SUMMARY OF THE RESPONSES TO THE PUBLIC CONSULTATION ON "RISK PROPORTIONATE APPROACHES IN CLINICAL TRIALS" RECOMMENDATIONS OF THE EXPERT GROUP ON CLINICAL TRIALS FOR THE IMPLEMENTATION OF REGULATION (EU) NO 536/2014 ON CLINICAL TRIALS ON MEDICINAL PRODUCTS FOR HUMAN USE

1. GENERAL REMARKS

The legislation for clinical trials has seen significant changes during the last decade, starting with the implementation, in 2004, of the Clinical Trials Directive 2001/20/EC ('Directive'), continuing with the publication of the Good Clinical Practice Directive 2005/28/ECi in 2005 and more recently with the Clinical Trials Regulation (EU) No. 536/2014 ('Regulation').

Despite the relative flexibility of the legislation and guidelines (for e.g. ICH Guideline E6(R2) for Good Clinical Practice), it has been observed that in general a 'one size fits all' approach to the design and conduct of clinical trials has been followed to comply with the ethical and scientific standards of Good Clinical Practice (GCP). Some clinical trials, however, pose only a minimal additional risk to subject safety and/or trial integrity compared to normal clinical practice.

A proportionate approach to the design and conduct of clinical trials is therefore supported by the Regulation. This approach should be adapted to the risk to the subject and/or trial integrity of the research carried out, as well as to the risk related to the reliability of trial results. The expert group on clinical trials developed a document *Risk proportionate approaches in clinical trials*, based on the requirements of the Regulation, which provides further information on how such a risk proportionate approach can be implemented and also highlights the areas identified in the Regulation which allow such adaptations.

With this public consultation the Directorate General for Health and Food Safety, DG SANTE, intended to seek the views of stakeholders – and other interested parties - on the document, in preparation for the implementation for the Clinical Trials Regulation (EU) No 536/2014.

This document presents a factual summary of the responses to the public consultation. It does not present the views of the European Commission.

2. CONTRIBUTORS TO THE PUBLIC CONSULTATION

The number of contributions received was 40. Eight contributors claimed confidentiality or anonymity over their submissions. Their contributions will therefore not be published or published only in anonymous form.

3. OUTCOME OF THE PUBLIC CONSULTATION

The following types of comments were received from contributors:

- General comments: 42

- Specific comments on the text (highlighted with track-changes): 261

The general comments were focused on:

- More emphasis that the risk adapted approach should take into account not only the risks to the subjects, but also the risks related to the reliability of trial results.
- In the Risk based quality management section, re-organisation of the text for clarity purposes was proposed.
- Alignment of the terminology in this document with the information provided in the Integrated Addendum to ICH E6.
- Clarification on the term 'risk assessment and mitigation plan'.
- Clarification on the requirements for centralised monitoring.
- Clarification on the application of risk adapted approaches to source data verification.
- In the section on the Trial Master File content, inclusion of examples of accepted combination of documents.
- Considering more examples, for illustrative purposes.

The specific comments on the text refer to:

- Editorial changes for consistent use of terminology and clarity purposes.

Section on low intervention clinical trials:

- Inclusion of a clarification that clinical trials with Investigational Medicinal Products (IMPs) which do not have a marketing authorisation cannot be considered low intervention clinical trials.
- Addition of text to clarify the role of the OECD recommendations in relation to Article 2(3) of the Regulation (EU) No 536/2014.
- Request to explain the cases where observational clinical trials become interventional only due to the randomisation process.

Section on risk proportionate approaches in clinical trials:

- Proposal to include in the list of references recommendations also from other initiatives, not only those issued by national/regional authorities.
- Continuous risk assessment may require that a low interventional trial is reclassified and no longer considered low interventional (for example following a protocol amendment, new safety information etc.).
- Request to include, as an example, a template for the risk assessment and mitigation plan.

Section on safety reporting:

- Clarification in the safety reporting section that the investigator has to report all adverse events and not only the adverse reactions. The risk –based approach has to start with considering all adverse events and subsequently, if justified, defining the exemptions of reporting all adverse events.

- The paper should further clarify which is the basis for the selection of adverse events to be recorded and reported.
- Inclusion of the clarification about Annual Safety Reports, that they should describe the risk adapted approach that was undertaken for safety reporting for each trial covered.
- Clarification that the option to completely replace on-site monitoring by centralised monitoring should remain only an exception to the rule.
- Refer also to remote monitoring.
- The extent of source data verification versus data privacy should be addressed.
- Include more details on the monitoring plan.

Section on the content of the Trial Master File (TMF):

- Request to add, as an annex, an example of TMF described in details.
- Comment that non-commercial organisations generally do not comply fully with ICH GCP and are not required to do so where data are not part of a regulatory submission.

Note: The above lists of comments are not exhaustive.

All comments that have been reviewed to-date, have been discussed, if agreed with, incorporated into the guideline and if not agreed with, a reason for this has been documented.

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i Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products