Article details: 2018-0096	
Title	Current use and costs of electronic health records for clinical trial research: a descriptive study
Authors	Kimberly A. McCord MSc, Hannah Ewald PhD MPH, Aviv Ladanie MSc, Matthias Briel MD MSc, Benjamin Speich PhD, Heiner C. Bucher MD MPH, Lars G. Hemkens MD MPH; for the RCD for RCT-initiative and the MARTA-Group
Reviewer 1	Ksenija Bazdaric
Institution	Department of Medical Informatics, Faculty of Medicine, Rijeka University, Rijeka, Rijeka, Croatia
General comments (author response in bold)	19. Methods Instead of: „...since 2000 that evaluated any medical intervention in any population on any medical outcome while utilizing EHR for any purpose. We determined the use of EHRs and the characteristics of respective RCTs.I would write: „ since 2000 that evaluated medical interventions while utilizing EHR. We determined..." **We have changed the text as suggested** The methods are very clear- Literature search and the protocol are explained in detail. **Thank you!** Statistical analysis: there is only descriptive statistics, why did you choose median and percentiles? you state in the results that something is more/less often but you did not use any test. there should be tests for categorical and quantitative variables included. **Our evaluation is a description of the current research in this area. We used medians and percentiles as descriptive measures, providing some orientation about the frequency and distribution of characteristics (reporting median and percentiles is valid if the data is not normally distributed).** **There is no hypothesis that we aimed to test. We agree that some of our statements might have been misleading in this regard and we have carefully adapted those to increase clarity. However, as per STROBE guidelines3, we did not report p-values on descriptive tables.** Results Please write: out in North America [153(81%)] and in all results with the same stile **We carefully revised the reporting accordingly and ensured consistency.** Remove percentage in : but instead used EHRs for recruitment (14 of 17; 82%) or outcome measurement (15 of 17; 88%). **We are not sure we understand this comment and have not changed thus far. The percentage is correct and in our view, it would provide the reader with an intuitive number.** Per patient cost: is there a median value? **We report all cost information in the table (i.e. there are 5 data points with per patient costs), we have now added the median cost value in the text as well (see revised manuscript, lines 262-263).** The results are not surprising, as the majority of the RCT comes from 2000 and in the US. it was interesting to read about the cost of the trials, and as this is the first study I believe we will have to investigate more in order to have a more clearer picture of the RCT cost. However I have major remarks on the presentation and analysis. Background Does the background accurately represent current knowledge in this field? Do the authors explain why they conducted the study? Is there a clear research question? The introduction has the rationale and objectives of the study. But, since this is a meta-epidemiological study I would like the authors to state the hypothesis **Our study is explorative and aims to evaluate this research field - as many other meta-epidemiological surveys (see for example [4,5]). We don't have a formal hypothesis that can be formally tested. Nonetheless we have now more clearly stated our aims and objectives so that this is clearer to the reader, and we have enhanced our background section.**
Reviewer 2	N. Nante
Institution	Department of Physiopathology, Experimental Medicine and Public Health, Università di Siena, Siena, Italy
General comments (author response in bold)	INTRODUCTION: -It could be more useful to insert the definition of table 1 in the Background paragraph, that it is poor and delete the table 1. **We feel that a specific table/box with definitions could be more useful as it separates the very specific details with the overall background. We feel that the specifics are complex and while well-known for some readers very novel to others. However, we carefully checked which definitions could be integrated in the Introduction and hope that our expanded example provides more information in general in the background section. In addition, we changed the table to a box (as suggested by the Editors).** -It could be better to explain the acronym USD on line 18. **We added the explanation.** METHODS: -As regards the methods, there may be a major aspect to consider. Authors did not evaluate whether risk adjustment techniques were included in the studies. So confonder effect due to different level/ risk/ etc within the same variable could have played a role to be aware of. Risk adjustment techniques are useful to take account of confounding effects in clinical data. Patient recruitment or outcome assessment which do not include risk adjustment could have changed the eligibility of RCTs and results throughout the study. **We agree that risk adjustment techniques are essential when trials are included in analyses that aim to use their estimated treatment effects. As the aim of our meta-epidemiological study was to see whether EHR trials were used, and if so, how they were used; the risk of bias and the quality of evidence were not particularly relevant. Please see our response to comment 11 by the Editors above.** The definitions mentioned, on Line 12 of page 4, should be moved to the Background as mentioned above. **We added this information.** The Appendix 1, referred to Line 33 of page 4, is not necessary, the keywords are sufficient. **We are strongly convinced that providing the complete search strategy in the appendix increases our transparency and reproducibility of our work. Please see PRISMA statement item 8: "present full electronic search strategy for at**

least one database..."and the corresponding item in the suggested reporting guideline by Murad & Wang.

Please explain The Acronyms CPOE/CDS at row 10 page 5, I know they are in table 1 but it could be better insert this also in the text.
We added the explanation of the acronyms in the text and added a link to the table here as well.

From line 25 to 33 the Authors repeat the acronym RCD, please explain it.
We have added the explanation of the abbreviation in the Introduction, where it is initially used.

Row 54 page 5 appendix 3, the Authors could insert the appendix directly in the text, what explained is part of the research. It is not necessary to separate from the text.
We inserted this as suggested.

RESULTS:
About the paragraph RCTs using HER for intervention, lines 55-56 page 8 and lines 3-10 page 9, it is poorly analyzed, also there are only the references of the studies, it might be helpful a resume table, as for HER-facilitated.
We have only briefly focused on the EHR-evaluating trials, because we were primarily interested in whether and how the technology could increase the ease of conduct of regular RCTs, i.e. trials that can be conducted with and without EHR, for example trials evaluating drug effects. Trials where the EHR is elementary for the intervention are a very specific subset (even when it is larger). We now made this focus more clear in the objectives stated in the Introduction (lines 113-115).

DISCUSSION:
-The Authors explain the part of the study about EHR-facilitated but not about EHR-evaluating part that has the most number of studies. This part needs to be expanded.
As mentioned above, while EHR-evaluating trials were more numerous, they were not our primary focus. We added a clear explanation and expanded the discussion.

As mentioned above, it might be helpful to add the risk adjustment part, or if it is completely absent in the study, the Authors should indicate this as a limit of the study.
We added this as a limitation in the discussion.

References:

1. Cristea IA, Ioannidis JPA. P values in display items are ubiquitous and almost invariably significant: A survey of top science journals. PLoS ONE 2018; 13(5): e0197440.
2. Goodman S. A dirty dozen: twelve p-value misconceptions. Semin Hematol 2008; 45(3): 135-40.
3. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. PLOS Medicine 2007; 4(10): e297.
4. Hemkens LG, Contopoulos-Ioannidis DG, Ioannidis JPA. Current use of routinely collected health data to complement randomized controlled trials: a meta-epidemiological survey. CMAJ Open 2016; 4(2): E132-E40.
5. Page MJ, Higgins JPT, Clayton G, Sterne JAC, Hróbjartsson A, Savović J. Empirical Evidence of Study Design Biases in Randomized Trials: Systematic Review of Meta-Epidemiological Studies. PLoS ONE 2016; 11(7): e0159267.