Author's response to reviews

Title: An electronic clinical trial tool to recruit large patient samples and assess selection bias in general practice research

Authors:

Stephanie Heinemann (sheinem3@gwdg.de)
Sabine Thüring (sthueri@gwdg.de)
Sven Wedeken (swedeken@gwdg.de)
Tobias Schäfer (tobias.schaefer@medizin.uni-goettingen.de)
Christa Scheidt-Nave (Scheidt-Nave@rki.de)
Mirko Ketterer (mirko.ketterer@it-choice.de)
Wolfgang Himmel (whimmel@gwdg.de)

Version: 3 Date: 23 April 2010

Author's response to reviews: see over
Author's response to reviews

Title: An electronic clinical trial tool to recruit large patient samples and assess selection bias in general practice research

Authors:

Stephanie Heinemann (sheinem3@gwdg.de)
Sabine Thüring (sthueri@gwdg.de)
Sven Wedeken (swedeken@gwdg.de)
Tobias Schäfer (tobias.schaefer@medizin.uni-goettingen.de)
Christa Scheidt-Nave (Scheidt-Nave@rki.de)
Mirko Ketterer (mirko.ketterer@it-choice.de)
Wolfgang Himmel (whimmel@gwdg.de)

Version: 2 Date: 16 April 2010

Author's response to reviews: see over
Both referees’ comments have been very valuable for us, especially the classification of our electronic tool as a sort of clinical trial alert (CTA) system. More precisely than in the first version, we now position the new version in the tradition of CTA and similar approaches to support research in practices and clinics. At the same time, we put more emphasis on those features of our electronic tool that may go a step beyond the hitherto existing tools: e.g. continual monitoring of a possible selection bias and integration of the clinical study itself into the alert system. Instead of using the CTA merely as a tool to recruit and refer patients to a study center for participation in a clinical trial, our tool combined patient recruitment in a primary care office setting with a clinical study that took place on the practice premises within a single patient consultation. Although we consider this to be a real novelty, we will follow the first referee’s suggestion to omit the word “novel” in the title of the paper. In the following, we show in detail how we have considered the referees’ suggestions and changed the manuscript accordingly.

Reviewer 1

Novelty aspect

1. *Title:* 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.

Authors’ response

We omitted the word “novel” in the title. Only those features of the tool that are really new aspects are still classified as “novel” in the body of the manuscript. Moreover, in the Abstract and in the body of the manuscript, we place our manuscript in the tradition of CTA and name the tool no longer recruitment tool but - more exactly - clinical trial tool (see especially the new title of the paper; Abstract and throughout the body of the text).

2. *Background:* 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).

Authors’ response

Thank you to the referee in helping us characterize those aspects of the tool that are really new. Moreover, we also emphasized two further aspects as a novelty: continuous
monitoring of a possible selection bias and the integration of the clinical study itself into the alert system. This tool is not just an “alert”, but a clinical trial tool which initiates the entire research process that is completed for an individual patient within minutes of its activation (page 3, lines 25ff; page 6, lines 8ff).

3. **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.**

Authors’ response

We now cite Embi’s and Rollman’s papers as preceding work and emphasize, as mentioned above, the use of the clinical trial tool in primary care settings for directly performing clinical studies as a further development of our work (page 3, lines 25ff; page 6, lines 8ff).

4. **Discussion section: 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).**

Authors’ response

Done. See page 11, line 6.

5. **Under “feasibility of the identification tool”. 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.**

Authors’ response

We changed the manuscript accordingly (see also #4); especially page 11, lines 8ff were modified.

**Physicians as target of the study**

6. **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.**

Authors’ response
We described in some more detail how the practices were selected (page 5, lines 17ff). However, we do not completely agree with the referee’s characterization of our study. Of course, this is a paper about methods and not about patients with osteoporosis, but we needed data about patients to evaluate the performance and effectiveness of the recruitment tool. Although we also mention the performance of doctors’ and practice staff, especially whether they have reached the target level of enrollment, these persons were not primarily in the center of our interest. In other words, the target of our study (i.e. the research subject) is neither the patients nor the physicians, but the performance of the EPR-based electronic tool in the midst of the “clinical study triangle” consisting of patients, practice personnel and study center (see page 8, lines 5ff). We hope the referee agrees with our point of view so that the comments in #8 and #9 (see below) can also be seen in a different light.

7. Results: Under “Electronic patient recruitment in general practices” – 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. The authors state, “only one practice reached the target to recruit 200.” 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.

Authors’ response

The characteristics of the participating practices (e.g. the number of patients seen per quarter, the number of older patients, the number of practice nurses and the number of doctors) were very different. It would have been an option, perhaps, to focus our study on single-handed practices, or joint practices, or large practices, etc. Instead, we chose to test the feasibility of our clinical trial tool in all practice types found in the primary care setting in Germany.

It could be argued that it was unreasonable to set the same target number of 200 enrolled patients (approximately one patient per workday) for all practices, given that the practices and their resources were so different. However, we chose this number as a minimum that (we thought) could be reached by all participating practices. In addition, the CTA technology cannot directly be related to the number of enrolled patients, since the CTA system regularly reminded the practice staff of eligible patients. The “real primary care practice conditions” like finding the time, the place and the personnel to immediately conduct a ca. 10-minute study within the practice setting also played an important role in the number of study enrollees. These factors had nothing to do with the technical functioning of the CTA system. Please see page 13, lines 1ff.

It is therefore difficult to follow the referee’s suggestion - for 2 reasons: (1) The recruitment tool was mainly handled by practice nurses and not physicians. (2) We have only data from the practice as a whole and not from individual physicians or practice nurses. The only thing we could do is to calculate and compare the performance of different
practices by simply dividing the number of patients who participated in the study by the number of physicians in the respective practice. But this could be rather misleading because physicians may work in different capacities (part-time or full-time, etc.) and physicians in a practice might strongly differ in their handling of the recruitment tool (some physicians recruited patients directly, others left this task up to the practice nurses). It is quite interesting that a single-handed practice with only one practice nurse was the only practice to reach the target of enrolling 200 patients.

8. Results: 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.

Authors’ response

Please refer to #6.

9. More attention in the methods should be paid to that clinician/practice group as the major “target” population for this study. 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.

Authors’ response

See our comments in #6. Moreover, we have clarified the target aspect in the new version on page 8, lines 5ff and are very interested to hear whether the referee agrees with our characterization of the study.

Technical details of the programming and data handling

10. Methods: The description of the software development and function is lacking in technical detail. This needn’t be extensive, but some technical detail about software platform, whether it 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.

Authors’ response

We revised the text below ‘software development’ and provided a more detailed technical description. We did not give detailed technical information about the way the software captures the information, since there is a specific solution for every individual practice software system, including highly-specialised programming-techniques not commonly known even to software developers (page 6, lines 14ff).
11. **Limitations:** Missing or misplaced limitation. 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"). 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.

Authors’ response

The adequate placement of this aspect, i.e. the regular adjustment of the identification tool to the changing practice software, is open to discussion. One might see this aspect as a limitation, but we think is not so much a limitation of our study but a characteristic of practice software that has to be considered when talking about the feasibility of the tool. Therefore, we would prefer to leave this sentence in the “feasibility” section.

12. 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.

Authors’ response

We revised the passages that were unclear about the transmitted data and added a clarification, why only praxis personnel could re-identify a patient and that this could only be done during the runtime of the study and not afterwards (page 6, lines 17ff).

13. Also under “software development, implementation and evaluation” 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.

Authors’ response

It was not technically possible to have every practice begin the study on the same day. Even so, the study was conducted in every practice over a 12-month period (Jan 1 - Dec 31, Nov 1 - Oct 31, etc.), regardless of the starting date. That is to say that each practice had the same number of days in which to recruit patients. Clarified now on page 6, line 13.

14. **Results:** 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. I sug-
gest 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.

Authors’ response

Since we consider the clinical trial tool to be the “target” of our study, the expression
“intention to treat” may be somewhat misleading. In any case, we have now made clear
that practices, or better said: two practice software systems, failed to adhere to the pro-
cotol and this is exactly the important information (page 9, lines 11ff).

15. Results: Under “Electronic patient recruitment in general practices” 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 ques-
tionnaire? This requires clarification.

Authors’ response

Indeed, this is just the advantage of our recruitment tool, that it allows practice nurses
or physicians to interrupt the questionnaire at any point and to continue it at a later
date. We only counted completed questionnaires as “successful” and non-completed
questionnaires as “open”, not differently than patients for whom a survey had not be-
gun. The number of started but not completed questionnaires was very small, since the
questionnaire itself was made as user-friendly as possible and took about 10 minutes to
complete. Said in other words, it would have been possible to stop the questionnaire
and complete it later, but patients and practice personnel usually didn’t start it unless
the 10 minutes needed were available. We now report the number of not completed
surveys (n=43) and describe this “middle option” in more detail (see page 7, lines 18ff;
page 10, line 14f).

16. Results: Under “Electronic patient recruitment in general practices”. 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.

Authors’ response

We agree with the referee and have toned down this expression. Now we report only in
a neutral sense that 20% did not give informed consent and leave it to the reader to de-
cide if this is a minor or major proportion [page 9, line 18].

17. In the Results section clarify that “joint” practice means “two-person” practice, if that is
the meaning.
Authors’ response

In Germany, there is an administrative difference between “Gemeinschaftspraxen” (joint practice where more than one doctor serves a single group of patients) and “Praxisgemeinschaften” (group practice where each doctor is individually responsible for his/her own patient group) for licensing and reimbursement. You might be able to say that in joint practices, the doctors work together and in group practices, the doctors work alongside or parallel to each other (sharing the facility and the practice staff). Often in joint practices, the doctors share a full-time job. That is to say that their workload would be similar to a single-handed doctor’s. Group practices normally offer services to twice as many patients as a single-handed doctor. In the end, this information would probably only be of interest to German readers, since the organization of primary care in Germany is relatively unique in this regard. We no longer differentiate between joint and group practices. We have re-written the text, differentiating now only between single-handed practices and practices with more than one physician (see page 9, lines 15f).

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

Authors’ response

We have clarified this point; see page 5, lines 22ff.

19. 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.

Authors’ response

The physicians in the participating practices are either members of a local GP network of about 100 individual practices or they are members of the German college of general practitioners (DEGAM), which is a Germany-wide organization.

Initial contact to members of locally organized GP networks was made by the local network administrators. In contrast, DEGAM members, who receive regular emails from the college, were contacted directly via email. This has now been clarified on page 5, lines 16ff.

Feasibility and Limitations

20. Under “Detection of selection effects”. 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.

Authors’ response

It is no problem to add a P-value. We did not report the P-value in the former version since statistical significance will be reached even in small differences when the sample
is a large as our sample. We now report the P-value (see Table), but do not overstress the strong significance in the text.

21. **Limitations: Missing or misplaced limitation.** 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.

Authors’ response

Done. See page 11, lines 27ff. Here we have added a reference to Embi’s and Rollman’s as fore-runners for the value of CTA-systems in comparison to traditional recruitment strategies.

22. **Limitations: Missing or misplaced limitation.** 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.

Authors’ response

Thank you for this suggestion. We included this remark in the Limitation section (page 11, lines 25f).

Referee 2

23. **My understanding from the paper it is that the software tool only interrogated the practice records for details of date of birth and sex, and not clinical data. If clinical data was accessed electronically (rather than when the clinician considered eligibility), this should be made clearer. There might be ethical and practical consequences of using clinical data, but doing so would make the tool more useful. It would be helpful to address this point in the discussion.**

Authors’ response

Thank you for this suggestion! On principle, our recruitment tool would allow us to use clinical data for inclusion criteria, but this will require a further development of the software. We now mention this fact in the discussion, see page 12, lines 21ff.

24. **I was struck that as software systems were updated, there was a need to update the recruitment software. This seemed important and I wonder if it should be added to the conclusions. - Otherwise others may think that such a system can be replicated without building in plans for maintenance.**

Authors’ response
We agree with the referee that this is an important point. Indeed, the clinical trial tool (or at least some of its features) have needed to be adapted in the case of software updates. Already in the first version, we mentioned this point under “feasibility of the identification tool” on page 12, lines 20ff. We have not changed the content but have added a paragraph break in order to draw more attention to this point.

25. The reference to participants providing informed consent at the bottom of page 5 presumably refers to participants recruited to the osteoporosis study, rather than all those screened for recruitment using this electronic tool. (This sounds pedantic but the wording could be a little clearer.)

Authors’ response

Done, see page 6, lines 4ff.

26. At the bottom of page 11, there is a misleading comparison with another study reporting differential recruitment between men and women. Part of the difference in the proportions recruited in the osteoporosis study was because the lower age range was different between men and women and thus the target sample was different. Thus the "80:20" participation ratio is largely a result of the study criteria, rather than differential recruitment. I would drop this comparison with ref 34.

Authors’ response

We agree with the referee and no longer refer to reference 34.

**Minor details**

27. It would be helpful if they could specify whether the data management aspects were approved by the ethics committee or was this just the project as a whole?

Authors’ response

All details of the management aspects of the recruitment were approved by the ethics committee and discussed in detail with the data security officer of the medical faculty (see page 6, lines 1ff).

28. Figure one was not readable when I downloaded this. It is good to include the screen, but it needs to be larger.

Authors’ response

We have made the figure larger and adapted it to a black and white format. We hope that the figure is more readable in the new version. We have now labeled two important places in the figure and offer a short explanation at the bottom.

29. Minor Essential Revisions such as missing labels on figures, the wrong use of a term, spelling mistakes.
Authors’ response

The labels for the figures can be found on page 20. It was not possible to add the title to Figure 1 because of its png format.