PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Randomized Controlled Pragmatic Clinical Trial Evaluating the Effectiveness of a Discharge Follow-Up Phone Call on 30-Day Hospital Readmissions: Balancing Pragmatic and Explanatory Design Considerations
AUTHORS	Yiadom, Maame Yaa; Domenico, Henry; Byrne, D; Hasselblad, Michele; Gatto, Cheryl; Kripalani, Sunil; Choma, Neesha; Marlow, Sarah; Wang, Li; Bhatia, Monisha; Morrison, Johnston; Harrell, F; Hartert, Tina; Bernard, GR

VERSION 1 – REVIEW

REVIEWER	James Harrison University of California San Francisco, USA
REVIEW RETURNED	24-Oct-2017

GENERAL COMMENTS	The authors present the study protocol for a pragmatic RCT evaluating the effectiveness of a nurse delivered discharge follow-up phone call program. The study is well designed and written up. The primary outcomes are 30-day readmission. Secondary outcomes are also clearly defined. The authors use appropriate data sources and ones that do not rely on direct contact with patients that increases the feasibility of data collection. The authors also provide a rationale for their approaches to design and implementation. Supplemental materials clearly define the intervention and other design/data elements. I have some minor questions for the authors: Can the authors provide some additional detail on what they expect control group participants to receive? What are standard VUMC policies and practices for patients discharged? It is highly likely that some patients will be readmitted during the study period – what will the process be for these patients and how will their data be dealt with? Will statistical analysis be completed blind to group allocation to limit bias? Does the nurse call program operate over the weekends? Does the sample size calculation take into account the various sub-group analyses that are being proposed?

REVIEWER	Irene Lie Oslo University hospital, Oslo, Norway
REVIEW RETURNED	05-Nov-2017

GENERAL COMMENTS	Dear authors. Congratulation with a very interesting article. I have some comments I would like you to consider to address. Abstract IRB approval and Trial registration are missing. Methods and analysis Study design Into my understanding none of study participants; control or intervention group, fill in a written informed consent. That would never have been allowed in my country. You collect data from medical record and so on for both groups? In addition to SPIRIT guidelines please also consider ”Improving the reporting of pragmatic trials: an extension of the CONSORT statement” by Merrick Zwarenstein, et al for the CONSORT and Pragmatic Trials in Healthcare (Practihc) groups (2008). The content of table 1 is seen on page 7 in the text. I suggest to delete the table. Figure 1. Normally it will be a consort flow diagram. The editor has to decide if your combination in the figure is in accordance with the journals acquirements. Supplement III before II in the text. Supplement III when you ask the patient how are you feeling and in the text page 7 line 32 a focused review of symptoms is conducted do you have the international A, B, C, D assessment as a framework in your approach? A short explanation of the Learning Healthcare System model for clinical research is not mentioned in the protocol article, only in the abstract. Re-visit data page 8 line 23. Readmission to hospital is mostly defined as 8 hours to 30 days after discharge. I do not understand your rationale to extend to day 31 and 32. Comparing your data with international research would have more power if you include data to 30 days. I cannot find table 2 reference in text

VERSION 1 – AUTHOR RESPONSE

REVIEWER ONE: JAMES HARRISON (JH)

JH COMMENT #1: Can the authors provide some additional detail on what they expect control group participants to receive? What are standard VUMC policies and practices for patients discharged?

Response: Upon hospital discharge patients receive documentation noting their new medication regimen with attention to medication changes, the follow-up appointment scheduling plan or scheduled appointment dates, education on new diagnoses, and symptoms for which to seek urgent care.
This detail was provided in the “Discharge Plan Review” sub-section of the “Study Procedure” section. It has been moved to the “Study Design” section of the “Study Methods and Analysis,” on page 5 where the intervention program is described, for clarity.

JH COMMENT #2: It is highly likely that some patients will be readmitted during the study period – what will the process be for these patients and how will their data be dealt with?
It is highly likely that some patients will be readmitted during the study period – what will the process be for these patients and how will their data be dealt with?

Response: Our primary analysis will consider each re-visit beyond 30 days as an independent event during which the patient could be re-enrolled and randomized again to either study arm. This is consistent with the methodology of the United States Center for Medicare and Medicaid Services (CMS) which his now cites as reference #17. We recognize, however, that visits for patients with repeat hospitalization are not truly independent. We plan a sensitivity analysis including only the first index visit for each unique patient. If this occurs sufficiently, we may also fit a mixed-effects model including the patient as a random effect so as to consider the within-patient correlation. We have included this detail in the 4th sentence of the “Study Design” section of the “Methods and Analysis” on page 5 and the 3rd sentence of the “General Approach” sub-section of the “Analysis Plan” section in “Methods and Analysis” on page 10.

JH COMMENT #3: Will statistical analysis be completed blind to group allocation to limit bias?

Response: The statistical code will be written blinded to group allocation. Once the dataset has been cleaned and locked, the code will be run without modification using group assignment. This approach will be used for both the interim and final statistical analyses to reduce the potential for bias. This detail has been included in the 3rd - 5th sentences of the “General Approach” subsection of the “Analysis Plan” section (end of page 9) within “Methods and Analysis.”

JH COMMENT #4: Does the nurse call program operate over the weekends?

Response: Calls are only made during week days. Patients who were discharge on a Fridays, Saturdays or Sundays are called the subsequent Monday. This detail has been added to the end of the first paragraph in the “Intervention Delivery” section of the “Study Procedure” section within the “Methods and Analysis” on page 8. We anticipate the needs of patients called on Mondays may be different than others given fewer active health service provider connections over the weekend. As a result we will examine day of the week in order to identify any association with patient’s ability to implementing the discharge plan in our exploratory analyses of “discharge implementation assistance needed.”

JH COMMENT #5: Does the sample size calculation take into account the various sub-group analyses that are being proposed?

Response: No. The study’s sample size and power calculations (Table 1) are based on our binary primary outcome (readmission within 30 days). All other analyses are considered exploratory in nature. This has been clarified in the first sentence of the “Statistical Analysis” section within “Methods and Analysis” on page 10.

REVIEWER TWO: IRENE LIE (IL)

IL COMMENT #1: IRB approval and Trial registration are missing.

Response: IRB approval and Clinical Trials.gov registration detail is included in the 4th and 3rd sentences of the “Study Design” section of the “Methods” at the top of page 5.

IL COMMENT #2: Methods and analysis: Study design - Into my understanding none of study participants; control or intervention group, fill in a written informed consent. That would never have been allowed in my country.
You collect data from medical record and so on for both groups?

Response: In the setting of clinical equipoise over whether the broad use of an intervention in a heterogeneous population will hurt or harm, we found it critical to request waiver of consent to maintain the ecology associated with the clinical practice environment. According to human subjects’ research regulations in the United States, a study needs to meet four criteria in order to be considered for waiver of consent by local Institutional Review Boards (IRB): 1) the study needs to be considered no more than minimal risk to participants; 2) the research could not practicably be carried out without waiver of consent; 3) when appropriate, participants will be provided with additional pertinent information about the study following their participation; and 4) the waiver will not adversely affect the rights and welfare of the participants. Given that the control group was receiving the standard of care and the intervention group was receiving a minimal risk intervention, waiver of consent was requested from the IRB. This request was granted. The waiver puts the study’s data access procedures on par with a retrospective study where medical record data can be used without patient consent. The United States Government’s Health and Human Service policy has been added as reference #18.

18. Code of Federal Regulations. "Protection of Human Subjects." National Institutes of Health Office for Protection from Research Risks. 2009;Title 45:Part 46.116:d1-4.

In 2008 the United States Secretary of Health and Human Services Advisory Committee on Human Research Protections (SACHRP) provided additional guidance for local IRBs on the interpretation of minimal risk related to waiver of consent. This citation has also been added as reference #19.

19. Department of Health and Human Services, Secretary's Advisory Committee on Human Research Protections, “SACHRP letter to HHS Secretary: Recommendations related to waiver of informed consent and interpretation of ‘minimal risk’.” January 31, 2008, available at: https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2008-january-31-letter/index.html Accessed: December 1, 2017.

IL COMMENT #3: In addition to SPIRIT guidelines please also consider ”Improving the reporting of pragmatic trials: an extension of the CONSORT statement” by Merrick Zwarenstein, et al for the CONSORT and Pragmatic Trials in Healthcare (Practihc) groups (2008).

Response: We have reviewed the manuscript for compliance with the CONSORT and Practihc Groups 2008 extension for pragmatic clinical trials, and assured adherence to the 22 point checklist as applies for a protocol study. Items 15-22 apply to results which are not available for this trial protocol. Adherence has been included in the last paragraph of the “Study Design” section of the “Methods and Analysis.” The checklist has been added as a review document.

IL COMMENT # 4: The content of table 1 is seen on page 7 in the text. I suggest to delete the table.

Response: Table 1 has been deleted as suggested.
IL COMMENT #5: Figure 1. Normally it will be a consort flow diagram. The editor has to decide if your combination in the figure is in accordance with the journals acquirements.

Response: We have not received a request from the Editor to replace Figure 1 with a more traditional CONSORT diagram. We chose to present the enrollment targets and patient flow in the context of our planned study analysis. We are glad to edit if a change is required.

IL COMMENT #6: Supplement III before II in the text.

Response: On pages 7 and 8 it appears that Supplement III is mentioned before II. However, the first mention of Supplement II is in the “Randomization and Blinding” sub-section of the “Study Procedures” section in the middle of page 6, with the first mention of Supplement III occurring on page 7. We are glad to re-order placement if the reviewers believe a change would be helpful.

IL COMMENT #7: Supplement III when you ask the patient how are you feeling and in the text page 7 line 32 a focused review of symptoms is conducted do you have the international A, B, C, D assessment as a framework in your approach?

Response: This review of symptoms and condition assessment of the study intervention does not specifically include this framework. The phone call intervention is semi-structured to permit intervention flexibility recommended by PRECIS-2 framework for the design of pragmatic clinical trials. (Reference #31: Loudon, et al The PRECIS-2 tool: Designing trials that are fit for purpose, Am J Pub Hlth, 2015).

IL COMMENT #8: A short explanation of the Learning Healthcare System model for clinical research is not mentioned in the protocol article, only in the abstract.

Response: The second paragraph of the Discussion includes a section on “Learning Healthcare Partnership.” In this section we present Vanderbilt University Medical Center’s (VUMC) engagement in a Learning Healthcare System (LHS) partnership with the Vanderbilt Institute of Clinical and Translational Research (VICTR) where “where clinical practice informs our research and research directly inform practice.” We had not included the abstract‘s comment on the importance of timely study completion. This has been added as the 6th sentence of the “Learning Healthcare Partnership” section paragraph in the main text of the “Discussion” section on page 13.

IL COMMENT #9: Re-visit data page 8 line 23. Readmission to hospital is mostly defined as 8 hours to 30 days after discharge. I do not understand your rationale to extend to day 31 and 32. Comparing your data with international research would have more power if you include data to 30 days.

Response: We are glad to clarify. In the US, fines are assessed for hospital readmissions within 30 days. The extension of the time window to 45 days allows assessment to exclude any unexpected increases in admissions at 31 or 32 days. This use of a binary outcome could mask a potential health care quality issue occurring just beyond the boundary of measure. As a result we added a 15 day “safety window” to permit us to compare the intervention and control group time to readmission curves for any difference in the readmission trend after 30 days that might suggest a delay in the primary outcome rather than a true reduction. This is clarified in the 2nd - 6th sentences of the “Re-Visit Data” sub-section of the “Data Collection” section in “Methods and Analysis” on page 8.

IL COMMENT #10: I cannot find table 2 reference in text

Response: The reference for Table 2 is in the 2nd sentence of the “More Robust Results with Randomization” section of the Discussion.
Thank you for accepting this manuscript for publication and the opportunity to respond to these comments. Our team is glad to address any further concerns.

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Corresponding Author
Assistant Professor, Emergency medicine
Vanderbilt University

VERSION 2 – REVIEW

REVIEWER	James Harrison University of California San Francisco, USA
REVIEW RETURNED	11-Dec-2017

GENERAL COMMENTS	I wish to thank the authors for responding to my questions. All have been answered and included where necessary in the revised manuscript.

REVIEWER	Irene Lie, RN, CCN, PhD Centre for Patient centered Heart- and Lung research/Cardiac surgery ICU Department of Cardiothoracic Surgery Division on Cardiovascular and Pulmonary diseases, Oslo University Hospital, Oslo, Norway
REVIEW RETURNED	22-Dec-2017

GENERAL COMMENTS	Dear authors. Thank you for your good feedback.