

The Lay Summary – Remember the Reader



As part of its Clinical Trial Transparency initiative, the EMA mandated a requirement for clinical trial sponsors to prepare a summary of the results of every clinical trial written in language understandable to lay persons (patients and others not in the pharmaceutical industry). The regulation (CTR EU No 536/2014) obliges the company to produce this summary of results for the lay audience one year after the end of the trial in the EU. This requirement was originally planned to take effect in 2018, but it seems likely that it will not now be implemented until 2019. The pharmaceutical industry is obviously aware of this coming requirement and serious discussions are occurring as to how best to respond to this challenge.

Overall, CTR EU No 536/2014 is a very positive development and is a welcome chance to deliver clinical study results to the broad and crucial audience of the general public – especially patients. Few things are more important to the future of the pharmaceutical industry than informing and involving patients in the process and decisions of drug development, and by extension, in the scientific process per se. The requirement to prepare a summary of the results of every clinical study, in a form that can be understood by anyone, is a major step forwards in transparency, an opportunity to explain drug development, and hopefully to increase public awareness and understanding of the industry.

However, there is a danger that this opportunity will be missed; either through lack of clarity in the requirements, or because writing for the layperson is notoriously difficult and so companies may be tempted to fulfill the letter rather than the spirit of the regulations. Confusion and misinterpretation of guidelines has happened historically. The Clinical Study Report (CSR) Synopsis ICH guidelines recommend “a brief synopsis (usually limited to 3 pages)” which was later extended to “for complex or large and important studies (e.g., to 10 pages)”. Unfortunately, few companies consider this guidance and CSR synopses of 20–25 pages are not uncommon. This likely arises from a misunderstanding of the purpose and use of the synopsis. It is mistakenly seen as an extended summary, rather than a brief description of the study for Module 2.7.6 of the CTD (where the synopses are gathered to provide a reviewer with a brief overview of all the registration studies). Many authoring teams seem unable to resist adding more and more information until the synopsis resembles the study methods and results sections of a full CSR.

The lay summary describes a single study – there is no context of wider clinical development to enable the reader to properly evaluate the benefit-risk of the drug, and there is a danger that ambiguity in the CTR EU No 536/2014 regulation may result in similar misinterpretation.

There are 10 suggested headings for the CTR lay summary; for some of them the information to be added is very clear and obvious, but for others, companies must make their own interpretation.

1. Clinical trial identification (including title, protocol number, EU trial number and other identifiers).

This section should have factual information, but how helpful it is for patients is questionable. If the title is complex, a simpler title should also be added, but care must be taken that when complex language is simplified, it does not become misleading.

2. Name and contact of sponsor.

This section is self-explanatory.

3. General information about the clinical trial (including where and when the trial was conducted, the main objectives of the trial and an explanation of the reasons for conducting it).

Describing objectives can be challenging. Secondary objectives can be very important, and so the company must decide what to present and how to present the facts. The methods section should be straightforward, but some companies believe that results for every single parameter should be mentioned in the methods. By itself this may be no bad thing, but as we have seen with CSR synopses, these ‘summary sections’ can mushroom into huge long lists of numbers and multi-page tables. Then there is the question of how the information is presented. It is well-known that tabular and graphical presentations are better for communicating data rapidly. Study designs can be very effectively communicated with carefully prepared, clear graphical schemes which are far superior to long passages of text.

4. Population of subjects (including information on the number of subjects included in the trial in the Member States concerned, in the union and in third countries; age group and gender breakdown; inclusion and exclusion criteria).

There can be huge numbers of inclusion and exclusion criteria, and long lists of complex terms can be very difficult to understand. Which criteria should be included, if the lists are too long?

5. Investigational medicinal products used.

Laypeople are unlikely to be familiar with generic names, and brand names can be different in different countries. For early phase studies, generic or brand names may not even have been allocated.

6. Description of adverse reactions and their frequency.

Discussing adverse events (AEs) can be very challenging. Any potential harms should be placed into context and weighed against potential benefits of the drug, but this is very difficult to do in the trial summary when the AEs section is presented to laypeople first. Even the term ‘adverse reaction’ can cause confusion, and the seriousness and frequency of each reaction should be explained and described. Most AEs are described in MedDRA (Medical Dictionary for Regulatory Activities) terms and so these should be explained in lay language. Underlying all of the challenges described in these sections is the more general

challenge of communicating benefit-risk information in terms that do not rely on statistical values or parameters to convince the lay audience to 'trust' them. How a drug's AEs are described can be crucial in how they are understood, and therefore in the outcomes that result.

7. Overall results of the clinical trials.

The results of the trial should be described but this can be very difficult considering that health numeracy levels (the ability to understand and interpret numbers related to health information) in the general population are even lower than those of health literacy. Technical terms such as 'number needed to treat', 'hazard ratio', 'confidence interval', etc. are particularly difficult to explain to a lay audience, and even more difficult for them to interpret. How do we expect the lay audience to interpret and react to a table of parameters from a Phase I pharmacokinetic study? Tables and graphs that are easy for those of us in clinical research to understand and interpret due to the familiarity that comes with long and repeated exposure, may not be so straightforward to the public. How confident can we be that patients will be able to correctly interpret at first glance a shift table, Forest Plot, or Kaplan-Meier survival analysis? Presenting only the top level or main results can also be interpreted as cherry-picking so a balanced, true representation of the results must be given. Using statistical terms to explain how much 'trust' the reader can place in a result can increase the perception of risk (Han 2011), and lead to a reluctance to take the drug.

Finally, there is the issue of what information to present. For efficacy results, a way must be found to discuss the difference between the interpretation of primary and secondary analyses, to say nothing of exploratory analyses. Giving the lay audience complex information does not help them to make decisions – especially if the information is numerical (Zikmund-Fisher 2013). It also calls into question the value of disclosing complex clinical trial results without context and explanation (neither of which is currently mandated by the regulation). Understanding the importance of increases of AEs above the general population level relies on the reader knowing what the baseline level of the population is, and being able to put this into context. How can we communicate that clinical studies are designed with statistical power such that statistically significant results for the

primary analysis indicate a clinically relevant effect, whereas for secondary analyses the interpretation is weaker and more complex? This is a challenge even for a scientifically literate audience.

Safety results might appear at first glance to be easier to communicate, but there are challenges here as well. Most adverse event results are given with a percentage indicating frequency. The accuracy of these frequencies, however, is very strongly dependent on the sample size; accuracy drops sharply in small studies, but how much it drops and the relative importance of different events can be very difficult to explain. Providing guidance to a lay reader on how to interpret adverse event frequencies is not trivial, and is crucial not least because of the nocebo effect (adverse effects occurring in patients receiving placebo due to expectation rather than any treatment). The nocebo effect could become a problem for companies if the presentation of safety data is not handled with care. Since all of these complex ideas and results can only be correctly interpreted in the context of other information, the likelihood of misunderstanding and thus misinformation is very high.

8. Comments on the outcome of the clinical trial.

This should be an overall summary of the results and their implications. However, it should be unbiased and should not sound promotional in any way. It is difficult to describe positive results so that they are not interpreted as promotional, but this is an excellent opportunity for companies to describe how clinically meaningful the results are.

9. Indication if follow up clinical trials are foreseen.

This section should explain if and when more studies will be done on the drug.

10. Indication where additional information could be found.

This section is self-explanatory, but links could also be given to more general sites, such as plain language dictionaries.

These challenges are not insurmountable and have not been ignored. The EMA have ongoing consultations with industry





and patient groups to try to improve the guidance for industry in communicating with the lay audience. There are also companies offering user testing services to allow testing of lay text with its intended audience. The continued dialogue between regulators and industry around the issues of transparency and communicating with laypeople offers the chance to develop guidelines that can lead to lay summary documents that truly aid the public's understanding of clinical research, and improve their trust and perception of the pharmaceutical industry, rather than just add still another document to the large pile of submission requirements for clinical research.

It would be a tragic waste of an opportunity if these new regulations simply lead to the addition of another overly long and hard-to-understand summary of clinical study results. Instead, everyone involved in either the writing or the designing of templates and procedures for lay summaries should invest time and resources in making sure that the resulting documents facilitate rather than hinder communication with the lay audience. The pharmaceutical industry has few opportunities to communicate directly with patients in Europe, and so it would be good to remember the reader when producing this document, and see the lay summary of the CSR not as yet another regulatory hurdle to be mechanically created and filed to gather dust, but rather as a unique chance to expand the science-public interface and perhaps improve the general understanding and acceptance of science into the bargain.

REFERENCES

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