

# Transferring regulation into practice: The challenges of the new layperson summary of clinical trial results

Kamila Sroka-Saidi, Barbara Boggetti, Thomas M. Schindler

*Boehringer Ingelheim Pharma GmbH & Co. KG  
Biberach an der Riss, Germany*

## Correspondence to:

Thomas M. Schindler  
Boehringer Ingelheim  
Pharma GmbH & Co. KG  
Birkendorfer Strasse 65  
88397 Biberach an  
der Riss, Germany  
thomas.schindler@boeh  
ringer-ingelheim.com

## Abstract

The new European Clinical Trials Regulation, published on 27 May 2014, requires sponsors to provide summary results of clinical trials in a format that is understandable to laypersons. The lay summary is to be made publicly available in the yet to be finalised EU database. In this article, we review the proposed content of the layperson summary and identify issues related to the writing of such documents.

**Keywords:** EU Clinical Trials Regulation, Disclosure, Transparency, Layperson summary

## Transparency of clinical trial results

The initiatives for greater transparency in clinical research and for public sharing of clinical trial results have been gaining momentum in recent years. In 2008, the updated Declaration of Helsinki included a statement that making study results available to the public was an ethical duty.<sup>1</sup> Starting in 2008, sponsors have been obliged to publish summary results of clinical trials on the US National Institute of Health website ClinicalTrials.gov. The results have to be posted not later than one year after trial completion or 30 days after approval of an investigational product in the US.<sup>2,3</sup> Since July 2014, EMA has required posting of summary results in the EUDRA CT database 12 months (or 6 months for paediatric trials) after study completion.<sup>4,5</sup> In July 2013, member companies of the European Federation of Pharmaceutical Industries and Associations and the Pharmaceutical Research and Manufacturers of America committed to publishing summary results of clinical trials for products approved in the US and the EU or its member states. Meanwhile several pharmaceutical companies have started sharing trial results with trial participants.<sup>6</sup>

The European Clinical Trials Regulation (no. 536/2014) introduced new requirements on data

disclosure for clinical trials with at least one site in an EU member state.<sup>7</sup> Once the regulation is fully implemented (the earliest by 28 May 2016), a lay summary of the trial results needs to be provided within a year of trial completion in the EU. This lay summary will be made publicly available via the EU database (Article 37 [4]) that is however yet to be established. Unfortunately, the guidance provided for the content of the lay summary is limited and consists only of a list of 10 items placed in Annex V of the regulation (see Box 1).

## General concerns

The list in Annex V can hardly be considered a guidance document, since the individual items are stated without any explanatory instructions. Each item needs interpretation and many important aspects of lay summaries are missing. These limitations of the guidance could either be intentional to give sponsors leeway in fulfilling the requirements or could indicate that the thinking on this topic has not yet been finalised.

There are no instructions on the format and the overall length of the lay summary. Sponsors are therefore required to make reasonable assumptions. Given the intention to summarise the trial results for non-specialists, anything beyond two pages seems inappropriate. Importantly, the EU regulation does not specify the target reading level for the lay summary (often expressed by the Flesch Kincaid grade level or readability ease score). This omission requires sponsors to set their own reading level target and depending on this decision, both content and style can vary considerably across companies. Another aspect that is not addressed is the language of the lay summaries. Usually key documents of clinical trials are written in English. Therefore, it seems straightforward to also provide the lay summary in English. However, English is just one of the languages in the EU. While

**Box 1**

The summary of the results of the clinical trial for laypersons shall contain information on the following elements:

1. Clinical trial identification (including title of the trial, protocol number, EU trial number and other identifiers);
2. Name and contact details of the sponsor;
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);
4. Population of subjects (including information on the number of subjects included in the trial in the Member State concerned, in the Union and in third countries; age group breakdown and gender breakdown; inclusion and exclusion criteria);
5. Investigational medicinal products used;
6. Description of adverse reactions and their frequency;
7. Overall results of the clinical trial;
8. Comments on the outcome of the clinical trial;
9. Indication if follow-up clinical trials are foreseen;
10. Indication where additional information could be found.

Source: Annex V of the European Clinical Trials Regulation<sup>7</sup>

proficiency in English is high in certain EU countries and in some age or professional groups, many citizens would still be excluded if the documents were provided only in English.

Summaries for a lay audience might increase the accessibility of clinical research data but they also have potential risks. People unfamiliar with clinical research might be in danger of drawing far-reaching but unwarranted conclusions. Each lay summary should therefore be accompanied by a disclaimer to prevent misinterpretation of trial results. It should alert readers that the results of any individual trial do not represent the complete medical knowledge about a substance and that patients should therefore not change their current therapy based on their understanding of the results.

### **Content of lay summaries of clinical trials according to the EU Clinical Trials Regulation**

In the following, we will go through the points provided in Annex V of the EU regulation and indicate where we see potential issues.

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

*2. Name and contact details of the sponsor.*

Providing the protocol number, the EU trial number, and the name and contact details of the sponsor is easily implemented. However, stating the full clinical trial protocol title is unlikely to be helpful for a lay audience. Protocol titles are designed to reflect the scientific and medical contents of a trial and are intended for a medical audience. Therefore, protocol titles are often long, and rich in technical terms and abbreviations.

Titles typically include dosages (e.g. 100 mg bid, 5 µg/day), study design features (e.g. multiple rising dose, two-way crossover), and descriptions of the patient population (e.g. patients with advanced non-squamous non-small cell lung cancer) that are usually not easily understandable for a layperson. Thus, we propose that a shorter, simplified lay title be provided. The challenge will be to formulate the lay title in such a way that it is succinct without being misleading or inaccurate.

*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).*

This requirement seems straightforward as the only difficulty is providing a clear and brief explanation of the trial's rationale. Issues may arise if details of a disease need to be included to make the rationale understandable for laypersons. For instance, the reasons for conducting a trial may involve discussing current treatment options and unmet medical needs for patients with a particular severity of a condition (e.g. stage IV chronic obstructive lung disease). Medical information such as severity gradings is often not useful for laypersons but might nevertheless be needed.

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

Providing the number of subjects in the member state concerned, the EU, and third countries has not been commonly done in the reporting of clinical trials; however, this requirement can be fulfilled easily. Age group and gender break-down are

self-explanatory and also not a problem. However, the lists of inclusion and exclusion criteria in the trial protocol might be too long for a lay audience and may contain criteria that are relevant only for specialised readers, e.g. the investigators. We therefore suggest limiting the number of inclusion and exclusion criteria to the most important ones; a total of five criteria or less might be desirable. It may be useful to mention those criteria that a layperson can observe by him- or herself or is likely to be familiar with. Some of the technical terms used to define a patient population (e.g. forced vital capacity percent predicted <50%) are not informative for a lay audience and could be omitted.

#### 5. *Investigational medicinal products used.*

Like some other elements in Annex V, this requirement is fulfilled easily. However, studies in early phases of clinical development may only be able to provide the sponsor's internal compound code, which will be completely uninformative. At later stages of drug development, the international non-proprietary name (INN) becomes available and can be used. For reports of studies in the more advanced stages of clinical development, it seems advisable to provide both the sponsor's internal compound code and the INN, as this would allow the reader to link the information to previous studies. The situation may become more complex for studies of marketed products that have several trade names across the EU. Ideally all identifiers, i.e. the sponsor's internal compound code, the INN, and the trade names should be provided. The same information for every comparator product, including placebo, should also be given, as they are considered investigational medicinal products under the regulation (Article 2 [2 (5)]).<sup>7</sup>

#### 6. *Description of adverse reactions and their frequency.*

To comply with this requirement, a number of decisions need to be made. First, we need to clarify the term 'adverse reaction'. The EU regulation defines adverse reactions in accordance with the EU directive 2001/83/EC as 'a response to a medicinal product which is noxious and unintended'.<sup>8</sup> This represents the concept of drug-related adverse events, i.e. those for which a causal relationship between the event and the medicinal product has either been established or cannot be ruled out. However, the concept of 'adverse reaction' and 'drug-related adverse events' might be challenging for a lay audience. Sponsors could therefore also consider reporting adverse events irrespective of them being deemed drug-related or not.

For the collection and description of adverse events, reports from patients about 'any untoward medical occurrence' need to be categorised to enable comparisons across study sites and across studies. This categorisation is commonly based on the Medical Dictionary

for Regulatory Activities (MedDRA). Although widely used by sponsors and regulatory agencies, many MedDRA terms are not easily understood by a layperson. MedDRA maps its terms to a number of hierarchical categories among them the lowest level terms (e.g. feeling queasy), the preferred terms (e.g. nausea), the high-level terms (e.g. nausea and vomiting symptoms), and system organ classes (e.g. gastrointestinal disorders). Commonly, the presentation of adverse events in clinical study reports is based on preferred terms and system organ classes. For the lay summary it needs to be decided, whether MedDRA terms will be used and if so which level of granularity is most appropriate. A translation of the MedDRA terms into lay language may often be necessary. Writers who write patient information leaflets face the same problem of translating MedDRA terms into lay language; it is therefore advisable to make use of the thesauruses they have developed.

Although not explicitly mentioned in Annex V, we believe that the section on 'adverse reactions' should also include information about deaths, serious adverse events, and adverse events leading to discontinuation. Furthermore, sponsors need to decide whether data on clinical laboratory findings and vital signs should be included.

#### 7. *Overall results of the clinical trial.*

The scope of this requirement is not clear. In most cases, 'overall results' of a trial would include both efficacy and safety results. As the safety results are largely covered by requirement 6 (see above), we suggest providing only efficacy data in this section. The primary and the key secondary endpoints should always be reported. Where applicable, data on endpoints related to quality of life can be included, as they might be of particular relevance for the patient. To be statistically and medically evaluable, endpoints in study protocols need to be phrased in a detailed, technical way. It will be a challenge for the writer to rephrase the results for the endpoints in such a way that the description is adequate and accessible for lay readers.

#### 8. *Comments on the outcome of the clinical trial.*

This is potentially the most problematic requirement for lay summaries. The word 'comments' leaves a wide spectrum of interpretation. It entails the notions of 'making a statement', 'expressing an opinion', and 'discussing the meaning'. Accordingly, we understand this requirement as the wish of the EU regulators to have a section in which the trial results are presented on an aggregate level and in which conclusions are provided.

As all summarising texts, such comments will need to use more general terms and will need to combine them to form high-level statements. For example, the efficacy results may be summarised by saying that

treatment with the study drug was efficacious (because the primary endpoint showed a highly significant difference to placebo/comparator). Similarly, the overall result of the different safety analyses may be summarised by ‘no critical safety issues could be identified’. The terms that need to be used for generalising statements (‘showed efficacy’, ‘raised no safety concerns’) are more comprehensive and hence open to misinterpretation. The need to use generalising terms may lead to legal issues because such statements could be perceived as being promotional. It might be for this reason that most of the lay summaries that are currently available on the internet (November 2014) do not contain a summarising or concluding statement. For the writer, the task is providing a high-level summary that does not overstate results. Therefore, the extent of comments on the outcome of the trial has to be considered carefully.

9. *Indication if follow-up clinical trials are foreseen.*

10. *Indication where additional information could be found.*

Requirement 9 can be addressed by a simple statement detailing whether additional clinical trials are ongoing or planned. Requirement 10 can be fulfilled by including a link to the sponsor’s homepage where further information such as the synopsis of the clinical study report may be available. However, this requirement might become even easier to comply with as the regulation (§ 67) states that the EU clinical trial results database will enable hyperlinking of ‘the summary, the layperson’s summary, the protocol and the clinical study report of one clinical trial, as well as linking to data from other clinical trials which used the same investigational medicinal product’.<sup>7</sup>

## Summary

Lay summaries of clinical trials will become standard in clinical research in the near future. While they are yet another commitment for the pharmaceutical companies, they will hopefully play a role in promoting health literacy in the general population. The current guidance, as provided by the EU regulation, is scant and key issues such as length, format, reading level target, and language of lay summaries are not

covered. For the time being, sponsors therefore need to make assumptions and need to define their own approach to lay summaries within the broad limits provided by the regulation.

## Declaration

The views expressed in this article are those of the authors and do not necessarily reflect those of Boehringer Ingelheim Pharma.

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## Author information

**Kamila Sroka-Saidi** has a PhD in Neurosciences from the University of Göttingen, Germany. After working as a post-doctoral researcher at Merz Pharmaceuticals, she joined Boehringer Ingelheim Pharma in 2012 as a medical writer.

**Barbara Boggetti** received her PhD in Plant Biology from the University of London and completed several post-docs in Germany and Italy. Most recently, she had gained a degree in clinical research at the mibeg-Institut. She is now a medical writer at Infill.

**Thomas M. Schindler, PhD** (Molecular Physiology). After his post-doc, he went into publishing as a popular science editor and has meanwhile gained some 18 years of experience in both medical affairs and regulatory medical writing. He is currently the head of the European regulatory medical writing group of Boehringer Ingelheim Pharma.