Reviewer’s report

Title: A novel electronic tool to recruit large patient samples and assess selection bias in general practice research

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Reviewer: Peter J Embi

Reviewer’s report:

General comments: The authors report on the implementation and use of a software intervention designed to improve identification and enrollment of research subjects that was incorporated into existing EPRs in a convenience sample of loosely affiliated primary care practices in Germany. This report is an important contribution because it adds to the limited literature on the use of EMR (EPR)-based clinical trial alert (CTA) approaches to improve recruitment to clinical research studies. The authors are to be commended for successfully conducting a challenging intervention across many practices that helps advance our understanding of how to improve participation by physicians and patients in primary care sites into clinical research studies. The authors do a fair job of explaining their approach, though, as noted below, more technical detail about the alert operation itself and a bit more detail about the methodology is desirable. Also, the report is less clear than it could be in parts. This confusion owes mainly to conflation of the “study” of the CTA approach, including the relevant “subjects” for that technological intervention (namely the physicians/practices) vs. the “study” of the patients whom they are trying to recruit to an osteoporosis study using the CTA approach. In several places (abstract, methods, results) this reviewer had to re-read the sections in order to determine whether the authors were referring to the “study” of the CTA intervention vs. the “study” of the patients with osteoporosis. It seems clear that the authors are mainly interested in reporting on the CTA intervention and its findings, but if so, then more emphasis and a bit more detail about methodology is required for that intervention (e.g. technical details, physician/practice recruitment methodology, analysis methodology used, etc.). Finally, and importantly, as further mentioned below the authors misstate that this approach is novel; the approach is not. In fact, EMR(EPR)-based CTA approaches in general practice settings that function in a real-time automated fashion have indeed been studied previously in the US despite the authors statement that their’s is the first such report. The fact that the approach described is not entirely novel is not a reason for not publishing this study in the least; it makes other important contributions. However, it should be noted that this is not novel, per se. The major contributions of this work include:

1. It is another example of a CTA approach being applied across multiple, disparate outpatient clinic environments (which due to the paucity of such reports is important and significant in and of itself).

2. It is the first such report of which I’m aware of this CTA approach being applied in general practice outpatient settings outside the US.
3. It does point out the value of this approach for potentially identifying selection bias in real-time, a novel insight, but probably not the major point of this article in my opinion.

- Major Compulsory Revisions/comments

1. Title: as I’ve noted elsewhere, the use of a point-of-care, EMR(EPR)-based clinical trial alert is not “novel” per se, even if the particular piece of software developed and implemented for use in conjunction with the EPRs noted in this study was. Said another way, while the particular software instance might be new, the approach of using such a tool for this purpose is not. Therefore, I suggest that the authors not note this as “novel” in the title and body of the manuscript. In fact, the authors should consider reporting this as a study of a “Clinical Trial Alert” approach in the title and/or abstract and/or body of the manuscript in order to acknowledge that it is another example of a previously reported approach. Again, the article is still a significant contribution without this aspect of novelty.

2. Abstract: particularly the methods section of the abstract does not adequately describe the “methodology” used for the deployment, evaluation of the approach used herein. For instance, a few words should be added about the way in how the practices/physicians (the “subjects” of this study of a CTA intervention) were selected, how analysis of the data were conducted, etc.

3. Background: Again, while the authors do cite the fact that prior research on enhancing recruitment “based on EPRs” has show promise over traditional methods, they do not accurately state in the background section that the very approach they are reporting, a clinical trial alert (CTA) approach, has indeed been performed before in similar settings. In fact, the appropriate acknowledgement of prior work in the literature upon which this manuscript builds is more accurately cited by stating that the current manuscript is a report of a CTA approach – and that it is a unique contribution and advance because (a) it is applied across multiple EPRs and practices that are not otherwise affiliated with one another, and (b) that it is the first such example of such a successful CTA application in an outpatient, general practice environment outside the US (just not the first in the world).

4. Methods: The description of the software development and function is lacking in technical detail. While this reviewer appreciates that the software was developed by a third-party vendor as stated in this section, it is still important for the authors to state a bit more about how this software works with the relevant EPRs. Without more detail, it is difficult for anyone to understand the main study’s intervention that is after all a technological one. This needn’t be extensive, but some technical detail about software platform, whether is was the same piece of software regardless the target EPR, how it was integrated into each EPR for point-of-care use (i.e. did it just use the EPR systems’ built-in capabilities, did the alerts appear via the target EPR’s interface or were they brought up via a separate window on screen), the way it captures and manages information from the source systems, a bit more about how secure exchange of
data were managed, whether any common standards were employed, etc.
should be offered. These are meant as example suggestions of how the authors
might respond to this reviewers’ desire for more detail and are not offered as an
exhaustive list nor as a hard requirements that each one be included necessarily.
Of course, if this has been described elsewhere, a citation to that source would
potentially be an adequate response to this point.

5. Under “software development, implementation and evaluation” section the
authors state that “a novel logistical approach…” was developed. Here is a
specific example of where the authors should instead note that applying
real-time, automated, EMR(EPR)-driven/based CTAs to primary care settings
has indeed been reported previously (i.e. first by Embi et al and then again
Rollman et al), two articles that the authors cite in other places but do not
appropriately acknowledge as preceding, if distinct, examples of this very CTA
approach.

6. Also under that section, the authors state that their software was implemented
in participating practices “consecutively”. As the time differential during which
each practice began to use the software is relevant to the final analysis and
determination of the significance of the numbers of patients recruited, this detail
should be offered.

7. Under Results:
a. I believe that the appropriate analysis of this CTA intervention should be that
of an “intention to treat” (or in this case, “intention to provide alert”) analysis. As
such, the exclusion of the 2 practices of the 27 who agreed to participate
because the practice software failed to function half-way through the study is
probably not appropriate. Excluding them could be considered analogous to
excluding a patient enrolled in a clinical trial because they decided not to take the
medication half-way through the study. I suggest the authors reconsider inclusion
of these two practices and/or state why they have decided not to employ an
“intention to treat” approach to their analysis in the methods section.
b. Under “Electronic patient recruitment in general practices” –
  i. I have a couple of analysis issues that should be addressed. One is that given
the wide differences in number of providers (and therefore potential patients
seen) between practices, it is probably better to re-analyze the outcomes data
using per-physician/provider basis rather than a per-clinic basis. That will allow
more of an apples-to-apples comparison.
  ii. The authors seem to state in that same section’s first paragraph that the
physician-subjects either fully completed the screening questionnaire on patients
(i.e. enrolled the subjects) or in 68% of cases clicked the alert off. Isn’t there a
middle-option wherein the physicians conduct screening of the patients (so they
don’t click it off), but don’t fully complete the questionnaire? This requires
clarification.
  iii. In the second paragraph of that section, the authors state that only a small
number of patients (n=387) chose not to give informed consent. This number
seems to represent 20% of the subjects invited (387/1913), and while not large
given most recruitment standards, 1 out of 5 refusing is probably best not
characterized as small number. This is a minor point, but I’ve left it here for ease of reference for the authors.

iv. The authors go on to state, “only one practice reached the target to recruit 200.” Again, this is a bit misleading in that practices varied widely in number of physicians, so using the same target for all practices regardless of whether they were 1 physician or multi-physician is not too informative in terms of the utility of the CTA. I think it would be reasonable to recalculate based on a per-physician and perhaps report both the per-clinic and per-physician numbers to better express the value of the main intervention.

v. Related point – the tables of data relate to the patients and not the actual subjects of this CTA intervention study – the physicians/providers who got the CTA. Some of the points above would be addressed by including a table of the practices/providers and the details of their participation and use of the alerts. This would be most informative and valuable overall.

c. Under “Detection of selection effects”

i. The performance of statistical analyses to test the statistical significance of the differences between the groups that the authors are reporting as representing biases is indicated. While these numbers appear to be different, one craves a statistics (e.g. a P-value) to demonstrate that with a degree of certainty – this could be included in the relevant table and/or the text.

8. Discussion section:

a. I agree with the authors that this is the first such application of a CTA in Germany in primary care settings.

b. In the first paragraph of the discussion section, the citations included after the sentence, “Worldwide, only few trials have reported the successful implementation of similar electronic tools,” omits the citation of the Embi et al. paper that was the first such successful implementation of a CTA (the authors’ citation #24).

9. Limitations:

a. Missing or misplaced limitations include:

i. This approach as described required significant oversight and ongoing and frequent (as often as quarterly) adjustment by the software vendor (as stated in the “Implementation, feasibility and precision of the identification tool section”). This is opposed to other approaches that specifically utilize the built-in capabilities of existing EPRs in order to allow for more widespread use (e.g. as reported by Embi et al.). The authors acknowledge this limitation in the last sentence of second paragraph under “feasibility of the identification tool”, and might consider moving this to limitations.

ii. The sentence under “Experience with the identification tool…” section that starts, “As we had no control group practices…” is probably better put under limitations section.

iii. While the authors’ finding and report about potential bias being discernable by use of the CTA is an important one most worthy of reporting (as in section
“patient recruitment and selection effects”), the authors should note under limitations section that the design of the study, including convenience sampling of practices of varying make-up, etc, did not allow them to draw conclusions about the source of the biases noted. It might have been related to EPR-based CTA or other reason.

10. Under “feasibility of the identification tool”

a. The considerable effort issue described above could be noted here instead of limitations – that might be more appropriate in fact.

b. The statement that “However, our system is the first to identify eligible patients during daily practice…” is not correct. Again, the Embi et al and Rollman et al studies both did this. In addition to noting this fact, the rest of that paragraph would need to be modified accordingly.

- Minor Essential Revisions

1. The authors discuss the “target” population definition for the patients for the related (and as far as this report of the CTA is concerned largely incidental) osteoporosis study, but they only refer to the “target population” definition for the physicians/practices in passing. More attention in the methods should be paid to that clinician/practice group as the major “target” population for this study. Again, the patients are the “target” for the osteoporosis study, the results of which are not the subject of this manuscript and presumably will be reported separately (which would be entirely appropriate, by the way and not a case of “double-reporting” of data because that is a discrete research study from the study of the CTA approach/technology being described herein).

2. Under “Electronic recruitment process”, the authors state that whenever an alert appeared, “anonymous” data was sent to the study centre via secure Internet connection, but that it did include identifiers like medical record number. While this statement of anonymous (i.e. no name) be technically correct, the inclusion of a medical record number technically means this is potentially identifiable information by the study personnel. However, it is later stated under “Data transfer and analysis” that pseudonymised data was the only data stored and that only practice personnel could re-identify the patient. This suggests that the medical record number mentioned above was not actually stored. This apparent discrepancy should be corrected.

3. Under results section – clarify that “joint” practice means “two-person” practice, if that is the meaning.

- Discretionary Revisions

1. Methods: The degree of compensation offered to participants is of interest.

2. Methods: more description of how these “loosely connected” general practices were contacted and invited to participate (i.e. phone call, email, in person, by mail) is of interest.

**Level of interest:** An article whose findings are important to those with closely
related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I have no financial conflicts of interest to report.
By way of non-financial conflicts to report, my only potential conflict to report is that I have in the past and currently continue to conduct research supported by the US National Institutes of Health on approaches that are very closely related to that reported by the authors in this manuscript.