DRAFT VERSION

For Public Consultation

Reshaping the trial protocol synopsis into a lay-friendly trial summary – recommendations of an expert group

A proposal based on the EU Clinical Trial Regulation Q&A document

Introduction

With the launch of the Clinical Trial Information System (CTIS) on 31 January 2022, the Clinical Trial Regulation (EU CTR) 536/2014 became fully applicable in the European Union (EU) and the European Economic Area (EEA).[1] Annex I of the EU CTR, Section D (24) specifies that the trial protocol shall be accompanied by a synopsis. The content expectations of the protocol synopsis were specified in a Question and Answers (Q&A) document published by the Clinical Trials Coordination and Advisory Group (CTCG) shortly before the go live of CTIS (version 4.1, January 2022). The Q&A clarified that the protocol synopsis should have a "maximum of 2 pages" and that the language requirements of the participating countries made available in Annex II of the Q&A needed to be adhered to. In addition, it is stated "Sponsors should consider to make the synopsis understandable to a layperson." Currently several terms are used for this document, e.g., "Protocol Plain Language Summary (PPLS)" or "Lay Summary of the Protocol Synopsis", however in this document the term "lay protocol synopsis (LPS)" is used.

Since the release of Q&A version 4.1 in January 2022, the requirements for the protocol synopsis have remained unchanged, despite numerous updates to the document (current version 7.1, released in March 2025)[2]. The synopsis requirements are outlined as a list of 9 numbered elements. Except for item #1, each element includes a numbered heading-like title and a description of the required content. While the numbering suggests a sequence, it is not explicitly stated that this sequence must be followed.

Neither the EU CTR nor the Q&A defines the target audience for the LPS. Industry perspectives vary, suggesting the audience extends beyond the general public, and includes trial participants, and those considering participation (and their caregivers), and also lay members of ethics committees (ECs) who need a quick, accessible overview of the protocol. In any case, sponsors need to produce LPS on a reading level that is suitable for all interested parties.

The content descriptions range from no detail (#1) or a single line (#2, #3) to a 13-line explanation for #9 "Ethical considerations" which requires extensive justifications of trial design features. These justifications duplicate content from the protocol and ICF, making it overly demanding for a document intended to be a concise synopsis.

Given the lack of additional guidance from the European Medicines Agency (EMA) or Clinical Trial Coordination Group (CTCG) on protocol synopsis content, and the mandatory nature of

the synopsis for clinical trial applications in the EU/EEA, sponsors have developed their own approaches. This has resulted in significant variability in protocol synopsis structures, as seen in publicly available documents in CTIS.

A sub-group of the working group that developed the Good Lay Summary Practice Guidance (GLSP)[3] and additional international experts such as lay language practitioners, lay summary experts, patient advocates, disclosure and transparency experts from pharmaceutical companies, strongly support the notion of a protocol synopsis that is understandable to non-specialists, hence the available guidance needs a more detailed elaboration. We have not included of recommendations on the use of plain language, the planning, writing, and translation of the LPS as the recommendations developed for lay summaries of study results made available in the GLSP are readily transferable to the development of the LPS.

In particular, we suggest that:

- In general, the presentation of the information in the LPS should be lay-friendly. Therefore, the guidance for the LPS should align with the principles for the writing of the lay summary of study results as provided by the GLSP which was endorsed by the European Commission and included into EudraLex Vol. 10.[3]
- Key aspects need further clarification, e.g., a firmer statement that the LPS is intended for non-specialists and that the document should be made available in all the languages of the participating countries.
- The guidance per section is often scant, it should be more balanced and should incorporate recommendations for best practices in lay-friendly communication.
- The guidance should encourage the use of graphics as they allow for a succinct summarisation of certain items, e.g. the trial design.

The LPS in the context of the other available information in CTIS

According to the revised CTIS transparency rules, in addition to the LPS, the protocol, the Informed Consent Forms (ICF), and patient-facing documents such as questionnaires become publicly available. Furthermore, the content in the structured data fields in CTIS is made available publicly. Thus, for each trial, extensive information is provided and the information is made available on different levels of detail: the LPS for a lay audience, the protocol for the investigator, the ICF for potential study participants. This permits that the LPS is written and designed in a way that it can fulfil its primary purpose of summarising a clinical trial in a structured way in a short text suitable for non-experts. While a high-level summary is provided in the LPS, details are provided in the protocol and/or the ICFs. It is therefore important to delineate the information provided in the LPS from that in the other documents. It is recommended to include references in a LPS to the more detailed information in the other publicly available documents. For example, due to the length limitation, a comprehensive description of potential benefits and risks cannot be provided in Section #9 “Ethical considerations”. At the same time, a detailed description of benefits and risks is available in the ICF. Therefore, in the LPS, a reference to the ICF should be provided

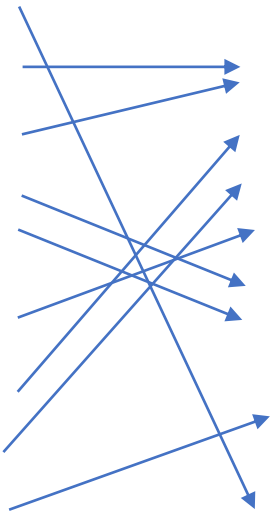
instead of a redundant elaboration particularly since both documents are written for non-experts.

Additionally, the full clinical trial approval pathway, i.e. dossier submission, competent authority and ethics committee review, approval, and ongoing regulatory oversight, safeguards participants' interests. Because these bodies critically assess benefits and risks, as well as the inclusion of minors and other vulnerable groups, extensive justifications on these points are not required in an LPS; they are addressed by the trial approval process itself.

Does the order of the items provided in the Q&A need to be adhered to? – A more lay-friendly presentation is highly recommended

The current sequence of items in the Q&A loosely follows the structure of the protocol as described in ICH E6 (R3). The guidance provided does not contain a statement, that the order is compulsory. While the protocol is intended for investigators to inform them about the background and conduct details of a trial, this sequence of topics might be less relevant for a lay audience. For example, for a lay reader, topics as a trial population with the description of eligibility criteria (trial population #7) and the interventions (interventions #8) might be of greater interest than the rationale (#2) or the endpoints (#3). Also, the sequence of topics should be chosen to best represent the clinical trial at hand. In summary, sponsors should strive to develop the appropriate sequence depending on the objective and trial design. Therefore, the sequence as provided in the Q&A should be adapted as to best inform a lay audience. Ideally input of patients should be sought when designing LPS templates for different trial types and the different clinical development phases.
The items in the Q&A are provided in a heading-like structure; however, these headings are not very informative for lay people. All topics should be presented in a question format because this format is more readily understood by non-specialists (see GLSP guidance).

Proposal for a lay-friendly structure of an LPS for an interventional study

Structure as represented in the Q&A	**Correspondence**	**Proposed new structure**
EU trial number and full trial title		Lay title
Rationale		Why is this study needed?
Objective		Who can participate in the study?
Main trial endpoints		What treatments are given?
Secondary trial endpoints		How is the study designed?
Trial design		What are the goals of this study and how will they be measured?
Trial population		What are the potential benefits and risks?
Interventions		Full scientific title
Ethical considerations		EU CT in header or footer

Length of the LPS: 2- 3 pages for the English version

In the answer to question 5.8 of the Q&A it is stated that the protocol synopsis should have a maximum of 2 pages. While the term synopsis implies the notions of brevity, overview, and summarisation, the reasons for the length limitation to 2 pages remain indeterminate. Most importantly it remains unclear whether the length limitation pertains to the English version of the LPS or also to the translations. For many sponsors the company language is English and therefore the LPS tends to be written, reviewed, and approved in English. Translation of the final document is an additional step. Translations of English texts into several national languages usually leads to an expansion of 20% to 40% in length. Hence an English text of 1000 words (roughly 2 pages of text) will result in a text of 1200 to 1400 words when translated into Spanish, Portuguese, German, Polish, or Hungarian.

Since the content requirements for a LPS are comprehensive, a very densely written text compressed into 2 pages will be substantially less readable and therefore less understandable than an adequately spaced text that uses white space to convey structure and coherence. Furthermore, graphics that facilitate understanding can much more easily be used in a document without a strict length limit. It is therefore recommended to allow the LPS to expand to 3 pages in the English version and to go beyond that in the translations. Many sponsors have adopted similar policies, and the ethics committees and competent authorities involved in the approval of clinical trials appear to accept LPS longer than 2 pages.

Language requirements for LPS: national language versions in all countries

The Q&A points to the national language requirements for LPS detailed in Annex II of the document. Of the 30 countries listed, 5 countries (Denmark, Estonia, Finland, Latvia, Portugal) whose national language is not English, and Ireland, accept LPS that are only provided in English; 24 countries require that the LPS is translated into their national language. Five countries (Czechia, Greece, Italy, The Netherlands, Slovakia) require that the version in the national language is supplemented by an English version, and Belgium requires the LPS be made available in all 3 national languages (Dutch, French, German). Clearly, the approaches vary across the EU/EEA countries which creates complexity both for sponsors in the production of the LPS and for participants and patient organisations looking for clinical trials; participants from Denmark, Estonia, Finland, Latvia and Portugal are currently not provided with an LPS in their national language.

To make the LPS a lay-friendly document it is recommended to generally provide the LPS in all languages of the participating countries plus a version in English. Such a single and straightforward recommendation would facilitate the production of the LPS and ensure that all interested readers have access to a copy in their national language in all the EU/EEA countries. Despite the absence of guidance, it has become common practice that ECs and competent authorities check the availability of the LPS in the national languages.

Who is a layperson? – LPS should aim for the general public

LPS are made publicly available on the CTIS public portal, and the LPS can be accessed by anybody who has some interest in a particular clinical trial. The Q&A takes this into account and expresses that the "sponsor should consider to make the synopsis understandable to a layperson". A layperson is generally understood as a person who is not an expert in a particular field. In the case of LPS, this may mean a person who is not an expert in clinical research or medicine. Given the fact that LPS of clinical trials are publicly available, the interested public should be considered as one of the main audiences. Consequently, the language used in the LPS should be easy to understand (follow plain language principles), not use (or explain) uncommon terms and abbreviations, and should avoid clinical research expert terminology. Clearly, there are other potential audiences with an interest in LPS, e.g., healthcare professionals, researchers and scientists, industry professionals, potential participants, members of patient advocacy groups, each with different expectations, background knowledge, and motivation, and preferences in regard to language level. Furthermore, in the context of the EU CTR and clinical trial authorisation, there is a more immediate audience for LPS, namely the lay members of the ethics committees (ECs) who contribute to the assessment of clinical trial applications.

The multitude of potential audiences is best served by using a simple straightforward language that follows plain language principles. Members of the public without prior knowledge will derive greatest benefit from LPSes written in simple clear language free of technical terms. Using simple sentences and focussing on core information will help keeping the LPS to the length limit. Developing an English "mother" LPS in simple language will also facilitate translation.

Should an LPS be redacted? – No, there should be no redaction

Particularly for early phase trials such as phase I trials in patients and healthy volunteers and in combined phase I/II trials, there is a potential tension between the requirements outlined in the Q&A and the need for sponsors to protect commercially confidential information (CCI). As in the protocol or in the ICF, CCI is redacted in the LPS by blocking the information with a black bar. There are several sections mentioned in the Q&A that could contain CCI, e.g. rationale (#2), objective (#3), endpoints (#4) trial design (#6), and interventions (#8). To be useful for a lay audience, the LPS should be fully accessible, i.e. not contain elements that are made inaccessible. To make an LPS lay-friendly, sponsors should strive to generate LPS that are free of commercially confidential content. Information on dosing, e.g., in a trial comparing 2 dose levels, should then be given in a way that does not require redaction. The trial could be described as testing a "low" dose versus a "high" dose without providing the exact numeric values.

Use of specialised terms and abbreviations

As LPSes are targeted for a lay audience, technical terms and specialist medical terms should be avoided. If technical terms are needed, they should always be followed by an explanation, potentially in brackets. Alternatively, as text with a lot of brackets is difficult to read, the LPS could be provided with a short glossary, preferably at the end of the document. If a glossary is included, the readers need to be informed of its availability at the beginning of the LPS. Also, a reference to an external glossary is possible.

Specific recommendations for the individual sections

1. **Q&A Text:** *EU trial number and full trial title*

   Our recommendation:
   While the EU CT number should be provided for reference to the record in the CTIS public portal it should not be overly prominent, e.g., it should be provided in the header or footer section of the document.

   Other main registries such as ClinicalTrials.gov have decided to first present the public or lay title of a study in their records. Lay titles are designed for the non-expert and are therefore more informative to the intended audience than the full scientific titles. Lay titles should not contain abbreviations, if possible. We recommend that the lay title (also called public title) of the protocol is to be provided on the first page of the LPS. The full scientific title should be provided towards the end of the document as a reference.

2. **Q&A Text:** *Rationale*
   (Specify background and hypothesis of the trial.)

   Our recommendation:
   The section title should be in question format, e.g. Why is this research needed? Why is this trial needed? Why do we want to perform this trial?

   The rationale should briefly introduce the selected indication and should then convey the rationale for the overall objective (e.g., testing an Investigational Medicinal Product, IMP versus Standard of Care, SOC) and the primary endpoint. The point of view should be that of the developer, i.e. the company / hospital conducting the research, not the presumed benefit of future patients.

3. **Q&A Text:** *Objective*
   (Specify the main and secondary objectives of the trial.)

   Our recommendation:
   The section title should be in question format, e.g. What are the goals of the trial? What does the trial want to find out?

This section could be combined with the Rationale (Section 2). The objectives should be detailed in primary and secondary goals, if applicable. Objectives could be presented in a table. While for the primary objective the assessment should be provided, the secondary objectives should be summarised, e.g., "investigating the safety". Exploratory objectives should not be mentioned.

4. **Q&A Text:** *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.)

Secondary trial endpoints

(Describe the secondary trial endpoints, and when they are assessed e.g. number of adverse events until 30 days post end of treatment.)

Our recommendation:

The section title should be in question format, e.g. What are the goals of the trial and how are they measured?

There should be a clear distinction between the primary endpoint and secondary endpoints, either by headings and / or by a different colouring. If a primary endpoint is related to safety, it should still be presented as primary endpoint and not under safety assessments.

Instead of the terms "Primary Endpoint" and "Secondary Endpoint" more lay friendly terms like "Main Goal" or "Main Objective" should be used. A tabular format was found most useful as it allows readers to directly see the link between an endpoint and the way it is measured.

Goals	How they will be measured
Main goals	
Secondary goals	

Patient-relevant secondary endpoints need to be summarised and limited to a few.[3,4] They should not be copied from the protocol but should be summarised and bundled into categories, e.g., pharmacokinetics, pharmacodynamics. The secondary endpoints presented in the LPS should be those also presented in the lay summary of results. The choice of secondary endpoints to be presented could be determined in discussion with patient groups that support the development of the protocol.

5. **Q&A Text:** *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.)

Our recommendation:

The section title should be in question format, e.g. How is the trial designed? How was the trial planned? "How does the trial work?", How did the researchers prepare the trial?

The trial phase (phase I, II, III) exploratory / confirmatory character should be included because it provides orientation for readers. The degree of blinding should be mentioned here (single, double-blind). The use of placebo should be described here (or in the rationale section).

The use of a graphic display is strongly encouraged. A graphic allows an easy separation of trial phases (screening, run-in, randomised phase, follow-up, Part A, Part B). However, in trials with a complex design (basket, umbrella, platform trials) a graphic display may become complex.

The required time investment of the participants should be spelled out per trial period and overall. The trial duration and the duration of treatment should be given; all the trial parts should be included (screening to follow-up). Depending on the indication a tentative wording may be appropriate, e.g., "…a participant may be treated for 8 months in total…or as long as he or she derives benefit from treatment". Overall, the description should remain high-level as details are provided in the ICF.

The frequency of participant-relevant procedures such as biopsies or blood sampling should be mentioned here.

6. **Q&A Text:** *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 ulcer or risk factors for a cardiac arrhythmia; healthy volunteers 18-60 years not exposed to X-Ray examinations during the last 12 months.)

Our recommendation:

The section title should be in question format, e.g. Who can take part in the trial? Who is eligible to participate in the trial?

Only the main inclusion and exclusion criteria should be given, limiting the list to 3 to 6 items.* However, the following should be included: age, sex, condition, disease-stage (if applicable), mutation status (if applicable).

In- and exclusion criteria should be bundled, i.e. those that belong together should be presented as one criterion, if possible. It should be indicated that the list presented is not complete and a reference be made to the complete list in the Informed Consent Form and the protocol. Specific criteria for sub-trials should be mentioned separately.

*To support LPS authors, trial teams should identify a low number of key inclusion and key exclusion criteria also in the protocol which could then be used in the LPS.

7. **Q&A Text:** *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.)

Our recommendation:
The section title should be in question format, e.g. “What treatments are given?” “Which treatments will the participants receive?” “What treatments are given during the trial?”
The planned number of participants in the trial should be provided, potentially as a range, to give an impression on the size of the trial. The randomisation ratio should be specified, e.g., 2 out of 3 or 66% will be receiving X. Ideally, the total numbers should be given, e.g., X will receive the test medicine, Y will receive placebo. The readers should not need to do the calculation. Alternatively, the probability of getting the active medicine could be provided.
The investigational treatment and the comparator should be named. Background treatment should not be mentioned, only if non-standard.
The route of administration should be described in non-technical terms. Also, the frequency of the treatments should be provided, e.g., “will be given every 3 weeks”.
If possible, the provision of the exact doses should be avoided because this information is often redacted, and redactions in LPS should be avoided. Potentially the doses can be described in relative terms, i.e. “high(er)”, “low(er)”.
The procedures and the blinding of the trial should be described in the design section (Section 6).

8. **Q&A Text:** *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 physical and physiological discomfort associated with trial participation)

Our recommendation:
The section title should be in question format, e.g. “What are the possible benefits and risks?" “What risks and benefits will participants experience?”

This section should be rather short and succinct. For a detailed description of benefits and risks, a reference to the relevant sections in the Informed Consent Form and the protocol should be included.

In all interventional trials, participants hope for an individual benefit when they decide on participation, even when they might be assigned to placebo. A group benefit is almost always possible. Therefore, no extensive benefit/risk justification is needed in a LPS. Instead, a cautionary statement could be included, e.g., “Participants may or may not benefit from the participation in this trial” or “The treatments used in this trial may or may not provide therapeutic benefit”.

Any description of potential adverse events (AE) should be avoided because the full list of AEs might not be known at the time of the trial and any list provided may quickly be outdated by subsequent development of a substance.

No detailed justification of potential burdens should be provided here. However, should the trial involve substantially more burdensome procedures than the standard of care, this should be mentioned.

A reference to the protocol section with the detailed description of the procedures is helpful as the protocol is also publicly available.

Procedures such as blood sampling or biopsies should be included in Section 6 “Trial design” not here.

References

1) Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance, https://eur-lex.europa.eu/eli/reg/2014/536/oj/eng

2) Clinical Trials Regulation (EU) No 536/2014 Questions & Answers Version 7.1, March 2025 https://health.ec.europa.eu/document/download/bd165522-8acf-433a-9ab1-d7dceae58112_en?filename=regulation5362014_qa_en.pdf

3) Good Lay Summary Practice Guidance (GLSP), EudraLex - Volume 10 - Clinical trials guidelines, Chapter 5, Additional Documents https://health.ec.europa.eu/document/download/8a42b8f5-4ec3-4667-969c-3dd89ea8b270_en?filename=glsp_en.pdf

4) Megnin M, Collyar D, Guerreiro D, Kashuba M, Klim L, Murray C, Patrick S, Schindler TM, Valencia J, Vashisht V: Presenting secondary endpoints in plain language clinical trial result summaries: Considerations for emerging practice, Medical Writing 2021, 30;2:58-67 https://journal.emwa.org/mentorship/presenting-secondary-endpoints-in-plain-language-clinical-trial-result-summaries-considerations-for-emerging-practice/