Publication of clinical trial protocols and statistical analysis plans on ClinicalTrials.gov

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Abstract
According to the final rule on "Clinical Trials Registration and Results Information Submission", clinical trial protocols and statistical analysis plans have to be published on ClinicalTrials.gov. The requirement affects all applicable clinical trials with a primary completion date on or after January 18, 2017. Personally identifiable information, as well as any trade secret and/or confidential commercial information can be redacted, before documents are made public. This article reviews the limited available guidance on how to prepare the documents for publication and the key questions to be addressed.

Once considered confidential documents, many clinical study protocols and statistical analysis plans (SAPs) are now publicly available on a variety of platforms: the Policy 0070 "Clinical Data" website of the EMA,[1] websites of some medical journals that follow the Recommendations of the International Committee of Medical Journal Editors, and clinical trial websites of a number of clinical research sponsors. However, following the implementation of the final rule on "Clinical Trials Registration and Results Information Submission", the most comprehensive source of original study protocols and SAPs for recent studies is by now ClinicalTrials.gov. As of March 3, 2019, the ClinicalTrials.gov registry held more than 3500 records of interventional studies with protocols (and/or SAPs) publicly available. More than 93% of these studies had a primary completion date on or after January 18, 2017, the effective date of the final rule.[2] This demonstrates the large impact that the final rule has already had.

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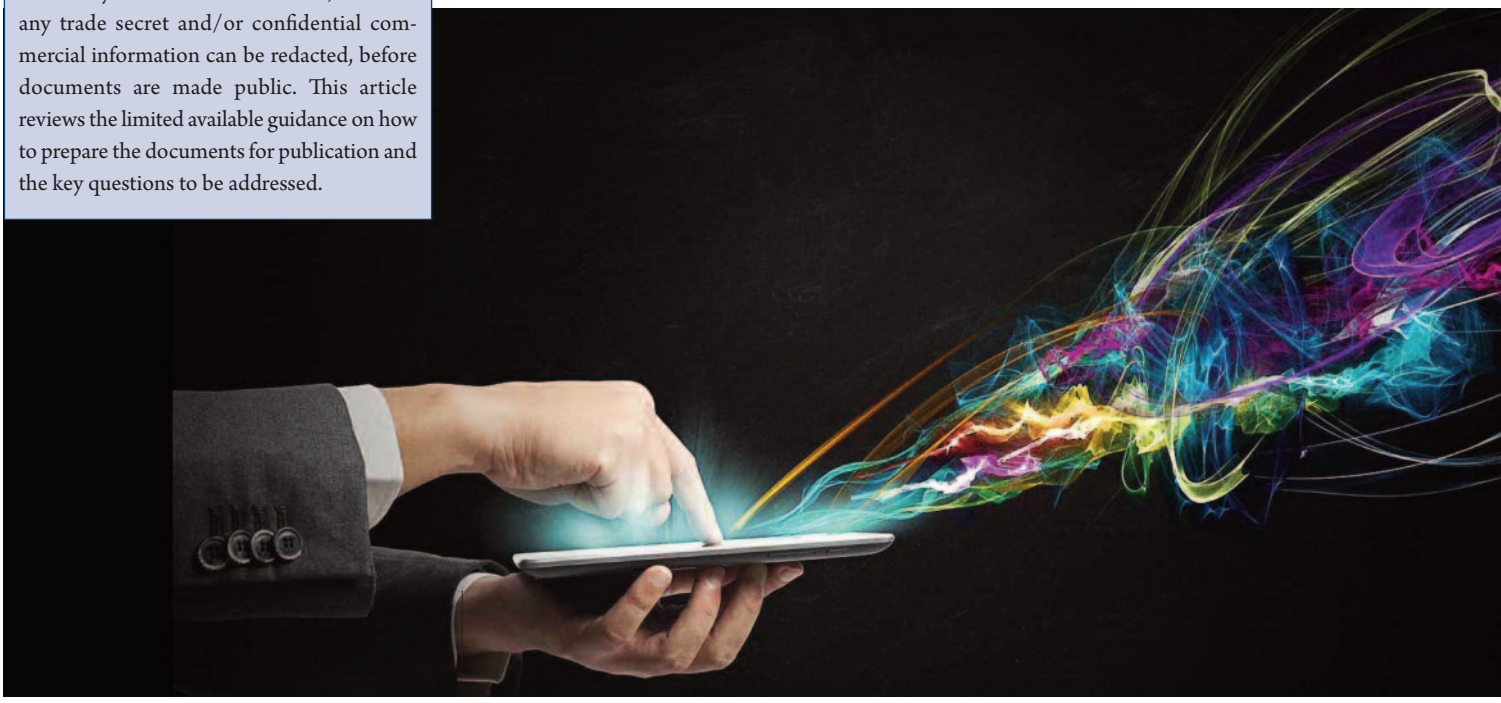
Section 801 of the US Food and Drug Administration Amendments Act of 2007 mandates the submission of registration and results information for certain clinical trials. Further rulemaking was foreseen by the Amendments Act to clarify and expand the requirements. Accordingly, the final rule was issued in September 2016 by the US Department of Health and Human Services.[3-5] This article focuses on the publication of study protocols and SAPs according to the final rule. The relevant key content of the Code of Federal Regulations is displayed in Figure 1. For a summary of the results-related requirements of the final rule, refer to Hanson.[6]

The results and document-related aspects of the final rule concern applicable clinical trials with a primary completion date on or after January 18, 2017. A study is considered an



applicable clinical trial, if it meets the criteria summarised in Figure 2. Primary completion date of a study is defined as the date that the final participant was examined or received an intervention for the purpose of final collection of data for the primary outcome.[7] According to the final rule, all applicable clinical trials that need results posted also require the publication of the clinical trial protocol and the SAP (if not part of the protocol). For both documents, at least the most recent version, i.e., after the latest global amendment, needs to be posted.[4]

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Interestingly, the Proposed Rule had not stipulated the publication of the full protocol and SAP but had invited comments on the benefits and burdens of such a potential requirement. Following an assessment of the comments received, the US Department of Health and Human Services concluded that the benefits of making protocol and SAP publicly available would clearly outweigh the burdens on responsible parties. The main advantages are cited as:

- Improves transparency and quality of reporting
- Is necessary for a full understanding of a study's results and replication thereof
- Safeguards against reporting bias
- Facilitates meta-analyses
- Improves the design of future studies
- Reduces unnecessary duplication of studies
- Promotes standardisation of protocol elements
- Avoids multiple individual requests for these documents.[4]

The default requirement is to make the protocol and SAP available at the same time as the results, i.e., within 12 months of the primary completion date. In certain cases, the results posting, and thus the publication of trial documents, may be delayed for up to two years. This is permitted, if the product was not yet initially approved by the FDA, when the primary completion date of the trial was reached. The delay is also possible, if a new use of the product (e.g., a new indication) has been filed with the FDA or is planned to be filed within one year. In exceptional cases, an extension of the submission deadline can also be requested for "good cause".[4,7]

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When a responsible party fails to submit the mandatory registration and/or results information (now also including the protocol and SAP), the FDA can seek civil money penalties of up to $10,000 per day.[3] Apparently, no fines have been imposed so far, for which the FDA has been heavily criticised by some transparency advocates.[8,9] In September 2018, the FDA issued a Draft Guidance summarising their intention on how to implement the monetary penalties.[10]

§ 11.48 What constitutes clinical trial results information?

(a) For each applicable clinical trial, other than a pediatric postmarket surveillance of a device product that is not a clinical trial, for which clinical trial results information must be submitted under § 11.42, the responsible party must provide the following:

… …

(5) ***Protocol and statistical analysis plan.*** A copy of the protocol and the statistical analysis plan (if not included in the protocol), including all amendments that have been approved by a human subjects protection review board (if applicable) before the time of submission under this subsection and that apply to all clinical trial Facility Locations. The responsible party must include the Official Title (as defined in § 11. 10b(2)), NCT number (as defined in § 11. 10a) (if available), and date of the protocol and the statistical analysis plan on the cover page of each document. The responsible party may redact names, addresses, and other personally identifiable information, as well as any trade secret and/or confidential commercial information (as those terms are defined in the Freedom of Information Act (5 U.S.C. 552) and the Trade Secrets Act (18 U.S.C. 1905)) contained in the protocol or statistical analysis plan prior to submission, unless such information is otherwise required to be submitted under this part. The protocol and statistical analysis plan must be submitted in a common electronic document format specified at *https://prsinfo.clinicaltrials.gov.*

Figure 1. Excerpt from Code of Federal Regulations mandating the publication of clinical trial protocols and statistical analysis plans.
Relevant key content of Part 11 in Title 42, Chapter I, Subchapter A of the Code of Federal Regulations is shown.[7]
Abbreviations: U.S.C., United States Code

While many affected studies have publicly posted results and documents, the overall compliance rate with the final rule leaves room for substantial improvement. The actual compliance in terms of timely posting can be monitored overall and for individual sponsors using the online tracker developed by the Evidence-Based Medicine DataLab at the University of Oxford, UK.[11-13]

Applicable clinical trials

- Interventional study, i.e., a clinical trial
- Any of:
  - At least one study site in the US or a US territory
  - Conducted under an FDA Investigational New Drug application or Investigational Device Exemption
  - Product manufactured, packaged, or labelled in the US or a US territory
- Product regulated by the FDA
- Not Phase 1 (for drug product) or not device feasibility study (for device product)

Figure 2. Definition of an applicable clinical trial per the final rule.
All four criteria must be met. For further details, refer to the National Library of Medicine checklist.[15]

How to prepare documents for publication

The regulations concede that the responsible party may protect certain information through redaction, before making the trial documents public. Per the Code, the following may be redacted: "personally identifiable information, as well as any trade secret and/or confidential commercial information … unless such information is otherwise required to be submitted under this part" (see Figure 1). The guidance on the extent and format of redactions is, at best, scarce. What is clear is that the responsible party, not the FDA, decides on the redactions and makes them. Also, "essential details necessary to understand the results" must not be redacted. Furthermore, although not expected, should personally identifiable information about individual clinical trial participants be present, "it should be redacted". The Agency reserves the right to provide "more specific guidance regarding redaction" later and to challenge a responsible party, if it appears that redactions are inappropriate.[4]

When approaching the redactions, responsible parties need to address many questions, some of which are listed below. The decisions are company-specific and affect, for example, the consistency of redactions on different public platforms and the effort needed to prepare redacted documents. Questions for consideration include: 1. Should redactions of personally identifiable information follow the same approach as employed for other transparency channels, e.g., EMA Policy 0070? 2. How much should be redacted as commercially confidential? Usually, product development is at an earlier stage when documents need to be published on ClinicalTrials.gov than for Policy 0070 publication. Therefore, more information may need to be considered commercially confidential than for Policy 0070. 3. Should copyrighted content, e.g., questionnaires or scales, be redacted? In contrast to the Policy 0070 "Clinical Data" website, no login or "acceptance of terms of use" is needed to view or download documents from ClinicalTrials.gov. Thus, the responsible party has no control over what a user of ClinicalTrials.gov might do with the documents. 4. Which style and format of redactions should be applied? 5. Should redacted documents on ClinicalTrials.gov be replaced by subsequent document versions with fewer redactions, once these become available on other platforms? Per the Code of Federal Regulations, there is no requirement to update the protocols and SAPs (unless for a protocol amendment).[4] Further questions – for example, when to prepare the redacted documents, which functions to involve, how to decide on redactions, and which software to use – are largely independent of ClinicalTrials.gov.

The regulations require the NCT number, i.e., the ClinicalTrials.gov identifier, on the cover page of each document, if this number is available. In addition, the official study title and the date of the document must be stated on the cover page (see Figure 1). Given that a study protocol is normally finalised before the NCT number is assigned, this number is typically not present in the original protocol. Thus, extra cover pages may be added or the NCT number could be inserted on the title

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pages of the redacted documents. Finally, the Code states that documents "must be submitted in a common electronic document format" (see Figure 1). This is specified on the website of the Protocol Registration and Results System as the Portable Document Format Archival (PDF/A) file format.[14]

A cursory review of a few randomly selected studies conducted by 20 mid-sized and large biopharmaceutical companies revealed that the extent and format of redactions are quite variable. Some documents have no or almost no redactions, while others have full paragraphs or occasionally even full sections redacted. Sometimes the redactions follow the Policy 0070 style, other times simple black bars without overlay text are used. Overall, some common principles emerge, i.e., redaction of names and addresses of certain sponsor and vendor personnel and a tendency to redact exploratory endpoints and related analysis methods.

Conclusions

Writing clinical documents that are as transparency-ready as possible will save time and resources later, when these documents need to be made public. Documents without or with few commercially confidential items and with little personally identifiable information require no or only few redactions (or anonymisation via other methods). This not only helps with the final rule but generally facilitates the compliance with the divergent transparency requirements.

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Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by her employer.

Conflicts of interest

The author is employed by Teva Pharmaceuticals International GmbH.

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