Article details: 2017-0134	
Title	A pilot study of a MEdication RAtionalization (MERA) Intervention
Authors	Rachel Whitty BScPhm RPh, Sandra Porter BScPhm RPh, Kiran Battu BScPhm RPh,Pranjal Bhatt Pharm D, Ellen Koo MSc, Csilla Kalocsai PhD, Peter Wu MD MSc, Kendra Delicaet MA, Isaac I.Bogoch MD MS, Robert Wu MD MSc, James Downar MD MHSc (bioethics)
Reviewer 1	Dr. Corrine Hohl
Institution	Vancouver Coastal Health Research Institute, Centre for Clinical Epidemiology and Evaluation
General comments (author response in bold)	This is an important area of work. The authors present a pilot study, yet do not define outcome measures or report outcomes consistent with that. **Clarification: Our main endpoints were typical pilot endpoints- feasibility, acceptability, time efficiency and effect. The justifications were provided in Appendix D.** They present comparisons, yet no robust methods for this. This is a poor quality comparative study, as the groups allocated to control and intervention are not likely comparable. In fact it is unclear how patients in the control group were screened for participation and if they consented. **See above comments and note the changes in terminology to comparison rather than control.** Having said that, this study could likely be refocused, by simply describing feasibility and process outcomes in the intervention group. If refocused, this may be a nice pilot study, but would require a re-write. **Clarification: Please note that the main focus of the study was on feasibility, acceptability and process elements as suggested by the reviewer. The comparison data accounted for only a single paragraph in the results section, and a single sentence in the abstract.** INTRODUCTION: 1. Page 7: Lines 8, and 14, please remove quotation marks. These are acceptable terms. Suggest replacing “deprescription” with deprescribing. **Quotations removed. Deprescription has been replaced with deprescribing throughout.** 2. Page 7: Line 19: reference 22 is not a peer-reviewed evaluation of medication reconciliation. In fact the benefit of medication reconciliation on patient-oriented outcomes is far from proven. Please make this statement more reflective of what has actually been shown, including unintended consequence, and reference peer-reviewed literature, such as these references. 1. Mueller SK, Sponsler KC, Kripalani S, Schnipper JL. Hospital-Based Medication Reconciliation Practices. Arch Intern Med. 2012;172:1057-69. 2. Kwan JL, Lo L, Margaret Sampson, Shojania KG. Medication Reconciliation During Transitions of Care as a Patient Safety Strategy. Ann Intern Med. 2013;158:397-403. 3. Stockton KR, Wickham ME, Lai S, et al. Incidence of clinically relevant medication errors in the era of electronically prepopulated medication reconciliation forms: a retrospective chart review. CMAJ Open. 2017;5:E345. **We thank the reviewer for these references and have modified the introduction accordingly. We have used the Stockton reference in our interpretation section, because it perfectly illustrates our own experience with medication reconciliation reversing the MERA recommendations in a number of cases.** METHODS: 3. Page 8: Please use completed sentences throughout the manuscript. **Done.** 4. Did you enroll consecutive eligible patients, or a convenience sample? Please provide details about how you identified them and approached them. **We enrolled consecutive patients for the intervention, and compared them to consecutive patients in the comparator group. Greater detail has been provided in the methods section.** 5. Inclusion criteria: How did you define elderly? How did you define frail? **See above.** 6. Please describe the criteria with which you determined the risk of 6-month mortality? As stated, this inclusion criterion makes no sense: Everyone alive is at risk of dying within 6 months. I think you mean “expected to die within 6-months? **The CARENET criteria originally described a population with a 50% mortality at 6 months, but that number has not always borne out in other studies. We have specified “elevated” risk of 6-month mortality.**

7. The participants in your study were patients. Healthcare providers were the individuals administering the intervention. Please clarify.

Health care provider criteria refer to eligibility to participate in the follow-up survey or the qualitative component. This has been clarified.

8. How did you train healthcare providers to deliver the intervention?

The MERA recommendations were presented to the patient or SDM by a member of the MERA team, either a physician or pharmacist, using the rationale presented in the guidelines (see Appendix B). The MERA team members were trained and experienced with such discussions as part of their role, and did not receive specific training for the study.

9. Page 8: please spell out all non-standard abbreviations (e.g., ICU, CTU), and for those that you do use, provide a definition prior to first use (should be limited to not more than a few).

ICU has now been spelled out. CTU is now written 9 times in the manuscript and spelled out in the first instance.

10. Page 8, lines 18-19: Please provide details of how you selected the controls amongst the two other wards.

See above.

11. Time frame for enrolment? Day of the week/time of day?

Screening took place during weekdays for any patient admitted in the previous 72 hours.

13. How did you collect data from the control group?

See above.

14. What were your primary and secondary outcomes?

Our co-primary outcomes were the enrolment rate and the acceptability of the MERA intervention to patients/SDMs - this has been specified in the methods section and in Appendix D.

15. Page 10, lines 6-7: Without knowing how your intervention and control groups were selected for enrolment, and without randomization or at least systematic allocation to intervention or control, the results of any comparisons between groups are difficult to interpret, and likely the result of how patients were allocated. How did you control for bias in this unblinded study?

See above.

RESULTS:
16. Page 10, line 14. (Figure 1). You present only the enrolment of patients allocated to the intervention. How did you enroll control patients? Their enrolment needs to be comparable.

See above.

17. Why did you have such a high physician refusal rate?

See above.

18. Page 10. Post intervention exclusions should be analyzed according to the group into which they were assigned in an intention-to-treat protocol (how you deal with this should have been specified and described in the methods).

We have clarified- these patients were included in feasibility endpoints (they were successfully enrolled) but not endpoints for effect and acceptability because they were unavailable at the time that this data needed to be collected.

19. Baseline characteristics: Please remove the p-values. Differences are likely attributable to the manner in which you allocated patients into the different groups (by ward), and none are likely to be due to chance alone. It is likely that the control group differs systematically from the intervention group because you did not allocate randomly or systematically. These are two different patient populations, and therefore comparisons should be removed.

See above.

20. The medication status at 3 months was unavailable for an unacceptably high proportion of

	patients. How did you follow-up patients not covered by the ODB? Did you try to contact them? **We regret that we did not as part of this project, due to concerns about the workload involved and the sensitivity of contacting patients who would be very near to death at that time. We are currently conducting a larger, multicentre, randomized study of less terminal patients that involves direct patient contact at 3-months post discharge.** DISCUSSION: 21. You state that the intervention was feasible, yet you reported a high rate of lack of physician participation. Please discuss. **See above. Physician "refusal" referred only to the specific patient in question, due either to conflict or concern about the patient/family member reaction based on goals of care.**
Reviewer 2	Dr. Mary Lynn McPherson
Institution	University of Maryland School of Pharmacy, Baltimore, Md
General comments (author response in bold)	The only thing I can say is that readers would probably LOVE to see (at least I would) the entire Appendix B - the 47 page document your pharmacists put together. Can it at least be an online supplemental document? **We would love to share the work but need to discuss this further within the team- the algorithms have been incorporated into a computer application in order to improve the efficiency of the process, and there may be copyright issues involved. If possible, we will share the document**.
Reviewer 3	Dr. Kenneth Chambaere and Kristel Paque
Institution	Vrije Universiteit Brussel, End-of-Life Care Research Group, Brussels (Jette), Belgium
General comments (author response in bold)	Overall, a clearly beneficial tool/instrument/intervention in deprescription in palliative care. There are however a number of issues that needed clarification and explanation. Abstract (issues also applicable in main manuscript text): 1. Endpoints effectiveness: not QoL or symptom control? **The endpoints were more about process than outcome given the pilot nature of the study. We are currently conducting a larger, adequately-powered study looking at more patient-centred outcomes.** 2. Why choice for 6-month life expectancy? **The project was focused on patients at elevated risk of death due to chronic or incurable conditions, for whom a medication rationalization approach might be more relevant.** 3. Why such a low enrolment rate? reasons for non-enrolment could be an indicator for (lack of) feasibility and acceptability! enrolment and results biased toward people who already believed they were taking too many different medications? **See above. We don't feel that a 53% enrolment rate is actually that low, but the concern about bias is valid and we have added comments about this in the discussion.** Methods 4. Design: perhaps provide more information on what the convergence triangulation design entails when first mentioning it. **We preferred not to describe this in depth due to the fact that we are not presenting the qualitative results here, and the manuscript is already lengthy.** 5. Participants: "at risk of 6-month mortality or ICU admission according to published criteria23": best to spell out the criteria in the report here. Target population in such feasibility research is pivotal! Also important in itself how this is operationalised. **We have added the CARENET criterai in Appendix G for the reader. Medical records of newly admitted patients were screened on weekdays to look for eligible patients.** 6. How acceptable is it to allow MERA team members to evaluate their own intervention? maybe perform sensitivity analysis: evaluation without MERA members, do they score differently than other HTMs? **MERA team members were only offered participation in the qualitative component of the study (this has been added to the methods section).** 7. Appendix B: I cannot judge the scientific rigor of the MERA guideline and algorithm development, nor whether it adheres to current state-of-the-art knowledge. It is not clear how the authors developed the intervention (no previous publication that describes the development of the intervention). They write about a 'guideline-based algorithm' and Appendix B page 28 contains a table with guidelines that are used for the elderly (including STOPP), followed by the MERA algorithm, which has been elaborated in great detail. It is not clear however how they switch from that table to the algorithm. Guidelines for PIMs in the elderly can not simply be transferred to palliative care. The example in the table (proton

	pump inhibitors) may have been somewhat unfortunate, because no "MERA" guideline is linked to this. **Clarification: The recommendations in the first 4 columns are derived from nationally- and internationally-accepted guidelines, which typically cover the PIMs in the elderly. The last column (MERA) is intended to cover medications in palliative scenarios that do not appear in the other columns- such as the examples provided. The recommendations in that column were derived based on the MERA algorithm depicted in the figure below. This has been clarified in the text for appendix B.** 8. Endpoints: I believe feasibility and acceptability are not measured by "enrolment rate", rather by acceptance rate of medication adaptation. Also, they rest with more than only the patient; what about the professionals involved? + effect is not effectiveness! Effectiveness suggests impact on patient outcomes such as QoL etc. **Agree with these points - see above clarifications, and changes made to the methods section and appendix D.** 9. A clear definition of deprescribing in palliative care or limited life-expectancy is missing. Is it about PIMs? **We tried to define this in the introduction- rationalization encompasses deprescription but also addition of comfort medications and changes to reduce the burden of treatments (e.g. changing injected medications to oral medications). See the MERA algorithm in appendix B.** 10. Did the authors have a "primary" outcome and if so, which one? Improving the use of medication or acceptability for the users? **See above.** 11. The number of medications in the control group is much lower than in the intervention group (significant difference). What is the explanation for this? The authors corrected for this in multivariable analysis, and it was shown to be an independent factor. **See above - this comparison group was not randomized and is provided only for context. Likely, the explanation is that the larger number of medications implies a larger number of inappropriate medications. But the treatment group was also an independent factor, suggesting that this baseline difference was not the explanation for our findings.** 12. What were the reasons for rejecting medication change by doctors and patients? important information for the acceptability of the guideline/intervention **We found it challenging to reliably record the rationale for rejecting a recommendation, as is often the case with such decisions. Disappointingly, the data was not helpful for interpreting our findings. We have explored this issue in paragraph 3 of the discussion, with several references for the readers.** 13. 3 months post-discharge: very little data due to the use of the Ontaria Drug Benefit program, which is a pity. The authors do mention this in the limitations, but it is difficult to judge the influence on the results. **See above explanation for our approach. We are studying this in greater detail in our current study.** 14. How did the authors, in their opinion, overcome barriers to deprescription - particularly where other interventions have failed? It "appeared" to "reassure" those involved, but why? It would be good to elaborate/speculate on what is/are the magic ingredients? **We have some insight into this explanation from our qualitative data, which we are publishing separately. We regret that we cannot include this data due to the length of the existing manuscript.** 15. The authors conclude that the MERA intervention is effective to change the use of medication: can you say this about a pilot study? There are also counterindications, such as restarts at discharge. Wouldn't the authors need to get to the bottom of that to judge and/or optimize effectiveness? **We agree that this study was not powered or designed to prove effectiveness. We will modify the abstract, interpretation and conclusion to read "possibly effective."**
Reviewer 4	Dr. Dick Bijl
Institution	Physician-epidemiologist, Netherlands
General comments (author response in bold)	I have only some minor comments and would advise to publish the article when the authors can adapt the text to these comments. Page 6. 1. Line 16. There is no need to call the control group 'retrospective' as data was collected

at the same time.

See above. We are changing the term to "comparison" group. We agree that the timing would not be "retrospective" but would be happy to keep or discard this term as the editors prefer.

Page 7.
2. Line 6 I am not familiar with the term 'comfort' medication. Can this be explained? See also page 13 line 18.

For the sake of simplicity we have provided the example of opioids in parenthesis.

3. Line 20. It is not clear what 'similar' refers to. The authors should explain it here.

We have removed the term "similar" to simplify the sentence.

Page 8.
4. Line 20. In Appendix A it is stated that nurses care across teams. Is there any chance that doctors and pharmacists were working on all 4 units or on more than 1 in the hospital? If so, is there a possibility that this might have influenced the outcome?

We have clarified that other team members typically do not care for patients across teams on a regular basis, limiting the opportunity for contamination.

Page 9.
5. Line 15. This clearly is a lesson that needs attention and improvement for a next study.
6. Line 21. BMQ was validated in 1999. It is reasonable to assume that opinions about drugs have changed since then. Can the authors discuss this point? Is there a need for a new validation?

We acknowledge the reviewer's concern but the BMQ results were not a major focus of the study, and we feel that this would be beyond the scope of our manuscript.

Page 10.
7. Line 9. The term 'correlation' refers to an inadequate statistical measure, it is better to use the term association.

Done.
Page 11
8. Line 10/13. I would like to see examples of drugs that have been added.

We have added a sentence to the results to describe these.

Page 12
9. Line 19. Also here it is better to use the term associated.

Done.

Page 13.
10. Line 1. Id.
11. Line 10. Delete the word 'large'.

Done.

12. Line 18. Is this the same as comfort medication then I would prefer this term.

Done.

Page 14.
13. Line 17. This is a very important factor. I would prefer to add the word 'unwarranted' and perhaps add some references of Freudenberg (Lethal but legal), Avorn, Frances or GØtzsche.

While we agree that the fear is often unwarranted, we would prefer to avoid this term as potentially controversial. The fear is just as formidable a barrier whether it is warranted or not.

Page 16.
14. Line 18. I hope these ties have been broken by this author.

Strangely, the invitations have become more scarce since I began this line of research…

Page 28.
18. Line 7. How did the authors perform the randomization?

See above.
