Author's response to reviews

Title: Heterogeneity prevails: the state of clinical trial data management in Europe - results of a survey of ECRIN centres

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Author's response to reviews: see over
Coverletter and list of corrections for manuscript 9990040063365136

RE.: MS: 9990040063365136 - Heterogeneity prevails: the state of clinical trial data management in Europe - results of a survey of ECRIN centres

Dear Editors, Dear Reviewers.

Thank you for the comments. The comments have been very useful and have improved the manuscript. All comments were incorporated and the manuscript has been corrected accordingly. In addition, the entire manuscript has been revised to improve readability. All figures have been formatted for 300 ppi, and correct size. The detailed list of reviewer comments and corrections made follows at the end.

Best wishes.

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Reviewer 1

Major compulsory revisions

1. “Mention of the poor response rate.” Correction: a new paragraph “Characteristics of the survey” was inserted that deals with the response rate (page 8, paragraph 2). The response rate is discussed in detail as a limitation of the study. Arguments are presented that the results are nevertheless valid and for many participating countries representative.

2. “The abstract should mention the response rate” Correction: the response rate is now indicated in the abstract: page 4, paragraph 2 (line 4) in parentheses.

3. “No mention of ethical approval” Because the survey does not refer to patient data or clinical procedures, an ethical approval is not necessary.

4. Results, last paragraph. “Thus, resources and experience to conduct successfully multinational clinical trials using CDMS are available in ECRIN centres. The authors cannot make this statement given the poor response rate.” Correction: this sentence was completely deleted.

5. Discussion 4th paragraph. “These are big statements that are difficult to support with the poor response rate. Can it be proven that centres involved in DM answered the survey or at that responding centres were representative of their country.” Correction: a new
paragraph was created “Characteristics of the survey” (page 8, paragraph 2). This paragraph contains the results of an additional question about the representativeness of data management for the respective country. The representativeness is discussed in view of differences in the response rate of different countries.

6. “Conclusion is concise and replicates the discussion. It should include the key points from the survey that will inform the new ECRIN system and the activities that will be undertaken as a result of this work. Correction: the “Conclusion” contains now (page 20, paragraph 1, line 16) a sentence about planned activities which are based on the results of our survey and which the ECRIN Transnational Working Group on Data Management will carry out.

Minor essential revisions

1. “Titles are missing from all Table and Figures which make interpretation difficult. This is particularly significant for Figure 1 where it is unclear what the numbers below the countries are, are they response rates for Survey1/Survey 2?” Correction: a title describing the meaning of the numbers was added to Fig. 1. The other figures and tables are described in detail in the accompanying legends (page 26 for figures).

2. “Grammar in the background needs to be revised.” Correction: grammar was corrected in the “Background” paragraph, and in addition the entire text was revised to improve readability (numerous corrections).

3. “Background, 1st paragraph last sentence. “It has been demonstrated that web-based EDC and CDMS can be employed very successfully in the academic area. Needs some sort of example.” Correction: three sentence dealing with academic trials and the example of the INVEST (University of Florida) study were inserted (page 6, end of paragraph 1, line 20).

4. “The manuscript would benefit from a linking paragraph from the background to the methods statement.” Correction: a small linking paragraph has been inserted at the end of “Background” (page 7, paragraph 3).

5. “Methods. The manuscript states that both surveys were sent to 167 centres.” Correction: the description of both surveys was revised. Now the exact number for both surveys is indicated (page 8, paragraph 1, line 8).

6. Results, 2nd paragraph, 1st sentence “The vast majority of centres/unit conducts DM. This is the first time we see DM.” Correction: this was corrected, the abbreviation is now explained at page 8, line 3).

7. Results, section entitled “Special cases of use of CDMS by ECRIN centres/units. This section should be a table.” Correction: the listing of special cases of CDMS is now formatted like a list / table (page 11-12).

8. Discussion, 1st paragraph: “I am not sure what this paragraph is stating, no clear discussion point.” Correction: the first paragraph has been completely rewritten; describing now the purpose of ECRIN data centres and the plan to use resources already available in ECRIN (page 14, paragraph 3).

9. “Discussion, 3rd paragraph. “ECRIN centres are using routinely EDC systems for their data collection needs, even though in only a small number of trials per centre”.

Correction: the concerning sentence was deleted. In fact the entire paragraph was rewritten. In the results section it is now made clear that the concerned CDMS are used routinely for clinical trials. (page 10, paragraph 2 (line 5). Also in table 1, row 2 CDMS in routine use are indicated.

equivalent of Part 11 the “EU GMP Guideline Vol. 4, Annex 11 Computerized Systems” is now mentioned (page 17, paragraph 2 (line 2))

**Discretionary revisions**

1. “Results. I would recommend that numbers as well as percentages were included in the manuscript”. **Correction**: for important values the numbers as well as percentages are indicated. For example in: page 10, paragraph “Clinical data management systems (CDMS) employed in ECRIN centres” and page 13 paragraph “Quality management and data management in ECRIN centres”

**Reviewer 2**

**Minor Essential Revisions**

1. “the use of 'less then' in line 6 on page 8.” **Correction**: this has been corrected; only “less then” is used.

2. “Page 12, there is a reference to a system being 'FDA compliant'”. Better to use the phrases: validated to meet FDA requirements” **Correction**: the sentence is changed into “the solution is validated to meet FDA requirements” (now page 11, paragraph 2)

3. The sentence in the conclusion: "But we identified as the most important task for clinical research centers to improve the quality management of CDMS... is not well-written and difficult to understand. … This sentence should probably be reworded to make a better transition between the need for data standards (data exchange as well as increased quality of data).” **Correction**: the sentence “identified as the most important task…” was rewritten. A new paragraph (page 20, paragraph 1) was added, about the relationship between a heterogeneous IT environment, the use of data standards and data quality.

**Discretionary Revisions**

1. “It may be appropriate or helpful to have a few sentences in the discussion around the move to encourage EHR adoption (i.e. the future beyond EDC) and the need to have CDMS that will also support such data collection methods....” **Correction**: in the last paragraph of “Discussion” now the topic of electronic health records (EHR) for trial data collection is discussed and the “CDISC healthcare link” is mentioned (page 19) and in addition a new reference [19] was added.

2. Perhaps a few sentences around this vision would bring a broader readership. **Correction**: in the last paragraph of “Discussion” the new vision of interoperability and data exchange is discussed, including ePRO and data warehousing (page 19, paragraph 1), which concludes that streamlining of clinical research may finally improve healthcare for patients