PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Implementation of a complex intervention to improve hospital discharge: Process evaluation of a cluster randomized controlled trial
AUTHORS	Rachamin, Yael; Grischott, Thomas; Neuner-Jehle, Stefan

VERSION 1 – REVIEW

REVIEWER	Bai, Shasha Ohio State University, Biomedical Informatics
REVIEW RETURNED	17-Feb-2021

GENERAL COMMENTS	This manuscript by Rachamin et al. described a mixed-method process evaluation of the implementation of an education intervention for polypharmacy at hospital discharge. This publication is part of a cluster randomized controlled trial. A total n=21 hospitals and 614 patients were recruited for the two arms (intervention vs control). The implementation used a tailored version of the framework for designing process evaluations of cluster-randomised trials with complex interventions (Grant et al, 2013), and generated informed results at multiple levels. Overall, the study is designed with care and details with clearly defined outcomes. The conclusion is well supported by the results. There are plenty of details on the reasons of refusal to participation at hospital level, resistance to medication change at discharge, and dropout at patient level. A few places need more clarifications in order to make the manuscript stronger: 1. In the Introduction, the authors stated, "process evaluations can help contextualize results for complex RCTs in terms of when, why and how interventions work". These intended benefits, however, are not obviously stated in the Results and Discussion sections, and could be added or stated more explicitly. 2. It is unclear what the specific adaptation to "extended Grant framework" is. Was it the separation of process and impact elements? What is the motivation of this adaption and how is this adaptation beneficial to the current work? 3. It is confusing to read that "relatives of GPs" were contacted when patients were not reachable. 4. Please explain the rationale of dichotomizing likert scale items. Why is it for most summaries but not all? 5. How is consensus reached among all authors regarding the themes? Are there any agreement statistics that can be reported?

	6. The objectives of implementations (fidelity, dose, feasibility, facilitators, barriers, and strategies) were clearly defined in the Methods section; however, some of these objectives were not mentioned in the Results or Discussion. 7. Is "Figure 3Bg" a typo and should be "Figure 3B"? 8. Figures 3 and 4 are difficult to understand with five categories presented but only three summary percentages. 9. It is understandable that COVID pandemic has limited recruitment and sample size. The current sample size is much smaller than anticipated (planned vs recruited: n=42 vs n=21 clusters, and n=2100 vs n=614 patients). Has the authors conducted a post-hoc power analysis to address the reduced statistical power?

REVIEWER	Zegers, Marieke Radboudumc, IQ healthcare
REVIEW RETURNED	18-Feb-2021

GENERAL COMMENTS	Generally, I really encourage process evaluations to improve the implementation of complex interventions in daily practice. However, the process evaluation described in the manuscript lacks clarity about the aims, implementation strategies, outcomes and recommendations for clinical practice. Title The ultimate aim of the intervention is missing in the title (to reduce hospital readmission and enhance quality of life). Abstract The abstract is vague and incomplete. Starting with the aim. 'Reporting' is not an aim. 'To study…' or 'To explain the results of the trial'. Because of a vague objective, the conclusion of the abstract is vague. Description of the implementation strategies lacks. A concrete description of the outcomes measures lacks in the section 'process evaluation components' (response rates, adherence rates and barriers and facilitators for the implementation of the interventions' are typical process evaluation outcomes). Important results (figures) are missing in the results section: number of hospitals and physicians who finally participated (response rates) and reasons for low rates (eg COVID pandemic), and adherence to the intervention. Also, a description of the main identified barriers and facilitators is missing. Please give more results (numbers and other outcomes). In the conclusion section, a conclusion of why the intervention succeed or failed is missing. The conclusion is now written for researchers. The aim of the study is to improve hospital discharge and to reduce readmissions. What are recommendations for clinicians to successfully improve clinical discharge practice? You mention 'positive results given', what are the results exactly? Introduction What is advanced age? Also, in the introduction, a clear aim is missing. See Stari guideline: implementation objective and intervention objectives.

In the introduction section is written: ‘when, why and how interventions work’. Be sure that this manuscript gives an answer on these questions.
A description of the implementation strategies lacks.

Methods
You are using the framework of Grant to conduct the process evaluation. I am not sure if I should use this model. I always use the model of Flottorp; very useful the classify the barriers and facilitators (https://implementationscience.biomedcentral.com/articles/10.1186/1748-5908-8-35).
Other process evaluation literature
‘The intervention was a teaching session’. What are the elements of this training session? What was learned? A process evaluation should include an extensive description of the intervention and implementation strategies; open the black box.
Control arm: usual discharge procedures. Idem: what are the elements?
I miss a section ‘outcome measures’.
There is a section objective, but that seems outcome measures.
Figure 1: what is ‘response’? The same as ‘adherence’? And recruitment? The same is response rate? Please, use implementation science terms.

Results
The results section is hard to follow. You write that the results are structured in quantitative results, qualitative results and implementation strategies. But on the next pages the distinction is made for recruitment, delivery and response per stakeholder. And what a want to read is information about implementation fidelity, intervention dose, feasibility and barriers and facilitators.
Start the results section with response and inclusion rates (hospitals, all kind of health care providers and patients) of the main study and thereafter response rates for the process evaluation (invited versus interviewed persons) and study characteristics in one section (thus not divided in several section throughout the results section).
Followed by the results per outcome (implementation fidelity, intervention dose, feasibility and barriers and facilitators).
One section with intervention adherence rates (intervention dose). Number of trainings session and attended health care providers. Compliance to discharge checklist. Please use implementation terms as compliance or adherence. Response is something else.
And one section with perceptions, barriers and facilitators: interview results from all perspectives together.
See the Stari guideline how to set up the results section.
Table 1: give the ‘n’; the number of chief physicians who were interviewed
Context: should be in the methods section

Discussion
Because a clear description of the objective and outcomes measures is missing, the discussion section is hard to read. No figures are given in the whole paper about the results of the main trial (process evaluation are set up to explain these results). In the first section of the discussion section is written: ‘implementation was successful ‘ and ‘implementation results were mixed’. Please provide figures (evidence) for these quotes; summarize main findings of the results section.

Conclusion

	What should I do, based on this process evaluation, to improve my clinical discharge practice to prevent readmission?

VERSION 1 – AUTHOR RESPONSE

Reviewer # 1 comment	**Response**	**Changes to the manuscript**
This manuscript by Rachamin et al. described a mixed-method process evaluation of the implementation of an education intervention for polypharmacy at hospital discharge. This publication is part of a cluster randomized controlled trial. A total n=21 hospitals and 614 patients were recruited for the two arms (intervention vs control). The implementation used a tailored version of the framework for designing process evaluations of cluster-randomised trials with complex interventions (Grant et al, 2013), and generated informed results at multiple levels. Overall, the study is designed with care and details with clearly defined outcomes. The conclusion is well supported by the results. There are plenty of details on the reasons of refusal to participation at hospital level, resistance to medication change at discharge, and dropout at patient level. A few places need more clarifications in order to make the manuscript stronger:	We thank the Reviewer for her encouraging feedback.	-
1. In the Introduction, the authors stated, "process evaluations can help contextualize results for complex RCTs in terms of when, why and how interventions work". These intended benefits, however, are not obviously stated in the Results and Discussion sections, and could be added or stated more explicitly.	The Reviewer rightly points out that we have not contextualized the results of our RCT in this article. This is due to the fact that the effectiveness has not yet been evaluated (the follow up period is not completed for all patients). We are however planning on basing the interpretation of the main results of the RCT on this process evaluation. We	Page 5, Background, last sentence: "The effectiveness outcomes will be published separately." And page 6, Methods section 'Design and setting':

	consider it a strength of our study that the evaluation was blind to the results of the study, which enables a less biased interpretation. To emphasize that we do not have the effectiveness outcomes yet, we added clarifying statements in the introduction and methods section.	"(…) effectiveness outcomes are still being collected and will be published separately."
2. It is unclear what the specific adaptation to "extended Grant framework" is. Was it the separation of process and impact elements? What is the motivation of this adaption and how is this adaptation beneficial to the current work?	We thank the Reviewer for raising that point, the adaptation of the Grant framework was indeed not clearly described: The separation of process and impact elements was already present in the original framework. The adaptation extended Grant et al.'s original framework for cluster RCTs with one level of clustering to trial designs with nested clustering on multiple levels. This allowed us to study the whole pathway of the intervention implementation, from the study team to the patient. We added this clarification to the manuscript.	Page 7, Methods section 'Design and setting': "The process evaluation was based on a framework of Grant et al.[16] which we then tailored to the specific multilevel nature of our intervention (Figure 1). The original framework of Grant et al. distinguishes process elements (recruitment, delivery, and response) of clusters and individuals from impact elements (effectiveness and unintended consequences). We added the levels "hospitals" (the entities being recruited by the study team) and "junior HPs" (who delivered the intervention to patients). " And page 20, Discussion section 'Strengths and Limitations': "Following our example, the framework could be further extended to handle any number of clustering levels."
3. It is confusing to read that "relatives of GPs" were contacted when patients were not reachable.	Actually, the sentence reads "relatives or GPs". We however altered the sentence to improve readability.	Page 7, Methods section 'Design and setting': "After repeated requests for pending answers, we contacted the patients'

		relatives and/or GPs for complete follow up data.”
4. Please explain the rationale of dichotomizing likert scale items. Why is it for most summaries but not all?	We dichotomized likert scale items for readability in the text. The Figures display all five likert levels. We changed the text to clarify that.	Page 9 Methods section ‘data analysis’: “Likert scale items were dichotomized for ~~most~~ text summaries.”
5. How is consensus reached among all authors regarding the themes? Are there any agreement statistics that can be reported?	We provided additional information about the method of the theme consensus process.	Page 9, Methods section, data analysis: “A theme was accepted if listed by both of the two researchers, and similar themes of the researchers’ list were merged by consensus. If there was disagreement between the two researchers, the third researcher (YR) operated as referee.”
6. The objectives of implementations (fidelity, dose, feasibility, facilitators, barriers, and strategies) were clearly defined in the Methods section; however, some of these objectives were not mentioned in the Results or Discussion.	Some of these objectives were not applicable to all sections of the results or discussion. For example, fidelity and dose were relevant in the “delivery” sections, while feasibility was most relevant in the “response of HPs” section, and facilitators/barriers as well as implementation strategies were relevant for “recruitment of hospitals”, “recruitment of patients” and “response of patients”. We added a clarification in the objectives section (newly termed Outcomes)	Page 8, Methods section “Outcomes”: “For the framework elements specified in Figure 1, we aimed to explore and describe implementation along the following dimensions (where applicable).”
7. Is "Figure 3Bg" a typo and should be "Figure 3B"?	It was not a typo; we referred to the last question (g) of the Figure 3B. However, since it seems to be confusing, we changed it to Figure 3B.	Page 11, Response of senior HPs, and page 12, Response of senior HPs: Figure 3Bg changed to Figure 3B
8. Figures 3 and 4 are difficult to understand with five categories presented but only three summary percentages.	We added clarifying statements to the Figure legends.	Figure legends page 28 (Figures 3 and 4): “The percentages given indicate 1) largely applies or applies, 2) partially applies, 3) does rather not or not apply.”

9. It is understandable that COVID pandemic has limited recruitment and sample size. The current sample size is much smaller than anticipated (planned vs recruited: n=42 vs n=21 clusters, and n=2100 vs n=614 patients). Has the authors conducted a post-hoc power analysis to address the reduced statistical power?	We thank the Reviewer for bringing attention to this this important issue. An insight into the impact of our smaller sample size (smaller than previously calculated) on the significance of the results as well as into the power required to detect smaller effects will be important. We will report on these issues in the main paper (effectiveness study, which will be published separately, see also our response to the second point above).	-

Reviewer # 2 comment	**Response**	**Changes to the manuscript**
Generally, I really encourage process evaluations to improve the implementation of complex interventions in daily practice. However, the process evaluation described in the manuscript lacks clarity about the aims, implementation strategies, outcomes and recommendations for clinical practice.	We share the Reviewer's assessment of the importance of process evaluations and hope that the changes we made to the manuscript may increase clarity for the Reviewer.	-
Title The ultimate aim of the intervention is missing in the title (to reduce hospital readmission and enhance quality of life).	We thank the Reviewer for her feedback. After the term "…improve hospital discharge…", we could add "… and reduce rehospitalisation". We hesitate to make the title even longer and would like to leave this decision to the editor.	-
Abstract The abstract is vague and incomplete. Starting with the aim. 'Reporting' is not an aim. 'To study…' or 'To explain the results of the trial'. Because of a vague objective, the conclusion of the abstract is vague.	We changed "reporting" to "study". Regarding conclusions, please see below.	Page 2, Abstract, objectives: "~~In this article, report on~~ To study the implementation of a cluster randomized controlled effectiveness-implementation hybrid trial (…)"

Abstract Description of the implementation strategies lacks.	We adopted the wording of the StaRI checklist and introduced the term implementation strategy throughout the manuscript.	Page 2, Abstract: “Implementation strategy: Two-hour teaching sessions for senior HPs on a patient-centred, checklist-guided discharge routine.”
Abstract A concrete description of the outcomes measures lacks in the section ‘process evaluation components’ (response rates, adherence rates and barriers and facilitators for the implementation of the interventions’ are typical process evaluation outcomes).	We added a section “Outcome measures” to the Abstract.	Page 2, Abstract: “Outcome measures: Intervention dose (quantitative), implementation fidelity (qualitative), feasibility and acceptability, facilitators and barriers, implementation support strategies.”
Abstract Important results (figures) are missing in the results section: number of hospitals and physicians who finally participated (response rates) and reasons for low rates (eg COVID pandemic), and adherence to the intervention. Also, a description of the main identified barriers and facilitators is missing. Please give more results (numbers and other outcomes).	We re-phrased the Abstract Results section according to the Reviewer’s inputs. We also agree that a more accurate description of barriers and facilitators would make sense; however, due to the limited word count, we did not expand on this in the Abstract (but we do in the manuscript).	Page 2, Abstract, Results: “Recruitment of hospitals was laborious but successful, with 21 hospitals recruited. Minimal workload and a perceived benefit for the clinic were crucial factors for participation. Intervention dose was high (95% of checklist activities carried out), but intervention fidelity was limited (discharge letters) or unknown (medication review). Recruitment and retention of patients was challenging, partly due to patient characteristics (old, frail) and the COVID-19 pandemic: Only 612 of the anticipated 2100 patients were recruited, and 31% were lost to follow up within the first month after discharge. The intervention was deemed feasible and helpful by HPs, and the relevance of the topic appreciated by both HPs and GPs.”
Abstract In the conclusion section, a conclusion of why the intervention succeed or failed is	We do not have final insight yet on whether the intervention succeeded or failed, we only know how it was implemented. Recommendations on how to	-

missing. The conclusion is now written for researchers. The aim of the study is to improve hospital discharge and to reduce readmissions. What are recommendations for clinicians to successfully improve clinical discharge practice?	improve clinical discharge practice, or which measures should be omitted due to lack of benefit, will be offered with the publication of the trial's effectiveness outcomes. See also next point.	
Abstract You mention 'positive results given', what are the results exactly?	This was an attempt to integrate a conclusion for clinicians: Under the condition that the effectiveness outcomes will be positive (as stated above, we do not know yet), the implementation part of the study will help to consider the contextual factors, in order to successfully disseminate the intervention. For not mixing up these two different conclusion issues, we now deleted this term in the Abstract.	Page 3, Abstract: "Conclusion: The results from this evaluation will support interpretation of the findings of the effectiveness study and **–** ~~positive results given – dissemination of our approach to further hospitals. In addition, the implementation strategies presented~~ may inform researchers and policy makers who aim at improving hospital discharge."
Introduction What is advanced age?	We re-phrased to a more precise term, i.e. "aged 60 years or older" (according to our inclusion criteria)	Page 5, Background: "~~at advanced age~~ aged 60 years or older"
Introduction Also, in the introduction, a clear aim is missing. See Stari guideline: implementation objective and intervention objectives.	We agree with this criticism and adapted the manuscript accordingly.	Page 5, end of Background section: "The aim of our study was to provide information about process evaluation outcomes on different levels of the complex intervention, in order to inform the interpretation of the effectiveness outcomes."
Introduction In the introduction section is written: 'when, why and how interventions work'. Be sure that this manuscript gives an answer on these questions.	Same point as point 2 of Reviewer #1: We can only answer these questions after the collection and analysis of the effectiveness outcomes are finished. The results described in this article will help interpreting (future) effectiveness outcomes.	-
Introduction	We discriminated intervention and implementation strategy	Page 5, Background: "We therefore performed a two-

A description of the implementation strategies lacks.	throughout the manuscript, and made the necessary changes in the manuscript.	armed cluster randomized controlled trial (RCT) investigating the effect of a medication review and improved information transfer at hospital discharge for patients aged 60 years or older with polypharmacy on rehospitalisation rates.[9] The intervention was implemented via a teaching session and patient-centred checklists for HPs, and adaptations to the discharge letters."
Methods You are using the framework of Grant to conduct the process evaluation. I am not sure if I should use this model. I always use the model of Flottorp; very useful the classify the barriers and facilitators (https://implementationscience.biomedcentral.com/articles/10.1186/1748-5908-8-35).	We thank the Reviewer for bringing the Flottorp framework to our attention. The widely used Grant framework (see References 32, 38-43 in our article) is based on process evaluation literature and the recognized and renowned RE-AIM framework and, most importantly, it accommodates for cluster RCTs with their multilevel structure. We considered this the "best match" for our study.	-
Methods 'The intervention was a teaching session'. What are the elements of this training session? What was learned? A process evaluation should include an extensive description of the intervention and implementation strategies; open the black box.	We thank the Reviewer for this very relevant input. We agree that for the reproducibility of our intervention, we should better describe the educational sessions. We added some clarification to the Methods section, and reduced the information in the Results section (to avoid redundancy).	Page 6, Methods section 'Design and setting': "In the teaching session, senior HPs were presented some background evidence on the significance of multimorbidity and polypharmacy, and on age-dependent target values, and were then instructed on how to apply a simple medication review tool to the patients' medication lists [18 19] (see also checklist, online supplementary appendix 1). This was demonstrated on an example patient with multimorbidity and polypharmacy. Senior HPs were encouraged to engage in a discussion. In the second

		hour of the teaching session, data collection procedures were explained.”
Methods Control arm: usual discharge procedures. Idem: what are the elements?	We added a clarifying statement.	Page 5, Methods section ‘Design and setting’: “In the control arm, senior HPs were given a “sham” instruction (covering the significance of multimorbidity and polypharmacy, and explaining data collection procedures) and patients were discharged according to the usual discharge procedures as established in the individual hospitals.”
Methods I miss a section ‘outcome measures’. There is a section objective, but that seems outcome measures.	We renamed it “Outcomes”	Page 8, subtitle: “~~Objectives~~ Outcomes”
Methods Figure 1: what is ‘response’? The same as ‘adherence’? And recruitment? The same is response rate? Please, use implementation science terms.	We used the terminology of the Grant framework: ‘Recruitment’ covers (amongst others) aspects of representativeness, as well as an in-depth understanding of why clusters participate (or not), and ‘Response’ includes but is not restricted to adherence (https://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-14-15)	-
Results The results section is hard to follow. You write that the results are structured in quantitative results, qualitative results and implementation strategies. But on the next pages the distinction is made for recruitment, delivery and response per stakeholder. And what a want to read is information about implementation fidelity,	As the first sentence in the Results says, they are presented along the elements specified in the framework (Figure 1), which are recruitment, delivery and response per stakeholder. They were then, within these elements, further structured into quantitative results, qualitative results, and implementation strategies. We	Page 9, Results, first sentence: “The results are presented along the elements specified in the framework (Figure 1) and within each element further structured into a) quantitative results, b) qualitative results, and c) implementation strategies.”

intervention dose, feasibility and barriers and facilitators.	added this clarification to the manuscript. Information about implementation fidelity, intervention dose, feasibility and barriers and facilitators is given in the appropriate places according to this logic.	
Results Start the results section with response and inclusion rates (hospitals, all kind of health care providers and patients) of the main study and thereafter response rates for the process evaluation (invited versus interviewed persons) and study characteristics in one section (thus not divided in several section throughout the results section). Followed by the results per outcome (implementation fidelity, intervention dose, feasibility and barriers and facilitators). One section with intervention adherence rates (intervention dose). Number of trainings session and attended health care providers. Compliance to discharge checklist. Please use implementation terms as compliance or adherence. Response is something else. And one section with perceptions, barriers and facilitators: interview results from all perspectives together. See the Stari guideline how to set up the results section.	We would like to sincerely thank the reviewer for going the extra mile and outlining a new structure of our results section. The proposed structure is well thought out and certainly a very valid alternative. However, as explained before, we have based our process evaluation on a framework that proposes a different approach (as well as terminology). In line with this framework and following the example of other authors (see e.g. https://implementationscience.biomedcentral.com/articles/10.1186/s13012-017-0547-2) we structured the methods section to reflect the multilevel hierarchy of our study, and it would seem odd not to follow the same logic (and use different terminology) in the results section. We believe that deviating from the chosen path now would compromise the structure and thus the readability of the whole manuscript. We still present the results listed by the StaRI guidelines, but according to the multilevel structure.	-
Table 1: give the 'n'; the number of chief physicians who were interviewed	We thank the Reviewer for bringing that to our attention; we added the number to the Table explanation.	Page 27, Table 1, explanation (below the table): Themes identified from the interviews (*n* = 15), with corresponding codes and example quotes from chief physicians (anonymized). Abbreviations:

		HP, hospital physician; GP, general practitioner
Context: should be in the methods section	Again, we chose to go with the structure of the Grant framework. Thus, the Context is part of our results (with a dedicated section, page 15)	-
Discussion Because a clear description of the objective and outcomes measures is missing, the discussion section is hard to read. No figures are given in the whole paper about the results of the main trial (process evaluation are set up to explain these results). In the first section of the discussion section is written: 'implementation was successful ' and 'implementation results were mixed'. Please provide figures (evidence) for these quotes; summarize main findings of the results section.	As clarified above, the effectiveness outcomes are still unknown and will be published later. The results of the process evaluation will then be used to interpret the effectiveness outcomes. If the intervention proves unsuccessful, then the process evaluation may provide insight into possible reasons. If it does work, then the process evaluation may help to develop dissemination strategies for our approach. We rephrased the first section of the Discussion (similarly to Abstract Results section, however without giving numbers, as they can be found in the Discussion below).	Page 16, Discussion: "Recruitment of hospitals was laborious but successful. Minimal workload and a perceived benefit for the clinic proved to be crucial for participation. Intervention dose was high, but intervention fidelity was limited (adaptations to discharge letter) or unknown (medication review). Recruitment and retention of patients was challenging, partly due to patient characteristics (old, frail) and the COVID-19 pandemic. The intervention was deemed feasible and helpful by HPs, and the relevance of the topic appreciated by both HPs and GPs."
Conclusion What should I do, based on this process evaluation, to improve my clinical discharge practice to prevent readmission?	We intend to address this question in the effectiveness study (see also similar comment to the conclusion in the Abstract). We also extended the conclusion to stress benefits that go beyond interpretation of our study.	Page 3, Abstract, Conclusion: "The results from this evaluation will support interpretation of the findings of the effectiveness study and may inform researchers and policy makers who aim at improving hospital discharge." (see also conclusion on page 20 in the manuscript)

VERSION 2 – REVIEW

REVIEWER	Zegers, Marieke Radboudumc, IQ healthcare
REVIEW RETURNED	16-Apr-2021

GENERAL COMMENTS	Thanks for the opportunity to review this article again. The article has certainly been improved by the authors. I also agree that they stick to the framework they used for setting up the process evaluation in the results section. The comprehensiveness of the framework makes the results section very long. But the rich description of the implementation process will help the researcher/authors to explain the results of the effectiveness study. And should be an example for other implementation scientists.