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Clinical Trial Data: The New EU Regime

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The European Medicines Agency moves to increase EU clinical trial transparency.

The last five years have seen a sea change in the attitude of EU authorities regarding the disclosure of clinical trial results, moving from a presumption of confidentiality to a willingness to disclose all but the most obviously commercially confidential information (CCI) and subject personal data.

The saga has three separate but related strands:

- Response to access requests under the EU transparency rules for information to an EU institution
- The European Medicines Agency's (EMA) policy on proactive release of clinical study reports (CSRs)
- The transparency rules under the new Clinical Trial Regulation

General EU Freedom of Information Principles

Under Regulation 1049/2001 (Transparency Regulation), there is a general obligation for EU institutions to release documents when requested. The exceptions are

- where disclosure would prejudice personal data privacy or
- where disclosure would undermine commercial interests.

An institution must consult the provider of the data where there is doubt about whether the information should or should not be disclosed.

The EMA recognises that CSRs can contain CCI, but any decision would be on a case-by-case basis reflecting the innovativeness or degree of difficulty involved in the design or conduct of the trial. For example, there will be a greater willingness to designate CCI information on a challenging trial in an ultra-orphan than a trial following established clinical research norms.

A team of EMA scientific reviewers will consult with the information originator and examine whether the CCI claim is justified. If a company disagrees with the EMA verdict, the company has to act quickly because it will only have 10 days from the decision to seek relief from the EU General Court.

The EMA Proactive Release Policy

This policy only applies to clinical trial data submitted after 1 January 2015 (applications before that time are subject to the Transparency Regulation) and does not apply to data held, other than under the Centralised Procedure.

Under the policy, only CSRs and summaries submitted to the EMA that are not in the public domain or publicly available and that undermine an applicant's legitimate economic interest are excluded from disclosure as CCI. Prior to the grant of the marketing authorisation (MA), an applicant submits a redacted set of the CSRs to the EMA based on redaction principles set out in the policy. That version of the CSR is then either accepted by the EMA or undergoes a consultation procedure to reach an agreed degree of redaction—ultimately, the EMA will have the final word.

The redaction principles are set out in Annex 3 to the policy, which lists the information that may be CCI. As with the Transparency Regulation, the EMA's view will be influenced by whether the information is in the public domain, including where the CSR follows standard regulatory guidance; whether economic harm could be caused; and the public interest in the disclosure.

Those who wish to view CSRs must agree to terms of use, which vary according to the access rights required. For simple screen access without the ability to download, there is an easy registration process. If an applicant wishes to download CSRs, the requirements are fairly extensive and include providing proof of identification and passport details. In either case, access must only be for noncommercial purposes and not for regulatory use, nor should there be any attempt to identify or contact the trial subjects. However, importantly, the EMA takes no responsibility for checking a user's compliance with the terms of use.

Because of unresolved difficulties about the treatment of personal data, the release policy has two phases: The first phase, which discloses only clinical reports without patient key codes, and the second, which takes effect once personal data issues are resolved through discussion with the European Data Protection Supervisor, will also include appropriately anonymised patient data.

In the EMA industry stakeholder meeting on 24 June 2015, further guidance was given about what constitutes CCI. It must be outside the public domain (for example, it cannot include information from websites, clinical trial registries, or patent applications); bear innovative features; and not reflect common knowledge shared within the scientific community. The 23 July 2015 meeting included further consideration of identifying and redacting CCI as well as on anonymising clinical reports for publication.

The CCI guidance presentation gives further detail on what does not constitute CCI, as well as the redaction proposal process and "justification table" required. Each piece of redacted text must be adequately justified to show how its disclosure would undermine an applicant's economic interest or competitive position.

New Clinical Trial Regulation

Article 81 of the Clinical Trials Regulation 536/2014 (CTR) provides for a new database that, once established, will contain all the data and information submitted under the regulation. All data are to be accessible, with the general exception of personal data and CCI. No data would be disclosed prior to approval of a trial, unless there is an overriding public interest. In general, however, CSRs would not be considered to be CCI once the MA was granted.

This regulation only takes effect when the database is ready (not before May 2016). However, in advance of May 2016, sponsors of any interventional clinical trials registered on the European Clinical Trials Database that ended on or after 21 July 2014 must post summary results as set out in Annex IV to the CTR with a layperson summary (Annex V) on the EU Database within six (if part of a paediatric plan) or 12 months at the end of a trial or intermediate data analysis date). Once the MA is granted, CSRs would be required. For trials that ended before that date, sponsors will need to submit summary results retrospectively.

A further recent consultation (EMA/42176/2014 of January 2015) explores certain opt-ins at the time of the CTA to

- limit disclosure to CCI Phase 1 studies (health volunteers) to trial number, sponsor name, site, and number of subjects and
- defer disclosure for authorised products until publication of the summary results.

There is an acknowledgement that certain documents may contain CCI, especially pre-MA grant, including the protocol, subject information sheet, investigator brochure, and the investigational medicinal product dossier (IMPD) and a presumption within the IMPD that the quality section would be CCI. There are four alternative proposals regarding other study-specific and IMPD documents respectively in relation to both authorised and unauthorised products, should they become accessible. The four alternatives range from publication in each the time of the trial decision to nine years after the first summary results are posted.

Getting Involved

The EMA regularly updates stakeholders on the progress of the implementation. These meetings also present the opportunity to continuously address those CCI and related issues that stakeholders perceive have not been sufficiently considered by the EMA.

Parallel to the above, EFPIA (the EU-level industry association) and PhRMA (the US trade industry association) launched their joint “Principles for Responsible Clinical Trial Data Sharing” to benefit patients, whereby, on request from qualified scientific and medical researchers, companies commit to sharing patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials for medicines and indications approved in the United States and the EU for legitimate research purposes.

These principles are a voluntary commitment from EFPIA and PhRMA members who will make their own determinations regarding how to implement these commitments and whether to exceed these common commitments to responsible data sharing.

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