PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of the application of an electronic medication management support system in patients with polypharmacy in general practice: a study protocol of cluster-randomised controlled trial (AdAM).
AUTHORS	Müller, Beate; Klaaßen-Mielke, Renate; GONZALEZ-GONZALEZ, ANA; Grandt, Daniel; Hammerschmidt, Reinhard; Köberlein-Neu, Juliane; Kellermann-Mühlhoff, Petra; Trampisch, Hans; Beckmann, Till; Düvel, Lara; Surmann, Bastian; Flaig, Benno; Ihle, Peter; Söling, Sara; Grandt, Simone; Dinh, Truc; Piotrowski, Alexandra; Meyer, Ingo; Karbach, Ute; Harder, Sebastian; Perera, Rafael; Glasziou, Paul; Pfaff, Holger; Greiner, Wolfgang; Gerlach, Ferdinand; Timmesfeld, Nina; Muth, Christiane

VERSION 1 – REVIEW

REVIEWER	Verloo, Henk University of Applied Sciences and Arts Western Switzerland, HES-SO Valais/Wallis
REVIEW RETURNED	01-Apr-2021

GENERAL COMMENTS	Overall evaluation of the topic and the readability of the manuscript: The study protocol is well written and easy to read and understand; the different steps are clearly stated. The integration of an interprofessional approach is robust in this study protocol. Title The title is covering the content of the study protocol. The study protocol includes an electronic support system to increase medication management in primary healthcare. Abstract The abstract is well structured and summarizes the study intention. It could be helpful to know the timeframe of the different steps to understand the trial. No comments on the content. Introduction – objective/aim • States the overall problem. • It could be reinforced with medication management strategies and include the medication-related problem as a rationale to develop the ADAM trial. • Well-documented study aims. • I did not found a clear theoretical framework for the study allowing me to identify the investigated concepts Methods The method section is well developed. • However, I did not find the PROMS, concepts SPIRIT, and approach as stated in the SPIRIT PRO guidelines and the SPIRIT

	Extensions (alvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan A-W, King MT; and the SPIRIT-PRO Group. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. JAMA. 2018;319(5):483-494). • I did not find the SPIRIT schedule: “Schedule Of Enrolment, Interventions, And Assessments” (https://www.spirit-statement.org/schedule-of-enrolment-interventions-and-assessments/) • COS criteria are not directly considered the Core outcome set (Beuscart J-B, Knol W, Cullinan S, Schneider C, Dalleur O, Boland B, et al. International core outcome set for clinical trials of medication review in multi-morbid older patients with polypharmacy. BMC medicine. 2018;16(1):1-9.) References Already mentioned and see attached files

REVIEWER	Fahey, Tom Royal College of Surgeons in Ireland, Department of General Practice
REVIEW RETURNED	07-Apr-2021

GENERAL COMMENTS	Thank you for asking me to review this protocol for a cluster RCT utilising a stepped wedge design. It examines the impact of an electronic medication management support system (eMMa) in patients taking five or more medicines in primary care. The study is taking place in a region of Germany (Westphalia-Lippe) for BARMER health-fund patients. I only have some minor comments: Overall, a well-written and clear protocol. My main concern is that the RCT seems to be finished with recruitment, intervention and outcome (from claims data) periods having been undertaken from May 2015 onward and finished in September 2020 (see rows 545-550 under "schedule and duration of the trial". This seems somewhat post-hoc to me and I would have expected the protocol to be written up and published before the actual cRCT took place. Some explanation as to the delay in preparing and submitting the protocol would be helpful.

VERSION 1 – AUTHOR RESPONSE

Revisions (R) made according to BMJ Open reviewer’s report (Reviewer 1) by queries (Q):
Q1- The study protocol is well written and easy to read and understand; the different steps are clearly stated. The integration of an interprofessional approach is robust in this study protocol.

R1- We would like to thank Reviewer 1 for the valuation of our manuscript and for the thorough comments.

Q2- Introduction – objective/aim: States the overall problem. It could be reinforced with medication management strategies and include the medication-related problem as a rationale to develop the ADAM trial.

R2 – We have revised the paragraphs in the introduction section that explain the importance of medication errors and the type of instruments that can help medication reconciliation to reinforce the

concept of the usefulness of medication management strategies.
• Introduction (lines 216-221): “Medication errors and omissions are important problems facing routine care in general practice, especially in patients with multimorbidity and multiple prescriptions (17–19). They may contribute to patient hospital admissions and mortality, thus additional understanding of such incidents is required (20). As most medication errors and omissions are preventable, raising physicians’ awareness of polypharmacy may help to ensure the safe, effective and appropriate use of medication (19,21,22)”.
• Introduction (lines 222-235): “Medication management strategies allow patients and families to actively participate with their physicians in developing complete and accurate medication lists. To ensure patients receive high-quality healthcare, physicians should be provided with tools that help them avoid risks in the treatment of their patients (22-24). Likewise, physicians should have access to continuously available data on quality-oriented aspects to support the control of their patients’ treatments (24). Few effective instruments are available to help physicians systematically monitor and optimise the medications their patients take (22). Such tools comprise computerised Decision Support Systems (CDSS) or complex multi-faceted pharmaceutical-care based approaches that may incorporate CDSS as part of the intervention. CDSS are computer-based systems providing “passive and active referential information as well as reminders, alerts, and guidelines” (25).

Q3 -I did not found a clear theoretical framework for the study allowing me to identify the investigated concepts

R3 – We have clarified the theoretical considerations which have been addressed by our intervention to provide the rationale for the AdAM trial, as follows:

• Introduction (lines 249-248): “Considering that individual, patient-related information relevant for the drug therapy is currently unavailable to physicians and that there is a lack of instruments helping physicians to regularly review their patients’ medication, an intervention with a web-based medication management system was developed within the AdAM [Anwendung für digital unterstütztes Arzneimitteltherapie-Management] project. The primary objective of the AdAM trial is therefore to assess whether such electronic medication management support system (complex intervention) reduces the combined endpoint of all-cause mortality and all-cause hospital admissions in patients with polypharmacy, compared to usual care and in the real context of a general practice setting.

Q4 – Methods: The method section is well developed. However, I did not find the PROMS, …

R4 – We thank Reviewer 1 for the suggestion. However, we were not able to include patient-reported outcomes such as PROMS, as our study design did not allow data collection from patients. We therefore stated in the strengths and limitations section, that claims-based outcome measures have disadvantages.

Q5 – [Methods: The method section is well developed. However, I did not find the] …. concepts SPIRIT, and approach as stated in the SPIRIT PRO guidelines and the SPIRIT Extensions (alvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan A-W, King MT; and the SPIRIT-PRO Group. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. JAMA. 2018;319(5):483-494). I did not find the SPIRIT schedule: “Schedule Of Enrolment, Interventions, And Assessments” (https://www.spirit-statement.org/schedule-of-enrolment-interventions-and-assessments/)

R5 – We have now included the Spirit checklist (see Additional file 6) in addition to the CONSORT 2010 checklist and The TIDieR (Template for Intervention Description and Replication) Checklist, which we have already provided with the first submission.

Q6 - COS criteria are not directly considered the Core outcome set (Beuscart J-B, Knol W, Cullinan S, Schneider C, Dalleur O, Boland B, et al. International core outcome set for clinical trials of medication review in multi-morbid older patients with polypharmacy. BMC medicine. 2018;16(1):1-9.)

R6 –We would like to thank the reviewer for the reference to the COS developed by Beauscart et al. Unfortunately, we were limited in the choice of outcomes which are available in claims. We selected as many outcome measures of the COS as possible (i.e., drugs related hospital admissions, underuse, potentially inappropriate medication). However, PROMs were not available to us (e.g., information about quality of life or pain relief was not available) – see also R4.

Revisions (R) made according to BMJ Open reviewer's report (Reviewer 2) by queries (Q):
Q7- Overall, a well-written and clear protocol. My main concern is that the RCT seems to be finished with recruitment, intervention and outcome (from claims data) periods having been undertaken from May 2015 onward and finished in September 2020 (see rows 545-550 under "schedule and duration of the trial". This seems somewhat post-hoc to me and I would have expected the protocol to be written up and published before the actual cRCT took place. Some explanation as to the delay in preparing and submitting the protocol would be helpful.

R7- We appreciate Reviewer 2 comments. Due to the difficulties in recruitment, the regular end of the intervention and the follow-up period were extended to March 2021. In addition, we had to change the design of the trail from a cluster-randomized trial to a stepped wedge design to increase the power of the trial. As soon as we completed all necessary design changes in the protocol, we submitted our manuscript (in December 2020). Therefore, submission date was well ahead of the completion of the trial and the start of any analyses. To be transparent about all changes made a priori to trial completion and starting of statistical analyses, we explained them in the manuscript at hand. Furthermore, we have faced difficulties to regularly update the status of the trial in clinicaltrials.gov, because the irregular structure of our consortium including members of the statutory health insurance company and other non-academic organizations did not match well with the structure of the registry forms. Therefore, our updates are still pending to be approved by the registry's staff. We have added information about this update process to the manuscript.

• Registration: ClinicalTrials.gov, NCT03430336. Registered on February 6, 2018. Last updates in 2019 (June 25, 2019), 2020 (July 4, 2020) and 2021 (June 5, 2021), waiting for approval. https://clinicaltrials.gov/ct2/show/NCT03430336

Q8 - Along with your revised manuscript, please include a copy of the SPIRIT checklist indicating the page/line numbers of your manuscript where the relevant information can be found (http://www.spirit-statement.org/)

R8 – We have now included the Spirit checklist (see Additional file 6) in addition to the CONSORT 2010 checklist and The TIDieR (Template for Intervention Description and Replication) Checklist, which we have already provided with the first submission.

Q9 - Along with your revised manuscript, please provide an English language examples of the patient consent form as a supplementary file as per item #32 of the SPIRIT checklist.

R9 – We have now included an English translation of the patient informed consent as Additional file 2.

Comments from the Editor:
Q10 – Please accept our apologies for the delay in reaching a decision on your manuscript.

- Along with your revised manuscript, please include a copy of the SPIRIT checklist indicating the page/line numbers of your manuscript where the relevant information can be found (http://www.spirit-statement.org/)

R10 – We have now included the Spirit checklist (see Additional file 6 in addition to the CONSORT 2010 checklist and The TIDieR (Template for Intervention Description and Replication) Checklist, which we have already provided with the first submission.

Q11 - Along with your revised manuscript, please provide an English language examples of the patient consent form as a supplementary file as per item #32 of the SPIRIT checklist.

R11 - We have now included an English translation of the patient informed consent as Additional file 2.

VERSION 2 – REVIEW

REVIEWER	Fahey, Tom Royal College of Surgeons in Ireland, Department of General Practice
REVIEW RETURNED	13-Jul-2021

GENERAL COMMENTS	Thank you for asking me to re-review this paper. The author's have addressed my concerns. From an editorial point of view, it is worth getting confirmation from the authors that approval has been granted by clinicaltrials.gov (see author's response to my comment).