

30 Aug 2016

Submission of comments on **Summary of Clinical Trials Results for Laypersons** – 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

Name of organisation or individual

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1. General comments

General comment (if any)

We welcome the opportunity to comment on this draft document and appreciate efforts to help authors when writing the lay summary. We recognise the value of lay summaries in promoting transparency as regards to clinical trials and their outcomes, and strive to prepare high quality and understandable documents. We also see that there is a balance to reach in providing comprehensive and complete information, often for complex studies, whilst keeping the document concise, readable and understandable. There is also a balance with regards to timing, to make this information available to participants, patients and others, in all EU countries where studies are run, in a timely manner after the end of the trial, whilst continuing to strive for the highest standards of quality and consistency. The comments below are aimed at further clarifying best practices to help implement lay summaries, and to highlight where flexibility may be warranted in order to reach the desired goals.

A global format for lay summary documents is required

The EU should collaborate with regulators worldwide to create a lay summary template that is readily understandable for audiences in all countries where the trial was performed. Today, clinical research is fully globalised and internet access will make published information accessible globally. The value of this new document will be jeopardized if it is written with an EU vs non-EU focus and it is not a good use of resources for clinical trial sponsors to write multiple versions of the lay summary for a global clinical trial. Hence, we strongly recommend this guidance be geographically agnostic to the extent possible.

Need for lay-friendly language of headings

Sponsors should have the flexibility to modify headings listed in Annex V of the EU Reg No 536/2014, in the same way as patient information leaflets can include more patient-friendly headings for the information required under Article 59 of Directive 2001/83/EC. As with the legislation concerning PILs, there is no clear requirement in the Clinical Trial Regulation to use the headings listed in Annex V: article 37(4) indicates that Annex V sets out the **content** of the lay summary; Annex V itself requires that the summary contains “information on” the “elements” listed. We understand that the Commission has advised that the wording of the 10 elements cannot be changed, but we respectfully request that this interpretation be reconsidered to provide flexibility and consistency within each lay summary.

Appropriate language for the headings in the template could be determined through user testing.

General comment (if any)

Dealing with multiple endpoints

The lay summary should report the results of the primary endpoint(s), at the minimum, to meet the goals of a short, high-level, balanced and factual document.

Lay summaries should describe the results of primary endpoints as the general standard for several reasons:

- (1) Primary endpoints address the main purpose of the study;
- (2) Studies are statistically powered to show differences in primary endpoints;
- (3) Unless pre-specified, some secondary endpoints or exploratory endpoints may lack statistical power and validation, which could lead to misinterpretation by the public and give more weight to a result than appropriate. This may be of particular concern for the lay summaries posted to the EU database and available to global audiences.
- (4) Selectively including “important” secondary endpoints risks introducing bias and may be misleading.
- (5) Lay summary should refer readers for further information, with a link to the scientific summary as already noted in Annex 1 section 7 (including the full list and results of secondary endpoints).

Timing of submission of lay summary for paediatric clinical trials

Sponsors of paediatric clinical trials have already raised concerns about the challenges of meeting the 6 months timeframe for reporting study results under the Paediatric Regulation. The additional need to prepare a lay summary will introduce significant further challenges. We assume that the submission of lay summaries for studies that include paediatric subjects are fully aligned with the requirements of the Clinical Trials Regulation to be submitted within 12 months after study end. (NOTE: If this assumption is correct, footnote to Table 1 of the EMA’s “Appendix, on disclosure rules, to the “Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014”” should be corrected, to clarify that the 6 months timeframe does **not** apply to lay summaries of paediatric studies.)

Preferably, the 6 months results reporting requirements and timeline for paediatric studies under the Paediatric Regulation should be fully aligned with the Clinical Trials Regulation and be waived for trials that are covered by Regulation 536/2014 to provide a consistent framework for all clinical trials which facilitates operational implementation and sponsor compliance.

General comment (if any)

Presentation of adverse reactions

We wish to reiterate that use of “adverse events” to report adverse reactions in lay summaries is preferred to clearly align with other key documents for the clinical trial, such as the technical summary, the clinical study report and the registries, to decrease the likelihood of confusion to patients and the general public. Adverse events are the most factual and transparent way to report side effects from clinical trials as they are derived directly and objectively from patient reports.

This preference notwithstanding, we recognize that the regulation uses the term adverse reactions. There is a lack of clarity regarding how to determine those events which may be categorized as “adverse reactions” and included in lay summaries. The Clinical Trial Regulation uses the definition of “adverse reaction” included in Directive 2001/83/EC (“A response to a medicinal product which is noxious and unintended”). This implies a causal relationship between the event and the investigational medicinal product

Multiple studies, however, are often needed to elucidate a causal relationship. In an individual clinical trial, the investigator will usually give an opinion on causality, but the sponsor/regulator’s assessment of causality may subsequently differ (e.g. when more extensive clinical trial or pharmacovigilance data are available). We recommend clarifying that the adverse events, which the investigator determines, are related to study treatment and are to be described and reported as “adverse reactions” in lay summaries. Standard text can be included in the lay summary to explain the differences between adverse events and adverse reactions. While we would prefer to use adverse events in lay summaries to align with the corresponding Annex IV summary, we propose describing and reporting “adverse reactions” as the best alternative in order to indicate a potential causal relationship in an objective and uniform manner.

Review of guideline to assess its business impact and value to the public

Based on our experience in developing and testing lay summary documents in close collaboration with stakeholders, we would like to point out the significant additional resource requirements that are required to produce high quality value adding documents in accordance with the Guideline recommendation for every trial; specifically for small and medium enterprises or sponsors who conduct hundreds of trials in several regions of the globe.

We recommend that the guideline be reviewed after an initial pilot phase to evaluate its functioning in light of the actual business experience and value to the public.

General comment (if any)

General Editorial remarks

Consistent terminology should be used for the naming of the summary of results for laypersons, to clearly identify and locate these new documents for the general public. We propose the term “plain language summary” should be consistently used, as feedback from patients has indicated that “lay summary” appears condescending.

Consistent terminology should be used throughout the guidance document (e.g. gender vs sex) that reflects accepted EU terms. Please replace US terminology with appropriate terms used in the EU framework. For example in the Annex 1, when used in the text of the lay summary, the word “drug” is open to misinterpretation and could create confusion in translations. We suggest a global change to “medicine”, “vaccine” or “consumer healthcare product” depending on the type of product being studied.

In addition, we suggest that that EU Expert Group on Clinical Trials makes available a common glossary of lay terms for medical and scientific concepts so that sponsors could use consistent language that is understandable to the general public.

In general, we recommend only including references to associations or plainly to terms like regulators/ethics committees/patients/health care professionals/industry/academia, who have contributed to the development of the draft guideline instead of listing specifically named individuals.

2. Specific comments on text

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
Lines 58-61, Lines 71-72 Lines 81-82, Lines 235-240, Lines 250-252, Annex 1, Section 4.2	<p>Comment:</p> <p>The document should be written for one primary audience – the general public. Research participants often have a different level of understanding and various levels of interest in the disease, treatment, the study design, population, etc. Although the document may be used by investigators to share information with the patients who were enrolled in the clinical trial the lay summary should provide comprehensive, basic information about the study and not assume that the reader was involved in the trial or has a high level of knowledge and understanding of it. Several sections of the guideline should be amended accordingly.</p> <p>Proposed changes:</p> <p>The lay summary should provide clarity to the question “Who is this document for? “. We’ve observed there isn’t a heading that explains why this document has been produced and what is its’ target audience. We suggest an additional heading for clarity as well as detailed explanation on the webpage that is being used to publish the documents.</p> <p>Lines 58-61 “This document provides recommendations and templates for the production of summaries of clinical trial results for laypersons by sponsors and investigators. These will only apply to lay summaries included in the EU database. The lay summary section of the EU database will be publicly available and research participants and the general public are is expected to be the primary audience of the lay summaries, but they may also be accessed by others such as research participants themselves, healthcare professionals and academics.”</p> <p>Lines 71-72 If the lay summary is to be written for the general public audience then it needs to include descriptions of the trial and the medical condition.</p>

Line number(s)
of the relevant
text

Comment and rationale; proposed changes

(If changes to the wording are suggested, they should be highlighted using 'track changes')

(e.g. Lines 20-23)

Lines 81-82

“Consider involving patients, patient representatives, or advocates in the development and review of the summary information to ~~ensure that it truly meets their needs~~ help meet the needs of the general public.”

Lines 235-240

“Where feasible, sponsors should consider testing the readability of an initial version of the study results summary with a small number of people ~~who represent the target population with the condition and a range of health literacy levels. Depending on the nature of the study, this could be patients with a particular disease or it could be members of the public. For example, studies which affect the general public such as vaccine studies would benefit from input from members of the public rather than patients.~~ Their feedback and suggestions can be ~~crucial~~ helpful in developing a summary that lay people will understand.”

Lines 250-252

“~~Patient friendly~~ Summaries of clinical trial results which combine clear infographics with explanatory text can be a good way of presenting complex information.”

Annex 1, Section 4.2

“Consider including a simple graphic that helps ~~people/patients~~ the reader understand the study”

Line 50-52

Comment:

The template recommendations may result in a lay summary that is longer than optimal for understanding by audiences with low health literacy level. We suggest providing a statement that it is not mandatory to include all the content recommended in the template and that it is not specifically required by the regulation.

Proposed change:

Add a sentence: “Suggested content, not specifically required by the regulation, is recommended but not mandatory.”

Line number(s)
of the relevant
text

(e.g. Lines 20-
23)

Comment and rationale; proposed changes

(If changes to the wording are suggested, they should be highlighted using 'track changes')

Lines 88-102

The description of people's reading ability is repetitive. Both Sections 5 and 6 cover this topic. We suggest shortening this information and confine it to one Section only.

Comment:

"Average proficiency level is 2-3." is **too broad** to be able to decide what an appropriate reading level is, because it suggests that the test is written for those who have completed high school and not the average person. It would be helpful to state a range for reading levels and to **add the reading age range** that corresponds with the high school level.

The grade level target is given as proficiency levels of 2-3, but with a suggestion that a level of 3 is the most common score across Europe. As a score of 3 corresponds to high school completion-level proficiency, this is in direct conflict with suggested grade level target later in the document. Please note that the EU schooling systems varies across Member States and that a reference to age range might be better understood instead of grade level.

Proposed change:

Based on research across Europe, suggests that text for the public lay summary should be aimed at a literacy proficiency level of 2 -3. The International Adult Literacy Survey (IALS) identifies five levels of proficiency ranging from level 1 (lowest level of proficiency in literacy, that is basic 90 identification of words and numbers) to level 5 (highest level of proficiency in literacy, that is able to understand and verify the sufficiency of the information, synthesize, interpret, analyze and discuss the information. At level 5 the individual demonstrates sophisticated skills in handling information).

Communications written for the public should use simple everyday language to ensure ease of reading and understanding.

- Text should be suitable for people with a low to average level of literacy. Across Europe the average proficiency level is 2-3. A proficiency level of 2 is defined as being able to identify words and numbers in a context and being able to respond with simple information e.g. being able to fill in a form. This level corresponds roughly with age 12-13. A proficiency level of 3 is defined as being able to identify, understand, synthesize and respond to information, be able to match given information which corresponds to a question. This level corresponds roughly with high school completion levels (14 to 18 years old).

Line number(s) of the relevant text (e.g. Lines 20-23)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')
	<ul style="list-style-type: none"> We recommend using language for the lay summary that corresponds to reading age 12-13."
Line 125	<p>Comment: The term "<i>big picture</i>" might be too vague and not accurate enough. The concept of "inverted pyramid style" might not be universally understood.</p> <p>Proposed change: "Presentation of the "big picture" <u>key information</u> before the details (inverted pyramid style)."</p>
Line 122-132	<p>Comment: We recommend highlighting the availability of existing tools that can assist in assessing readability, including aspects such as layout, formatting, and use of visual elements. These are an important adjunct to the text metrics already provided. Embedded weblinks in the guidance and templates may become outdated over time and a maintenance process is needed.</p> <p>Proposal: Briefly describe and cross-refer to the CDC Clear Communication Index and AHRQ toolbox (which are both already included in the references list). We propose to update to the next versions of the Harvard MRCT documents which are now publically available (Guidance v2.1 and Toolkit v2.2 (accessed at http://mrctcenter.org/wp-content/uploads/2016/07/2016-07-13-MRCT-Return-of-Results-Guidance-Documnet-Version-2.1.pdf and http://mrctcenter.org/resources/2016-07-13-template-mrct-return-results-toolkit-version-2-2/ respectively). All links will be checked periodically to make sure they do not become outdated.</p>
Lines 148-155	<p>Comment/Proposed change: This information should be combined and aligned with Section 5 to avoid redundancy and add clarity. As outlined above, the grade level target is given as proficiency levels of 2-3.</p>

Line number(s)
of the relevant
text

Comment and rationale; proposed changes

(If changes to the wording are suggested, they should be highlighted using 'track changes')

(e.g. Lines 20-23)

Line 238

Comment:

We agree and consider a good idea to test the readability of an initial version of the study results summary with a small number of people who represent the target population in order to develop appropriate writing skills for lay summaries. We note that the guidance recommends that this should be completed 'where feasible' and appreciate this flexibility, as it may prove difficult to achieve within the timelines for preparation of the lay summary and be quite resource intensive. In addition, we propose that further wording is added to offer other ways to achieve this outside of the routine process for lay summary preparation.

Proposed change:

"Readability scores are useful but not in themselves enough to ensure that a text is easy to understand. Where feasible, sponsors should consider a review by an appropriate target population. ~~testing the readability of an initial version of the study results summary with a small number of people who represent the target population.~~ Alternatively, other ways to obtain feedback may be possible, for example through questionnaires or surveys after publication.

Lines 244-247

Comment:

Please add the link to the numeracy publication – the perspective from the IOM.

In addition, it would be helpful to include the core principles within this document given that clinical study results will most certainly contain numerical data. Such principles could include "use whole numbers rather than decimals, use consistent denominators and timeframes. Research suggests that less literate readers may interpret numbers as more risky when in frequency form (1 out of 10) versus percentage form (10%). This could be because frequencies elicit emotional imagery, where percentages are more abstract or meaningless" etc.

Proposed change:

"Strategies to Enhance Numeracy Skills " by Andrew Pleasant, Megan Rooney, Catina O'Leary, Laurie Myers, and Rima E. Rudd
<http://nam.edu/strategies-to-enhance-numeracy-skills/>

Line number(s)
of the relevant
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Comment and rationale; proposed changes

(If changes to the wording are suggested, they should be highlighted using 'track changes')

(e.g. Lines 20-23)

Line 133

Line 138

Lines 253-256,
Annex 1. Section
4.2

Comment:

It is not clear what would constitute unnecessary imagery other than logos.

The guidance on visuals in Annex 1 suggests avoiding figures that present more than one message. However we believe that this could be misinterpreted. Also visuals that only convey a single simple message could be replaced with a single line of text. The figure in Annex 1. Section 4.2, Figure 1 is a good example.

We recommend that use of such tools is at the discretion of the sponsor, and propose that the text clarifies that this decision is based on whether the graphic improves the reader's understanding of the text.

We agree that visuals should only be used where they aid reader understanding, and as such, authors should be advised to use visual materials that communicate messages more clearly.

Propose changes:

Line 133: "Limited use of unnecessary imagery that does not enhance understanding (icons, logos, etc.)

Line 138: "Use visuals and infographics (e.g. simple graphs) if helpful to clearly convey complex messages."

Replace Lines 253-256 with the following wording "Avoid visuals that are overly complicated and difficult to interpret. Consider how a visual aid helps reduce the need for lengthy text. Any visuals and logos should still be clear if printed in black and white."

Delete Figure 1 in Annex 1 Section 4.2.

Line 260-261

Comment:

Research shows that people vary in terms of learning styles and this flexibility could benefit how understandable lay summaries are. Hence, we support the concept that sponsors would be allowed to use different modalities to provide study results.

However, the guidance suggests that sponsors include videos, cartoons and animation in the lay summary. We believe these may not be suitable for a pdf file and may lead to confusion.

Line number(s) of the relevant text (e.g. Lines 20-23)	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
	<p>Proposed changes: Delete line 260.</p> <p>In addition, we propose to delete or update the link to “Drug Trials Snapshots” as the current link opens to “Drug Trials Snapshot: CORLANOR”. Perhaps a better link would be as follows: http://www.fda.gov/drugs/informationondrugs/ucm412998.htm</p>
Lines 264-268	<p>Comment: As described in the general comments above, the preparation and submission of translations of lay summaries of paediatric studies within 6 months of the end of the trial will be very challenging.</p> <p>Proposed change:</p> <p>“As a minimum, the summary is expected to be provided in the local language of each of the EU countries where the trial took place. <u>Only the local language in which the informed consent had been provided should be required as a minimum.</u> A pdf version in each language used will need to be uploaded separately. Where resources allow, sponsors should consider including an English version if the trial did not include the UK, as the use of a common language will allow greater accessibility across the EU, however this is not mandatory. <u>For all studies, including paediatric studies, lay summaries will be available within 12 months of the study end.</u>”</p>
Lines 271-276	<p>Comment: The guidance suggests that sponsors should consider providing some direct feedback to patients who have taken part in their trials. We would like to clarify that the sponsors are prohibited from directly contacting patients who were enrolled in studies.</p> <p>Please also note that in compliance with ICH E6 GCP (1.16 – 1.21 – 4.8.10 (o) obligation to maintain the confidentiality of subjects’ identities) subject identity is completely blinded to the sponsor (except the CRA who access the medical records), mostly even after the end of the trial. Sending such direct acknowledgements to former trial participants would trigger the creation of lists in total contradiction with the long implemented GCP principles within pharma sponsors. Hence, it will be necessary to revise ICH E6 before recommending such</p>

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
	<p>return of results to study participants within the EU guideline.</p> <p>Proposed change: The summary for lay persons in the EU database should not be regarded as the only way of communicating with trial participants. Whilst study participants may find the lay summary useful, sponsors may providing some direct provide study results to <u>investigators or third parties to</u> feedback to patients who have taken part in their trials including along with an acknowledgement of their contribution and an expression of thanks for their time <u>appreciation</u>.</p>
Annex 1. Introduction	<p>Comment: Sponsors must have the flexibility to modify headings listed in Annex V of the EU Reg No 536/2014, in the same way as patient information leaflets can include more patient-friendly headings for the information required under Article 59 of Directive 2001/83/EC. As with the legislation concerning PILs, there is no clear requirement in the Clinical Trial Regulation to use the headings listed in Annex V: article 37(4) indicates that Annex V sets out the content of the lay summary; Annex V itself requires that the summary contains “information on” the “elements” listed. We understand that the Commission has advised that the wording of the 10 elements cannot be changed, but this interpretation is unhelpful and we respectfully request this to be reconsidered to provide flexibility and consistency within each lay summary.</p> <p>Proposed change: It should be noted that the <u>content of the lay summary must include information fulfilling all ten elements in Annex V.</u> wording of the ten elements cannot be changed but that Sponsors can, if they wish, combine categories where this aids understanding For example, some sponsors might wish to combine section 3.1 (where the trial was conducted) with 4.1 (the number of subjects included in the trial). <u>Sponsors and</u> may also decide to change the order of the <u>categories headings</u> if they feel this is appropriate and if they feel this is <u>appropriate makes the summary easier to understand.</u> and add sub-headings as required</p>
Annex 1, Section 1, example	<p>Comment: Please consider avoiding the terms 'best' or 'safest' and replace with 'to understand the overall benefit and overall risk for patients' as this</p>

Line number(s) of the relevant text (e.g. Lines 20-23)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')
language	<p>may be considered promotional language.</p> <p>Proposed change: Researchers look at the results of many studies to decide which drugs work best and are safest for patients understand the overall benefit and overall risk for patients.</p>
Annex 1, section 1	<p>Comment: “[R]ationale for these trials should be explained”. This information is already included in section 3.3 and should be deleted from section 1 to avoid redundancy.</p> <p>The guidelines indicate "<i>Other identifiers refer to WHO ICTRP number, US NCT number, ISRCTN number if available, etc.</i>" Providing too many trial identifiers might be confusing to the general public, and a large majority of trials are registered on ClinicalTrials.gov.</p> <p>Proposed change: We recommend using NCT number to clearly identify the trial across multiple registries and provide other identifiers as optional and when available.</p>
Annex 1, section 2	<p>Comment: Please note that the provision of sponsors’ contact information could be interpreted as an invitation for the public to discuss outcomes of interventional studies with the sponsor. We’d like to reiterate it is neither customary nor appropriate to do so. In our experience, putting contact names, even generic ones, in the public domain often results in inquiries that are not for the intended purpose. Sponsor contacts may be included however sponsor would be limited as to the information that could be provided other than general results and the contract information for the study site/investigator. We feel strongly that patients who are interested in learning more about results of a study and potential implications for them individually should discuss results with their investigator or with their treating physician who is familiar with their medical history and treatment. It is also not feasible to have sponsor contacts available to speak with patients in every language possible which limits the value of requiring a sponsor contact.</p>

Line number(s)
of the relevant
text

Comment and rationale; proposed changes

(If changes to the wording are suggested, they should be highlighted using 'track changes')

(e.g. Lines 20-23)

Proposed change:

"Give the name and address of the sponsor organization, ~~and how to contact (not a specific person in most cases).~~"

Annex 1,
section 3

Comment:

Please consider using alternative wording to "new treatment" for early phase studies when the agent has yet to be approved. For example "experimental treatment" or "investigational medicinal product" (which would match the wording of the 10 elements) so that the lay public do not think that early phase studies are looking at the results of a new approved product.

Proposed changes:

Suggested wording for Phase 2 trials: 'In this study, researchers were trying to find out if this ~~new~~ test treatment could help patients with a particular condition. '

Suggested wording for Phase 3 trials: "In this study, researchers compared the ~~new~~ test treatment to the standard treatment used for [disease/condition] or placebo.'

Suggested wording for Phase 4 studies: "Researchers looked at the effect of the new treatments in a larger number of people".

Annex 1,
section 4.1,
p. 15

Comment:

This section has significant overlap with section 3.1, and repeats long list of EU specific breakdown information such detailed EU specific information will make it difficult to use the template for reporting on global clinical trials. This information is already available from the EU clinical Trials Portal.

Proposal:

Preferable this EU specific information should be deleted from the lay summary.

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(e.g. Lines 20-23)

Annex 1,
section 4.2,
p. 16

Comment:

Due to the global nature of clinical research, a breakdown of age and gender in EU vs non-EU countries is not very informative, not required by the regulation, and will make the document longer and less accessible to the reader. We recommend providing only the breakdown for the overall trial population.

Also, please clarify that a summary of the overall statistics, eg, mean, median, range, is sufficient.

Proposed change:

“Provide basic breakdown of participants by age range and gender break down in the EU (and non-EU if the studies includes countries outside of the EU).”

Annex 1,
section 5,
Bullet 1,
p. 17

Comment:

Including all brand/trade names for **all products in all countries** in multi-country studies will create confusion and add to the length and complexity to the lay summary. Additionally, if the sponsor of the study is not the marketing authorisation holder of a treatment used in a comparator arm, it may be difficult to obtain and accurately report all brand names. The use of brand names may also be suggestive of an approval status which could be misleading to the patient. Only generic name/INN (if available) should be required, and sponsors should have flexibility to determine what other name(s) are appropriate to include. For example, internal compound codes may be relevant for some trials in early clinical studies.

Proposed change:

This should include both the interventional drug and any comparator products, and should refer to generic (international non-proprietary name (INN)). and all brand/trade names used in the countries where the trial took place. The most common brand names of the interventional drug used in EU member states where the trial took place may be provided at the end of the summary.

Annex 1,
section 5,

Comment:

There are scientifically valid reasons for single blind studies and these are appropriately discussed with regulatory agencies. We suggest

Line number(s) of the relevant text (e.g. Lines 20-23)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')
p. 17	<p>deleting as this can be a confusing statement for a lay person.</p> <p>Proposed change: A single blinded trial may mean that the results may be biased by knowing who received each treatment.</p>
Annex 1, section 6	<p>Comment: The information provided in the guideline is insufficient to describe “adverse reactions” as defined by the Regulation and for sponsors to determine what to include in a lay summary. Below are some issues that need further clarification and required explicit guidance in the document. In addition, it may also be useful in the lay summary to refer to the full summary results and/or the product information for an approved medicine:</p> <ul style="list-style-type: none"> - As explained in the general comments above, there is a lack of clarity regarding how to determine which information should be provided to describe and report “adverse reactions” in the lay summaries, we recommend that the lay summary includes the adverse events for which the investigator determines there is a reasonable possibility of a causal relationship with the investigational medicinal product. - It is also unclear whether events not related to the investigational product are to be reported in this section. (The section heading, “Adverse reactions,” indicates a causal relationship to the drug, yet there is a statement that “<i>deaths</i>” and “<i>any adverse events</i> which have led to ... the withdrawal of patients” are to be reported, which may include both related and unrelated events.) Please make the section internally consistent and consistent with the heading. - The guidance states that adverse drug reactions reported in the lay summary should be presented with a similar layout to that in the Patient Information Leaflet (PIL) required for marketed products. It should be noted, however, that the objective and context for the PIL is different than for the lay summary. The PIL is designed to provide patients with comprehensive information about a medicine, based on multiple clinical trials and other data sources, to help ensure that the patient uses a prescribed medicine correctly and takes appropriate action in specific situations (e.g. if they have a contraindication, experience an adverse reaction or

Line number(s)
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23)

Comment and rationale; proposed changes

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take the wrong dose). The lay summary on the other hand is designed to report the results of a single study to a general audience not necessarily familiar with the disease area or possible treatments at all.

- There is still some confusion in regards to **seriousness and severity** of adverse reactions which are specifically defined terms in the regulatory framework. It is stated that “The most serious adverse reactions need to be listed first,”. How should ‘most serious’ be judged (by medical judgment, intensity of AE)?
- Serious Adverse Reactions are covered by a later bullet point but the description does not seem to refer to Serious Adverse Events according to the definition in ICH E6, but rather to adverse reactions that are considered to be medically “serious”. Clarification on this issue is requested. We suggest to state: Serious adverse events need to be listed first and (non-serious) adverse events should be presented separately in a table sorted by frequency.
- Lastly, the European Commission’s Readability guideline does not include any guidance regarding the listing of adverse drug reactions in patient information leaflets: that guidance is provided in the EMA QRD templates for product information (see page 32 at [this link](#)). Reference to such guidance is, however, inappropriate, as the PIL and lay summary serve different purposes (see general comments).

Proposed changes:

“Sponsors should note that the lay summary calls for a description of adverse reactions whereas the technical summary refers to adverse events. This difference is intentional and means that text should not be simply copied across from one document to the other. For the purposes of this guidance, “adverse reactions” means an adverse event for which the investigator has indicated there is a possible causal relationship between the event and the investigational medicinal product.”

The reference to the European Commission’s Readability guideline is not helpful and should be deleted.

- ◆ ~~Sponsors should follow guidance used for listing adverse reactions in patient information leaflets included in the European Commission’s Readability guideline (http://ec.europa.eu/health/files/eudralex/vol-2/c/2009_01_12_readability_guideline_final_en.pdf) on how to~~

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~~comply with the legal requirement of article 59(3) of Directive 2001/83 and render a package leaflet that it is legible, clear and easy to use.~~

We recommend to outline one or more unambiguous options for reporting, eg, present AEs reported by the investigator as treatment related and with a frequency > 5%, and SAEs reported by the investigator as treatment related and with a frequency > 1%, or other criteria that can be objectively applied within the framework of a single trial.

~~“The side effects should be laid out as they would be in a regular Patient Information Leaflet. The most serious adverse reactions need to be listed first, followed by all other side effects listed by frequency (starting with the most frequent) and not repeating the most serious side effects listed above.~~

~~The number of serious adverse reactions and deaths-fatal adverse reactions should be clearly stated together with any adverse events reactions which have led to the early closure of the trial or the withdrawal of patients... Where deaths and adverse reactions may be attributable to the treatment rather than the condition, this needs to be made clear.”~~

Paragraph following bulleted list:

~~“Side effects are unwanted medical events (e.g. headache) that happen during the study, and are reported because they are thought the study doctor (investigator) believes the side effects were to be related to the treatments in the study.”~~

Annex 1,
Section 7

Comment:

As explained in the general comments above, lay summaries should describe the results of primary endpoints as the general standard. As explained under the general comment section, providing the primary endpoint(s) is essential to a high-level summary. However, including descriptions and explanation of additional endpoints may add considerable length and complexity to the summary and thereby be counterproductive to the overarching goal of the lay summary. Studies that measure “Patient relevant secondary endpoints” and “Key patient reported outcome measure” are not necessarily powered or designed to test the significance of a treatment effect on these endpoints, and instruments may not be validated. Including a reference to the full results summary will provide additional information to

Line number(s)
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Comment and rationale; proposed changes

(If changes to the wording are suggested, they should be highlighted using 'track changes')

the interested public.

Please add guidance as to how numerical differences vs statistically significant differences are to be reflected in lay language. For example, the statement, “This means that more patients in Group B had tumours that shrunk.”—should this be reserved only for cases where statistical testing demonstrated a significant between-arm difference? We recommend that if numerical differences were seen but significance was not reached or was not assessed, this needs to be explained to the reader.

Proposed changes:

“This section should describe each of the study arms including the name of the drug (generic only) and the results of the primary outcome(s) measures ~~at a minimum~~ (both positive and negative), using text and graphics where appropriate. ~~including information on whether the study completed as planned, or terminated early along with the reason. Where statistical testing was performed, indicate whether results were statistically significant, using lay language. Where statistical testing was not performed, state this in lay language.”~~

Proposal for example text in the table:

“Statistical testing showed this difference [*was unlikely to have been*] OR [*could have been*] due to chance alone”

“Researchers did not test whether the difference between Group A and Group B could have been due to chance alone”

“The primary endpoint(s) and results by study arm which were pre-specified by the statistical analysis plan as a primary endpoint.

- ~~● Patient relevant secondary endpoints and results by study arm~~
 - ~~● Key patient reported outcome measures (PROMS) or other quality of life indicators of interest to patients (Any scales used for measurement should be explained).~~
 - When dealing with multiple endpoints,
 - ~~● Where additional endpoints are reported, these endpoints should be reported by study arm~~
- ~~In some cases, It may be possible to summarize closely related endpoints together.~~
- Sponsors should include patient relevant secondary endpoints as some of the quality of life measures and PROMs are likely to be of

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~~interest to patients~~ Sponsors may wish to point out that a complete list of outcomes based on all endpoints is available on the website in the technical result summary for each clinical trial. ~~is available on the website.~~

- They may also reference the registries that contain more detail.

Annex 1,
section 7

Please list the best practices document and link Health Literacy Missouri website to ensure readers can find the information.

Comment:

We recommend using the definition of the attached publication of Sorensen K et al., Health literacy and public health: A systematic review and integration of definitions and models; BMC Public Health 2012, 12:80 doi:10.1186/1471-2458-12-80:

Health literacy is linked to literacy and entails people's knowledge, motivation and competencies to access, understand, appraise, and apply health information in order to make judgments and take decisions in everyday life concerning healthcare, disease prevention and health promotion to maintain or improve quality of life during the life course.

The definition is the result of a systematic review of definitions and has been used as a basis for the European Health Literacy Survey (sponsored by the European Commission).

Annex 1,
section 7, p.20-23

Comment:

Dose Escalation: The "highest dose that is tolerated" is not called a "dose limiting toxicity". This should be removed.

DLT and MLT are not the same as implied by the document. One causes serious side effects the other does not.

- DLT: Describes side effects of a drug or other treatment that are serious enough to prevent an increase in dose or level of that treatment.
- MTD: The highest dose of a drug or treatment that does not cause unacceptable side effects. The maximum tolerated dose is determined in clinical trials by testing increasing doses on different groups of people until the highest dose with acceptable side effects is found.

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Proposed change:

Please define DLT to capture the true definition.

Comment:

Endpoint morbidity: Please consider adding 'or when the patient experiences a new illness or condition' to the end of the sentence.

Proposed change:

"Morbidity endpoints are those that measure the severity of disease, or ~~when a new disease begins~~ when the patient experiences a new illness or condition."

Comment: PFS:

Descriptions of OS and PFS: The example data presentations for PFS and OS are misleading. These endpoints are often evaluated using a hazard ratio. Both endpoints are related to time alive (example given for OS) and the percentage of patients with certain outcomes (example given for PFS), but providing percentages does not accurately reflect PFS or OS analyses. All key efficacy assessments in oncology are based on time-dependent estimates, thus the representation of these endpoints in percentages is incorrect and misleading. We suggest including better wording or leaving it up to sponsors to develop appropriate descriptions.

Comment:

Change "Surrogate" to "Surrogate Marker" in the first column.

Annex 1,
Section 8

Comment:

As explained above, differences between subgroups may be described, if they have been examined in a trial as a part of the original statistical analysis plan. However, this guidance should not impose this expectation otherwise.

In addition, the information conveyed regarding subgroups in the FDA's Drug Trials Snapshot represents data from multiple clinical trials in

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the post-authorization context. The lay summary on the other hand is a summary of data from one clinical trial with limited numbers of patients, especially if Phase I/II.

Proposed changes:

Describe if there were any significant differences between sub-groups; in particular by age, gender and ethnicity where the same size is sufficient to show statistical differences. The Drug Trials Snapshots produced by the FDA provide a useful model for this, for example:

~~Were there any differences in how well the drug worked in clinical trials:~~

~~Were there any differences in how well the drug worked in clinical trials?~~

- ~~• Sex: Treatment A worked similarly in men and women.~~
- ~~• Ethnic group: Treatment A worked similarly in all groups.~~
- ~~• Age: Treatment A worked similarly in patients younger than 65 years and patients 65 years and older.~~

~~Were there any differences in side effects?~~

- ~~• Sex: Treatment A had a similar side effect profile in men and women.~~
- ~~• Ethnic groups: The number of patients from ethnic minority groups was limited. This means that it was not possible to make any conclusions regarding differences in side effects among ethnic groups.~~
- ~~• Age: All patients who took Treatment A had a similar side effects no matter how old they were.~~

Annex 1,

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Comment and rationale; proposed changes

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section 9

Due to the fast dynamic of clinical development this information may only be accurate at the time of publication and becomes quickly out of date. In addition, disclosing plans for follow-up trials could be perceived as promotional, and interpreted to be indicative of the sponsor's confidence in particular products or disclose company confidential information.

Proposed change:

This section should explain whether other trials are ongoing already or provide public domain information about related trials. ~~if any further, related clinical trials are likely to be undertaken, and if so, what the foreseeable timelines might be~~

To learn whether there are follow-up trials ongoing or planned, go to [URL] and search on the medicine name, "X".

Alternative: Based on the findings of this study there are no future studies planned at this time."

Annex 1,
section 10,
p. 25

Comment:

Sponsors should be responsible for the content of the lay summary, but not for any information that is above and beyond their control. When providing web-links within the lay summary, sponsors will not be able to take on responsibility for the content of a webpage they have no direct access to; there might be no promotional language on a certain webpage by the time of linking to a lay summary, but as long as the sponsor is not in charge of the referenced content, promotional language might be added on that webpage at a later stage and it is not possible to ensure that contents of webpages do not change over time. In addition, there is inconsistency in the document related to the number of links the sponsor should provide in the summary. Line 130 says only minimal links should be provided whereas this section seems to suggest providing a number of links to all available information.

Proposed changes:

Links to "General information about clinical trials" would be more appropriate to maintain on the EU portal landing page than for sponsors to recreate for each individual study.

Please delete the requested specific links in this section and provide more general information on the EU CT Portal.

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
Lines 77-78 Annex 2	<p>Comment: We strongly support the aim of the document to ensuring that no promotional content is included in the lay summary and we appreciate the inclusion of neutral language guidance in Annex 2 to assist with this. We do foresee some areas of uncertainty, for example regarding on how the presentation of patient reported and quality of life results is to be handled, since some measures have assessments that are not factual (e.g. for the question 'are you feeling better?' stating that 60% of population reports "feeling better" could be construed as promotional).</p> <p>Proposed change: We would propose that Annex 2 is continuously updated to include good examples of neutral language to serve as examples for other sponsors. These examples can then be considered by sponsors, along with those already provided in Annex 2, to help with learning and improvement as the new lay summary document is implemented.</p>

Please add more rows if needed.