To: Dr Lorraine Nolan, Chair, EMA Management Board

Cc:
Ms Emer Cooke, EMA Executive Director
Mr Sylvain Giraud, Mr Christophe Didion, Ms Linda Abdelall, DG SANTE D2, European Commission
Ms Emily O'Reilly, European Ombudsman

Please respond to: Rita Kessler, Prescrire, rkessler@prescrire.org

17 October 2022

Dear Dr Nolan,

We urge you to place the issue of the European Medicines Agency's proposed deferral of publication of Phase II and Phase III investigative drug trial protocols onto the agenda of the next meeting of EMA's Management Board.

EMA's proposed deferral of publication of these protocols within the Clinical Trials Information System (CTIS) by up to 5 years after trial end clearly runs counter to the spirit and the letter of the Clinical Trials Regulation. For EMA to unilaterally decide to allow sponsors to hide trial protocols for long after the results of those same trials have been made public is unacceptable and is not in the best interests of science, patients, or of furthering medical innovation.

We urge the EMA Management Board to direct the agency to protect and promote patient interests by fully implementing the transparency provisions set out in European law. Specifically, this requires EMA to disclose unredacted clinical trial protocols for Phase II and Phase III trials on CTIS at the time that the summary results of the related trials are made public on CTIS.

In draft guidance put out for consultation this spring, the European Medicines Agency (EMA) laid out its plans for protecting personal data and commercially confidential information (CCI) in documents uploaded to CTIS.[1] While sponsors are obliged to upload the tabular summary results of clinical trials

within one year of trial completion at the most, EMA plans to allow sponsors to defer publication of the underlying trial protocols for Phase II and Phase III trials for up to 5 years after trial end.[i] According to EMA, this provides "the possibility to delay the publication of clinical trial information with the objective to protect commercially confidential information".[ii]

The 2014 Clinical Trial Regulation, which sets out the legal framework for the new CTIS registry, requires sponsors to include detailed information in protocols.[iii] This includes descriptions of the measures taken to minimise bias, of the statistical methods to be employed, and the "justification for the dosage, the dosage regime, the route and mode of administration, and the treatment period."

Crucially, the Regulation contains no provision which could be used as basis for delaying the publication of protocols. To the contrary, it clearly states that "[t]he information in the EU database should be public, unless specific reasons require that a piece of information should not be published."[iv]

A trial protocol is defined in the regulation as "a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial.[v] EMA has never provided 'specific reasons' why any of these protocol elements should be assumed to contain commercially confidential information and thus warrant deferral of publication by several years.

In fact, in a 2015 document, EMA noted that for Phase II and III trials, "[t]he more confidential details of the IMPs [investigative medicinal products] and their development can be addressed in the Investigator Brochure and IMPD [Investigational Medicinal Product Dossier]".[2] In other words, sponsors can choose not to include such details within the protocol itself.

While its 2022 consultation was still open, EMA was already granting trial sponsors deferrals for protocols, with 9 such deferrals granted in July of this year alone.

According to EMA, these deferrals are "a functionality implemented in CTIS that has been introduced to reduce the burden of redaction (deletion) of commercially confidential information."[3] The legal basis for EMA's introduction of this 'functionality' remained unexplained; its rationale, obscure.

If EMA persists with this approach, medical researchers, systematic reviewers, and public health bodies worldwide will find themselves in a profoundly absurd situation. They will be able to rapidly access a summary of the outcomes of European drug trials, but will not be able to discover precisely how those outcomes were generated.

This is not a trivial issue. Researchers need access to detailed information on trial design, including measures taken to minimise bias, statistical methods, and dosage regimes in order to fully interpret trial outcomes.

For example, researchers in the United States recently detected what they alleged were significant deviations from the pre-planned statistical analysis plan in an early-stage clinical trial of an investigative drug for Alzheimer's disease. Based on this and other concerns, they lodged a citizens petition with the U.S. Food and Drug Administration urging it to place a halt on imminent follow-on trials, arguing that these might endanger the health of more than 1,800 planned trial participants.[4]

[i] Cf. table page 22 of the consultation document
[ii] Cf. lines 343-344 of the consultation document
[iii] Cf. Annex I-D of the regulation
[iv] Cf. Recital 67 of the regulation
[v] Cf. Article 2(22) of the regulation

It appears unlikely that the US drug regulator had previously been aware of these protocol deviations; the early-stage trial in question had never been included in a submission aimed at securing market authorisation.

The information that the whistleblowers provided in their petition has reportedly sparked a criminal investigation into the company that sponsored the trial. [5] Even more importantly, their findings have led experts to re-evaluate the rationale underpinning multiple concurrent large-scale Alzheimer's research programmes premised upon the same, possibly unreliable, evidence base.[6]

Protocols are essential for interpreting the outcomes of clinical trials. The alternative public source of information on trial design and trial conduct, data entered into trial registries during initial trial registration, is often incomplete or inaccurate.[7–9]

Even if these data quality issues were addressed within the new European CTIS registry, such registrations alone remain insufficient to allow independent researchers to fully evaluate trial outcomes.[10,11]

As sponsors and investigators do not routinely make protocols public on a voluntary basis,[11,12] regulatory intervention is the only means by which consistent and timely protocol disclosure can be assured.

We urge you to place this issue onto the agenda of the next meeting of EMA's Management Board, and we urge the Board to direct the agency to disclose unredacted clinical trial protocols for Phase II and Phase III trials on CTIS at the time that the summary results of the related trials are made public on CTIS.

Please let us know whether and when the EMA Management Board will discuss this issue.

Thank you for your time, best wishes,

Supporting organisations and academic experts

- TranspariMED
- Prescrire
- Health Action International (HAI)
- International Society of Drug Bulletins (ISDB)
- Consilium Scientific
- BUKO Pharma-Kampagne
- Access to Medicines Ireland
- Salud por Derecho
- The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists **(**ASCEPT)
- Standing Committee of European Doctors (CPME)
- Grupo de Ativistas em Tratamentos (GAT)
- Joel Lexchin MD, Professor Emeritus, School of Health Policy and Management, Faculty of Health, York University, Toronto
- Dr Agnes Vitry, Adjunct Senior Research Fellow, Clinical and Health Sciences, University of South Australia
- Carl Henegan, Professor of EBM & Director Centre for Evidence-Based Medicine, University of Oxford
- Florian Naudet, professor of therapeutics, Univ Rennes, CHU Rennes, Inserm, Centre d'investigation clinique de Rennes (CIC1414), service de pharmacologie clinique, Institut de recherche en santé, environnement et travail (Irset), UMR S 1085, EHESP, 35000, Rennes, France

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