur.

Furthermore, the signatories of this declaration commit, within 12 months, to devise and implement a policy setting out mandatory deadlines for prospective registration and public disclosure of the results of the clinical trials that they fund, co-fund, promote or support. They also agree to implement a monitoring system for trial registrations and publicly share the outcomes of this monitoring public.

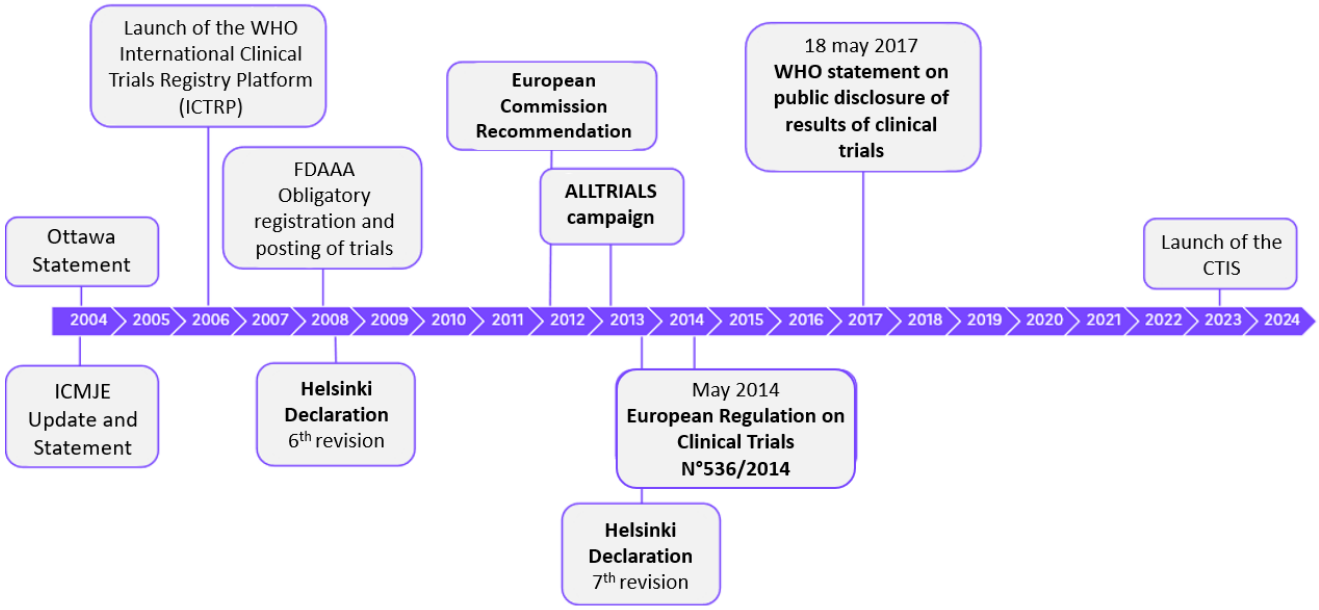
The European registry is evolving: from EudraCT to the Clinical Trials Information System (CTIS)

Articles 80 and 81 of the European regulation no. 536/2014 assigned to the EMA the task of creating a European Union portal and database. The first registry created was EudraCT, where over 40,000 clinical trials have been registered. It was later decided that a new portal, the Clinical Trials Information System - CTIS, would become the single point of entry, effective 31 January 2023, for transferring data and information relatied to clinical trials, as required by European regulations. CTIS will replace the EudraCT portal. All interventional clinical trials with at least one recruitment site in the EU, and with the last visit of the last patient scheduled after 30 January 2025, must be transferred to CTIS. Trials that are planned to end before 30 January 2025 will remain on the EudraCT database and do not require transfer to CTIS.

It should be noted that, according to those managing it, this registry is exclusively for drug-related trials.

[12] https://www.who.int/news/item/18-05-2017-joint-statement-on-registration

Development timeline of registries and result posting.



Changes in French legislation since July 2022

According to Article L1128-12 of the French Public Health Code, non-compliance with Articles 37, 42, 43 and 93 of European Regulation (EU) No. 536/2014 of the European Parliament of April 16, 2014 on clinical trials of medicinal products on the communication of information intended to be made available to the public in the database of the union is punishable by one year's imprisonment and a fine of 15,000 euros[13] .

[13] https://www.legifrance.gouv.fr/codes/article_lc/LEGIARTI000046122248

Despite the existence of these registries, regulations and laws, concerns about publication bias and selective posting persist

The situation in Europe and throughout the world

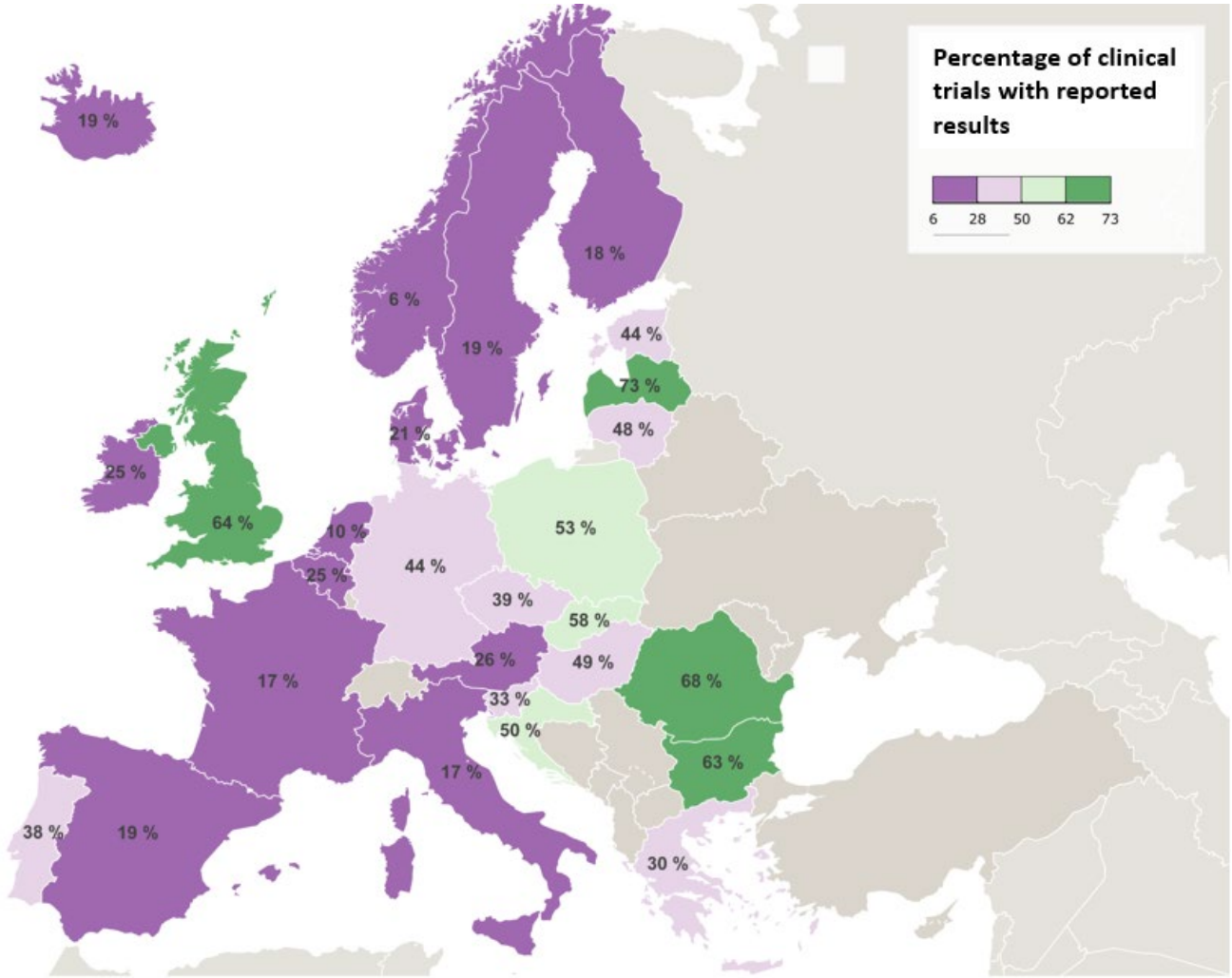
Several studies have confirmed that widespread publication bias and "selective reporting"[14] persists, particularly in trials with academic sponsors.

In Europe, an analysis published in 2018 showed that out of the first 7,274 trials registered in EudraCT with pending results, only 49.5% (95% confidence interval: 48.4% to 50.7%) had their results posted. Trials conducted by private sponsors were significantly more likely to post results posted compared to those by non-commercial sponsors (68.1% compared to 11.0%, adjusted odds ratio 23.2, 95% confidence interval: 19.2 to 28.2). Additionally, the quality of the posted results was often poor, including errors, omissions and contradictory data (Goldacre, BMJ 2018).

In a more recent random sample of 500 trials registered on EUCTR with completion dates exceeding two years, the availability of the results posted on EUCTR was 53.2% (95% confidence interval (CI) from 48.8% to 57.6%) and the median time period to post results was 1,142 days (95% CI = 812 to 1,492). Of the 383 trials with results available, 55 (14.4% 95% CI = 10.9% to 17.9%) were only posted on EUCTR. Finally, for 117 trials (23.4% 95% CI = 19.7% to 27.1%), results were unavailable both in the registries and as published articles (DeVito BMJ Med 2024).

[14] "*Selective reporting*" refers to the practice of only reporting certain evaluation criteria, or even to replacing the primary evaluation criterion with a secondary one.

Percentage of clinical trials with posted results by country
(Source: TranspariMed, EUDRACT)[15]



Data: TranspariMED. 2021. Map credits: Ouvrirlascience.fr Licence CC BY.

The situation in France is that only 36% of trial results are posted or published one year after the trial ends

The results of a TranspariMED report show that the results reporting rate in France is very low[16]. These performances are confirmed by the French Open Science Monitor, which was created in 2021 as part of the National Open Science Plan (see Appendix 1 for more details). This Monitor shows that the results of only 36% of French clinical trials were reported (through either posting or scientific publication) within 12 months after the trial ends. The percentage is higher when the indicator is calculated for results posted within three years of the trial ends. It reaches an average of 52% ranging from 74% for trials with

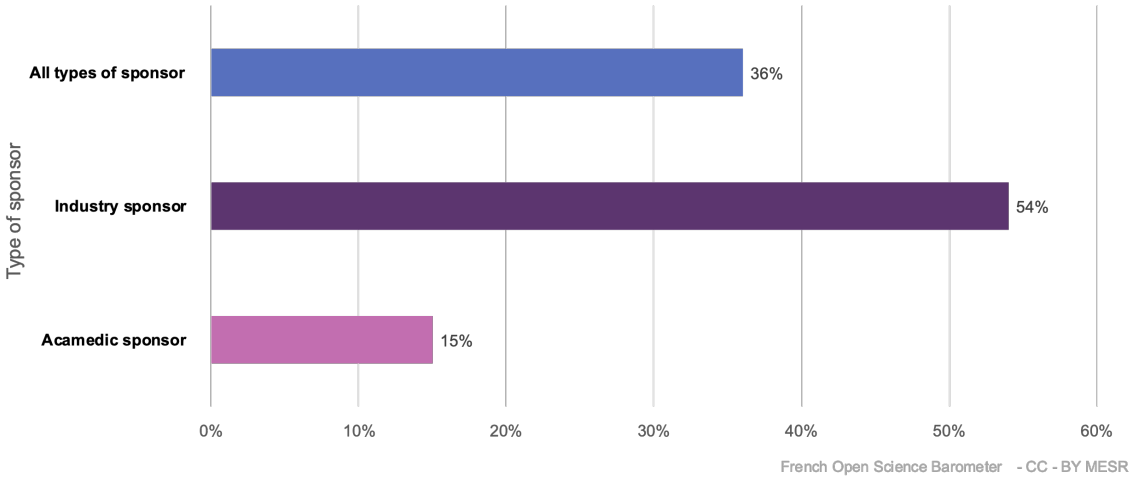
[15] Data source: Missing clinical trial data in Europe. Assessing and comparing the performance of national medicines agencies Paris (France), Amsterdam (NL), and Bristol (UK), 5 July 2021.https://transparency-france.org/wp-content/uploads/2021/07/TranspariMED-NCA-report_final_20210705.pdf

[16] Clinical Trial Transparency in France. Mapping unreported drug trials, Paris (France) and Bristol (UK), March 16th 2021

https://transparency-france.org/wp-content/uploads/2023/10/Clinical-Trial-Transprency-in-France-CONFIDENTIAL-20210206-FR-PDF.pdf

industry sponsors to 28% for trials with academic sponsors. However, even when extending the posting delay to 3-year after trials end, still half of the results of French clinical trials are not reported at all.

Percentage of registered clinical trials that ended in 2022 where the result has been posted and/or a scientific publication has been declared within one year of clinical trial ending



Posting results: a scientific integrity issue for all stakeholders

The issue of publication bias and selective results posting is a major challenge to scientific integrity. The Helsinki Declaration emphasizes this by asserting that researchers are obligated to make the results of their research on human subjects publicly available. The Declaration specifies the responsibility for maintaining integrity in research applies to researchers, authors, sponsors, editors and publishers, all of whom are ethically obligated to ensure the proper publication and dissemination of research results.

According to the WHO's joint statement of 2017, the prospective registration and timely public disclosure of results from all clinical trials are of critical scientific and ethical importance. This statement highlights that the timely disclosure of clinical trial results reduces research waste, enhances the value and efficiency of funds use, and mitigates reporting bias, ultimately contributing to improved decision-making in healthcare.

It states that reducing the current bias in reporting results would enable more informed decisions making, particularly in the following areas:

1. The granting of licenses and marketing authorisations for treatments (including risk-benefit assessments),
2. Public health policy recommendations on treatment usage (including cost-effectiveness), and funding decisions by public procurement bodies and multilateral agencies,
3. Personal treatment choices made by doctors and patients.

Finally, the European Code of Conduct for Research Integrity does not explicitly address the posting of results, but it emphasizes that authors should make their work available to peers in a timely, open, transparent and accurate way, and that both authors and editors

should consider negative results to be just as equally valid as positive ones for publication and dissemination (see Appendix 9).

Decreasing publication bias and increasing the posting of results

In addition to regulatory measures, the impact of various experiments aimed at increasing results posting and decreasing publication bias has been assessed

Actions carried out by Investigators

Various approaches have been tested to improve the rates of result posting. In Maruani *et al*.'s randomised trial, in the intervention group, investigators of randomised trials registered in clinicaltrials.gov received a reminder message that reminded them that their trial was subject to FDA Amendments Act 801 and that they were required to post their trial results and that warned them of potential fines for non-compliance. Six months after the intervention, the percentage of trial result posting was 24% in the intervention group versus 14% in the control group. Therefore a simple intervention (sending a reminder message) resulted an increased number of trial results posted, 10 messages sent resulted in one additional results posting.

Actions carried out for Sponsors

Several European groups, particularly TranspariMED, publish reports showing the results by country for the main sponsors, particularly universities and university hospitals. This approach involves publicly sharing the information, sometimes using direct messages on social media to name the worst offenders and urging them to take measures to improve their indicators.

Oxford University's Bennett Institute for Applied Data Science has developed the TrialsTracker tool which is updated every month (https://eu.trialstracker.net/) for trials registered in Europe. This tool identifies the number of trials for which a result should be posted on the European registry and the number of trials presenting inconsistent registrations, such as international trials for which end date differs across participating countries trial registries or trials with missing completion date (Goldacre B et al., BMJ 2018). It also produces a ranking of sponsors with the greatest numbers of registered and unregistered trials. Finally, a page can be consulted for each sponsor, showing the number of trial results posted and listing these trials, thus enabling the sponsors to easily identify and correct any failures to post results.

In Germany, a semi-automatic approach has been introduced to assess how well transparency practices are adhered to. This involves posting the results of interventional trials sponsored by a University Medical Centre (UMC). It takes into account clinical trials registered in ClinicalTrials.gov, the German clinical trial registry (DRKS) or the EU clinical trial registry (EUCTR) through the use of the EU Trials Tracker. An interactive dashboard[17] displays the rates of posting results by German University Medical Centres (UMC), both individually and overall.

[17] Franzen DL, Carlisle BG, Salholz-Hillel M, Riedel N, Strech D. Institutional dashboards on clinical trial transparency for University Medical Centres: A case study. PLoS Med. 2023 Mar 21;20(3):e1004175.

In addition to aggregated results posting, there is a need for overall improvements in the transparency of clinical trials and their publication

Of course, improving the transparency of clinical trials is not limited neither to reducing publication bias nor simply posting results.

Included in the taxonomy of poor reporting practices, there is also:

1. *Non-publication:* a failure to publish a report on a completed study, despite having it been presented at a conference.
2. *Selective reporting*: biased reporting of data, for example the primary judgment criterion is not reported but a secondary judgment criterion is,
3. *Incomplete reporting:* a lack of key information, for example, the procedure is insufficiently described, so it cannot be replicated,
4. *Misleading presentation:* for example, claiming that the study is a randomised controlled trial when it is not; retrospective change in direction (spin); etc.,
5. *Inconsistencies between sources:* for example, contradictory information between the publication and the protocol.

An important aspect is the need to report randomised trials following precise reporting guidelines. In 2010, EQUATOR (Enhancing the Quality and Transparency of Research) developed the definition of a reporting guideline as being: *"a checklist, flow diagram or structured text to guide authors in reporting a specific type of research, and which has been developed using explicit methodology."* For randomised trials, the ***CONSORT Statement*** is the recommendation to follow**,** with both a main version (*main CONSORT*) and extensions to these recommendations depending on the type of experimental plan or the type of intervention. All of these documents can be found on the EQUATOR network website[18].

Providing access to clinical trial protocols also increases the overall value of these trials. The protocol is the core document for clinical trials and describes the methods used in detail. Sharing this document is an important part of transparency.

Sharing the clinical trial data is considered to be an essential element of research integrity and is increasingly encouraged, or even required, by scientific journals, funders, research bodies and other stakeholders in research. As such, the U.S. Office of Science and Technology Policy (OSTP) announced in 2022 that, by January 2026 at the latest, all publications resulting from research funded by the U.S. federal government should be made immediately and freely accessible to the public[19]. This policy also applies to the underlying data reported in the articles: *"Scientific data underlying peer-reviewed scholarly publications resulting from federally-funded research should be made freely available and publicly accessible by default at the time of publication, unless subject to limitations"*. This is part of a significant effort in the United States, notably by the National Institute of Health (NIH), to share health research data[20]. Sharing clinical trial data is indeed a crucial aspect of research transparency and serves to maximise the usefulness of these trials. Sharing data means that it is possible to reanalyse the trials, to perform further analysis that were not initially planned and to perform meta-analysis from individual data. It refers to the practice of sharing underlying individual data, analysis codes and other parts of

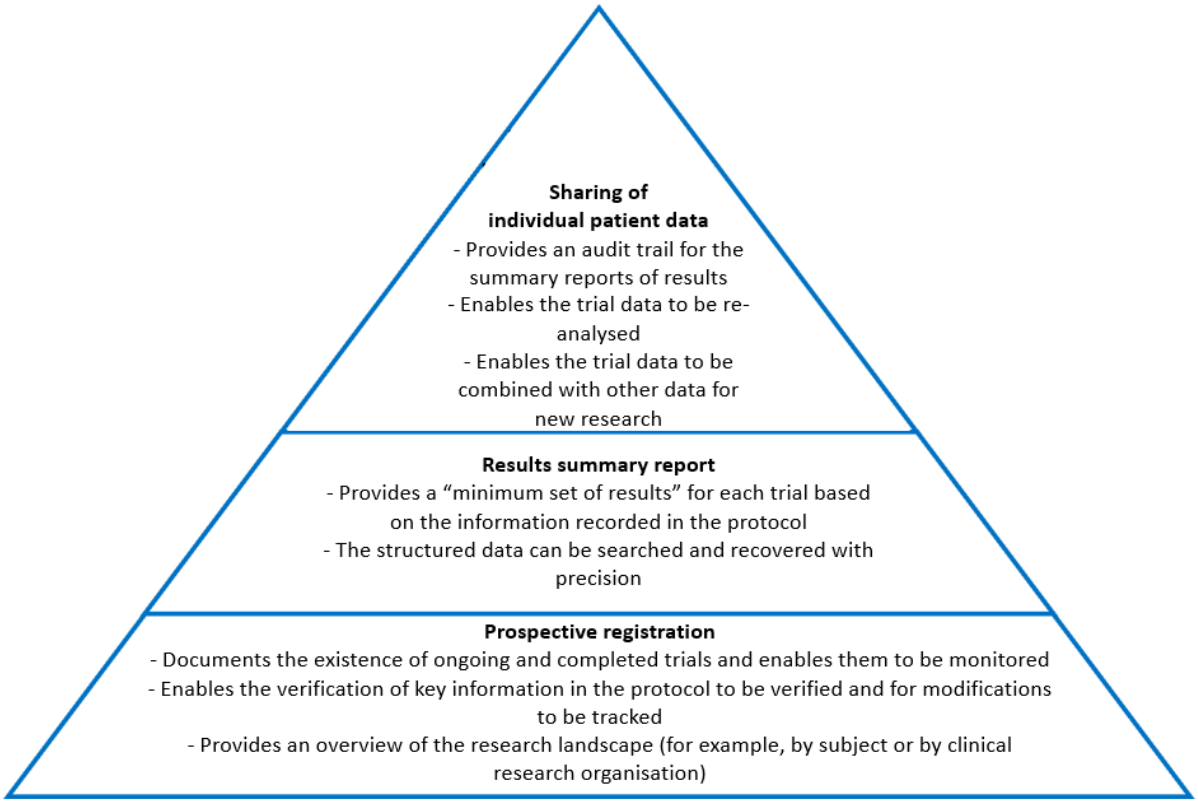
[18] https://www.equator-network.org/

[19] https://www.whitehouse.gov/wp-content/uploads/2022/08/08-2022-OSTP-Public-Access-Memo.pdf

[20] Ross Joseph S., Waldstreicher Joanne, and Krumholz Harlan M. "Data Sharing — A New Era for Research Funded by the U.S. Government". *New England Journal of Medicine* 389, nº 26 (27 December 2023): 2408-10. https://doi.org/10.1056/NEJMp2308792.

the completed study. However, it is important to acknowledge that sharing sensitive individual data is more complex than sharing aggregated data, and may raise regulatory issues related to data protection.

Diagram showing the functions of three key components of the trial reporting system[21].



[21] Zarin, Deborah A., and Tony Tse. "Sharing Individual Participant Data (IPD) within the Context of the Trial Reporting System (TRS)". *PLOS Medicine* 13, nº 1 (19 January 2016): e1001946. https://doi.org/10.1371/journal.pmed.1001946.

Recommendations for clinical trials

These recommendations cover all types of clinical trials (on drugs or not). Their goal is to ensure that the need of reporting clinical trial results is adequately taken into account by the whole chain of stakeholders in clinical research, from government ministries to principal investigators, including regulatory authorities, sponsors, trials registries and stakeholders in scientific integrity. The specific aim is to promote good adherence to the principles of transparency in research in order to guarantee that the recommendations are followed at every stage of the clinical trial process, without assigning sole responsibility to a single stakeholder in the chain.

1. For French Ministries of Research and Health: define a clear action plan to promote systematic posting of results for all clinical trials

1.1 Publish a guide for clinical research stakeholders

- Publish a guide to inform the scientific community about the **need for results transparency for all clinical trials.**
- Inform the scientific community that posting results on a clinical trial registry has no impact on publishing of trials results in high-quality peer-reviewed scientific journals.
- Inform the ethical committees, sponsors and funders of a clinical trial, that **the date of the final visit of the last participant for the primary judgment criterion** should be defined in each protocol and included as an information to be filled in protocol templates.

1.2 Improve transparency for all types of clinical trials by systematically posting results

- Implement the posting of clinical trial results within 12 months after the trials end, as required in the European regulations on clinical trials and clinical investigations.
- Change the assessment criteria of sponsors and take into account results posting in the funding indicators, particularly via SIGREC (the French Information System for the Management of Research and Clinical Trials) when the sponsor is a healthcare institution.

1.3 Widen the obligation to post trials results to cover all kinds of clinical trials

- Starting in 2025, via regulation, make it mandatory to post the results of all clinical trials as defined by WHO, beyond solely drug trials.
- As soon as possible, via legislation, make it mandatory to post the results of all clinical trials as defined by WHO, beyond solely drug trials.

1.4 Ensure a smooth, straightforward transition from the current widespread use of Clinicaltrials.gov to the adoption of the European registry, Clinical Trials Information System (CTIS), as requested by the legislator.

Recommendations to be shared with sponsors:

- For registered clinical trials ending prior to 2025, the results should be posted on registration registry.

- For new clinical trials:
    - Use CTIS for drug trials
    - Use ClinicalTrials.gov for other trials. When the EudaMed registry, dedicated to medical devices, will open, it will have to be used for this kind of trials.

1.5 Assess the feasibility of developing an online assistant for posting results in a format that is identical to ClinicalTrials.gov and compatible with Appendix IV of the European Regulation on Clinical Trials

In order to simplify and standardise the task of posting results on CTIS, assess the feasibility of developing an open source assistant for posting results, based on the format used in ClinicalTrials.gov and compatible with Appendix IV of the European Regulation on Clinical Trials. This generator should at least be available online.

1.6 Continue to develop and implement the French Open Science Monitor for clinical trials: first inform sponsors individually, then make the indicators publicly available

- Conduct regular quantitative monitoring of the rates at which trials results are posted and published, utilizing data from both the European registries (EudraCT and CTIS) and the U.S. registry Clinicaltrials.gov
- Share the indicators and data used to calculate them to each sponsor, to encourage improvements in their posting rates

1.7 Provide methodological support to sponsors to help them improve the quality of their own indicators

- Assign the CNCR the task of providing methodological support to sponsors during a transitional period of 12 to 18 months.
- Send each sponsor a report that includes a list of their trials with unposted results in order to prompt them to identify and correct posting failures.
- Make the indicators for each sponsor public after a transition period of one year following the receipt of this report.
- Allow the investigator to submit requests in the Monitor database.
- Encourage sponsors to implement a local dashboard for their trials that would display the indicators that they deem relevant (based on the template of local open science monitors).

1.8 Advocate for changes in European policies on the transparency of clinical trials

- Advocate for changes in European policies to expand the scope of regulations on results posting in registries to cover all types of clinical trials, beyond existing european regulation.

1.9 Influence the European registry managers

Exert influence, in particular via the national point of contact of ANSM for the "Clinical Trials Coordination and Advisory Group" (CTAG) group, to:

- Ensure that the CTIS becomes a registry that works smoothly and is recognised by the scientific and publishing community.
- Develop a posting template in CTIS.

1.10 Continue the work on improving clinical trial transparency by creating a working group on clinical trials data sharing

On several occasions, the Working Group has discussed the need to put forward proposals of guidelines for data and documentation sharing in clinical trials. Given the complexity of the task, the group suggests initiating a new, dedicated project once this group's recommendations on trials results posting have been published.

2. For clinical trial sponsors: organise, raise awareness, issue warnings and reminders

2.1 Clearly define the role of each stakeholder in posting results and establish a schedule of actions

- Appoint an "open science" correspondent to take responsibility for implementing the open science policy and to act as a point of contact for transparency concerns for the clinical trials sponsored.
- Introduce a dashboard for trial transparency and make this public. This dashboard should include: a list and number of sponsored trials that have been funded, whether they are started and finished, and the finished one indicate when results are posted or published.
- Plan for an annual institutional discussion of the dashboard data (percentage of trials with posted results, time gap between the expected posting data and the actual posting date) and decide of corrective actions if necessary.
- Fully assume responsibility for posting results.
- For all sponsored trials, introduce a clear organisational procedure for posting results in collaboration with the principal investigator and the clinical research support teams.
- Introduce a procedure to manage the posting of results in case the principal investigator leaves the project or is absent for an extended period of time.
- Promote the use of the posting generator when available.
- If investigators repeatedly fail to follow the posting organisation procedure, inform their main employer that should remind them the need to be aligned with European regulation and scientific integrity.
- Implement measures to enable registries and the French Open Science Monitor to effectively record the results of clinical trials, along the lines of the vade-mecum provided in Appendix 2.

2.2 Train the principal investigators: raise awareness, issue warnings and reminders

- **Raise awareness** to the principal investigators about the need, by law, to report the results of completed clinical trials.
- **Issue warnings** to principal investigators once their trial is completed about the need to post the results within one year after the trial ends.
- **Send reminders** to principal investigators who have not transmitted to the sponsor the information needed to post the results of completed trials, before the deadline (one year after the trial ends) is reached.

2.3 Include posting results in the protocol templates and patient information leaflets

- In the protocol templates, introduce a section on the commitment to post results, that defines the date of end of the trial (date of the final visit of the last participant for the primary judgment criterion).
- Include a note in the patient information leaflets stating that the results will be posted in the right registry and will be available to participants in the research.

3. For clinical trial funders: include posting of results upstream and downstream of the financing process

3.1 Train principal investigators and sponsors

- As soon as funding applications for clinical trials have been submitted, systematically inform investigators and sponsors that it is mandatory to post the results in a clinical trials registry within 12 months following the end of the trial (whether the findings are positive or not).
- Remind investigators and sponsors who have selected for funding that posting results (be they positive or negative) in a clinical trial registry has no impact on the possibility of scientific publication of the results of this trial in any peer-reviewed journal.

3.2 Include the posting of clinical trial results in the assessment procedures for projects and their funding: commitment, assessment of compliance in past trials, final funding instalment

- As soon as a project is submitted to obtain funding, ensure that a written commitment is signed, involving to systematically post the clinical trial results within twelve months after the trial ends, independently of any scientific publication (as a preprint or in a peer reviewed journal), which will also be recommended.
- Update the financial regulations by indicating that principal investigators and sponsors should meet the obligation of having posted the results of previous ended trials they have conducted.
- Where sequential funding is involved, make payment of the final funding instalment conditional on posting results within twelve months after the trial ends.

3.3 Assume responsibility, as a funder to promote scientific integrity

- Remind the funders that they are also responsible for following good practice towards scientific integrity and particularly for the need to disseminate research results, including if these are negative (cf. European Code of Conduct for Research Integrity, 2.7, p.9).
- When a scientific integrity clause exists in the funding statement, issue a reminder that a condition for the funding may include the dissemination of results (posting and/or scientific publication).

3.4 Introduce a dashboard

Every year, all funders should publish indicators on the posting and scientific publishing of results for the trials they fund, which could provide information on whether the corrective measures implemented are followed by improved posting results statistics.

4. For European authorities : improve CTIS

For the European Commission, the Clinical Trials Information System (CTIS), the EMA (European Medicines Agency) and the "Clinical Trials Coordination and Advisory Group" (CTAG) group.

4.1 Ensure that all types of clinical trials have a registry for posting their results

- Take into account the systemic role of clinical trials registry for the entire scientific community and for public health, beyond the simple requirement to regulate drugs.
- Ensure that all types of clinical trial have a registry enabling their results to be posted on a register recognised by WHO.

4.2 Improve the interface for posting clinical trial results in the European registry, CTIS

- Introduce a template so that results can be posted in a structured way in the European registry.
- Ensure that editors validate the quality of the results submitted for posting.

4.3 Ensure that the CTIS becomes a registry that functions smoothly, as a working tool recognised by the scientific and publishing community

- Organise regular and structurally open wide-ranging consultations with users (sponsors, researchers, supervisors, evidence synthesis experts, specialists in research on research, specialists in clinical trial transparency, etc.) to build and develop a template for clinical trial posting.
- Ensure compliance with the principles of open data: 1) make it easy to browse and carry out searches in the web interface, 2) create a powerful, documented and unlimited API, 3) allow data downloads (bulk download).
- Cooperate with the Clinical Trials Transformation Initiative (CTTI) to improve the potential for using the European registry - https://ctti-clinicaltrials.org/

5. For clinical trial regulators: include posting results, both upstream and downstream of the process

5.1 Include the posting of results in the template forms for sponsors/investigators

For CPPs (French Committees for the Protection of Persons)

- Include the concept of posting results in the participants information forms and in the template form for sponsors available on the CNRIPH page.
- Include the general recommendation to post results in the ethical opinions issued by the CPPs (recommendation by the CNRIPH)

5.2 Reminder of the issues involved in posting results for all clinical trials

For ANSM (Agence Nationale de Sécurité du Médicament et des Produits de ***Santé, French National Agency for the Safety of Medicines and Health Products)***

- Remind sponsors of their obligation to post results
  - During inspections of clinical trial sponsors
  - At meetings of the "clinical trials" sub-group of the ANSM Interface Committee
  - During ANSM communications on clinical trials
- Take into account the most recently published Open Science Monitor indicators as part of ANSM's monitoring activities.

6. For universities: train stakeholders and interact with their staff

6.1 Include the posting of results in training programmes and courses on clinical research, for both initial training programmes and ongoing training for working professionals

Ensure that all clinical research training programmes include a section rules on posting results as part of their teaching content.

6.2 Provide assistance when a sponsor is experiencing difficulties in obtaining the data required from an investigator

When the sponsor is having difficulties in obtaining the data required for results posting from an investigator, the main employer, for example the university in the case of Professors of Universities-Hospital Practitioners - PU-PH), can be called upon to remind the investigators their obligations in terms of scientific integrity.

7. For bodies assessing institutions, research structures and researchers: include the posting of results in their assessment criteria

7.1 Assessment of clinical trial sponsor organisations: assess their policies regarding the posting of results

In the context of assessments by HCERES of sponsor of clinical trials' organisations: examine the strategies, organisations, procedures and results of the clinical trial sponsor organisations in terms of posting ended trial results, specifically based on the indicators produced by the French Open Science Monitor.

7.2 Assessment of research structures: examine their strategies regarding the posting of clinical trial results

In the context of assessments by HCERES and INSERM, of research centres/units and clinical investigation centres (CIC) involved in clinical trials: examine their strategies, organisation, procedures and results regarding the posting of ended trial results, in particular based on indicators produced by the French Open Science Monitor.

7.3 Assessment of researchers: plan a dedicated section on posting of clinical trial results

As part of assessing sponsorships and activities by the Conseil National des Universités (French National Council of Universities, CNU) and INSERM's Specialised Scientific Committees (CSS), request elements relating to the posting of trial results in the section on clinical trials conducted as principal investigator.

8. In the research integrity policies of the organisations and the French Office of Scientific Integrity (Ofis): include the posting of trial results as a criterion of integrity

8.1 Explicitly include the objective of posting clinical trial results in the scientific integrity policies of clinical trial sponsoring organisations

Explicitly include the objective of communicating trial results into the scientific integrity policies of clinical trial sponsoring organisations, whether they are health or research institutions.

8.2 Educate researchers, sponsors and scientific integrity officers about scientific integrity issues related to the posting of trial results

- Make researchers and sponsors aware that deliberately withholding the publication or dissemination of results, including negative ones, is a violation of scientific integrity.
- Make scientific integrity officers aware about appropriate methods for addressing reports of potential breaches, particularly regarding non-compliance with the obligation to post trial results.

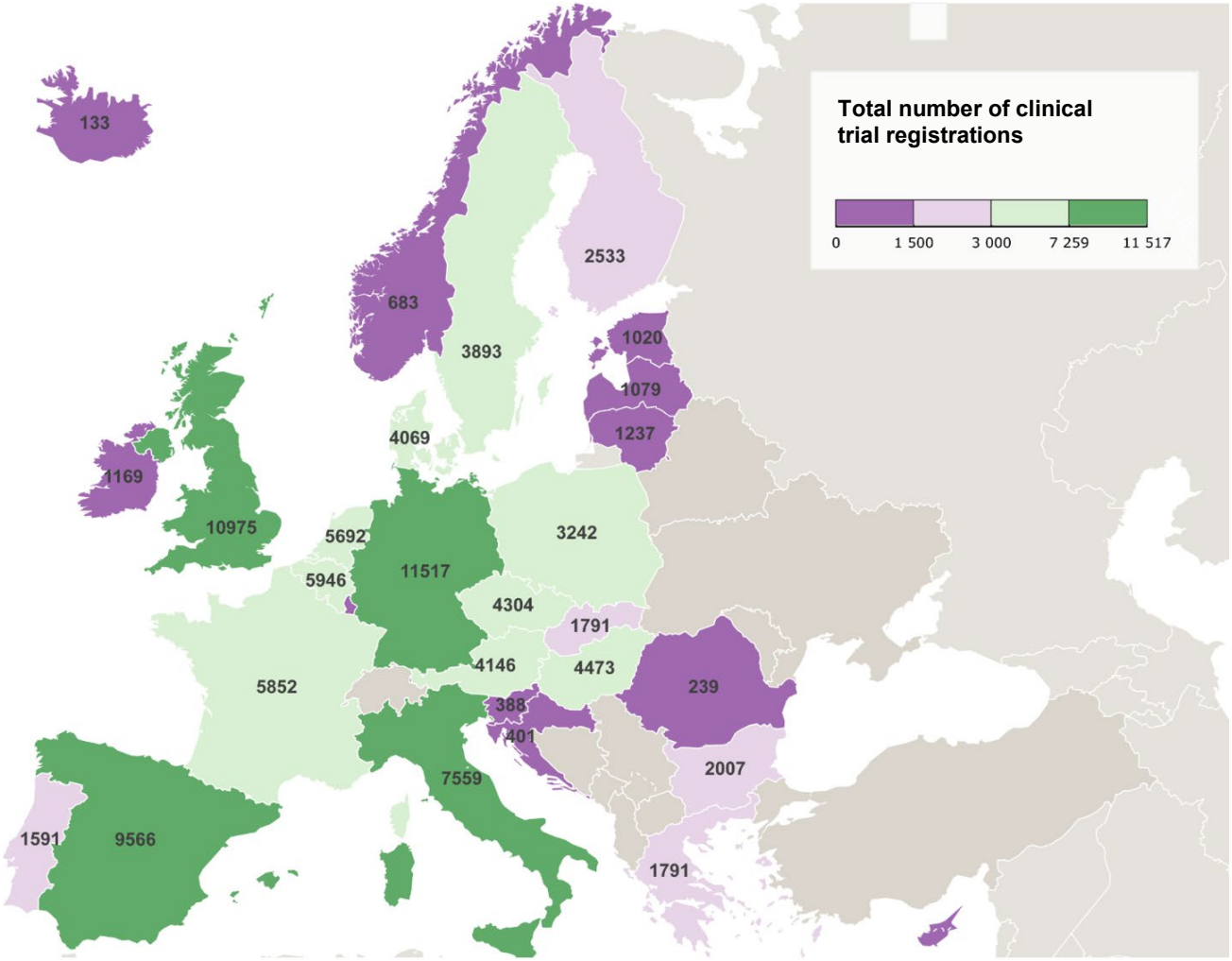
Appendices

Appendix 1. Main indicators on clinical trials results reporting (in may 2024)

Appendix 1.1. European indicators from TranspariMED (drug trials on EUDRACT)

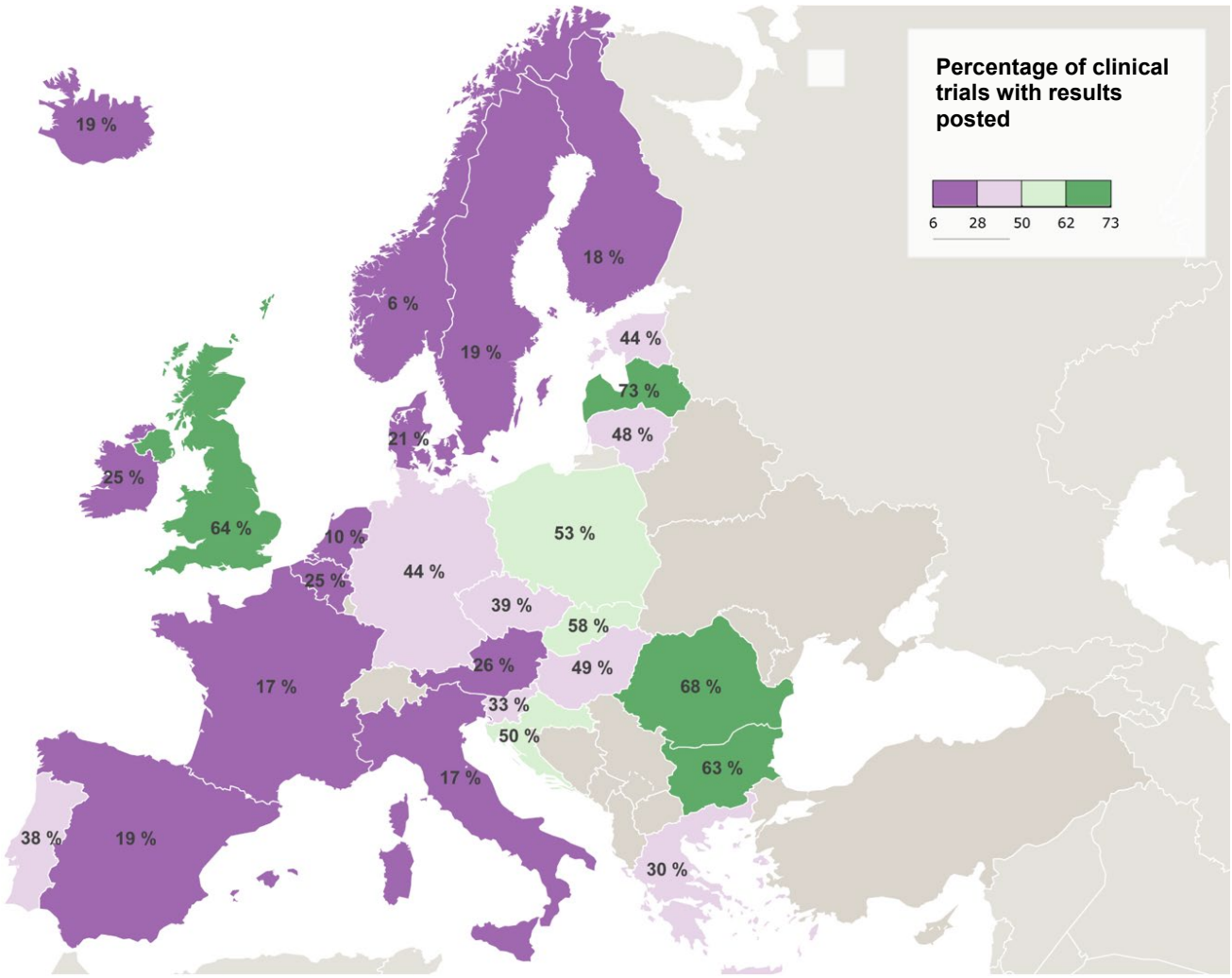
Source: Missing clinical trial data in Europe. Assessing and comparing the performance of national drugs agencies Paris (France), Amsterdam (NL), and Bristol (UK), 5 July 2021. https://transparency-france.org/wp-content/uploads/2021/07/TranspariMED-NCA-report_final_20210705.pdf

Number of clinical trials per country



Data: TranspariMED. Map credits: Open Science Committee Licence CC BY.

Percentage of clinical trials with results posted, by country [22]



Data: TranspariMED. Map credits: Open Science Committee Licence CC BY.

[22]Source of the data: Missing clinical trial data in Europe. Assessing and comparing the performance of national medicines agencies Paris (France), Amsterdam (NL), and Bristol (UK), 5 July 2021.https://transparency-france.org/wp-content/uploads/2021/07/TranspariMED-NCA-report_final_20210705.pdf

Table of indicators on clinical trials in Europe by country (Source: TranspariMed)

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

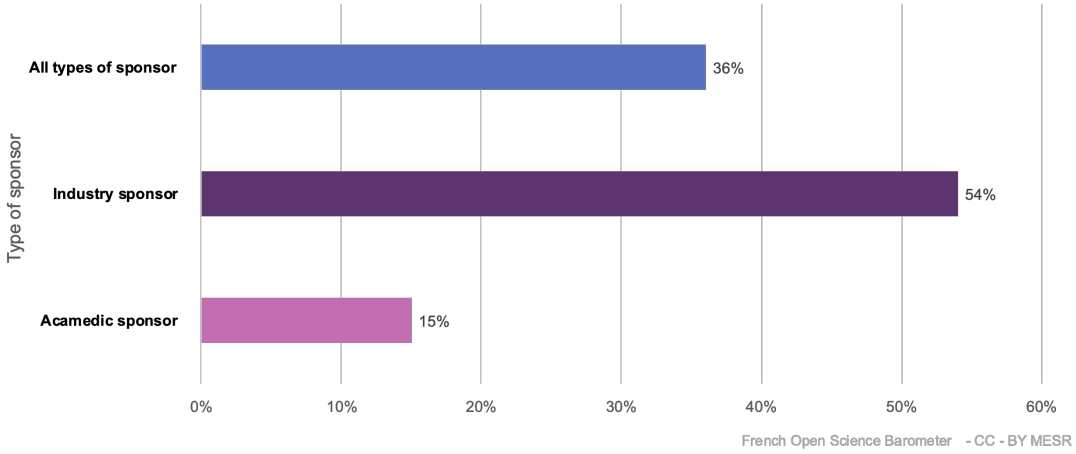
Table legend:

- Total CTAs (#) : Total number of registered clinical trials (CTA = Clinical Trial Applications)
- Registration (%) : Percentage of clinical trials registered in publicly available registries
- Results rep. (%) : Percentage of clinical trials with posted results
- Results missing (#) : Total number of clinical trials with unknown results

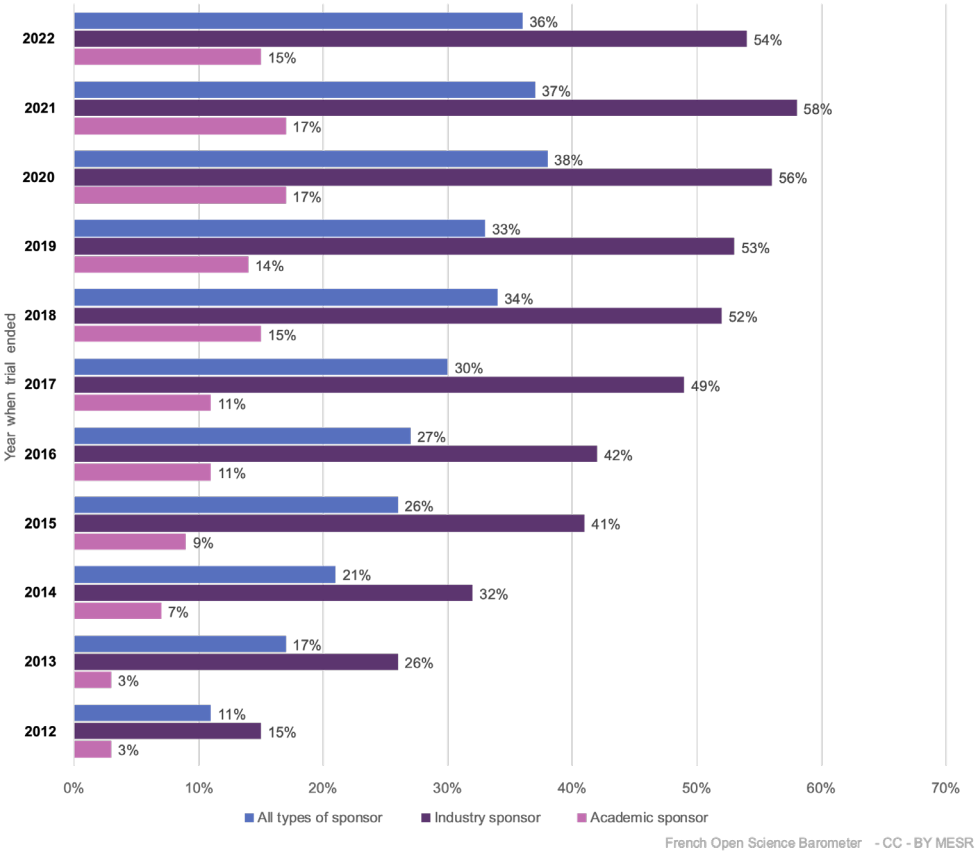
Appendix 1.2. National indicators from the French Open Science Monitor

Indicators 12 months after the end of a clinical trial

Percentage of registered clinical trials that ended in 2022 where the result has been posted and/or a scientific publication has been declared within one year of clinical trial ending

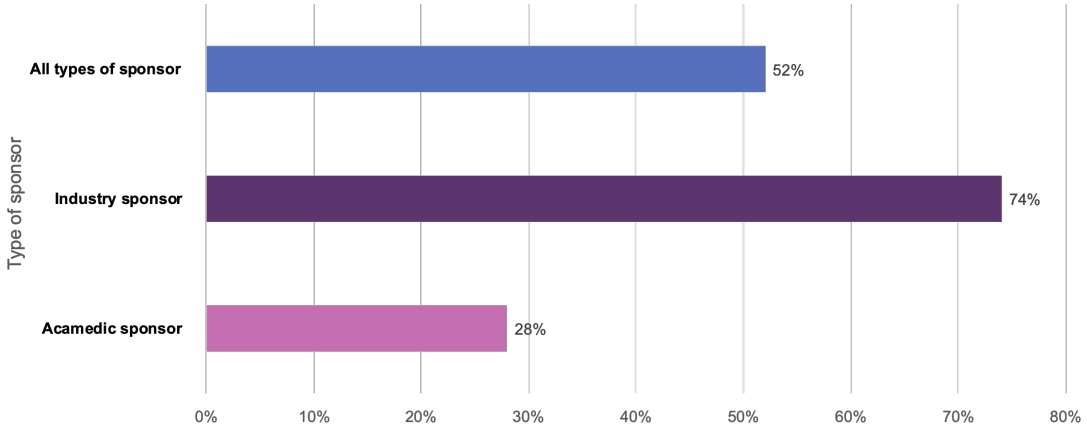


Percentage of registered and completed clinical trials where a result has been posted and/or a scientific publication has been declared within one year of clinical trial ending, by year of trials ends (2012-2022)

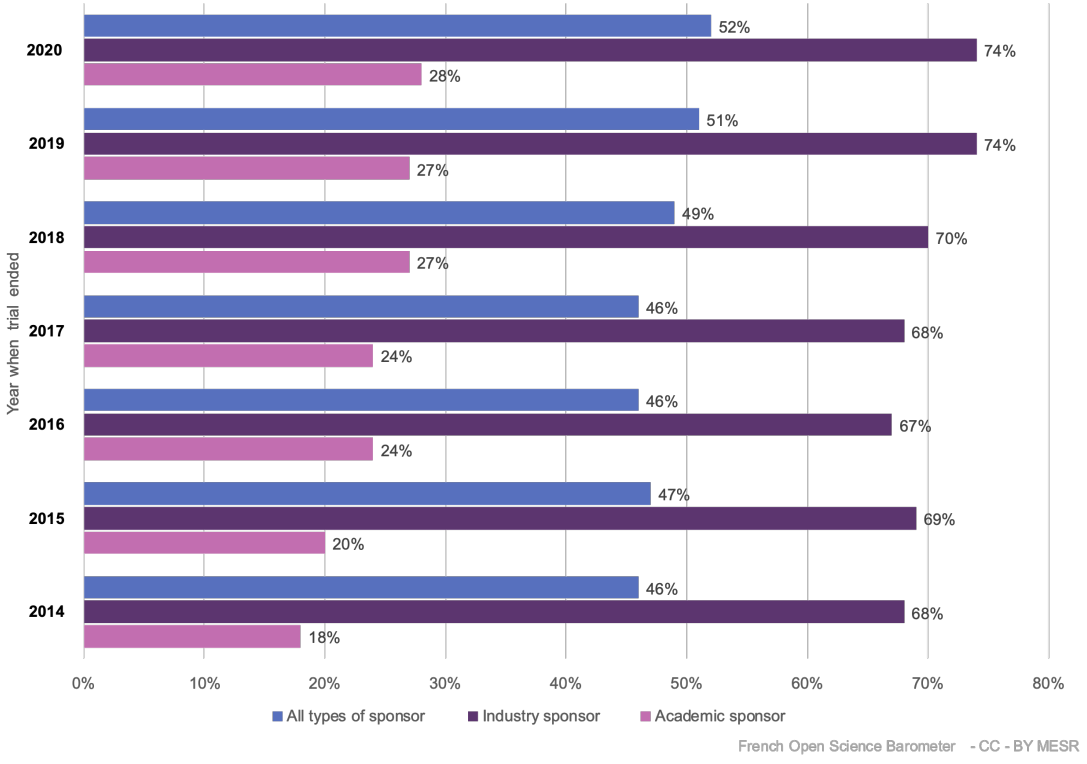


Indicators 36 months after the end of trials

Percentage of registered clinical trials that ended in 2022, where a result has been posted and/or a scientific publication has been declared within 3 years of clinical trial ending



Percentage of registered and completed clinical trials where a result has been posted and/or a scientific publication has been declared within three years of clinical trial ending, by year of trials ends



Appendix 2. *Vade-mecum* to report the results of completed clinical trials

Communication of clinical trial results is a key issue for scientific integrity, public health, and the proper use of research budgets. The results can be published in a peer-reviewed scientific journal, released as a pre-print, or posted in a clinical trial registry. The French Open Science Monitor (BSO) automatically tracks the results that are published or posted. This vademecum provides a series of recommendations for sponsors to improve the quality of the recording of clinical trial results.

A/ Anticipate automatic recording

To ensure that the results are easily found, they must appear in clinical trial registries, for example, through the following actions:

Step 1: Systematically posting results

For all completed studies, the results should be posted in the trial registry within one year of the end of the trial.

Step 2: Including the registration number in the abstract

In all publications of studies that have been registered in a registry, include the registration number (e.g. NCT) in the abstract so that it can be automatically detected, and in order to enable to link the publication to the trials' registry.

B/ Manual recording if necessary

When a publication has not been automatically detected by the registry, the sponsor must update it manually, for example, through the following actions:

Step 1: Using unique identifiers in your database

Identifying each study by using its identification number (e.g. NCT) in your institution internal databases.

Step 2: Identifying any publication of the results

Identifying any publications of the results by differentiating between the main publication (analysis of the primary evaluation criteria for the whole study population) and any secondary publications[1] (other publications, sometimes before or after the study):

- In your internal database
- In SIGAPS
- In Google Scholar by using the study identifier (e.g. NCT)
- By searching on PubMed
- By contacting the principal investigator or the project leader

Step 3: Updating the registry

Once a publication has been found, reporting it in the registry, indicating if possible the difference between the main publication and any secondary publication.

Note

Where no main publication is found, it is even more important to post the results in the registry. Posting is mandatory even if the results have been published. Under no circumstances does posting prevent publication (Cf. ICJME recommendations[2]).

Further reading

This procedure takes its inspiration from the following study:
https://www.researchsquare.com/article/rs-3782467/v1
You may consult it for further details on the approach.

[1] Pre-print publications are taken into account. However, scientific outputs such as protocols, methodologies, as well as communications and abstracts presented at scientific conferences, are not considered publications.
[2] https://www.icmje.org/recommendations/

Appendix 3. WHO framework for clinical trial registries

FIFTY-EIGHTH WORLD HEALTH ASSEMBLY (18 April 2005)[23]

The Fifty-eighth World Health Assembly, Having considered the Mexico Statement on Health Research resulting from the Ministerial Summit on Health Research (Mexico City, 16-20 November 2004);

CALLS UPON the global scientific community, international partners, the private sector, civil society, and other relevant stakeholders to establish a voluntary platform to link clinical trials registers in order to ensure a single point of access and the unambiguous identification of trials with a view to enhancing access to information by patients, families, patient groups and others;

[23] https://apps.who.int/gb/ebwha/pdf_files/WHA58-REC1/english/A58_2005_REC1-en.pdf

Appendix 4. Ottawa Statement

Principles for international registration of protocol information and results from human trials of health-related interventions : Ottawa statement

Reference : Krleza-Jerić K, Chan AW, Dickersin K, Sim I, Grimshaw J, Gluud C. Principles for international registration of protocol information and results from human trials of health related interventions: Ottawa statement (part 1). BMJ. 2005 Apr 23;330(7497):956-8.

A. Objective

The Ottawa Statement aims to establish internationally recognised principles for trial registration (Part 1) as well as their proposed operationalisation (Part 2).

B. Definitions

'Trial' refers to a prospective controlled or uncontrolled research study evaluating the effects of one or more health-related interventions assigned to human participants. For example, a trial may investigate interventions related to one or more of the following: prevention, health promotion, screening, diagnosis, treatment, rehabilitation, or organisation and financing of care. 'Intervention' refers to a deliberate act applied to an individual or group of individuals. Health-related interventions include but are not limited to the use of pharmaceuticals, biological products, surgery, procedures, radiation, devices, education, counselling, behaviour change, complementary health modalities, and management or economic policies.

Registration' of a trial involves the assignment of a unique identification number; the recording and public release of protocol information; as well as the recording and public release of trial results. 'Protocol' refers to a document written before participant enrolment to describe the objectives, methodology, statistical analyses, organisation, and administrative details of a trial. 'International' refers to the applicability of the principles presented in this document to trials conducted in any country or countries worldwide. 'Sponsor' is defined as an individual, company, institution, or organisation that takes responsibility for the initiation, management, and/or financing of a trial. The sponsor does not actually conduct the investigation unless the sponsor is an investigator-sponsor. 'Principal investigator' is defined as the person responsible for the overall conduct of the trial

C. Rationale for international trial registration

C.1. Ethical rationale

C.1.1. Above all, international trial registration is necessary to fulfill ethical obligations to research participants. When members of the public agree to participate in trials, it is on the understanding that they are contributing to the global body of health-related knowledge. It is thus unethical to conduct human research without ensuring that valid descriptions of the study and its findings are publicly available.

C.1.2. Potential trial participants, care providers, researchers, institutional review boards/independent ethics committees (IRBs/IECs), and sponsors should have access to valid information about trials that have been previously performed.

C.1.3. Potential trial participants, care providers, researchers, IRBs/IECs, and sponsors should have access to valid information about trials that are currently open for enrolment. C.1.4. The availability of unbiased information about all initiated trials contributes to global open access to knowledge, which constitutes a public good.

C.2. Scientific rationale Public access to trial protocol information (as approved by the IRB/IEC) and results will help to:

C.2.1. Minimise known risks and potential harm arising from unnecessary exposure to previously tested interventions;

C.2.2. Accelerate research by making knowledge available about prior experiences with interventions;

C.2.3. Identify and deter unnecessary duplication of research and publications;

C.2.4. Identify and deter selective reporting of research (reporting biases);

C.2.5. Provide a means of comparing the original protocol upon which ethics approval was based with the study as it was carried out;

C.2.6. Enhance collaboration among researchers by informing them of ongoing trials.

D. Principles regarding the scope and nature of international trial registration

D.1. Types of trials to be registered Protocol information (D.4) and results (D.5) from all trials related to health or healthcare – regardless of topic, design, outcomes, or market status of interventions examined – should be registered and publicly available.

D.2. Elements of registration Registration of each trial comprises three distinct parts: obtaining an internationally unique identification number (D.3), registering the original protocol approved by the IRB/IEC along with subsequent amendments (D.4), and registering the trial results (D.5). A general time-line for registration is shown in the Figure.

D.3. Principles relating to unique identification number (Unique ID)

D.3.1. Assignment of Unique ID Every trial should have a Unique ID assigned by a single international source prior to participant enrolment. The Unique ID should be verifiable and have builtin error-detecting logic.

D.3.2. Application of Unique ID The Unique ID should appear on all trial documentation, including the consent form given to participants as well as subsequent presentations and publications.

D.4. Principles relating to protocol registration

D.4.1. Definition of protocol information to be registered Protocol information in the register should consist of (1) a minimum set of standardised, structured, key items from the protocol approved by the IRB/IEC ("minimum protocol items"); (2) the consent forms approved by the IRB/IEC; and (3) any subsequent protocol amendments. Protocol information from each of these components should be irreversibly recorded and dated at the time of submission to the register (D.4.2). The minimum protocol items registered should be sufficient to enable critical appraisal of trial methodology and statistical analyses. Furthermore, the full protocol as approved by the IRB/IEC, and the data collection forms, should be available in the public domain to enable the interpretation of trial findings.

D.4.2. Timing of protocol registration Registration of the minimum protocol items and the consent forms should occur prior to enrolment of trial participants. Amendments to the registered protocol information should be dated and registered as they occur.

D.4.3. Timing of public access to registered protocol information The public should have cost-free access to the Unique ID, minimum protocol items, and consent forms prior to participant enrolment. Registered amendments should be made publicly available as they occur. The full protocol as approved by the IRB/IEC, and the data collection forms, should be made publicly available as soon as possible and no later than the date of completion of data analysis.

D.5. Principles relating to registration of trial results

D.5.1. Definition of trial results to be registered At a minimum, results for outcomes and analyses specified in the protocol (as approved by the IRB/IEC), as well as data on harms, should be registered regardless of whether or not they are published. If a trial is terminated prematurely, any available results should be registered along with the reason for termination. The summary results recorded for each outcome should be sufficient for valid interpretation, and should not enable identification of any individual trial participant to the public.

Full citations to trial publications should be registered as they become available. However, listing of study publications alone does not constitute adequate registration of results.

D.5.2. Timing of registration of trial results Trial results should be registered once the analyses are completed and verified.

D.5.3. Timing of public access to registered results Investigators should have sufficient time to publish their findings in a peerreviewed electronic or print forum before the registered results are released for public, free-of-charge access. Timely public access to results should ultimately be assured regardless of their publication status.

D.6. Organisation and language of registries

The source assigning the Unique ID can exist separately from the register or registers that contain protocol information and trial results. However, all three components (Unique ID, protocol information, trial results) must be cross-referenced. To facilitate efficient searching, multiple national or regional registers should be linked. Furthermore, registered information must be presented at least in English and also preferably in the major language(s) of the region where the main study site is located. E. Responsibilities of involved parties E.1. Sponsors The sponsor(s) of the trial has ultimate responsibility for obtaining the Unique ID (D.3) as well as for registering the protocol information (D.4) and results (D.5). The sponsor should also ensure that the full protocol as approved by the IRB/IEC, and the data collection forms, are made publicly available. When there are multiple sponsors, each sponsor is individually responsible for ensuring that these tasks are fulfilled.

E.2. Investigators

The principal investigator has a responsibility to ensure that the sponsor(s) obtains a Unique ID and registers his or her contact information, the protocol information (D.4), and the trial results (D.5). Investigators also have the responsibility to perform analyses in a timely fashion and to submit the findings for publication in a peer-reviewed electronic or print forum.

E.3. Institutional review boards/independent ethics committees

IRBs/IECs have a responsibility to ensure that approved trials have a Unique ID; that minimum protocol items and consent forms, as approved by the board, are registered prior to participant enrolment; and that subsequent protocol amendments are reported and registered. They are also responsible for ensuring that the Unique ID appears on the consent form. Furthermore, they are responsible for encouraging the publication of trial results in a peer-reviewed electronic or print forum. When a trial receives approval from multiple IRBs/IECs, each board is responsible for ensuring that these tasks are fulfilled.

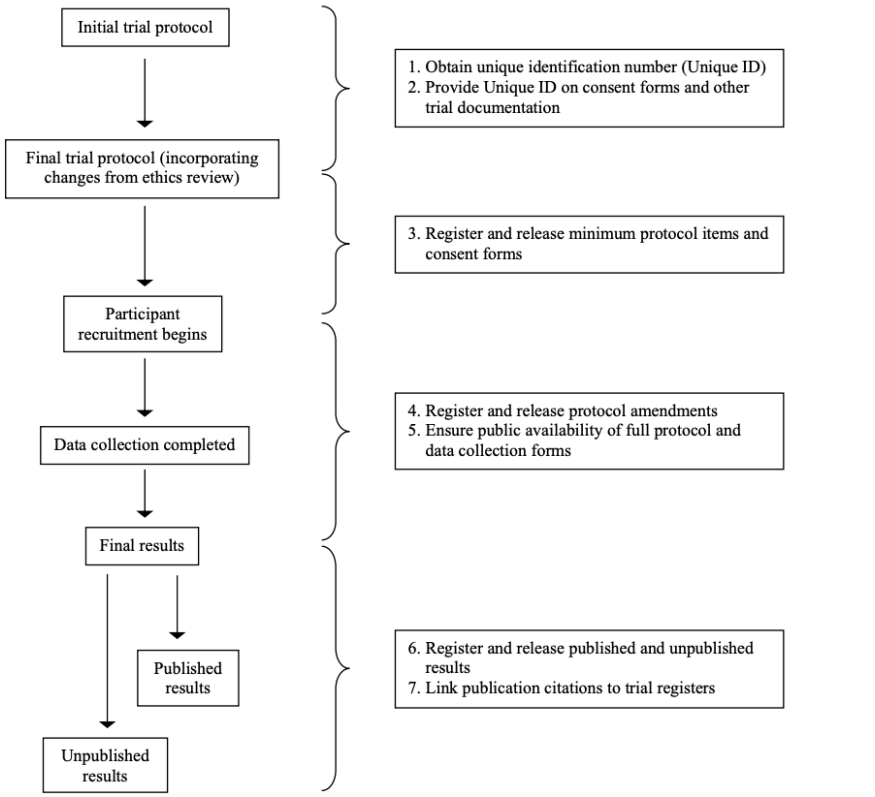
E.4. Journal editors

Journal editors have a responsibility to promote trial registration by requiring that any trial being considered for publication has a Unique ID, and to include the Unique ID in any resulting publication.

E.5. Policing and sanctions

Trial registration should be a legal requirement, with enforcement of meaningful sanctions against those found to be in violation.

General time-line for process of trial registration



Appendix 5. Helsinki Declaration (64th General Assembly of the World Medical Association, Fortaleza, Brazil, October 2013)

There are two items in the Helsinki Declaration that cover research registration, and the publication and dissemination of results.

Reference:
https://www.wma.net/fr/policies-post/declaration-dhelsinki-de-lamm-principes-ethiques-applicables-a-la-recherche-medicale-impliquant-des-etres-humains/

35. Every research study involving human subjects must be registered in a publicly accessible database before the first subject taking part in the research is recruited..

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make the results of their research on human subjects publicly available. All parties are responsible for the providing complete, accurate reports. They should adhere to the accepted guidelines for ethical reporting. Negative and inconclusive results, as well as positive results, must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared within the publication. Research reports which do not comply with the principles of this Declaration should not be accepted for publication.

Appendix 6. Recommendations of the ICMJE (International Committee of Medical Journal Editors)

Reference: https://www.icmje.org/icmje-recommendations.pdf

The ICMJE's clinical trial registration policy is detailed in a series of editorials (see News and Editorials and FAQs).

Briefly, the ICMJE requires, and recommends that all medical journal editors require, registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication. Editors requesting inclusion of their journal on the ICMJE website list of publications that follow ICMJE guidance should recognize that the listing implies enforcement by the journal of ICMJE's trial registration policy.

ICMJE uses the date trial registration materials were first submitted to a registry as the date of registration. When there is a substantial delay between the submission of registration materials and their posting at the trial registry, editors may inquire about the circumstances that led to the delay.

The ICMJE defines a clinical trial as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention and a health outcome. Health-related interventions are those used to modify a biomedical or health-related outcome; examples include drugs, surgical procedures, devices, behavioural treatments, educational programs, dietary interventions, quality improvement interventions, and process-of-care changes. Health outcomes are any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE does not define the timing of first participant enrollment, but best practice dictates registration by the time of first participant consent.

The ICMJE accepts publicly accessible registration in any registry that is a primary register of the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/clinical-trials-registry-platform/network/whodata-set) that includes the minimum acceptable 24-item trial registration data set or in ClinicalTrials.gov, which is a data provider to the WHO ICTRP. The ICMJE endorses these registries because they meet several criteria. They are accessible to the public at no charge, open to all prospective registrants, managed by a not-for-profit organization, have a mechanism to ensure the validity of the registration data, and are electronically searchable. An acceptable registry must include the minimum 24-item trial registration data set (http://prsinfo.clinicaltrials.gov/trainTrainer/WHO-ICMJE-ClinTrialsgov-Cross-Ref.pdf or www.who.int/clinical-trials-registry-platform) at the time of registration and before enrollment of the first participant.

The ICMJE considers inadequate trial registrations missing any of the 24 data fields, those that have fields that contain uninformative information, or registrations that are not made publicly accessible such as phase I trials submitted to the CTIS (Clinical Trials Information System) and trials of devices for which the information is placed in a "lock

box." In order to comply with ICMJE policy, investigators registering trials of devices at ClinicalTrials.gov must "opt out" of the lock box by electing public posting prior to device approval. Approval to conduct a study from an independent local, regional, or national review body (e.g., ethics committee, institutional review board) does not fulfill the ICMJE requirement for prospective clinical trial registration. Although not a required item, the ICMJE encourages authors to include a statement that indicates that the results have not yet been published in a peer-reviewed journal, and to update the registration with the full journal citation when the results are published.

The purpose of clinical trial registration is to prevent selective publication and selective reporting of research outcomes, to prevent unnecessary duplication of research effort, to help patients and the public know what trials are planned or ongoing into which they might want to enroll, and to help give ethics review boards considering approval of new studies a view of similar work and data relevant to the research they are considering. Retrospective registration, for example at the time of manuscript submission, meets none of these purposes. Those purposes apply also to research with alternative designs, for example observational studies. For that reason, the ICMJE encourages registration of research with non-trial designs, but because the exposure or intervention in non-trial research is not dictated by the researchers, the ICMJE does not require it.

Secondary data analyses of primary (parent) clinical trials should not be registered as separate clinical trials, but instead should reference the trial registration number of the primary trial.

The ICMJE expects authors to ensure that they have met the requirements of their funding and regulatory agencies regarding aggregate clinical trial results reporting in clinical trial registries. It is the authors', and not the journal editors', responsibility to explain any discrepancies between results reported in registries and journal publications. The ICMJE will not consider as prior publication the publications. The ICMJE will not consider as prior publication the posting of trial results in any registry that meets the above criteria if results are limited to a brief structured abstract or tables (to include trial participants enrolled, baseline characteristics, primary and secondary outcomes, and adverse events).

The ICMJE recommends that journals publish the trial registration number at the end of the abstract. The ICMJE also recommends that, whenever a registration number is available, authors list this number the first time they use a trial acronym to refer either to the trial they are reporting or to other trials that they mention in the manuscript.

Editors may consider whether the circumstances involved in a failure to appropriately register a clinical trial were likely to have been intended to or resulted in biased reporting. Because of the importance of prospective trial registration, if an exception to this policy is made, trials must be registered and the authors should indicate in the publication when registration was completed and why it was delayed. Editors should publish a statement indicating why an exception was allowed. The ICMJE emphasizes that such exceptions should be rare, and that authors failing to prospectively register a trial risk its inadmissibility to our journals.

Appendix 7. WHO Joint statement on public disclosure of results from clinical trials

Reference:

https://www.who.int/news/item/18-05-2017-joint-statement-on-registration

Joint statement

The current 2013 Declaration of Helsinki states that "Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject." and that "Researchers have a duty to make publicly available the results of their research .... Negative and inconclusive as well as positive results must be published or otherwise made publicly available." In addition to the ethical imperative, poor allocation of resources for product development and financing of available interventions, and suboptimal regulatory and public health recommendations may occur where decisions are based on only a subset of all completed clinical trials.

The signatories of this joint statement affirm that the prospective registration and timely public disclosure of results from all clinical trials is of critical scientific and ethical importance. Furthermore, timely results disclosure reduces waste in research, increases value and efficiency in use of funds and reduces reporting bias, which should lead to better decision-making in health.

Within 12 months of becoming a signatory of this statement, we each pledge to develop and implement a policy with mandated timeframes for prospective registration and public disclosure of the results of clinical trials that we fund, co-fund, sponsor, or support. We each agree to monitor registration and endorse the development of systems to monitor results reporting on an ongoing basis. We agree to share challenges and progress in the monitoring of these policies. We agree that transparency is important and therefore the outputs from the monitoring process will be publicly available.

Benefits and costs of requiring public disclosure of results

The benefits of implementing and monitoring policies on public disclosure of results relate to access to more complete information about the results of clinical trials. The benefits are summarised below.

- The current bias in the reporting of results will be reduced allowing for more informed decisions in the following areas:
    - Licensure/marketing authorization (including risk-benefit assessments),
    - Public health policy recommendation on use (including cost-effectiveness), and
    - Financing decisions by public procurement bodies, and multilateral agencies
    - Optimal implementation and delivery
    - Individual treatment choices by doctors and patients

- Research funding allocation will be more efficient (avoiding the current situation, whereby funds may be allocated to answer scientific questions that have already been answered in unreported clinical trials, and waste occurs because learning from previous trials cannot be taken into account in design of current trials)
- The development of interventions will be more efficient
- Ethical requirements for dissemination of information will be met, potentially increasing trust of trial participants in the utility of clinical research
- The scientific state-of-the-art will be based on a more complete cross-section of clinical trial data; in particular the many negative clinical trials will be more available for assessments.

A further benefit is that doctors, professional bodies and the general public will be able to access the results from a larger proportion of clinical trials.

Finally, patients seeking enrolment in clinical trials will be able to access results from previously completed clinical trials in their area, as they make decisions on which clinical trials, they may wish to seek enrolment into.

There will be modest costs associated with public disclosure of clinical trial results. The costs of disseminating the results of research are a minor component of the overall costs of conducting such research, and results reporting is an essential component of the research enterprise. The resource allocation, public health, and scientific benefits - together with the need to meet ethical imperatives - far outweigh the costs.

Proposed common elements of agencies' policies on results reporting

Principles that could be included in harmonized policies on results reporting include the following:

Registration of clinical trials

Before any clinical trial is initiated (at any Phase) its details must be registered in a publicly available, free to access, searchable clinical trial registry complying with WHO's international agreed standards (www.who.int/ictrp). The clinical trial registry entry must be made before the first subject receives the first medical intervention in the trial (or as soon as possible afterwards). Clinical trial registry records should be updated as necessary to include final enrolment numbers achieved, and the date of primary study completion (defined as the last data collection timepoint for the last subject for the primary outcome measure). If clinical trials are terminated, their status should be updated to note the date of termination, and to report the numbers enrolled up to the date of termination.

Completeness and accuracy of the clinical trial registry records can be a limiting factor for use of information from the registries, and it is encouraged that care is taken to ensure good quality registry entries.

Reporting timeframes for clinical trials

We jointly agree that summary results of clinical trials should be made publicly available in a timely manner following primary study completion. There are two main modalities for this to occur. By posting to the results section of the clinical trial registry and by journal publication. We will work towards a timeframe of 12 months from primary study completion (the last visit of the last subject for collection of data on the primary outcome) as the global norm for summary results disclosure. As timelines for publication in a journal are not fully within the control of the sponsor or investigator, this joint statement focuses on use of registries – such as clinicaltrials.gov and EU-CTR - to meet

this results disclosure expectation. Publication in a journal is also an expectation, with an indicative timeframe of 24 months from study completion to allow for peer review etc. Access to a sufficiently detailed clinical trial protocol is necessary in order to be able to interpret summary results. Therefore, we also encourage development of requirements that the protocols are made publicly available no later than the time of the summary results disclosure as part of the clinical trial registry summary results information (including amendments approved by ethics committees/institutional review boards, and either as uploaded electronic document formats such as pdfs or links to the pdf).

At the time of the initial grant submission, the plan for public disclosure of results should be included, including specific time bound commitments. Reasonable funds to enable compliance with these considerations is a cost eligible item in clinical trial budgets.

Trial ID in clinical trial publication

The Trial ID or registry identifier code/number should be included in all publications of clinical trials, and should be provided as part of the abstract to PubMed and other bibliographic search databases for easy linking of trial related publications with clinical trial registry site records. This is essential for linking journal publications with registry records.

Registration and reporting of past trials

Reporting of previous trials realises the value of funding; therefore, the contribution made from reporting previous trials, whatever their results, will be considered in the assessment of a funding proposal. When a PI applies for new funding, they may be asked to provide a list of all previous trials on which they were PI within a specified timeframe and their reporting status, with an explanation where trials have remained unreported.

A note on sharing of individual participants' data

As trials are registered, this sets a basis for development of IPD sharing. The benefit of sharing individual participants' data (IPD) and the facilitation of research through greater access to primary datasets is a principle which we consider important. This statement is not directed towards sharing of IPD. However, we are all actively engaged with initiatives related to IPD sharing, and support sharing of health research datasets whenever appropriate. We will continue to engage with partners in support of an enabling environment to allow data sharing to maximise the value of health research data. We will support activities that enable the development of explicit ethical and legal frameworks that govern data collection and use and enable development of international norms and standards for sharing of IPD from clinical trials.

A note on open access policies

We are all supporters of open access policies, and consider that publications describing clinical trial results should be open access from the date of publication, wherever possible. Open access fees should be included in clinical trial budget requests, if necessary.

A note on the scope of this statement

While this statement focuses on clinical trials, transparency and reduction of waste and reporting bias are important for other types of research including public health intervention studies, observational studies, implementation research and pre-clinical studies of experimental therapeutics and preventives.

We encourage formative work on development of possible transparency frameworks for these types of research, including how best to develop registries that publicly disclose research studies in the above categories.

Appendix 8. European regulation on clinical trials and medical devices

ON CLINICAL TRIALS

Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance

Reference:
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0536

Considering 37 : "In order to allow patients to assess possibilities to participate in a clinical trial, and to allow for effective supervision of a clinical trial by the Member State concerned, the start of the clinical trial, the end of the recruitment of subjects for the clinical trial and the end of the clinical trial should be notified. In accordance with international standards, the results of the clinical trial should be reported within one year from the end of the clinical trial"

Considering 67 : "In order to ensure a sufficient level of transparency in the clinical trials, the EU database should contain all relevant information as regards the clinical trial submitted through the EU portal. The EU database should be publicly accessible and data should be presented in an easily searchable format, with related data and documents linked together by the EU trial number and with hyperlinks, for example linking together the summary, the layperson's summary, the protocol and the clinical study report of one clinical trial, as well as linking to data from other clinical trials which used the same investigational medicinal product. All clinical trials should be registered in the EU database prior to being started. As a rule, the start and end dates of the recruitment of subjects should also be published in the EU database. No personal data of data subjects participating in a clinical trial should be recorded in the EU database. The information in the EU database should be public, unless specific reasons require that a piece of information should not be published, in order to protect the right of the individual to private life and the right to the protection of personal data, recognised by Articles 7 and 8 of the Charter. Publicly available information contained in the EU database should contribute to protecting public health and fostering the innovation capacity of European medical research, while recognising the legitimate economic interests of sponsors."

Article 37

End of a clinical trial, temporary halt and early termination of a clinical trial and submission of the results

« (…) 4. Irrespective of the outcome of a clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the EU database a summary of the results of the clinical trial. The content of that summary is set out in Annex IV.

It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of that summary is set out in Annex V.

However, where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

In addition to the summary of the results, where the clinical trial was intended to be used for obtaining a marketing authorisation for the investigational medicinal product, the applicant for marketing authorisation shall submit to the EU database the clinical study report within 30 days after the day the marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed, or the applicant for marketing authorisation has withdrawn the application.

For cases where the sponsor decides to share raw data on a voluntary basis, the Commission shall produce guidelines for the formatting and sharing of those data. »

« (…) 8. Without prejudice to paragraph 4, where the clinical trial protocol provides for an intermediate data analysis date prior to the end of the clinical trial, and the respective results of the clinical trial are available, a summary of those results shall be submitted to the EU database within one year of the intermediate data analysis date. »

ANNEX IV

CONTENT OF THE SUMMARY OF THE RESULTS OF THE CLINICAL TRIAL

The summary of the results of the clinical trial shall contain information on the following elements:

A. CLINICAL TRIAL INFORMATION:

1. Clinical trial identification (including title of the trial and protocol number);

2. Identifiers (including EU trial number, other identifiers);

3. Sponsor details (including scientific and public contact points);.

4. Paediatric regulatory details (including information whether the clinical trial is a part of a Paediatric Investigation Plan);

5. Result analysis stage (including information about intermediate data analysis date, interim or final analysis stage, date of global end of the clinical trial). For clinical trials replicating studies on already authorised investigational medicinal products and used in accordance with the terms of the marketing authorisation, the summary of the results should also indicate identified concerns in the overall results of the clinical trial relating to relevant aspects of the efficacy of the related medicinal product;

6. General information about the clinical trial (including information about main objectives of the trial, trial design, scientific background and explanation of rationale for the trial; date of the start of the trial, measures of protection of subjects taken, background therapy; and statistical methods used);

7. Population of subjects (including information with actual number of subjects included in the clinical trial in the Member State concerned, in the Union and in third countries; age group breakdown, gender breakdown).

B. SUBJECT DISPOSITION:

1. Recruitment (including information on the number of subjects screened, recruited and withdrawn; inclusion and exclusion criteria; randomisation and blinding details; investigational medicinal products used);

2.Pre-assignment Period;

3.Post Assignment Periods.

C. BASELINE CHARACTERISTICS:

1. Baseline Characteristics (Required) Age;

2. Baseline Characteristics (Required) Gender;

3. Baseline Characteristics (Optional) Study Specific Characteristic.

D. END POINTS:

1.End point definitions (*1)

2.End Point #1

Statistical Analyses

3.End Point #2
Statistical Analyses

E. ADVERSE EVENTS:

1. Adverse events information;

2. Adverse event reporting group;

3. Serious adverse event;

4. Non-serious adverse event.

F. ADDITIONAL INFORMATION:

1. Global Substantial Modifications;

2. Global Interruptions and re-starts;

3. Limitations, addressing sources of potential bias and imprecisions and Caveats;

4. A declaration by the submitting party on the accuracy of the submitted information.

(*1) Information shall be provided for as many end points as defined in the protocol.

ON MEDICAL DEVICES

Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (Text with EEA relevance.)

Référence : https://eur-lex.europa.eu/eli/reg/2017/745/oj?uri=CELEX:32017R0745

Considering 70: "The sponsor of a clinical investigation should submit a summary of results of the clinical investigation that is easily understandable for the intended user together with the clinical investigation report, where applicable, within the timelines laid down in this Regulation. Where it is not possible to submit the summary of the results within the defined timelines for scientific reasons, the sponsor should justify this and specify when the results will be submitted"

Article 77 : "Information from the sponsor at the end of a clinical investigation or in the event of a temporary halt or early termination"

« (…)5. Irrespective of the outcome of the clinical investigation, within one year of the end of the clinical investigation or within three months of the early termination or temporary halt, the sponsor shall submit to the Member States in which a clinical investigation was conducted a clinical investigation report as referred to in Section 2.8 of Chapter I and Section 7 of Chapter III of Annex XV.

The clinical investigation report shall be accompanied by a summary presented in terms that are easily understandable to the intended user. Both the report and summary shall be submitted by the sponsor by means of the electronic system referred to in Article 73.

Where, for scientific reasons, it is not possible to submit the clinical investigation report within one year of the end of the investigation, it shall be submitted as soon as it is available. In such case, the clinical investigation plan referred to in Section 3 of Chapter II of Annex XV shall specify when the results of the clinical investigation are going to be available, together with a justification.

6. The Commission shall issue guidelines regarding the content and structure of the summary of the clinical investigation report.

In addition, the Commission may issue guidelines for the formatting and sharing of raw data, for cases where the sponsor decides to share raw data on a voluntary basis. Those guidelines may take as a basis and adapt, where possible, existing guidelines for sharing of raw data in the field of clinical investigations.

7. The summary and the clinical investigation report referred to in paragraph 5 of this Article shall become publicly accessible through the electronic system referred to in Article 73, at the latest when the device is registered in accordance with Article 29 and before it is placed on the market. In cases of early termination or temporary halt, the summary and the report shall become publicly accessible immediately after submission.

If the device is not registered in accordance with Article 29 within one year of the summary and the report having been entered into the electronic system pursuant to paragraph 5 of this Article, they shall become publicly accessible at that point in time. »

Appendix 9. Framework relating to research integrity

Reference documents on research integrity, and extracts relating to the reporting of research results.

Research code

Reference:
https://www.legifrance.gouv.fr/codes/texte_lc/LEGITEXT000006071190/

Article L211-2: Definition of requirements for scientific integrity "aiming to guarantee that the nature of their [research projects] is honest and scientifically rigorous, and to reinforce the relationship of trust with society. Scientific integrity contributes to ensuring the impartiality of research projects and the objectivity of their results."

The regulatory section of the French Research Code, article D211-2, introduces a requirement for *public establishments contributing to the public service of research and foundations which are recognised to be publicly useful, where the main activity is public research*:

- To ensure "that the research projects they conduct or participate in fulfil the demands of scientific integrity",
- To promote "the dissemination of open access publications and the making available of methods, protocols, data and source codes associated with the research results",
- To define "the conditions for conserving, communicating and reusing raw data from scientific work conducted within their organisation."

Order no. 2021-882 dated 1st July 2021 provides a list of public establishments with by-laws which include research activities:https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000043742033 and Decree no. 2021-1135 dated 30 August 2021 amending Order no. 2021-882: https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000044000628

These two texts state that this refers, in particular, to universities and other EPSCPs [scientific, cultural and professional public establishments], research bodies [ESPTs, scientific and technically-based public establishments, EPICs, industrial and commercial public establishments] and public health establishments.

The European Code of Conduct for Research Integrity (ALLEA, 2023)

References:
https://allea.org/wp-content/uploads/2023/06/European-Code-of-Conduct-Revised-Edition-2023.pdf

https://www.allea.org/wp-content/uploads/2018/01/FR_ALLEA_Code_de_conduite_europeen_pour_lintegrite_en_recherche.pdf (2018 French translation)

The European Code of Conduct for Research Integrity was published in 2011. It is a framework text that defines good practice in scientific integrity, and provides a classification of breaches in scientific integrity. The latest revised edition was published in 2023. The European Commission recognises the European Code of Conduct as a reference document for research integrity for all EU-funded research projects.

The code refers to the 4 principles of scientific integrity:

- **Reliability** meaning ensuring the quality of research, reflected in the design, methodology, analysis and use of resources.
- **Honesty** meaning developing, undertaking, reviewing, reporting, and communicating research in a transparent, full, fair and unbiased way.
- **Respect** for colleagues, research participants, research subjects, society, ecosystems, cultural heritage and the environment.
- **Accountability** for research activities right from the concept to publication, for managing and organising them, for training, supervision and mentoring, and for the wider societal impact of the research.

The code does not only apply to individual researchers, it also highlights the responsibility of all those parties concerned: "Researchers, academies, learned societies, *funding bodies, public and private research organisations*, those responsible for scientific publications and other organisations concerned, all assume a specific responsibility for following and promoting these practices, and the principles on which they are based."

This responsibility applies to the diffusion of results, including negative results: **"Authors and editors** acknowledge that **negative results** may be **just as relevant as** positive findings for the purpose of **publication and dissemination**."

Consequently, the list of breaches of scientific integrity highlights certain unacceptable practices regarding the diffusion of research results:

- Allowing funders, sponsors or others to jeopardise the independence and impartiality of the research process or the reporting of the results by introducing or favouring bias.
- **The withholding of research data or results without reasonable justification.**
- Quoting in a selective or inaccurate way.

Research integrity in the European Regulation of 16 April 2014 on clinical trials on medicinal products for human use

Referring to non-compliance with the European Regulation of 16 April 2014 on clinical trials on medicinal products for human use, concerning the publishing of the results of clinical trials in this category:

- Failure to comply with the regulation is also considered to be a breach of scientific integrity, in the same way as the failure: "breach or abuse of, or non-compliance with, ethical laws and protocols".
- The European Code of Conduct makes the following recommendations: "Researchers, institutions and research organisations will comply with the regulations, codes and rules that apply to them."

Appendix 10. Glossary for clinical trials and posting them in registries

** This definition is used in the glossary available here (in French): https://notre-recherche-clinique.fr/lexique/.*

ANSM - French National Health Products Safety Agency*

The ANSM is tasked with providing fair access to innovation for all patients, and guaranteeing the safety of healthcare products throughout their lifecycle, from the initial trials up to oversight once marketing authorization has been issued.

It covers drugs, medical devices, biological products, cosmetic and tattooing products and other health products.

It is responsible for issuing authorisations for the sponsors of all interventional clinical trials that entail an intervention that may pose a risk to persons, and which is not justified in their routine care provision. This concerns interventional clinical trials on drugs, in vitro diagnostic medical devices and biological products, as well as clinical trials on non-health related products taking place in France. The agency can request additional information or amendments to the trial protocols.

ANSM is the competent authority for clinical trials conducted in France. It can suspend or stop a trial at any time.

Investigator*

The investigator of a clinical trial is a health professional who manages and oversees the carrying out of the trial. They must have the relevant experience in conducting clinical trials. When the trial is conducted in several sites in France, the sponsor appoints a *coordinating investigator*. If the research is carried out by a team on one site, the investigator responsible for the team is named the *main investigator*. The Ethics Committee (EC) ensures that the investigator or investigators is/are appropriately qualified for the research project.

Ethics Committee (EC)*

Ethics Committees are independent bodies comprising equal numbers of members of the medical-scientific domain (18) and civil society (18). They are accredited by the French Ministry of Health. Their composition is designed to guarantee independence and a wide range of expert knowledge. Each EC member should declare any direct or indirect relationships, or the lack of such relationships, with the sponsors and investigators of the trial. The members undertake their work on a voluntary basis.

Their role is, based on the careful analysis of the research documents and the information given to participants before they are included in the trial, to oversee the safety of research participants, the soundness and relevance of the research and compliance with the legislation on research in France. The documents to be analysed are divided up between the 39 ECs randomly. The committee that will assess the project is selected at

random from the committees that are available at the earliest opportunity and have the competence required to oversee the project.

A favourable opinion from an EC must be obtained before starting clinical research.

Date of trial end – Last patient, last visit

In Europe, the end of trial is defined in European regulation No. 536/2014 on clinical trials on medicinal products. The ending of the trial is defined as the last visit of the last patient included in the study (Last patient, last visit – LPLV) or a later date as defined in the protocol. For Europe (CTIS), the rules stipulate that the results should be posted in the registries within 1 year following the trial end.

Internationally (WHO declaration, FDA Amendments Act), the end of the study is defined as the last visit of the last patient in the study (Last patient, last visit – LPLV) for the primary evaluation criteria.

Clinical trial

A common point with all these definitions is that they are not limited solely to drug trials.

- Definition in the European regulation[24]: "a clinical trial fulfils one of the following conditions:
    6. Assigning the subject to a particular therapeutic strategy is decided in advance, and it does not fall within normal clinical practice in the Member State concerned;
    7. The decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study;
    8. Diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects;"
- WHO definition: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes."
- ICJME definition: The ICMJE defines a clinical trial as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention and a health outcome. Health-related interventions are those used to modify a biomedical or health-related outcome; examples include drugs, surgical procedures, devices, behavioral treatments, educational programs, dietary interventions, quality improvement interventions, and process-of-care changes. Health outcomes are any biomedical or health related measures obtained in patients or participants, including pharmacokinetic measures and adverse events.".
- NIH definition: "Clinical trial" is defined in Section 102(b) of the revised IRB regulations (the 'Common Rule') as: "a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes."

[24] Definition in the (EU) regulation No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

Posting of summary results

Posting of summary results refers to the structured disclosure of clinical trial results in public clinical trial registries. The structure and content are defined in Appendix IV of the European Regulation on Clinical Trials. ClinicalTrials.gov gives examples of recognised posting templates.

Sponsor*

The sponsor is an individual, a company, institution or organisation which takes responsibility for initiating, managing and setting up the funding of the clinical trial. In practice, the sponsor is responsible for all of the organisation, implementation and oversight of the clinical trial: nominating the investigator, recruiting the Clinical Research Associate (CRA) quality controllers, obtaining a favourable opinion from the Ethics Committee and authorisation of the competent authority where necessary, taking out insurance and declaring any adverse events that occur in the course of the research to the competent authority.

Research involving human subjects (*Recherche impliquant la personne humaine*, RIPH)*

Article L.1121-1 of the French Public Health Code. Research organised and practiced on humans in order to advance biological or medical knowledge is referred to as "research involving human subjects".

The law identifies 3 categories of research involving human subjects:

- Interventional research involving an intervention on a person that is not justified by their usual treatment,
- Interventional research that carries only minimal risks and constraints, the list for which is defined by the order of the French Ministry of Health, based on the opinion of the General Director of ANSM.
- Non-interventional research that does not carry risks or constraints, in which all of the procedures are enacted, and all of the products are used, in a routine manner.

Appendix 11. Results posting templates

Templates available on ClinicalTrials.gov

In ClinicalTrials.gov, the results should be posted following the predefined templates and the very precise description of the elements to be posted. These elements can be considered as de facto standards that are developed, recognised and practised by the global scientific community.

Reference: https://clinicaltrials.gov/submit-studies/prs-help/support-training-materials

1. Participant flow Data Preparation Checklist

Participant Flow Template

Example number 1: first page of the "Participant Flow Data Preparation Checklist".

More details available in the Results Data Element Definitions. April 2017

Participant Flow Template ***ClinicalTrials.gov***

Recruitment Details	
[*] Pre-assignment Details	

Period ①

* Period Title	Overall Study ①		
* Arm/Group Title			
*§ Arm/Group Description ②			
	Number of Participants ④	Number of Participants ④	Number of Participants ④
* Started			
[*] Milestone Title ③			
[*] Milestone Title ③			
[*] Milestone Title ③			
* Completed			
Not Completed	*(automatically calculated)*		
Reason Not Completed Type ③			
[*] Adverse Event			
[*] Death			
[*] Lack of Efficacy			
[*] Lost to Follow-up			
[*] Physician Decision			
[*] Pregnancy			
[*] Protocol Violation			
[*] Withdrawal by Subject			
[*] Other Reason			
[*] Other Reason			
[*] Other Reason			

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

① Complete a Period table for each stage of the study. If only one Period, the Title is "Overall Study". For multiple Periods, include descriptive Titles for each Period.
② Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
③ [Optional] Add as many Milestone Title or Other Reason Not Completed rows as needed. A descriptive title for each row is required.
④ Number and Type of Units Assigned may also be specified.

The complete document is available at: https://cdn.clinicaltrials.gov/documents/data-prep-checklist-pf.pdf

2. Baseline Characteristics Data Preparation Checklist

Baseline Characteristics Data Preparation Checklist

- Baseline Characteristics Template - Age
- Baseline Characteristics Template - Sex/Gender
- Baseline Characteristics Template - Race, Ethnicity, Region
- Baseline Characteristics Template - Study Specific Measure

Example number 2: Baseline Characteristics Template - Age.

More details available in the Results Data Element Definitions. April 2017

Baseline Characteristics Template *Age* (use at least one)* **ClinicalTrials.gov**

* Arm/Group Title								Total	
*§ Arm/Group Description ①									
* Overall Number of Baseline Participants ②								③	
[*] Baseline Analysis Population Description									
Age, Categorical									
<=18 years								③	
Between 18 and 65 years								③	
>=65 years								③	
* Unit of Measure	Participants								
Age, Continuous									
* Measure Type	* Measure of Dispersion								
(Select One) Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM	(Select One) Standard Deviation Inter-quartile Range Full Range								
* Unit of Measure									
Age, Customized									
* Measure Type	* Measure of Dispersion								
(Select One) Count of Participants ④ Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units ④	(Select One) Not Applicable ⑤ Standard Deviation Inter-Quartile Range Full Range								
[*] Row/Category Title ⑥			④⑤		④⑤		④⑤	③	④⑤
[*] Row/Category Title ⑥			④⑤		④⑤		④⑤	③	④⑤
* Unit of Measure									

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

① Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
② Overall Number of Units Analyzed and Type of Units Analyzed may also be specified.
③ Total values are automatically calculated for Overall Number of Baseline Participants and for data reported with a Measure Type of Number, Count of Participants, or Count of Units.
④ If Measure Type is a "count," percentage of participants/units is automatically calculated from Overall Number of Baseline Participants/Units Analyzed. The percentage can be hidden (display is optional).
⑤ Not Applicable should be used only if Measure Type is Number, Count of Participants, or Count of Units. No dispersion value is needed if Measure of Dispersion is Not Applicable.
⑥ [Optional] Add as many Rows/Categories as needed. If more than one is entered, a Row/Category Title and Baseline Measure Data are required for each row.

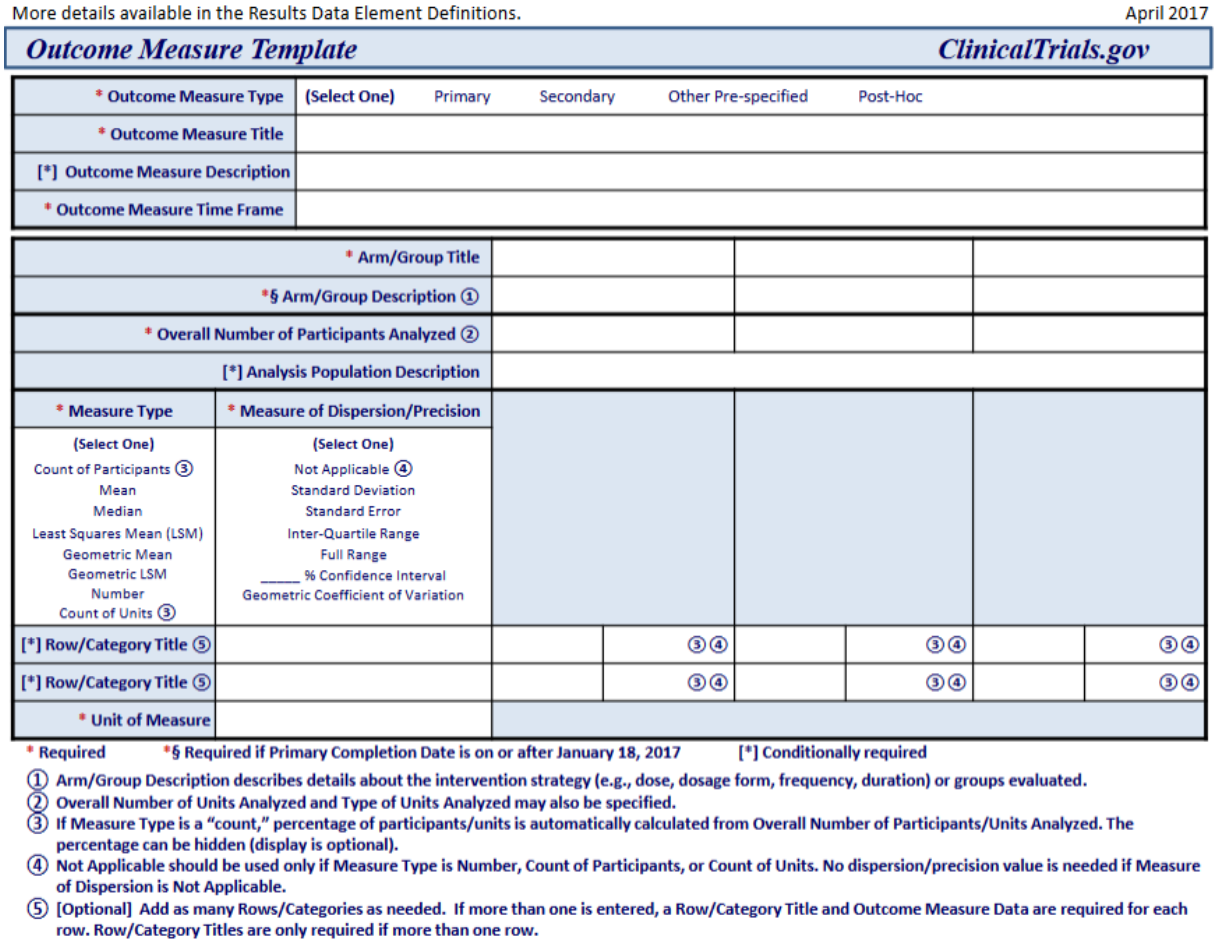
The document is available here: https://cdn.clinicaltrials.gov/documents/results_table_layout/DataEntryTable_BaselineAgeForm.pdf

3. Outcome Measure and Statistical Analysis Data Preparation Checklist

Outcome Measure and Statistical Analysis Data Preparation Checklist

- Outcome Measure Template
- Outcome Measure Template Examples
- Statistical Analysis Template

Example number 3: Outcome Measure Template.



More details available in the Results Data Element Definitions. April 2017

Outcome Measure Template ClinicalTrials.gov

* Outcome Measure Type	(Select One) Primary Secondary Other Pre-specified Post-Hoc
* Outcome Measure Title	
[*] Outcome Measure Description	
* Outcome Measure Time Frame	

* Arm/Group Title						
*§ Arm/Group Description ①						
* Overall Number of Participants Analyzed ②						
[*] Analysis Population Description						
* Measure Type (Select One) Count of Participants ③ Mean Median Least Squares Mean (LSM) Geometric Mean Geometric LSM Number Count of Units ③	* Measure of Dispersion/Precision (Select One) Not Applicable ④ Standard Deviation Standard Error Inter-Quartile Range Full Range _____ % Confidence Interval Geometric Coefficient of Variation					
[*] Row/Category Title ⑤			③④		③④	③④
[*] Row/Category Title ⑤			③④		③④	③④
* Unit of Measure						

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

① Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
② Overall Number of Units Analyzed and Type of Units Analyzed may also be specified.
③ If Measure Type is a "count," percentage of participants/units is automatically calculated from Overall Number of Participants/Units Analyzed. The percentage can be hidden (display is optional).
④ Not Applicable should be used only if Measure Type is Number, Count of Participants, or Count of Units. No dispersion/precision value is needed if Measure of Dispersion is Not Applicable.
⑤ [Optional] Add as many Rows/Categories as needed. If more than one is entered, a Row/Category Title and Outcome Measure Data are required for each row. Row/Category Titles are only required if more than one row.

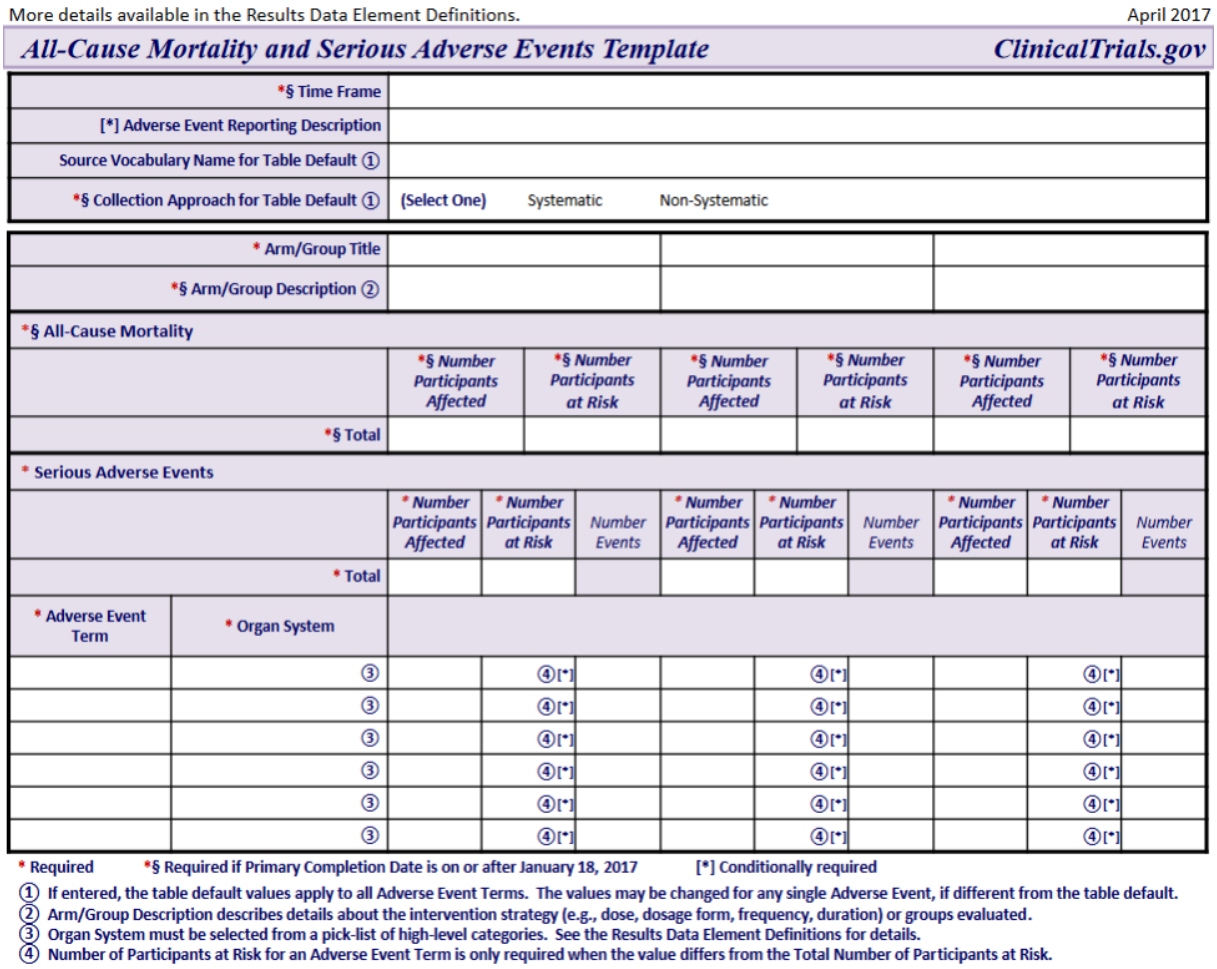
The document is available here:
https://cdn.clinicaltrials.gov/documents/results_table_layout/DataEntryTable_OMForm.pdf

4. Adverse Events Data Preparation Checklist

Adverse Events Data Preparation Checklist

- Serious Adverse Events Template
- Other (Not Including Serious) Adverse Events Template

Example number 4: Serious Adverse Events Template.



More details available in the Results Data Element Definitions. April 2017

All-Cause Mortality and Serious Adverse Events Template ClinicalTrials.gov

*§ Time Frame						
[*] Adverse Event Reporting Description						
Source Vocabulary Name for Table Default ①						
*§ Collection Approach for Table Default ①	(Select One) Systematic Non-Systematic					
* Arm/Group Title						
*§ Arm/Group Description ②						
*§ All-Cause Mortality						
	*§ Number Participants Affected	*§ Number Participants at Risk	*§ Number Participants Affected	*§ Number Participants at Risk	*§ Number Participants Affected	*§ Number Participants at Risk
*§ Total						

* Serious Adverse Events										
		* Number Participants Affected	* Number Participants at Risk	Number Events	* Number Participants Affected	* Number Participants at Risk	Number Events	* Number Participants Affected	* Number Participants at Risk	Number Events
* Total										
* Adverse Event Term	* Organ System									
	③		④[*]			④[*]			④[*]	
	③		④[*]			④[*]			④[*]	
	③		④[*]			④[*]			④[*]	
	③		④[*]			④[*]			④[*]	
	③		④[*]			④[*]			④[*]	
	③		④[*]			④[*]			④[*]	

* Required *§ Required if Primary Completion Date is on or after January 18, 2017 [*] Conditionally required

① If entered, the table default values apply to all Adverse Event Terms. The values may be changed for any single Adverse Event, if different from the table default.
② Arm/Group Description describes details about the intervention strategy (e.g., dose, dosage form, frequency, duration) or groups evaluated.
③ Organ System must be selected from a pick-list of high-level categories. See the Results Data Element Definitions for details.
④ Number of Participants at Risk for an Adverse Event Term is only required when the value differs from the Total Number of Participants at Risk.

The document is available here: https://cdn.clinicaltrials.gov/documents/results_table_layout/DataEntryTable_SAEForm.pdf

Appendix 12. European Commission Guideline

Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 (2012/C 302/03)

2. SCOPE

This guidance document addresses the posting and publication of clinical trials as defined in Article 2(a) of Directive 2001/20/EC with at least one of the following characteristics: — the clinical trial is regulated or was regulated by Directive 2001/20/EC, which took effect at the latest on 1 May 2004 (on the posting of result-related information on clinical trials which have ended in the past, see section 4.6.1). This implies that at least one investigator site of the clinical trial is located in the European Union (EU) or in a contracting State of the European Economic Area, — the clinical trial forms part of a paediatric investigation plan including those where the investigator sites are outside the European Union (EU) (8), — the clinical trial falls within Article 45 of Regulation (EC) No 1901/2006, — the clinical trial falls within Article 46 of Regulation (EC) No 1901/2006.

3. CONTENT OF POSTED RESULT-RELATED INFORMATION

The result-related information should be posted in accordance with this Guideline for all clinical trials referred to in Section 2. The content of the results-related information is set out in the Guideline 2009/C28/01. The information set out there applies for paediatric as well as non-paediatric clinical trials. The implementing technical guidance on the format of the data fields (hereinafter 'full data set') is published in a separate document in 'EudraLex — the rules governing medicinal products in the European Union', thus completing the two implementing technical guidances on the 'List of fields to be made public from EudraCT for Paediatric Clinical Trials in accordance with Article 41 of Regulation (EC) No 1901/2006' and the 'List of fields contained in the "EudraCT" clinical trials database to be made public, in accordance with Article 57(2) of Regulation (EC) No 726/2004.' (9). The data fields in that detailed technical guidance take account of international harmonisation efforts. The content of the data fields is kept identical with the U.S.-database 'clinicaltrials.gov', with limited exceptions to take account of particularities like the EU paediatric investigation plan, as well as evolving changes of international databases or international harmonisation efforts.

4. MODALITIES OF POSTING AND PROCESSING OF RESULT RELATED INFORMATION

By posting result-related information to the European database referred to in Article 11(1) of Directive 2001/20/EC (hereinafter 'EudraCT') the sponsor, the addressee of the decision on a paediatric investigation plan or the marketing authorisation holder, as appropriate, comply with Article 41(2) of Regulation (EC) No 1901/2006. Moreover, this posting is considered as the submission of the clinical trial summary report as part of the end-of-trial-declaration to national competent authorities as set out in Section 4.3 of the detailed guidance CT-1. Where the result-related information is published (see Section 5), it is considered as submission to the Ethics Committee as set out in Section 4.2.1 of the detailed guidance CT-1. 4.1. Posting of data The result-related information is posted to EudraCT either directly entering data using a web interface provided by the European

Medicines Agency (hereinafter 'the Agency'), by uploading a XML file via the web interface, or using a gateway technology. The data are posted to a secure module of EudraCT. The information should be provided in accordance with an XML schema established and published by the Agency. The information is posted: — by the addressee of the decision on a paediatric investigation plan, where the clinical trial forms part of a paediatric investigation plan, — by the marketing authorisation holder, where the clinical trial falls within Articles 45 and 46 of Regulation (EC) No 1901/2006, — by the sponsor of the clinical trial for all other clinical trials referred to in Section 2. To this end the party responsible for posting the information is provided with a secure account to enable uploading and editing of these data in the system. That party has access only to their own data. This access will enable the posting and maintenance of the data in a secure part of the system. The further processing and making public of this information is controlled by the Agency. Certain fields of the protocol-related data will be used to present the context of the trial facilitating the presentation of the result related information. The corresponding protocol-related information will automatically be loaded, from EudraCT, into these fields when result-related information is provided via the web interface or on a pre-populated XML downloaded. On the occasion of posting result-related information, these fields may be updated by means of the web interface or alternatively via posting of an updated XML-file with protocol-related information. In general, a comment field is made available linked to data fields other than free text fields. The comment field is intended to allow for inclusion of information supplementing the fixed field contents. The structure of the collected data accommodates the large majority of clinical trials; however, the comment field may be used if data fields do not adequately accommodate the required information. 4.2. Processing In the secure part of the system, an automated technical validation may take place. In case issues are identified, the posting of the information will be blocked. A validation report will be provided to the posting party with instructions on how to resolve or clarify the issues. The data are then entered into EudraCT, and information on clinical trials to be made public are selected by the applicable business rules and made public in the EU Clinical Trials Register of EudraPharm (see Section 5). They will be linked to the protocol-related data, where the latter are available in EudraCT. It is not possible for the public to access the secure module. The posting of result-related information does not overwrite existing protocol-related information that is stored in EudraCT. C 302/8 Official Journal of the Europea

4.3. Timing

Result-related information should be posted within the timeframes set out in the Regulation (EC) No 1901/2006 and the guidelines referred to under Section 1, i.e. (relating to paediatric clinical trials) within six months (10) and otherwise within one year of the end of the trial (11). It is recommended that result-related data should be posted prior to these dates if such information is already available. This is the case, for example, if results have already been published in scientific journals, or if a primary completion date is foreseen before the end of the trial. If the clinical trial ends prematurely, that date should be considered the end of the trial. Only one set of result-related data may be provided per planned analysis and trial. If the outcome is analysed on several occasions, each of these analyses should be posted.

4.4. Language

The result-related information is largely numerical, or based on value list definitions, using pre-defined options or terminology lists. Regarding free text fields the system will permit the entry of more than one language (from the official languages of the EU). In accordance with WHO standard and to facilitate the international use outside the EU, information

should be posted in English. In addition, the information may be posted in any other official EU language.

4.5. Data updates and follow-up posting

Some protocol-related information, as well as the result-related information (e.g. contact points for further information or enrolment status), will be available for update by the posting party, in such a way that the updated information is made directly available in the public domain subject to technical controls being met. Each version of protocol-related information and result-related data will be stored and posting of new versions will not result in deletion of previously posted versions, thus providing a record of changes.

4.6. Provisions for results of clinical trials which have ended in the past 4.6.1.

Clinical trials within the scope of Directive 2001/20/EC Result-related information on clinical trials which ended less than one year prior to finalisation of the programming referred to in Section 6 should be posted within one year of the finalisation of the programming by using the full data set (see Section 4.1). Result-related information on clinical trials which ended one year or more prior to finalisation of the programming referred to in Section 6 may be posted either by using the full data set (see Section 3) or by using the method for clinical trials within the scope of Article 45 of Regulation (EC) No 1901/2006 (see below). This should be done within 24 months of the finalisation of the programming referred to in Section 6. 4.6.2. Clinical trials referred to in Regulation (EC) No 1901/2006 An alternative posting process will be made available for clinical trials referred to in Article 45 of Regulation (EC) No 1901/2006. For these clinical trials the posting of result related information to the Agency for the purpose of publication may be done as a copy, authorised by the copyright-holder, of a medical journal article (as PDF file), as the synopsis in accordance with Annex I to the ICH Topic E 3 guidance (as PDF file), or any other appropriate document containing the information of that synopsis (as PDF file). For these cases, a set of fields will be established in EudraCT to identify the clinical trial involved, to facilitate searching and to allow attachment of the PDF file. This result-related information should be posted within 24 months of the finalisation of the programming referred to in Section 6. Result-related information of clinical trials included in an agreed paediatric investigation plan (Article 41(1) of Regulation (EC) No 1901/2006), and of marketing authorisation holdersponsored trials which involve the use in the paediatric population of a medicinal product covered by a marketing authorisation (Article 46 of Regulation (EC) No 1901/2006), and which ended prior to finalisation of the programming referred to in Section 6, should be posted within one year of the finalisation of the programming by using the full data set (see Section 4.1).

4.7. Non-compliance, factual inaccuracy

Member States should verify that for clinical trials authorised by them the result-related information is posted to the AgencyClinical trials for which no result-related information has been posted 9 months after the end of the trial (see Section 4.3) for paediatric trials or 15 months for other trials will be flagged. This information will be publicly available. The anticipated duration of the trial is entered at the time of the clinical trial application. The actual end of the trial is notified through the 'Declaration of the end of trial form'. All corrections to published information will be made by the party posting that information, sometimes upon request by the Agency f inspections of compliance with good clinical practice (GCP) reveal that there are serious doubts about the accuracy or reliability of the result-related data, the Agency will be informed immediately. The Agency will retain the possibility of: — removing information from the public view, — highlighting that the result-related information may not be valid in view of GCP non-

compliance, or — adding a notice to the public record, where necessary for reasons of factual accuracy or compliance with regulatory requirements.

5. PRESENTATION OF THE RESULT-RELATED INFORMATION TO THE PUBLIC

The posted result-related information is made public through the EU Clinical Trials Register of EudraPharm in accordance with the Commission guidance documents set out under Section 1, i.e. only result-related information on non-paediatric Phase-I clinical trials is not made public. The result-related information is made public within 15 working days from the posting of a valid data set. The results-related information of each clinical trial is linked to the corresponding protocol-related information which is already stored in the system. Regarding follow-up posting (see Section 4.5), by default, the current version will be presented first for public access, but previous versions may also be viewed by the public. In addition to being readable in situ on the web, the data will also be made available in a printable format and in a downloadable format. The web interface is going to provide tools to facilitate the searching, reading and browsing of the public information on clinical trials and their results.

6. IMPLEMENTATION

This guidance document applies as soon as the programming of the relevant databases has been finalised. Finalisation of the programming will be publicly announced by the Agency

Appendix 13. Reference websites

- Agence nationale de sécurité du médicament et des produits de santé – ANSM
  https://ansm.sante.fr/qui-sommes-nous/nos-missions/faciliter-lacces-a-linnovation-therapeutique/p/encadrer-les-essais-cliniques
- Baromètre de la science ouverte (santé)
  https://barometredelascienceouverte.esr.gouv.fr/sante
- Clinicaltrials.gov
  https://clinicaltrials.gov/
- Clinicaltrials.gov : Support and Training Materials
  https://clinicaltrials.gov/submit-studies/prs-help/support-training-materials
- Clinical trials in the European Union
  https://euclinicaltrials.eu/
- The EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network
  https://www.equator-network.org/
- International Clinical Trials Registry Platform (ICTRP)
  https://www.who.int/clinical-trials-registry-platform
- The Clinical Trials Transformation Initiative (CTTI)
  https://ctti-clinicaltrials.org/
- TranspariMED
  https://www.transparimed.org/

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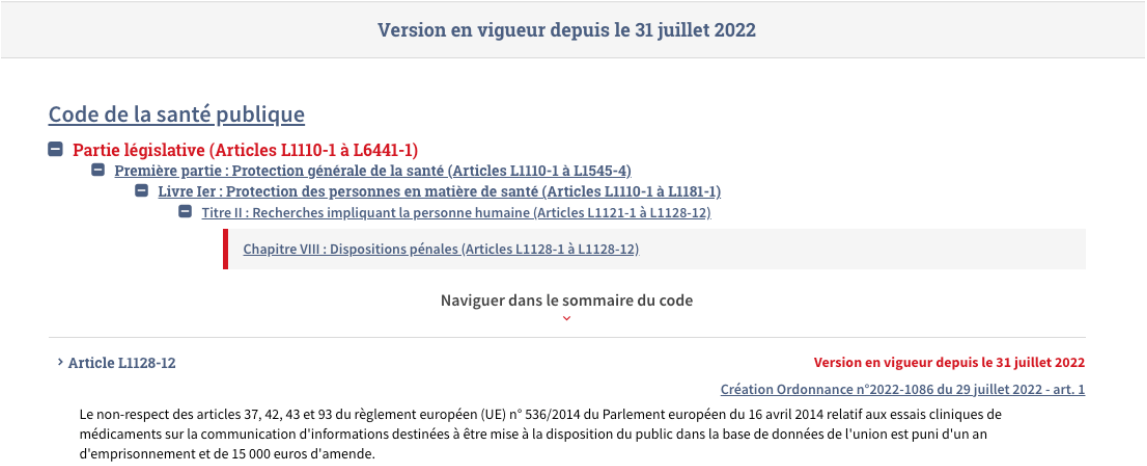
Appendix 15. Article L1128-12 of the French Public Health Code



Version en vigueur depuis le 31 juillet 2022

Code de la santé publique

Partie législative (Articles L1110-1 à L6441-1)

Première partie : Protection générale de la santé (Articles L1110-1 à L1545-4)

Livre Ier : Protection des personnes en matière de santé (Articles L1110-1 à L1181-1)

Titre II : Recherches impliquant la personne humaine (Articles L1121-1 à L1128-12)

Chapitre VIII : Dispositions pénales (Articles L1128-1 à L1128-12)

Naviguer dans le sommaire du code

› Article L1128-12

Version en vigueur depuis le 31 juillet 2022

Création Ordonnance n°2022-1086 du 29 juillet 2022 - art. 1

Le non-respect des articles 37, 42, 43 et 93 du règlement européen (UE) n° 536/2014 du Parlement européen du 16 avril 2014 relatif aux essais cliniques de médicaments sur la communication d'informations destinées à être mise à la disposition du public dans la base de données de l'union est puni d'un an d'emprisonnement et de 15 000 euros d'amende.

"Failure to comply with Articles 37, 42, 43 and 93 of European Regulation (EU) No 536/2014 of the European Parliament of 16 April 2014 on clinical trials of medicinal products on the communication of information intended to be made available to the public in the union database is punishable by one year's imprisonment and 15,000 euros."

Appendix 16. List of abbreviations and acronyms

- ANSM - Agence Nationale de Sécurité du Médicament et des Produits de Santé
- AP-HP - Assistance publique – Hôpitaux de Paris
- CHU - Centre Hospitalier Universitaire
- CNCR - Comité National de Coordination de la Recherche
- CPP - Comité de Protection des Personnes
- CTAG - Clinical Trials Coordination and Advisory Group
- CTIS - Clinical Trials Information System
- EMA - European Medicines Agency
- EUDRACT - European Union Drug Regulating Authorities Clinical Trials Database
- FDA - Food and Drug Administration
- GIRCI - Groupements Inter-Régionaux de Recherche Clinique et d'Innovation
- HCERES - Haut Conseil de l'évaluation de la recherche et de l'enseignement supérieur
- ICMJE - International Committee of Medical Journal Editors
- INSERM - Institut National de la Santé et de la Recherche Médicale
- OMS - Organisation Mondiale de la Santé
- OSTP - Office of Science and Technology Policy
- RIPH - Recherche Impliquant la Personne Humaine
- WHO-ICTRP - World Health Organization International Clinical Trials Registry Platform