New European Clinical Trial Regulation: The Requirement for Lay Summaries and Its Impact on Medical Communicators

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INTRODUCTION

The European Clinical Trial Regulation (EU No. 536/2014)[1] published by the European Parliament in May 2014 introduced new requirements for authorization, conduct, reporting, and transparency of clinical trials with at least 1 site in a European Union (EU) member state. According to this regulation, sponsors will be obliged to provide results of clinical trials in a summary that is understandable to laypersons. This summary shall be publicly available in an EU-wide database that is yet to be established.

For globally acting sponsors, data disclosure policies need not only comply with requirements from the US Food and Drug Administration (FDA) but also with the EU regulations. This article gives an overview of the recent developments in regard to transparency of clinical trial data in the EU and the provision of lay summaries of clinical trial results. We highlight the implications and challenges associated with the new regulation for medical writers.

RECENT DEVELOPMENTS IN TRANSPARENCY IN THE UNITED STATES AND THE EUROPEAN UNION

At the time of launch of the NIH database ClinicalTrials.gov in 2000, it included only a subset of clinical studies conducted in the United States.[2] With the FDA Amendment Act of 2007, the requirements for registration on ClinicalTrials.gov were expanded, and it became obligatory for sponsors in the United States to post summary results of studies of approved products on the website by 2008.[3,4]

In contrast to the United States, the European Union did not have a legally binding obligation to publish trial results in existence at that time. In 2001, the EU directive 2001/20/EC was released. It aimed at harmonizing requirements and ensuring data quality for clinical trials across all EU member states.[5] The EU directive stipulated the creation of an EU-wide database, later called EUDRA CT, in which clinical trials conducted in the EU had to be registered. Then, in 2012, a European Commission guideline obliged sponsors to post summary results of all clinical trials conducted in at least 1 EU member state.[6] The results were to be posted in EUDRA CT; however, the functionality for posting did not become available before June 2014.[7]

In 2009, an assessment by the European Commission of the impact of the EU directive revealed that the operational requirements imposed had resulted in an increased administrative burden and higher expenses for sponsors and that, because of this, the number of clinical trials conducted in the EU had decreased.[8,9] To counteract this decline, the European Parliament issued regulation No. 536/2014,[1] which came into force on June 16, 2014. Unlike the former directive, the new regulation is directly applicable and overrules the respective national laws in all EU member states. Shortly after release of the Clinical Trial Regulation, the European Medicines Agency (EMA) adopted policy 0070, which became effective Jan 1, 2015, setting the scene for proactive publication of entire clinical trial reports and clinical submission documents by the EMA.[10]

In July 2013, member companies of the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA) recognized the need of greater transparency and proactively committed to publishing summary results of clinical trials for products approved in the United States or the EU and its member states.[11] This commitment to some extent preempted some of the requirements introduced by the European Clinical Trial Regulation. Since then, several pharmaceutical companies have started sharing their trial results with the trial participants on a voluntary basis.

CONTENT AND IMPLEMENTATION OF THE NEW REGULATION

Even though the European Clinical Trial Regulation was released in June 2014, it will become effective "not earlier than 28 May 2016," or once the new EU database has become available. The main content of the regulation is a harmonized clinical trials application procedure via a new EU database, which will document the procedure, assessment, and timelines for each clinical trial. Thereby, the regulation is thought to "create an environment that is favorable to conduction of clinical trials in the EU with the highest standards of safety for participants." In addition, the regulation introduces increased transparency concerning clinical trials.[1, 12]

SPECIFIC REQUIREMENT FOR LAY SUMMARIES OF CLINICAL TRIAL RESULTS

As part of the transparency efforts, Article 37 of the new European Clinical Trial Regulation states that sponsors are obliged to submit a technical summary of results of clinical trials. This technical summary will be very similar to the postings of clinical trial results on ClinicalTrials.gov and EUDRA CT. However, unlike in the United States, the posting "shall be accompanied by a summary written in a manner that is understandable to laypersons." The requirements for this lay summary are delineated briefly in Annex V of the regulation (Box 1) and were added only "at the last stage of negotiations," according to a recent position paper of the European Patients Forum.[13] Although discussions about returning summary results of clinical trials to patients and the public have been ongoing for some years in the United States and the EU,[14,15] this is the first time that a list of items that should be included in such a document has been given by a regulatory agency (Box 1).

Box 1. Content of the Summary of the Results of the Clinical Trial for Laypersons

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: Regulation EU No. 536/2014 on clinical trials on medicinal products for human use, Annex V[1]

IMPACT ON MEDICAL COMMUNICATORS

As the writing of lay summaries of clinical trial results requires expert understanding of clinical research and the specific skills associated with communicating to lay audiences, medical writers are ideally suited for this task.

Unfortunately, Annex V of the European Clinical Trial Regulation provides only scant guidance on the content of a lay summary. As most of the 10 items provided (Box 1) need interpretation and adaptation, there is a large potential for professional medical communicators to contribute. Sponsors, whether from academia or the pharmaceutical industry, will have to make reasonable assumptions about the implementation of the requirements.[16] Medical writers can support the implementation by developing lay summary templates and providing expertise for the writing in lay language. Although at first reading the requirements appear straightforward, on closer inspection many issues arise. Some of the requirements can be readily implemented (Nos. 2, 10), however all others need further specifications.[16] In Table 1 we list these issues and propose potential solutions.

Beside the issues that need interpretation, there are more general aspects that need to be considered in the writing of lay summaries of clinical trial results.

Annex V gives no guidance on format, length, and structure of the lay summary, therefore each sponsor will have to develop its own approach. In addition, the European Clinical Trial Regulation does not specify the language of the lay summary. While it might be reasonable to assume that the summary could be provided in English, it is obvious that this would exclude a large number of European citizens, because there are 23 other official languages in the EU. If the objective of increased transparency is taken seriously, lay summaries will have to be provided in all EU languages.

The European Clinical Trial Regulation provides no guidance on a target reading level, therefore medical writers need to determine the target reading level and need to devise strategies for achieving it. Current guidance in the United States

Table 1: Requirements for Lay Summaries, According to the European Regulation EU No. 536/2014: Identification of Potential Issues and Proposal for Implementation

Requirement[a]	Issue	Proposal for Implementation
1. Clinical trial identification (including title of the trial)	The trial title is usually written for a specialist audience in a technical language.	Devise an additional lay title that is shorter and simpler than the full trial title and provide it along with the full trial title.
3. Main objectives and rationale of the trial	Objectives and rationale are usually described in the trial protocol for a specialist audience in a technical language.	Provide a simplified description avoiding specialist terms, but also provide important medical terminology (like disease stages) to maintain specificity.
4. Inclusion and exclusion criteria	The clinical trial protocol usually contains many inclusion and exclusion criteria written for a specialist audience in a technical language.	Reduce the lists of inclusion and exclusion criteria from the trial protocol to the most important ones, like age, body mass index, and indication-specific criteria.
5. Investigational medicinal product	Depending on the product development stage, different drug identifiers are usually available, such as internal compound code, international non-proprietary name, or trade names. In addition, trade names often differ among countries or regions.	Provide the compound code for early trials and all available identifiers for later stages. If feasible, all available identifiers for comparator medication(s) should be given. Provide information if a placebo was used.
6. Description of adverse reactions and their frequency	By definition, the term *adverse reactions* refers to the concept of drug-related adverse events. Especially in early drug development programs, this concept might not be appropriate, and it would be reasonable to report all adverse events. In addition, there are several levels of granularity in frequencies of adverse events and in reporting of adverse events (eg, MedDRA preferred terms and system organ class).	To keep consistency with other sources, provide adverse events using MedDRA preferred terms as default and system organ class level only if useful. The medical terms may need an additional explanation in lay terms. Provide frequencies of all adverse events, deaths (if any), adverse events leading to trial discontinuation. Provide clinical laboratory data only if considered useful for the reader.
7. Overall results of the trial	Because clinical trials usually have several different end-points (primary, secondary, further), it is not clear if this section should contain all efficacy and safety data, and to what extent numerical data should be presented. Quality of Life data might be of special interest for patients, but these are often not included as primary/secondary endpoints.	Focus on the primary and the key secondary endpoints. Provide numerical results to make the data comparable to other resources (clinical trial reports, publications, trial results databases). Include Quality of Life data, if relevant results were obtained in the trial.
8. Comments on the outcome of the trial	This item might refer to the trial objective or the primary endpoint, but it is not clear on what the sponsor is supposed to comment. Because reporting of the trial results is already mentioned above, this might require qualitative statements. However, qualitative summary statements are easily perceived as promotional.	Provide a high-level factual statement on whether the trial fulfilled its objective.
9. Follow-up trials	Whereas the terms *trial* and *study* are precisely defined in the regulation, a definition of what should be considered a follow-up trial is missing. All planned trials investigating the same product might be mentioned. Likewise, already recruiting trials only, or any planned future trials could be reported as well. However, this might be perceived as advertising future studies conducted by the same sponsor.	Only true extension trials related to the trial in question should be reported.

[a]*Items 2 and 10 can be readily implemented and are therefore not included in this table. MedDRA=Medical Dictionary for Regulatory Activities*

and in the United Kingdom recommend that information for patients is written at a reading level of 6th to 8th grade.[17–19] Once a reading level target is agreed upon, medical writers of lay summaries will need to develop criteria to assess whether their texts fulfill the requirements associated with this target. This may involve the development of thesauruses for clinical research terms and their lay language translations, and the use of software tools to measure readability.

The development of lay summaries provides an opportunity to involve patients and patient organizations, if not for the routine process then for the development of an appropriate template. In a recent position paper, the European Patients Forum suggests ensuring the "layness" of result summaries by including patients or patient representatives in the review in a yet to be defined process.[13] Implementing this proposal, however, would have logistical challenges as it will be difficult to find appropriate patient representatives for all diseases studied in clinical trials.

One of the major issues for sponsors of clinical trials is how to maintain consistency between the many different communication channels for sharing clinical trial data with various audiences. To achieve full transparency, the data mentioned in lay summaries need to be linked to the more technical summaries provided on ClinicalTrials.gov and in the EU database. Describing results in a manner understandable to laypersons will need to account for the level of numerical literacy in the general population. This means that details of the statistical analyses will likely have to be omitted, as, eg, odds ratios, P values and confidence intervals will not be informative for a lay audience with a reading level of 6th to 8th grade. As a result, it might be difficult for a lay reader to relate the content of a lay summary to the detailed data provided in the corresponding technical summaries. Sponsors will have to find a balance between the possible low numerical literacy of lay readers and consistency throughout different public sources.

CONCLUSION

The discussions about returning results of clinical studies to participants and the provision of summary results to lay audiences have been ongoing for several years. With the new European Regulation lay summaries of clinical trials will become mandatory in the EU. Because expectations on returning clinical trial data to patients are also increasing in the United States,[20,21] it is highly likely that such summaries will become a standard in clinical research that is conducted on a global level. Although the summaries are yet another requirement for the pharmaceutical sponsors, they have the potential to play a role in improving health literacy among the general public. Very likely, though, because of the lack of detailed guidance on their content, lay summaries will be of varying quality and content depending on the sponsors' interpretation of the regulation.

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

Author disclosure: *The authors declare no conflict of interest.*

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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). http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.158.01.0001.01.ENG. Accessed April 30, 2015.
2. National Institutes of Health launches "ClinicalTrials.gov." National Institutes of Health website. www.nih.gov/news/pr/feb2000/nlm-29.htm. Published February 29, 2000. Accessed May 13, 2015.
3. ClinicalTrials.gov. https://clinicaltrials.gov/. Updated October 2014. Accessed April 30, 2015.
4. Section 801 of the Food and Drug Administration Amendments Act of 2007. US Government Publishing Office website. www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf. Accessed April 30, 2015.
5. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf. Accessed May 15, 2015.
6. Commission Guideline—guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006. http://ec.europa.eu/health/files/eudralex/vol-10/2012_302-03/2012_302-03_en.pdf Accessed May 15, 2015.
7. Posting of clinical trial summary results in European Clinical Trials Database (EudraCT) to become mandatory for sponsors as of 21 July 2014 [press release]. European Medicines Agency website. www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/06/news_detail_002127.jsp&mid=WC0b01ac058004d5c1. Published June 19, 2014. Accessed April 29, 2015.
8. Assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC, public consultation paper. http://ec.europa.eu/health/files/clinicaltrials/docs/2009_10_09_public-consultation-paper.pdf. Published October 9, 2009. Accessed April 23, 2015.
9. Assessment of the functioning of the 'Clinical Trials Directive' 2001/20/EC, summary of responses to the public consultation paper. March 30, 2010. http://ec.europa.eu/health/files/clinicaltrials/2010_03_30_summary_responses.pdf. Accessed April 23, 2015.
10. European Medicines Agency policy on publication of clinical data for medicinal products for human use (Policy/0070). 2 October 2014. www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf. Accessed May 13, 2015.
11. European Federation of Pharmaceutical Industries and Associations, Pharmaceutical Research and Manufacturers of America: Responsible transparency. Principles for responsible clinical trial data sharing: our commitment to patients and researchers. 18 Jul 2013. http://phrma.org/sites/default/files/pdf/PhRMAPrinciplesForResponsibleClinicalTrialDataSharing.pdf. Accessed April 30, 2015.

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