August 16, 2016

Submission of comments on 'Summary of Clinical Trial Results for Laypersons'

Comments from:

Name of organisation or individual
Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard

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).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Overall we applaud this effort by HRA to ensure that clinical trial results are routinely returned to trial participants. Specifically, the focus on patient-friendly, concise summaries written with health literacy principles will be key towards successful implementation. The EU Consultation document's recommendations and templates for summaries should be commended as the first regulatory guidance publicly to: • Address specific recommendations and templates for the production of summaries of clinical trial results for laypersons by sponsors and investigators (line 56-57) • Provide the lay summary section of the EU database in a publicly available database for research participants and the general public • Build upon published material from the MRCT Center (http://mrctcenter.org/news/updated-versions-of-return-of-results-guidance-document-and-toolkit-released/ • Provide guidance in a clear, concise, succinct language • Refer to literacy proficiency and readability in detail and make detailed recommendations for specific countries • Encourage patient involvement in the review and development of the summary to ensure it meets their	

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	needs [line 81ff] We note the following areas of concordance with MRCT Return of Results (ROR) Guidance Document: • Ensure no promotional content [line 77]; Neutral Language Guidance in Annex 2 is taken from MRCT ROR Toolkit (http://mrctcenter.org/wp-content/uploads/2016/07/2016-07-13-MRCT-Return-of-Results-Toolkit-Version-2.2.pdf) • Follow health literacy principles: #5, line 87ff "Health Literacy Principles and Writing Style" uses content from Annex 3 of MRCT ROR Guidance Document (http://mrctcenter.org/wp-content/uploads/2016/07/2016-07-13-MRCT-Return-of-Results-Guidance-Document-Version-2.1.pdf) Endpoint table from MRCT ROR Toolkit has been integrated into Annex 1 – Templates, "#7. Overall results of the clinical trials" We note that a harmonized approach benefits those that have participated in clinical trials by enabling the timely return of high-level, patient-focused and non-promotional aggregate results summaries. We commend the EU Consultation for the concordance of its recommendations, propelling international uniformity that will help to ensure that all participants, in all countries, benefit from access to identical information,	

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	consistent with ethical principles of justice.	
	Role of the Ethics Committees (RECs) – There is currently no international agreement on the obligations and involvement of RECs in the process of returning aggregate results to research participants. This was an area of considerable debate and discussion in the development of the MRCT Guidance and Toolkit. We believe that the appropriate level of REC involvement should be based on the timing of returning results as delineated in the MRCT Return of Results Guidance Document, Version 2.1, Section 2.3, pp 21-22. There are three primary time frames in which sponsors/investigators consider the process of returning results: 1) the introduction of the concept in study planning (and therefore in the informed consent and occasionally the study protocol, 2) during ongoing clinical trials when primary endpoint results are available but the study remains open for secondary endpoint data collection, and 3) return of results for studies that are completed and closed. These scenarios will require differing levels of REC engagement; we suggest that the HRA include specific language in this regard. The companion document in the MRCT Toolkit Version 2.2, p. 24 provides a checklist to assist IRBs/RECs in defining their role to support this initiative. Specifically, the checklist assists RECs in balancing risks and benefits of returning results. In general we	

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	believe that in the event of returning of results in the midst of a study (e.g. contemporaneous with the scientific publication of primary endpoints but the study to remain open for collection of secondary endpoints, a longitudinal observational study, etc.), the IRB/REC, throughout an open trial, has oversight responsibilities and should review planned interactions or communications with participants. If interim studies will be communicated by contacting the participants directly, the IRB/REC should review and approve the communication. If, on the other hand, interim study results are communicated by public dissemination (e.g. posting results on a website such as is proposed in the present draft consultation), the REC does not have jurisdiction. At the end of a study, however, the situation changes. In the U.S. and in the EU, IRBs/RECs are not required to review the plan for, or materials used in, the return of RRS to participants -- unless these plans are described in the study protocol -- *so long as* the results will be returned after the study has been closed by the IRB/REC.	

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)*
Line 265-267		"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." We believe that this requirement may cause an undue burden; we suggest that the EU consultation instead consider that translation be provided in the local language if the informed consent document was translated and if participants were enrolled.	
Pg.13 Annex 1		We recommend the following changes to be consistent with health literacy principles: "1. Clinical trial identification" to "Title of the study"	
Pg. 14 Annex 1		"3. General information about the clinical trial" to "Why the study was done"	
Pg.15 Annex 1		"4. Population of subjects" to "Study Information: Trial participants"	

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Pg.17 Annex 1		"5. Investigational medicinal products used" to "Study Information: Drugs (Devices) used in this trial"	
Pg.17 Annex 1		"6. Description of adverse reactions and their frequency" to "Side effects"	
Pg. 19 Annex 1		"7. Overall results of the clinical trials" to "How the study worked"	
Pg.24 Annex 1		"8. Comments on the outcome of the clinical trials" to "Summary of results"	
Pg.25 Annex 1		"9. Indication if follow up clinical trials are foreseen" to "Final Comments"	
Pg.25 Annex 1		"10. Indication where additional information could be found" to "Final Comments"	
Pg.17 Annex 1		Template, "5. Investigational medicinal products used."	

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		Change “to reduce differences between the groups” to “so that each patient had the same chance to be selected for any group in the study.” Utilizing the MRCT ROR Template, we found that the latter was more useful than the former.	
Pg. 19 Annex 1		Template, “7. Overall results of the clinical trials” <u>Redefine which endpoints to include at a minimum in the lay summary</u>: We suggest to include only: ○ Primary endpoints at a minimum by study arm. ○ Additional *safety data* that impacts the primary endpoint. ○ Secondary endpoints may be communicated by sponsors if there is a strong rationale for inclusion (e.g. safety, clinically meaningful).	
Pg. 19 Annex 1		We suggest not including the term “patient relevant secondary endpoints” such as “key patient reported outcomes” as it may have the	

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		potential for bias; these results may be the most "accessible" to patients yet lack statistical significance and rigor. In some cases, addition of these endpoints may lead to greater weight being given to these endpoints by patients versus the primary outcome.	
Line 62		• delete "be" in front of "take" at the beginning of the line	
Line 79		• change section 6 to 5 where it refers to "Health Literacy Principles and Writing Style"	
Line 127		• change section 8 to 7 where it refers to numeracy principles	
Line 247		• Refer to latest versions of MRCT ROR documents: Guidance Document Version 2.1 (http://mrctcenter.org/wp-content/uploads/2016/07/2016-07-13-MRCT-Return-of-Results-Guidance-Document-Version-2.1.pdf) and Toolkit Version 2.2	

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		(http://mrctcenter.org/wp-content/uploads/2016/07/2016-07-13-MRCT-Return-of-Results-Toolkit-Version-2.2.pdf), also in References. • Refer specifically to Appendix 4 in MRCT ROR Toolkit for "Health Literacy Missouri Best Practices for Numeracy"	
Pg. 11		• Reference "A user-friendly checklist to apply health literacy principles" is incomplete.	
Pg. 19 Annex 1		• "Overall results of the clinical trials": make "trials" singular since each summary reports only from one trial	
Pg. 25 Annex 1		Template: Overall: change to parallel active wording throughout the template, start bullet points with an action verb; e.g., #"10. Indication where additional information could be found": ○ *Provide* links to helpful websites with further information… ○ *Ensure* that readers are not exposed to	

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		promotional language … ○ *Provide* links to generic sites…	