

The Lay Protocol Synopsis: Requirements and feasibility

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Abstract

The EU Regulation 536/2014 included a requirement for companies to produce a Protocol Synopsis with a recommendation for a version in lay language. This requirement stated, among other things, a maximum length of two pages. This article outlines the requirements of the regulation with respect to the Protocol Synopsis, and discusses their feasibility in light of the maximum page limit.

In 2014, the EU introduced a new regulation: EU CTR 536/2014.¹ This regulation replaced the previous Clinical Trials Directive 2001/20/EC,² and became mandatory with the opening of the Clinical Trials Information System (CTIS) on January 31, 2022. The new regulation was introduced to ensure that the rules for the assessment of clinical trial applications and the conduct of clinical trials were identical throughout the EU. There were many new aspects introduced by the regulation, and as part of the EMA's drive towards transparency and openness, it included requirements for sponsor companies to produce a Lay Summary of Clinical Trial Results, as well as a recommendation for a Protocol Synopsis in lay language.

Both of these requirements have caused much discussion in the industry, because they called upon a completely different writing skill set. For the first time, companies were required to explain complex scientific and clinical information clearly, concisely, without being biased or promotional in any way, and in a manner that is also understandable to the general public. The content requirements of the Lay Summary of

Clinical Trial Results are outlined in full in Annex V of the Regulation, but in contrast, the Protocol Synopsis is only mentioned in one line in Annex 1 (D.24), which states simply, "the protocol shall be accompanied by a synopsis of the protocol".

In response to requests for more guidance, the Protocol Synopsis content requirements were discussed in more detail in the latest Question & Answer document (version 6.2), which was issued by the Authority in September 2022.³ These requirements are extensive and include a maximum page allowance. This article will look at the requirements for the Protocol Synopsis in lay language and discuss if it is feasible to produce the document as required.

What is the Protocol Synopsis?

Quite simply, the Protocol Synopsis is a summary of the main aspects of the protocol, and there is a recommendation from the Authority to produce a version in language that is "understandable to a layperson." The latest guidance does not state what a "layperson" is considered to be, but it does outline the nine sections that should be included in the synopsis, with some description:³

1. **EU trial number and full trial title**
2. **Rationale:** Specify the background and hypothesis of the trial.
3. **Objective:** Specify the main and secondary objectives of the trial.
4. **Main trial endpoints:** Describe the main trial endpoints and when they are assessed, e.g. the main trial endpoint is the percent change in the number of events from baseline to a specified time, or the total number of adverse reactions at a particular time after baseline.
5. **Secondary trial endpoints:** Describe the secondary trial endpoints, and when they are assessed, e.g. the number of adverse events until 30 days after the end of treatment.
6. **Trial design:** Describe the design and the expected duration of the trial for the individual subjects, e.g. double-blind, placebo-controlled clinical trial, where subjects are participating for X weeks.
7. **Trial population:** Describe the trial population, indicating the main inclusion

criteria, including age and disease/healthy volunteer and the main exclusion criteria to protect the subject, e.g. patients with moderate asthma, 18–55 years, with normal kidney and liver function and without gastrointestinal ulceration or risk factors for a cardiac arrhythmia; healthy volunteers, 18–60 years, who have not been exposed to radiographic examinations during the last 12 months.

8. **Interventions:** Describe interventions and treatment duration, also including background treatment if any, e.g. one group receives a 10 mg tablet of product X twice daily for Z weeks while also receiving product Y as background treatment, and the other group receives a placebo tablet twice daily, as well as product Y. Also describe trial-related diagnostic and monitoring procedures used.
9. **Ethical considerations** relating to the clinical trial, including the expected benefit to the individual subject or group of patients represented by the trial subjects, as well as the nature and extent of burden and risks: A benefit-risk analysis should be done for the trial-specific treatments and interventions, clearly explaining if the trial involves an expected individual benefit (e.g. as required in emergency situations) or a group benefit. When a trial is placebo-controlled, a brief justification should be given. If a non-therapeutic trial is carried out in vulnerable groups, e.g. in minors, incapacitated persons, pregnant or breastfeeding women, their inclusion has to be justified, and it should be explained why the risks and burden are considered minimal and why the trial can only be performed in this particular patient group. The trial-specific risks and burdens for subjects and caregivers (if applicable) related to diagnostic, therapeutic, and monitoring procedures should be justified, e.g. the amount and number of blood samples, the number of site visits, physical examinations, or other tests, as well as any physical and physiological discomfort associated with trial participation.



Furthermore, unlike the Lay Summary of Clinical Trial Results, the Protocol Synopsis has a required maximum page limit of two pages.

Challenges

Aside from the general challenges of writing for the general public (which are outside of the scope of this article), there are a number of specific challenges associated with the Protocol Synopsis requirements as set by the Authority.

There is no guidance about how much background should be given in section 2, or how many secondary objectives should be given in section 3 (the implication being that all of them should be included). The

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objectives, main, and secondary trial endpoints (which must be described in sections 4 and 5) can be very complex and take a large amount of space to explain in plain language, a problem that is compounded by the requirement to not only describe, but state the timeframe of the assessments. The trial design and population (sections 6 and 7) can also be very complex and potentially confusing, and are often most easily explained using infographics, which can work very well but do take up a lot of space.

Section 7 also requires the inclusion and exclusion criteria to be described, which can be extensive, involving a lot of complicated clinical and technical terms and assessment criteria. A description of the inclusion and exclusion criteria in clinical regulatory language often takes a page

alone (and we must consider that extra words are often necessary to explain concepts in plain language), and the requirement to include a description of the background treatment and trial-related diagnostic and monitoring procedures (section 8) could be extremely lengthy, depending on the therapy area.

Similarly, section 9's requirements for an ethical discussion and a benefit-risk analysis would be extremely challenging to condense into a meaningful, plain-language document.

Conclusions

Considering that the guidance on the requirements of the Protocol Synopsis runs to a page and a half on its own, and that in general, it takes more words (and therefore, more space) to explain complex concepts in plain language, the two-page limit would make a fit-for-purpose document almost impossible to achieve for all but the most simple of studies. This is a great shame (and cause of much frustration) because arguably a plain



language Protocol Synopsis is most needed for more complex studies.

Some companies are ignoring the recommendation completely. Some are exploring the use of a glossary to allow them to circumvent the two-page limit by adding explanations of terms and abbreviations to a separate document. Unfortunately, this not only risks uncoupling the glossary from the main text, but also requires the reader to do quite a lot of memory work and cross-referencing, just to be able to understand the document – surely the opposite of what any plain language document, but especially the Protocol Synopsis, is trying to achieve.

However, the Authority must be applauded for recommending a version of the Protocol Synopsis in lay language. The concept is sound – providing a simplified, easy-to-understand summary of how and why a study was done for the general public is necessary. Additionally, the Protocol Synopsis could and should form a great basis for the Lay Summary of Clinical Trial

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Results document, and the plain language used in the Informed Consent Form could be brought forward to both documents, thereby minimising effort and simplifying the messaging for the general public.

A suggested page limit is a very sensible strategy to avoid long, convoluted, unclear documents (whether in plain language or not!), but I fear that having a strict limit disincentivises companies to even try to produce these documents in plain language – the task in many cases is just too daunting, if not unachievable. My hope is that the Authority allows some flexibility on this page limit. Surely it would be better to have a three-page Protocol Synopsis that is clear and understandable, than a two-page document that the public cannot understand.

Disclosures and conflicts of interest

The author declares no conflicts of interest.

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