EPF's response to the European Commission's public consultation on the "Summary of Clinical Trial Results for Laypersons"

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1. Introduction

EPF welcomes the Commission's public consultation on a guideline for drafting the summary of clinical trial results for lay persons. As we stated in our position statement of March 2015, we believe a set of guidelines at EU level is necessary to ensure that the lay summaries written for the EU database are consistent in their approach and quality.

We would also like to thank the UK Health Research Authority (HRA), which led the development of the draft guidelines on behalf of the EU expert group on clinical trials. EPF participated in the multi-stakeholder task force led by the HRA, comprising patient representatives as well as industry and other stakeholders.

Below, we provide some further feedback from a patient perspective on the draft guidelines now released for public consultation.

2. General remarks

In order to achieve meaningful patient involvement in research, it is crucial that at every stage of the research process, information is available to patients in a way that enables them to understand it. Lay-friendly information is needed, for example, at the stage of seeking funding and ethics approval. It is important not only for patients, but also for lay persons and non-specialist health professionals.

EPF warmly welcomes the improved transparency provisions in the Regulation. We particularly welcome the fact that all clinical trials results must include a "lay summary", which will be available on a publicly accessible, user-friendly EU clinical trials database. Nevertheless, if the EU database is to become the main point of reference for patients for information about clinical trials, then it needs to establish a high standard of patient-friendliness for the information that is presented, the way it is presented, and the user experience of the electronic interface. Summary results should be communicated in a way that is unbiased, comprehensive, relevant, and understandable to patients (see EPF position paper on clinical trial results – communication of the lay summary, March 2015).

We believe that the draft guideline addresses these issues to a large extent. As we state below, we strongly support the use of templates and explicit guidance to sponsors regarding the avoidance of promotional or misleading language, including the way numbers and visuals are presented.

Conveying scientific information in simple language – especially where the interpretation of results may depend on some quite nuanced details – is not easy. Even with the best intentions there is a risk of introducing bias when simplifying. Therefore, easy understanding and readability of the lay summary must be balanced with factual accuracy.

3. Comments by section

2. *Scope*

Line 63:	We would recommend moving the footnote from page 2 here as it is the first time the term “health literacy” is introduced.

3. *Responsibility of the sponsor*

Line 66-67:	It might be appropriate to state here that it is also the responsibility of the trial sponsor *to ensure that the lay summary is accurate and unbiased*.

4. *General principles*

Line 71-72:	It should not be assumed that lay readers will have any prior knowledge of the trial, *or of clinical research in general*.

5. *Health literacy principles and writing style*

Line 93-94:	Here, rather than describing literacy proficiency level 5 which is not relevant for the lay summaries, it would be more helpful to describe level 2-3, which is the level that the lay summary should aim for. (That description is actually given further down, on lines 98-103.

6. *Readability and use of plain language*

Line 143-145:	We recommend that an appropriate larger font (than 12 pt) should be used not only when the clinical trial relates to visual impairment or involves older people, but also when it relates to clinical trials for people with cognitive impairment / dementia.
Line 148-155:	This section describing literacy proficiency levels appears to repeat the section under heading 5, above.
Line 161-232:	We would prefer to move the descriptions of national readability systems into an annex, as they are not relevant for all readers.

8. *Visuals*

Line 250-252:	Some people respond better to visuals, whereas other people find it easier to understand text. Therefore, we recommend that *visuals, especially graphs, should always be complemented by a simple textual explanation* of the information given in the visual representation.

9. *Language*

Line 267-269:	We consider that the lay summary *should always be provided in English*, regardless of what other languages are used. Without an English language version, access for those people who do not speak to national languages of the countries in which the trial took place will be severely hampered, as will be the ability to compare lay summaries from a number of different trials.

10. Communication of return of results to participants

Line 272-276:	We strongly support the recommendation that sponsors should find ways of providing *direct feedback* to those patients or volunteers who have taken part in the trials, as long as the patients have agreed that they can be re-contacted. This provision should be already built into the informed consent process at the start of a trial.

Annex 1 – templates

The elements that must be included in the lay summary are set out in Annex V of the Clinical Trials Regulation. Unfortunately, the list in Annex V was developed without any consultation with patient organisations. As a result, some of the 10 headings are in themselves not easily understandable for laypersons (e.g., "population of subjects", and "investigational medicinal products"). We would strongly recommend that the headings be revised in consultation with patient representatives to ensure that they are lay-friendly.

Templates increase predictability and consistency – important health literacy principles – and will thus help patients make sense of the results. It also improves the comparability of lay summaries from a number of different trials, which patients may well wish to do. Therefore, EPF strongly supports the use of templates.

We do not believe that changing the order of the headings, as suggested on page 13, is helpful to lay readers, as it can impede the comparability and predictability of the templates. The addition of sub-headings to aid understanding is, however, recommended.

A note concerning language: Besides unbiased and non-promotional language, it may be good to have a reminder in the guideline about the use of language in a way that is respectful and empowering for patients. As an example, in the case of trials in dementia terms such as "demented" should be avoided, and in any case terms such as "sufferers" or "victims" that have negative connotations should be always avoided. "People living with…" or "people affected by… " Are some of the terms that can be used instead.

Our specific comments regarding the templates provided in Annex I are as follows:

1. **Clinical trial identification**

   1.1. Title of the trial

   - We recommend the inclusion of both the full, specific title of the trial and a shorter or simplified "lay friendly title" .

2. **Name and contact of sponsor**

   - It is important to give a clear point of contact for further information.

3. **General information about the clinical trial**

3.2. When the trial was conducted

- We strongly support the inclusion of information on the reasons why a clinical trial may have closed early.
- In addition, patients should also be informed about who conducted the study and who funded it, and the financial and other relationships between the researchers and the pharmaceutical companies or other organisations funding the study. A link to the relevant section of the protocol, assuming the information can be found there, can be inserted.

3.3. The main objectives of the trial and an explanation of reasons for conducting it

- "Why the comparator was chosen…" From the patient perspective it is indeed important to include information on why the comparator was chosen.
- In addition, information about which end points were used and why should be included.
- "Any critical changes made during the study." It is not clear who is to decide what are considered "critical" changes. We would prefer a reference to substantial modifications and protocol changes made during the study, for reasons of full transparency and to minimise the risk of introducing reporting bias.
- In addition to the suggested wordings for the different phases of clinical trials (which should not really mix specific and general statements), it would be helpful for lay readers to provide a short description of the different phases of clinical trials in a separate glossary. Patients often do not realise, for example, that a phase 1 trial is the first of many stages and that to complete the research process will take considerable time.

4. Population of subjects

4.2. Age group and gender breakdown

- The title of the figure provided as an example ("Baseline demographics by sex") is not an example of lay-friendly language.

4.3. inclusion and exclusion criteria

- It is helpful to refer to *disease stage or severity*, but a reference to disease stage alone (e.g. stage III) is not always straightforward to understand for lay persons.

5. Investigational medicinal products used

- The rationale for using placebo, where that is the case, should be briefly explained.
- Randomisation and blinding arrangements should always be described in a simple way. It is important that patients know what steps were taken to minimise biases in the study design.

6. **Description of adverse reactions and their frequency**
    - Frequencies of adverse events should be given following numeracy principles, so "when communicating fractions or ratios, compare risks out of the same number—do not change the base number." So compare 1 of 10 patients with 2 of 10 patients, rather than 1 of 10 with 1 of 5. (Source: MRCT Return of Results Guidance Document, Annex 4. Version 2.1, July 13, 2016.)

7. **Overall results of the clinical trial**
    - "The primary endpoint(s)…" The concept of endpoint needs to be explained in simple words.
    - "Patient-relevant secondary endpoints": it is unclear who is to decide which secondary endpoints are "patient relevant".
    - At least, *all* patient-reported outcome measures and quality of life indicators should be reported, as they are all potentially of interest to patients. In addition, there should be a cross-link to the relevant section of the full summary results for those patients who may wish to have more information.
    - While we agree that technical terms such as "number needed to treat", "odds ratio" and "confidence interval" are not easy for a lay audience to understand, we believe this information should be included, in simple language as it is relevant for understanding the validity of the results.

8. **Comments on the outcome of the clinical trial**
    - In our view, this is a key section for patients to understand the significance of the trial results and put them in the right context.
    - We strongly recommend the inclusion of key limitations and caveats under this section. We have previously noted with some concern that whilst Annex IV of the Regulation includes a mention of limitations and caveats, it was omitted from Annex V. However, this information is equally vital for patients and it should be clearly included in the lay summary.
    - Similarly, we recommend the inclusion of text that reinforces understanding of the results from a single trial in a wider context where other trials may have different results.
    - We also support the inclusion of sub-group analysis where this is possible.

9. **Indication if follow up trials are foreseen**
    - Under this section, it would be good to provide contact information for those patients who are interested in knowing more about forthcoming clinical trials.

10. Indication where additional information could be found

- EPF strongly supports links to additional information. However, we believe that as a first reference there should be a link to the full summary results of the trial, for those patients who are interested in delving further into the results. Secondly, a link to the website of the trial, if applicable, should be provided.
- However, we would be cautious about providing links to commercial or industry websites unless the website is specifically about the trial. It should also be clearly flagged that the link in question is to a commercial source of information. We doubt it would be possible in real life to prevent readers from being "exposed to any promotional language … in the process of accessing the relevant pages".
- We also support the inclusion of links to generic sites of interest, which should be non-commercial in nature, such as the EMA or the Cochrane library, or an international registry.

4. Additional comments

Glossary of terms

EPF believes that a glossary of key terms is needed to help patients and laypersons to makes sense out of clinical trial results, even lay summaries. Many patients will also wish to refer to the full summary results, which contain more comprehensive information. Concepts such as different types of endpoints, terminology around adverse reactions, and basic statistical concepts needed to understand the reliability and validity of trial results should be included in the glossary. A glossary should therefore be integrated into the EU database, and we believe can easily be developed taking as a basis existing patient-friendly glossaries on clinical trials. The glossary should be developed in consultation with patient organisations to ensure it meets patients' information needs.

Patient involvement

EPF strongly recommends that the lay summary should include a section outlining how patients/the patient community were involved in the design of the trial, protocol and setting of the research priorities, selecting clinically relevant endpoints, patient reported outcome measures, or developing methodologies. The Regulation recommends that patients should be more involved in the design of trials, and that such involvement should be described in the protocol. (Annex I of the Regulation, point 17) Many lay patients are not likely to read the protocol, however, so the inclusion of disinformation in the lay summary would be welcome. At the very least there should be a cross-reference and link to the relevant section of the trial protocol.

In clinical trials involving children (minors), lay summaries should contain a paragraph with information about to what extent the parents and children were involved in the trial process; basic information about relevant national legislation, such as the legal age of majority; mandatory or suggested age ranges for assent (or consent if assent is not used); what signatures were required from parents or guardians; a link to the relevant national legislation; and a reference to Article 32 of the Regulation. Because clinical trials in minors are sensitive, involving parents and explaining their particular role would contribute to a more inclusive and transparent system and potentially increase the number of children participating in clinical trials.

The same principles should apply to other vulnerable groups, such as persons with incapacity (Article 31 of the Regulation).

Review of lay summaries

To enhance patients' trust in the lay summaries, it would be desirable to introduce a system of reviews by patient representatives. Ideally patients should be involved in the development of a lay summary, but it would also be useful to review (some of) them after publication to check that the authors of the lay summaries are indeed adhering to the guidelines for patient-friendliness and presenting information in an objective and unbiased way.

The European Medicines Agency has an existing system for patient reviews of package information leaflets and EPARs, which is working well. However, we recognise that currently the Agency is not likely to have adequate resources to check every summary. Possible reviewers could also include member states' national competent authorities as well as medical and scientific organisations. Some patient and consumer organisations may also have the desire capacity to do this, but would need to be resourced. EPF would welcome further discussion around this topic to explore the feasibility of such a system and how it might operate in practice.

For more information, see:

- **EPF position paper: Clinical Trial Results – Communication of the Lay Summary** (2015) available here
- **EPF position paper: Clinical Trials Regulation: Informed Consent and Information to Patients** (2016) available here
- **EPF position paper on the European Commission proposal for a Regulation on Clinical Trials** (2013) available here

Contact: policy@eu-patient.eu