

Clinical trial results disclosure on ClinicalTrials.gov and EudraCT

Holly Hanson

ICON Clinical Research United Kingdom Ltd

Correspondence to:

Holly Hanson
ICON Clinical Research UK Ltd
6 Stonecroft Rise
Chandlers Ford
Eastleigh
SO53 3LD
United Kingdom
+44 (0)162 849 3642
Holly.Hanson@iconplc.com

Abstract

The range of clinical trial results information that must be made publicly accessible is ever increasing both in the United States and the European Union. This brings a number of challenges, not least maintaining consistency across the publicly available data for a given trial. Furthermore, differences exist in the specific requirements for data disclosure on the ClinicalTrials.gov and European Union Drug Regulating Authorities Clinical Trials databases. The planning of disclosure of clinical trial results must occur alongside preparation to author the Clinical Study Report in order to meet this important legal obligation.

With the US Final Rule for Clinical Trials Registration and Results Information Submission (42 Code of Federal Regulations Part 11)¹ coming into effect on January 18, 2017, and the Clinical Trial Regulation EU No. 536/2014² entering into force on June 16, 2014, the expanding scope of the public disclosure of clinical trial data has become increasingly important for sponsors of clinical trials.

Why publicly disclose trial results?

The US Final Rule clarifies and expands the requirements for submitting clinical trial registration and results information to ClinicalTrials.gov in accordance with Section 801 of the FDA Amendments Act of 2007 (FDAAA 801).³



Failure to comply with these requirements can result in civil penalties of up to \$10 000 per day if required results are not submitted, and the withholding of grant funds for trials supported by federal agencies. However, the FDA has been criticised for never having imposed a fine on sponsors failing to publish clinical trial results.

The EU Clinical Trial Regulation will become applicable six months after the European Commission confirms that the EU clinical trials portal and database are fully functional, which is currently expected to occur early to mid-2020. The EU regulation requires member states to impose and implement penalties when the requirements are not met, stating that “The penalties provided for shall be effective, proportionate and dissuasive.”²

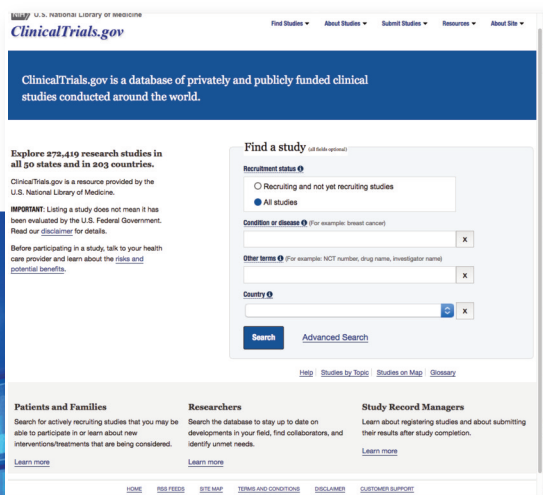
In addition to these regulatory penalties, the Inter-

national Committee of Medical Journal Editors now has requirements that clinical trials reported in their member journals contain a data sharing statement, either within the manuscript (as of July 2018) or within the trial’s registration (for trials that begin enrolling on or after January 1, 2019).⁴ Data sharing statements must indicate whether individual de-identified participant data (including data dictionaries) will be shared, what data in particular will be shared, whether additional, related documents will be available (e.g., study protocol, statistical analysis plan, etc.), when the data will become available and for how

long, and by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism).

Recently, the Evidence Based Medicine DataLab at the University of

The EU Clinical Trial Regulation covers all interventional clinical trials with medicinal products for human use conducted within the EU.



Oxford, UK, has developed and delivered an online tool which publicly monitors compliance with FDAAA 801 and the Final Rule, further increasing the public pressure on sponsors to adhere to the disclosure requirements.⁵

Which trials must be disclosed?

In the US, the Final Rule now requires results for all applicable clinical trials (ACTs) with a primary completion date on or after January 18, 2017, to be disclosed on ClinicalTrials.gov, regardless of approval status. Previously, results were only required for approved products. Device investigations are now also within the scope of ACTs. Table 1 summarises which studies are considered within the scope of an ACT.

The EU Clinical Trial Regulation covers all interventional clinical trials with medicinal products for human use conducted within the EU. This includes Phase I trials, which were previously exempt from the EU Clinical Trials

Directive (2001/20/EC) and are not considered ACTs per the Final Rule. However, Phase I trials conducted solely in adults which are not part of an agreed Paediatric Investigation Plan (PIP) are not made public. Non-interventional trials and trials without medicinal products (e.g., device studies, surgery, etc.) are not within scope.

Where are trial results posted?

Records can be prepared for disclosure on ClinicalTrials.gov directly in the web-based data entry system Protocol Registration and Results System (PRS). ClinicalTrials.gov establishes one PRS account for an organisation and this is managed by the organisation's PRS administrator. The PRS administrator can then grant individuals access to specific trials as required.

Similarly, records for disclosure in the EU can be authored directly in the EU Drug Regulating Authorities Clinical Trials databases (EudraCT) database. A primary user is assigned for a trial via the Clinical Trial Assignment Request Letter. The letter must be completed either by the sponsor, or the addressee of the decision on a PIP, or the marketing authorisation holder. The European Medicines Agency (EMA) then grants access for one primary user for the clinical trials listed in the letter who can then assign one backup user and multiple delegated results preparers and posters for each listed trial. Individual users apply for a single, personal account and are then assigned specific trials to edit by the primary user of the

trial. A template for the letter and accompanying instructions are available on the EMA website.⁶

In addition to authoring directly in the databases, there are specialist vendors who can offer tailored authoring software allowing users to manage the authoring, approval and release of records to PRS and EudraCT.

What trial results are disclosed?

US results disclosure

The US Final Rule requires that all primary and secondary outcome measures (endpoints) are disclosed on ClinicalTrials.gov, whether or not target accrual was met, the trial was terminated, or planned analyses were expected to yield statistical significance. Careful consideration should therefore be given to which endpoints are defined as primary and secondary when drafting the protocol. Trial endpoints need to be specifically defined to avoid ambiguity over what must be disclosed at a later date. For example, stating that the pharmacokinetics (PK) of Drug X is a secondary endpoint means all derived PK parameters should be disclosed. If only certain PK parameters are of interest as secondary endpoints, these should be specified, e.g., maximum plasma concentration, area under the plasma concentration-time curve from time zero to infinity, and half-life of Drug X. If data are collected and analysed at multiple time-points, consideration should be given as to whether it is appropriate to restrict primary or secondary endpoints to particular time-point(s) of interest.

The definitions for results data that must be submitted to ClinicalTrials.gov are provided in

Table 1. Applicable clinical trials per the Final Rule

In Scope	Out of Scope
Interventional clinical trials initiated on or after January 18, 2017	Phase I trials
Trials with one or more treatment arms	Device feasibility
Trials with one or more pre specified outcome measures (endpoints)	Expanded access use
Trials with at least one trial facility located in the US or a US territory	
Trials conducted under a US FDA Investigational New Drug application or Investigational Device Exemption	
Trials involving a drug, biological, or device product that is manufactured in and exported from the US (or a US territory) for investigation in another country	
Trials evaluating at least one drug, biological or device product regulated by the US FDA	
Paediatric post market surveillance of a device product	

Table 2. Content of trial results record submitted to ClinicalTrials.gov

Module	Content
Participant Flow	A tabular summary of the progress of participants through each stage of the trial, by trial arm or comparison group. Includes the numbers of participants who started, completed, and dropped out of each period of the trial based on the sequence in which interventions were assigned.
Baseline Characteristics	A tabular summary of the data collected at the beginning of the trial for all participants, by trial arm or comparison group. These data include demographics, such as age and gender, and trial-specific measures as appropriate.
Outcome Measures	A tabular summary of outcome measure values, by trial arm or comparison group. Includes tables for each pre-specified primary outcome and secondary outcome and may also include other pre-specified outcomes, post hoc outcomes, and any appropriate statistical analyses.
Adverse Event Information	A tabular summary of all serious adverse events and a tabular summary of other non-serious adverse events exceeding a specified frequency threshold (>0%, >1%, >2%, >3%, >4% or >5%). For each serious or other adverse event, the summary includes the adverse event term, affected organ system, the number of participants at risk, and number of participants affected, by trial arm or comparison group.
Limitations and Caveats	Describes significant limitations of the trial. Such limitations may include not reaching the target number of participants needed to achieve target power and statistically reliable results, or technical problems with measurements leading to unreliable or uninterpretable data.
Certain Agreements	Information indicating whether an agreement exists between the sponsor or its agent and the principal investigators (unless the sponsor is an employer of the principal investigators) that restricts in any manner the ability of the principal investigators, after the completion of the trial, to discuss the results of the trial at a scientific meeting or any other public or private forum, or to publish in a scientific or academic journal information concerning the results of the trial.
Results Point of Contact	Point of contact for scientific information about the clinical trial results information.

the ClinicalTrials.gov Results Data Element Definitions for Interventional and Observational Studies.⁷ The record is divided into seven modules: Participant Flow, Baseline Characteristics, Outcome Measures, Adverse Event Information, Limitations and Caveats, Certain Agreements and Results Point of Contact. The general content of each module is provided in Table 2.

EU results disclosure

In contrast, the EU Clinical Trial Regulation has a less definitive description of which endpoints are required. At least one primary endpoint is

required, and the EMA recommends that data for key endpoints are disclosed rather than mandating reporting of all primary and secondary endpoints.⁸ The EMA has previously advised that there is no link between results that must be disclosed and the primary and secondary endpoints specified in the protocol.⁹

Importantly, if trials are conducted both within the EU and the US, consideration must be given to ensuring the results presented on ClinicalTrials.gov and EudraCT are consistent given the different regional reporting requirements.

The definitions for results data that must be submitted to EudraCT are provided in the EudraCT Result Related Data Dictionary.¹⁰ The record is divided into six modules: Trial Information, Subject Disposition, Baseline Characteristics, End Points, Adverse Events and More Information. The general content of each module submitted to EudraCT is provided in Table 3.

Data considerations

Data requirements should be checked carefully, ideally during production of the Statistical Analysis Plan, to ensure all required data will be tabulated and summarised. Some data, such as non-serious adverse events and the number of participants enrolled per country, are not commonly summarised for the Clinical Study Report (CSR). Detailed information on the requirements for each module can be found in the guidance documents.^{7,10} However, a few points are worth noting and should be shared with any persons performing quality control (QC) of these records to avoid redundant QC findings:

- Fields within the database are annotated with symbols to indicate information which is mandatory, information which is conditionally required, or optional information.
- Some of the fields may only be completed by selecting from a drop-down menu thus restricting the content.
- Some fields have character limits restricting the amount of free text that can be included.

When must trial results be disclosed?

FDAAA 801 requires results to be submitted for ACTs no later than 12 months after the primary completion date, defined as:

The date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Results may then need to be updated following the study completion date, defined as:

Table 3. Content of trial results record submitted to EudraCT

Module	Content
Trial Information	Includes trial identification details, paediatric regulatory details, sponsor details, results analysis stage, general information about the trial, the number of participants enrolled per country and a breakdown of the trial population by age group.
Subject Disposition	Includes details of recruitment of trial participants, screening, blinding implementation, trial products, and a tabular summary of the progress of participants through each stage of the trial, by trial arm or comparison group.
Baseline Characteristics	A tabular summary of the data collected at the beginning of the trial for all participants, by trial arm or comparison group. These data include demographics, such as age and gender, and trial-specific measures as appropriate.
End Points	A tabular summary of endpoint values, by trial arm or comparison group. Includes tables for primary endpoint(s) and secondary endpoint(s) and may also include other pre-specified endpoints, post hoc outcomes, and any appropriate statistical analyses.
Adverse Events	A tabular summary of all serious adverse events and a tabular summary of other non-serious adverse events exceeding a specified frequency threshold (>0%, >1%, >2%, >3%, >4% or >5%). For each serious adverse event, the summary includes the adverse event term, affected organ system, number of participants at risk, number of participants affected, number of occurrences, number of occurrences causally related to treatment, number of fatalities, and number of fatalities causally related to treatment, by trial arm or comparison group. For each non-serious adverse event, the summary includes the adverse event term, affected organ system, number of participants at risk, number of participants affected, and number of occurrences, by trial arm or comparison group.
More Information	Includes details of substantial global protocol amendments, global interruptions to the trial, limitations and caveats and online references.

Given that no such process currently occurs for records submitted to EudraCT, addressing these NIH review comments may further contribute to inconsistencies between results disclosed in the US and EU.

The EU Clinical Trial Regulation requires a summary of results of a clinical trial to be submitted to EudraCT within 12 months of the end of the clinical trial, i.e., the last visit of the last participant, or at a later point in time as defined in the protocol. However, the regulation permits results to be submitted after this deadline if there are valid scientific reasons detailed in the protocol. In these cases, the summary of results must be submitted as soon as possible, and the protocol must specify when the results will be submitted, together with a justification for the delay. Results for paediatric trials within the scope of Article 41 or Article 46 of the Paediatric Regulation,^{11,12} or in an agreed PIP, should be posted to EudraCT within six months of the end of the trial, unless this is not possible for objective scientific reasons.¹³ Results for non-paediatric trials included in an agreed PIP should be posted within 12 months of the end of the trial.

Planning results disclosure

The length of time it takes to prepare results records will mainly be driven by the number of endpoints and any associated statistical analyses, and the number of serious and non-serious adverse events that occurred during the trial. Data can be entered manually or uploaded using Extensible Mark-up Language (XML) files. XML schemas are available online for both ClinicalTrials.gov¹⁴ and EudraCT.¹⁵ If both US and EU results records are required, efficiencies can be made if one record is completed prior to starting the other. Preparation of the required records should be part of the overall study timeline to ensure compliance with the regulations.

Conclusion

The requirements for public disclosure of trial results, including data that are not readily available as part of the CSR summary tables, should be considered in a timely manner to allow the regulations to be met. Consistency of publically available data must also be taken into account given that lay summaries and redacted CSRs will now also be released for public viewing in the EU. Although seemingly burdensome,

The date the final participant was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (for example, last participant's last visit), whether the clinical study concluded according to the pre-specified protocol or was terminated.

that an ACT reached its study completion date before the drug, biologic, or device was initially approved, licensed, or cleared by the FDA for any use, or that the trial investigates a new use (i.e., not included in the labelling). A request to extend the deadline for submission of results for “good cause” can also be made.

Once results have been released via PRS, the record undergoes a QC review by the National Institutes of Health (NIH) to ensure the clarity and completeness of the information submitted. It is important to

Of note, if the primary completion date and study completion date occur in close proximity, it may be possible to submit one record within the 12-month deadline.

Results disclosure on ClinicalTrials.gov may be delayed by submitting a certification

Preparation of the required records should be part of the overall study timeline to ensure compliance with the regulations.

note that the record will not be released publically until it passes this QC step and to do so may take several iterations.



complying with the disclosure regulations can only have a positive impact on the wider public perception of the pharmaceutical industry.

Disclaimers

The views expressed in this article are those of the author and do not necessarily reflect those of ICON Clinical Research United Kingdom Ltd or EMWA.

Conflicts of interest

The author is employed by ICON Clinical Research United Kingdom Ltd.

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Author information

Holly Hanson, PhD, trained as a pharmacokineticist before moving into medical writing. Holly has over 15 years of medical writing experience. Her areas of expertise are Phase I/II studies and public disclosure of clinical trial results. Holly is currently a medical writing manager with ICON Clinical Research United Kingdom Ltd.