EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 February 2015

# Submission of comments on "Draft proposal for an addendum, on transparency, to the 'Functional specifications for the EU portal and EU database to be audited -- EMA/42176/2014'"

## Comments from:

| Name of organisation or individual |
| --- |
| Multi-Regional Clinical Trials (MRCT) Center at Harvard University |

*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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February 18, 2015

RE: Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited – EMA/42176/2014"

Dear Colleagues:

The Multi-Regional Clinical Trials (MRCT) Center at Harvard University respectfully submits the comments below on EMA's Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited – EMA/42176/2014." This proposal will support the implementation of the new European Clinical Trial Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. This Regulation aims to foster innovation through simplification of the clinical trial application process and to increase transparency and availability of information on clinical trials and their results.

The MRCT Center at Harvard has three primary goals: (1) to improve the design, conduct, and oversight of multi-regional clinical trials, especially trials sited in or involving the developing world; (2) to simplify research through the use of best practices; and (3) to foster respect for research participants, efficacy, safety and fairness in transnational, trans-cultural human subjects research. The MRCT Center at Harvard does not fund, plan, conduct, or monitor clinical trials, but rather studies their regulatory, practical and ethical aspects, in order to improve design and conduct of clinical trials. The MRCT Center at Harvard has convened a number of working groups, including a group to study ways to facilitate greater access to participant-level clinical trials data while maintaining the security of private health information and a separate working group to plan and hold a conference in late March 2015 designed to promote shared governance and a shared data platform for a wide variety of industry and academic sponsors of clinical trials.

In this capacity, the MRCT Center at Harvard applauds the proposed application of transparency requirements, data and documents to be made public through the EU portal and EU database. While we support the proposed addendum on transparency, we wish to submit the following focused comments for your consideration. The comments follow on the form requested by the EMA.

The MRCT Center at Harvard thanks the EMA for the opportunity to provide comments. We hope the agency finds these comments helpful as you finalize the addendum.

Respectfully submitted,

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Mark Barnes, JD

Carmen Aldinger, PhD

On behalf of the Multi-Regional Clinical Trials Center at Harvard University

# 1. General comments

| Stakeholder number<br>*(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)<br>*(To be completed by the Agency)* |
|---|---|---|
| | The draft appendices 1-7 to the draft proposal are clearly laid out in color-coded blocks with respect to the data fields required and the timing of submission in relation to market approval. However, the guidance does not specify the required format of the data to be uploaded into the database and, importantly, whether EMA intends to harmonize these requirements with NIH's structured tabular data entry system (currently found on ClinicalTrials.gov). The data entry system of ClinicalTrials.gov provides maximum flexibility for results submission, permits effective searching, and facilitates cross-trial comparisons. However, the ClinicalTrials.gov data entry process places significant burden upon responsible parties and sponsors by requiring the manual placement of individual results data points into the website or XML file. This burden is further compounded when the responsible party must comply with a separate data format when submitting to the Food and Drug Administration. For this and other reasons, the MRCT Center at Harvard urges that the EMA amend its proposed rule by adopting a standard data format consistent with CDISC SDTM and ADAM Data Submission Standards, to which the Food and Drug Administration has already made a commitment, and to which the MRCT Center at Harvard has urged that the | |

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| | NIH and ClinicalTrials.gov also commit. This would allow sponsors to create one clinical trial results file that is in compliance with both EMA and FDA standards. This approach would allow interoperability of the data, minimize data mapping requirements, and permit maximal utilization of the data for science and the public good. Further, this requirement may encourage academic investigators and other sponsors that do not submit to the FDA to adopt the CDISC Data Submission Standards, thereby facilitate the merging of datasets for analyses. | |
| | We applaud the inclusion of the requirement for a layperson summary, proposed in Annex 6 of the draft proposal EMA/42176/2014, which is consistent with Regulation (EU) 536/2014 Annex V. We have drafted a guidance document – the *MRCT Center at Harvard Return of Results Guidance Document* and the *MRCT Center at Harvard Return of Results Toolkit* which were developed by a multi-stakeholder workgroup comprised of more than 50 members from industry, academia, patient advocacy groups and non-profit centers, coordinated by the MRCT Center at Harvard. Our detailed guidance document is fully consistent with the layperson summary proposed in the Regulation. | |

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| | In addition, the *MRCT Center at Harvard Return of Results Toolkit* includes templates and sample summaries for returning results to study participants, a table with common clinical trial endpoints in simple language, guidance on neutral language, a sample notification to third party form, and checklists for Research Result Summaries Reviewers and Ethic Committees. These resources provide user-friendly tools for implementing the guidance and for reporting in lay language and are publicly available.<br><br>Furthermore, the *MRCT Center at Harvard Return of Results Guidance Document* recommends compliance with health literacy and numeracy standards and use of non-promotional language. These are critically important considerations, and we suggest the EMA adopt language supporting this approach in its current communication. Lay summaries will have maximum impact if they are written in compliance with health literacy and health numeracy principles. Health literacy principles include the use of short active-voice sentences, familiar vocabulary, descriptive headings and subheadings, and bullet points. Health numeracy principles include the proper use of graphs and tables, use of numerical examples, and the inclusion of absolute risk as context for relative risk. In order to facilitate the use of health literacy and numeracy principles, the MRCT Center at | |

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| | Harvard recommends further that the EMA release guidance on how to format and write lay summaries that are easy for the general public to understand.<br><br>The MRCT Center at Harvard strongly believes that non-technical lay summaries can be written using neutral language that is not promotional. To facilitate the use of neutral language, we recommend that the EMA release guidance on how to write summaries that are non-promotional.<br><br>We recommend that the EMA provide resources including user-friendly tools and templates to facilitate the implementation of and compliance with the final Regulation. | |

## 2. Specific comments on text

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
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| 382-410 | | Comment: EMA's proposal to release the names and CVs of principal investigators and their staff is not consistent with widely accepted principles of the protection of personally identifiable information. In some cases of controversial drugs or trials, (such as abortifacients) this breach of privacy may have significant implications for the personnel involved.<br><br>Proposed change: We propose that investigator and study staff names and CVs are redacted and only the institution wherein the study was conducted be included. | |
| 610-642 | | Comment: We agree that "regardless of marketing authorisation status the IMPD-Q section on IMP quality and the related lists of questions, responses and assessment report sections should be considered to be commercially confidential and not be made public for any trial at any time, as this deals with the manufacturing and related pharmaceutical development information which continues to be CCI, indefinitely, post marketing authorisation." Since the Investigational Medicinal Product Dossier (IMPD) includes manufacturing and related pharmaceutical development information, we agree that this continues to be commercially confidential information that should not be made public at any | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
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| | | time.<br><br>Proposed change (if any): NONE | |
| 643-654 | | Comment: We concur with Proposal 3 – a differential treatment based on clinical trial stage that would treat data release more conservatively in the earlier stages of development but less conservatively for those trials that have progressed through Phase 3. This would most balance the public's interest in the data pertaining to a compound that has advanced into pivotal trials with the appropriate protection of commercially confidential information important to sponsors that may be considering the next development steps for a product without marketing authorisation. Further, this more conservative approach protects the public from any assumptions of accuracy in small data sets on products that have not yet been shown to be safe or effective (or unsafe or ineffective), and then from relying on analyses that are potentially significantly flawed.<br><br>Proposed change (if any): NONE | |
| 655-708 | | We concur with Proposal Two: "The Study specific and product specific documents (with the exception of the IMPD-Q section, which would not be made public at any stage) should only be made public after the earlier of the conditions set out in paragraph 6.5 below are met." This would most appropriately | |

| Line number(s) of the relevant text<br><br>*(e.g. Lines 20-23)* | Stakeholder number<br><br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br><br>*(To be completed by the Agency)* |
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| | | balance protections for commercial confidentiality with the public's interest in the data.<br><br>Proposed change (if any): Choose Proposal Two. | |
| 726-746 | | We concur with the proposal to give the sponsor the option to have only very minimal public information at the time of decision on the Phase I trial (EU number of the trial, sponsor, investigator site, phase of trial [Phase I], number of trial subjects, population under study [healthy volunteers], decision on trial). However, we do not agree that the summary results of the Phase I trials should be released due to concerns regarding potential commercially confidential information, whose sensitivity and commercial importance may be highest during this early product development stage and propose sponsors have the option to defer for these reasons.<br><br>Proposed change (if any): lines 739-744<br><br>740 The decision on the trial would also be made public, but identifying the trial only by this minimum set of information. The information that would 741 usually have been made public at the start of the trial and during the trial will, in case of a 742 deferral, be made public at the point when the summary of trial results is published only in cases in which serious and unexpected adverse events have occurred in healthy volunteers 12 months 743 after the end of the trial. This option for deferral will not apply to Phase I trials | |

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| | | conducted in 744 paediatric populations. | |
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