29 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
TransCelerate BioPharma, Inc

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Dealing with multiple endpoints The lay summary should report the results of the primary endpoint(s) 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 will address the main purpose of the study; (2) Studies are statistically powered to show differences in primary endpoints; (3) 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 in the context of lay summaries posted to the EU database. (4) Selectively including “important” secondary endpoints risks introducing bias and may be misleading . (5) Lay summary should refer readers with a link to the scientific summary for further information, as 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	

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	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. If this assumption is correct, footnote p 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 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.	
	Presentation of 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	

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	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'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 that the investigator determines are related to study treatment 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 drug 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.	

2. Specific comments on text

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Stakeholder number ***(To be completed by the Agency)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	Outcome ***(To be completed by the Agency)***
Lines 58-61, Lines 81-82, Lines 235-240, Lines 250-252, Annex 1, Section 4.2,		Comment: 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 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. Several sections of the guideline should be amended accordingly. Proposed changes: 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 healthcare professionals and academics."	

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		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. ~~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"	

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Lines 88-102		Comment: 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. 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 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. 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).	

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Lines 253-256, Annex 1. Section 4.2		Comment: 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. Proposed change: 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. " Delete Figure 1 in Annex 1 Section 4.2	
Line 260		The guidance suggests that sponsors include videos, cartoons and animation. We believe these may not be suitable for a pdf file and may lead to confusion. Proposed change: Delete line 260.	
Lines 273-275		Comment: The guidance suggests that sponsors should consider providing some direct feedback to patients who have taken part in their trials. Sponsors do not directly contact patients who were enrolled in studies due to law and privacy protections in the various jurisdictions. Proposed change: The summary for lay persons in the EU database should not be regarded as the only way of	

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		communicating with trial participants. Whilst study participants may find the lay summary useful, sponsors should ~~providing some direct~~ provide study results to investigators to 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~~ appreciation.	
Annex 1. Introduction		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 we respectfully request that this be reconsidered to provide flexibility and consistency within each lay summary. Proposed change: It should be noted that the content of the lay summary must include information fulfilling all ten elements in Annex V. ~~wording of the ten elements cannot be changed but that~~ Sponsors can, if they wish, combine categories where this makes sense ~~For example, some sponsors might wish to~~	

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		~~combine section 3.1 (where the trial was conducted) with 4.1 (the number of subjects included in the trial). Sponsors~~ and may also decide to change the order of the categories ~~headings~~ if they feel this is appropriate. ~~and add sub-headings as required~~	
Annex 1, Section 1, example language		**Comment:** Please consider avoiding the terms 'best' or 'safest' and replace with 'to understand the overall benefit and overall risk for patients' as this may be considered promotional language. **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.	
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.	

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		Proposed changes: Suggested wording for Phase 2 trials: 'In this study, researchers were trying to find out if this ~~new~~ experimental treatment could help patients with a particular condition. " Suggested wording for Phase 3 trials: "In this study, researchers compared the ~~new~~ experimental 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 treatment~~s~~ in a larger number of people".	
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~~	

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		~~includes countries outside of the EU).~~"	
Annex 1 Template Section 5 Bullet 1		Comment: Including all brand/trade names for all products in all EU countries in multi-country studies could create the need for a long list of names that adds 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, for example, 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. We propose reporting only the most common EU brand name of the interventional treatment 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		Comment: As explained in the general comments above, there	

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6		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. Although our preference would be to report adverse events, this objective approach to reporting adverse drug reactions could be specifically described in the text of the lay summary. Proposed change: 1st paragraph "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." *Paragraph following bulleted list:* "Side effects are unwanted medical events (e.g. headache) that happen during the study, and are reported because ~~they are~~	

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		~~thought~~ the study doctor (investigator) believes the side effects were ~~to be~~ related to the treatments in the study."	
Annex 1. Section 6 1st and 3rd bullets		Comment: The reference to the European Commission's Readability guideline is confusing. This 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, unnecessary, as the PIL and lay summary serve different purposes (see general comments), and as Section 6 of Annex 1 already provides necessary detail as to requirements for lay summaries. Proposed change: • ~~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 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.~~ • ~~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…	
Annex 1, Section		Comment: The guidance states that adverse drug reactions	

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6		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 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. Proposed Change: ~~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.~~	
Annex 1. Section		Comment: As explained in the general comments above, lay	

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7		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. Because sponsors will need to carefully consider the inclusion of additional information against the length, clarity and understandability as well as the balanced and non-promotional nature of the summary, sponsors should have the discretion to add further information regarding secondary endpoints or refer to the more detailed and comprehensive Annex IV summary Proposed change: 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. • ~~Patient relevant secondary endpoints and results by study arm~~ • ~~Key patient reported outcome measures (PROMS) or other~~	

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		~~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 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 results summary for each clinical trial. ~~is available on the website.~~	
Annex 1, Section 8		Comment: Where examined in a trial as a part of the original statistical analysis plan, differences between subgroups may be described, however, this guidance should not imposed this expectation otherwise. In addition, the information conveyed regarding subgroups in the FDA's Drug Trials Snapshot represents data from multiple clinical trials in 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. Proposal: ~~**Describe if there were any significant differences**~~	

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		~~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 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, Section		Comment: Disclosing plans for follow-up trials could be	

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9		considered company confidential information. This may also be perceived as promotional, and interpreted to be indicative of the sponsor's confidence in particular products. 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~~	

Please add more rows if needed.