



A pilot study of a Medication Rationalization (MERA) Intervention.

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More Detailed Keywords:	Deprescriptions; Potentially Inappropriate Medication List; Palliative Care; Patient Comfort; Quality Improvement; Pilot Study
Abstract:	<p>Background: Many seriously ill and frail inpatients receive potentially inappropriate or harmful medications, and do not receive medications for symptoms of advanced illness. We developed and piloted an interprofessional medication rationalization (MERA) approach to deprescribing inappropriate medications and prescribing appropriate comfort medications.</p> <p>Methods: Single centre pilot study of inpatients at risk of 6-month mortality from advanced age or morbidity. The MERA team reviewed medications and made recommendations based on guidelines. We measured endpoints for feasibility, acceptability, efficiency, and effectiveness.</p> <p>Results: We enrolled 61 of 115 (53%) eligible patients with a mean age (SD) of 79.6 (11.7). Patients were taking an average (SD) of 11.5 (5.2) medications prior to admission, and had an average of 2.2 symptoms with >6/10 severity on the Edmonton Symptom Assessment System. The MERA team recommended 263 medication changes, of which 237 (90%) were</p>

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	<p>accepted by both the medical team and the patient. MERA recommendations resulted in the discontinuation of 162 medications (mean 3.1 per patient), dose changes for 48 medications (mean 0.9 per patient), and the addition of 13 medications (mean 0.2 per patient). Patients who received the MERA intervention stopped significantly more inappropriate medications than similar retrospective non-MERA comparison patients (3.1 vs. 0.9 medications per patient, $p < 0.01$). The MERA approach was highly acceptable to patients and medical team members.</p> <p>Interpretation: The MERA intervention is feasible, acceptable, efficient, and possibly effective for changing medication use among seriously ill and frail elderly inpatients. Scalability and effectiveness may be improved through automation and integration with medication reconciliation programs.</p>

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	
Objectives	3	State specific objectives, including any prespecified hypotheses	3-4	
Methods				
Study design	4	Present key elements of study design early in the paper	4	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5	
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-5	
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls		
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants		
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	4	
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4, Appx C,D	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4, Appx C,D	
Bias	9	Describe any efforts to address potential sources of bias	Appx D	
Study size	10	Explain how the study size was arrived at	(Pilot study)	

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	5
		(c) Explain how missing data were addressed	--
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	Appx D
		(e) Describe any sensitivity analyses	--
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, Fig 1
		(b) Give reasons for non-participation at each stage	6, Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, Supp Table
		(b) Indicate number of participants with missing data for each variable of interest	--
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Page 7-8, Fig 2
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	Page 7-8, Fig 2
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	--
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	--
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	--
		(b) Report category boundaries when continuous variables were categorized	--
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	--

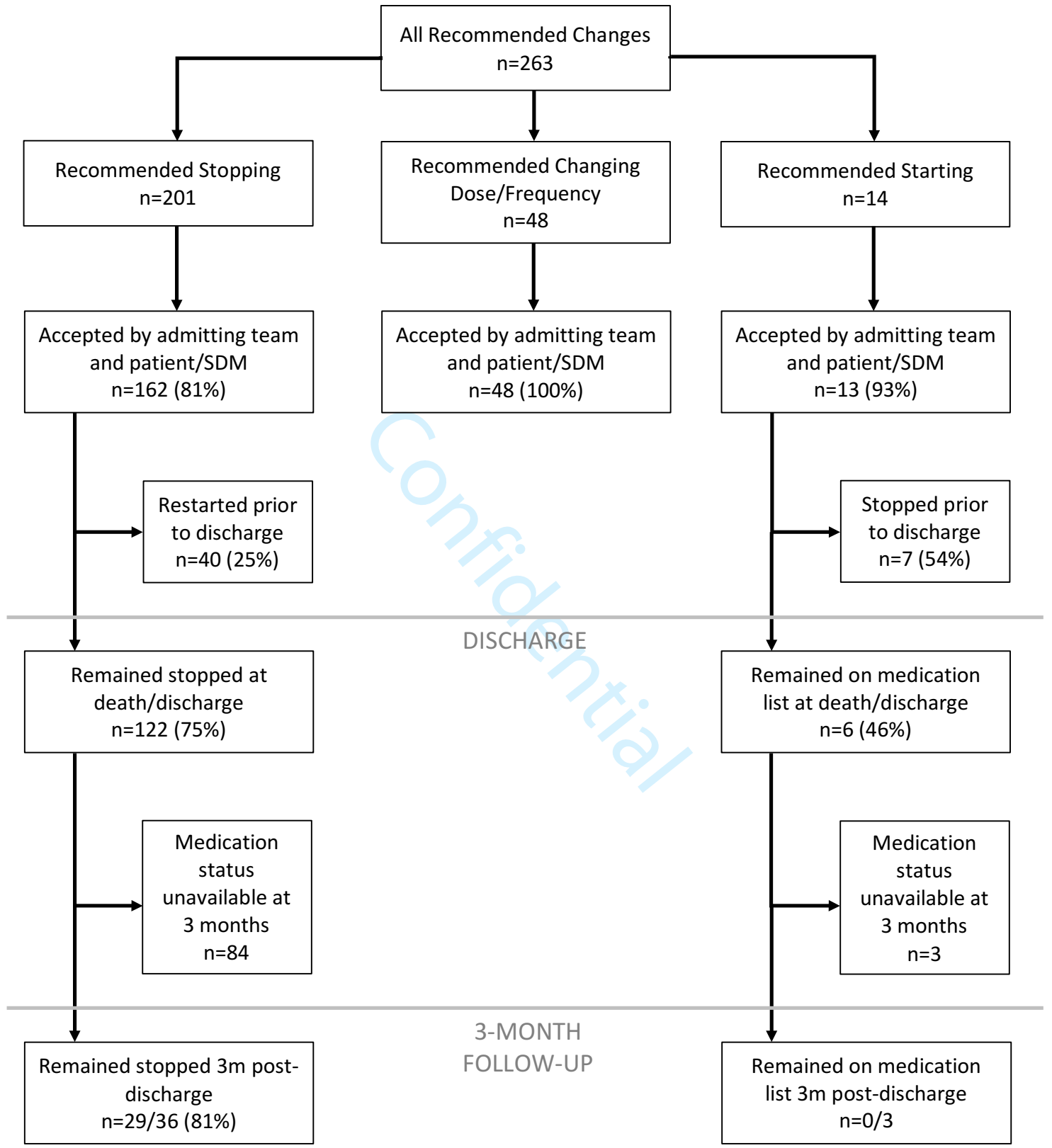
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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 8-9, Fig 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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3 **1 Title.**

4 2 A pilot study of a MEdication RAtionalization (MERA) Intervention.
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6 4 **Running Title.**

7 5 MEdication RAtionalization (MERA).
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26 24 Abstract Word Count: 248

27 25 Word Count: 2795
28 26

29 27
30 28 **Key Points:**

- 31 29
 - 32 30 • An interprofessional, pharmacist-led team was effective for rationalizing the medications prescribed to seriously ill and elderly medical inpatients.
 - 33 31 • Our MEdication RAtionalization (MERA) approach was highly acceptable to patients, caregivers and staff alike, and played a role currently unfilled by other members of the care team.
 - 34 32 • Scalability and effectiveness of the MERA approach may be improved through automation and integration with medication reconciliation programs.

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3 **1 Abstract.**
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5 **2 Background:** Many seriously ill and frail inpatients receive potentially inappropriate or harmful
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7 **3 medications,** and do not receive medications for symptoms of advanced illness. We developed and
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9 **4 piloted** an interprofessional medication rationalization (MERA) approach to deprescribing inappropriate
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11 **5 medications** and prescribing appropriate comfort medications.
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14 **6 Methods:** Single centre pilot study of inpatients at risk of 6-month mortality from advanced age or
15
16 **7 morbidity.** The MERA team reviewed medications and made recommendations based on guidelines. We
17
18 **8 measured** endpoints for feasibility, acceptability, efficiency, and effectiveness.
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21 **9 Results:** We enrolled 61 of 115 (53%) eligible patients with a mean age (SD) of 79.6 (11.7). Patients were
22
23 **10 taking** an average (SD) of 11.5 (5.2) medications prior to admission, and had an average of 2.2 symptoms
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25 **11 with** >6/10 severity on the Edmonton Symptom Assessment System. The MERA team recommended 263
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27 **12 medication** changes, of which 237 (90%) were accepted by both the medical team and the patient.
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30 **13 MERA** recommendations resulted in the discontinuation of 162 medications (mean 3.1 per patient),
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32 **14 dose** changes for 48 medications (mean 0.9 per patient), and the addition of 13 medications (mean 0.2
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34 **15 per** patient). Patients who received the MERA intervention stopped significantly more inappropriate
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36 **16 medications** than similar retrospective non-MERA comparison patients (3.1 vs. 0.9 medications per
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38 **17 patient,** $p < 0.01$). The MERA approach was highly acceptable to patients and medical team members.
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41 **18 Interpretation:** The MERA intervention is feasible, acceptable, efficient, and possibly effective for
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43 **19 changing** medication use among seriously ill and frail elderly inpatients. Scalability and effectiveness
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45 **20 may** be improved through automation and integration with medication reconciliation programs.
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48 **21**
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50 **22 Key Words.**

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52 **23 Deprescriptions;** Potentially Inappropriate Medication List; Palliative Care; Patient Comfort; Quality
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54 **24 Improvem3ent;** Pilot Study
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3 1 *Introduction.*

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5 2 Polypharmacy (the concomitant use of 5 or more medications) is present in more than half of the
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7 3 seriously ill and frail elderly^{1,2} and is associated with medication errors, drug interactions, adverse drug
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9 4 reactions and nonadherence³. Even as patients approach death, they are often prescribed a substantial
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11 5 number of non-comfort medications that are likely inappropriate and burdensome to patients and
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13 6 healthcare providers alike⁴. At the same time, many dying patients are not given comfort medications
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15 7 (e.g. opioids)⁵, suggesting that the problem is not simply overtreatment but a mismatch between care
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17 8 and values. In order to promote deprescribing, different organizations have published lists and criteria
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19 9 for medications that are potentially inappropriate in older adults⁶⁻⁸. Palliative Care (PC) practitioners
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21 10 have also developed lists of medications with questionable benefit in patients with end-stage or
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23 11 terminal illnesses^{4,9-12}; for example, preventive medications with only long-term benefits. Yet there are
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25 12 many barriers to deprescribing^{3,13} and to providing comfort-oriented medications (e.g. opioids)¹⁴, even if
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27 13 these would appear to be rational choices for a patient nearing the end of life.

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32 14 An effort to rationalize medications in the seriously ill and frail elderly, by deprescribing
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34 15 inappropriate medications and prescribing appropriate comfort medications, may simultaneously
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36 16 improve care while reducing costs^{15,16}. Deprescribing has been studied extensively in the general
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38 17 medical population¹⁷⁻¹⁹, but there is little published research on this approach in patients nearing the
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40 18 end of life²⁰. Other medication-focused quality improvement initiatives have been broadly implemented,
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42 19 such as Antibiotic Stewardship²¹ and Medication Reconciliation²², although they may not always improve
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44 20 patient care^{23,24}. In this study, we sought to develop and pilot a MEDication RAtionalization (MERA) team
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46 21 that would systematically rationalize medications for seriously ill and frail elderly patients admitted to a
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48 22 medical ward.

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54 24 *Methods.*

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5 2 *Design.*
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8 3 We conducted a pilot study using a mixed-methods triangulation design (convergence model) in two
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10 4 populations (Patients/Substitute Decision-Makers (SDM) and Healthcare Providers). We are presenting
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12 5 the quantitative results in this report.
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16 7 *Participants.*

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19 8 1. Patients. Inclusion Criteria: We enrolled seriously ill or frail elderly patients admitted to the General
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21 9 Internal Medicine ward, at elevated risk of 6-month mortality or Intensive Care Unit admission
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23 10 according to published criteria²⁵ (Appendix G), or followed by the PC service. Exclusion Criteria
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25 11 included refusal of consent to participate, or refusal by attending physician or delegate to enrol that
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27 12 particular patient. If the patient was not capable of providing consent, we approached their SDM to
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29 13 offer enrolment.
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32 14 2. Healthcare Team Members. Inclusion Criteria for the follow-up survey and qualitative components:
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34 15 We offered enrolment to any consenting physician, medical trainee, or pharmacist members of
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36 16 General Internal Medicine Clinical Teaching Units (CTU). Physician or pharmacist members of the
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38 17 MERA team were also offered participation in the qualitative component of the study. Exclusion
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40 18 Criteria included refusal of consent to participate.
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46 20 *Setting/Duration.*

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48 21 The intervention was delivered on two of six General Internal Medicine CTUs at Toronto General
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50 22 Hospital between August and December 2015, and we screened the medical record of every patient
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52 23 admitted to those CTUs over that period to look for eligible patients. Screening took place during
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54 24 weekdays for any patient admitted in the previous 72 hours. We also collected medication data
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3 1 retrospectively on a comparison group consisting of consecutive eligible patients admitted concurrently
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5 2 to two other CTUs where the MERA intervention was not delivered. A description of the units is
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7 3 provided in *Appendix A*.
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12 5 *Intervention.*
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14 6 The study coordinator screened the charts of newly admitted patients each day on the General Internal
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16 7 Medicine wards to identify patients who met inclusion criteria, obtained informed consent to
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18 8 participate, collected demographic and clinical data (including the Clinical Frailty Score), administered
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20 9 baseline questionnaires to the patient or SDM, and prepared a list of their current medications for the
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22 10 MERA team. A MERA physician and pharmacist reviewed this information in the context of the patient's
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24 11 clinical history, symptoms and medications, and made recommendations to stop, start, or change doses
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26 12 of specific medications using a guideline-based algorithm (described in *Appendix B*). Any disagreements
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28 13 about recommendations were resolved by consensus within the team. The study coordinator then
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30 14 arranged a meeting between the CTU attending physician (or delegate), CTU clinical pharmacist, and a
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32 15 physician and/or pharmacist from the MERA team to review the recommendations and discuss the
33
34 16 potential need for additional symptomatic medication (e.g. opioids). If the admitting team disagreed
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36 17 with the rationale behind any MERA recommendation, the recommendation was dropped and not
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38 18 presented to the patient or family member.
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43 19 A summary of the medication recommendations was then discussed with the patient or SDM by
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45 20 a member of the MERA team. Medication changes were only made with the consent of the patient or
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47 21 SDM. A written summary report of all medication changes made including rationale was provided to the
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49 22 patient or SDM. Note that all patients admitted to our facility undergo both admission and discharge
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51 23 medication reconciliation; the discharge reconciliation does not always involve a pharmacist.
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1 *Endpoints and Analysis*

2 Our baseline data included demographic data and other pertinent information; the Patient Attitudes
3 Towards Deprescribing (PATD) questionnaire, a validated 15-item exploratory measure of acceptance of
4 deprescribing²⁶; the Beliefs about Medicines Questionnaire (BMQ), a validated 17-item questionnaire
5 assessing beliefs about the necessity, toxicity and overuse of medications²⁷ (*Appendix C*); and the
6 Edmonton Symptom Assessment System-revised²⁸ (ESAS). We collected pilot endpoints to evaluate the
7 feasibility, acceptability, time efficiency, and effect of MERA (justification in *Appendix D*), and we
8 analyzed medication use 3 months post-discharge using the Ontario Drug Benefit (ODB) program
9 database (which would have information for many medications taken by participants over age 65). Our
10 co-primary outcomes were the enrolment rate and the acceptability of the MERA intervention to
11 patients/SDMs.

12 Data were analyzed descriptively for most outcomes. Demographic comparisons between the
13 intervention and non-MERA comparison groups were made using a t-test for continuous variables and
14 chi-square test for categorical variables. Comparisons of numbers of medications prescribed,
15 recommended discontinuations, and accepted discontinuations between non-MERA comparison and
16 interventions groups were made using a Mann-Whitney U test as the data were non-parametric.
17 Comparisons involving more than 2 categorical predictor variables were made using a Kruskal Wallis
18 ANOVA. Multivariable linear regression was used to measure the association between demographic and
19 baseline data and the number of medications discontinued. This study was approved by the Research
20 Ethics Board at our facility (REB# 15-8840-A).

21 *Results.*

22 Overall, we enrolled 61 of the 115 (53%) eligible patients admitted during the study period (Figure 1).
23 For eight patients, the MERA team made recommendations to the treating team but these could not be
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1 discussed with the patient or SDM prior to the death or discharge of the patient. These patients were
2 excluded from the analysis of effect and acceptability to patients/SDMs. Participant demographics are
3 presented in Table 1.

4 Baseline patient perception and symptom data are provided in Supplementary Table 1. Taken
5 together, the BMQ scores indicate that participants generally believed that their medications were
6 necessary (but this belief was not strong), and they did not have strong concerns about harm and
7 overuse (more detailed explanation provided in *Appendix E*). The PATD questionnaire indicated that
8 participants generally felt that they were taking a large number of medications (61%) and only 29 (55%)
9 felt that their medications were necessary. There was a strong willingness to stop one or more
10 medications (91%) or take additional medications (68%) if suggested by a physician. Participants were
11 comfortable with the idea of a pharmacist stopping a medication, provided that their physician was
12 informed (75%), and there was a strong preference for a face-to-face encounter to follow-up any
13 decision to stop a medication (66%). Average patient symptom severity scores on the ESAS-r were in the
14 low to moderate range (1.3-5.2), but each patient had an average of 2.1 symptom scores greater than 6
15 (severe).

16 The median (range) duration of MERA meetings with the admitting team was 7 minutes (1-12),
17 and the MERA team recommended a total of 263 medication changes, affecting 51/53 (96%) enrolled
18 patients (Figure 2). Of the 201 recommendations to stop medications, the medical team accepted 176
19 (88%) and the patient/SDM accepted 162, for a combined acceptance rate of 81%. Sixty-one of 62(98%)
20 recommendations to change doses/frequencies or add medications were accepted by both the medical
21 team and the patient/SDM, for an overall recommendation acceptance rate of 223/263 (85%).MERA
22 recommendations resulted in the discontinuation of a mean (SD) of 3.1(2.6) medications, dose changes
23 in 0.9 (1.5) medications, and the addition of 0.2 (0.5) medications per patient (Table 2). The most
24 common recommended discontinuations were vitamins/minerals, lipid lowering agents,

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3 1 homeopathic/herbal supplements, proton pump inhibitors, and docusate (Table 3). These five
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5 2 medications/classes accounted for 55% of all recommended discontinuations. The medications added
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7 3 were opioids (3), mirtazapine (3), inhaled bronchodilators (2), non-opioid analgesics (2),
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9 4 metoclopramide (1), rivaroxaban (1), and paroxetine (1).
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12 5 Of the 162 medications that were stopped, 40 (25%) were restarted during hospitalization or at
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14 6 the time of discharge (Figure 2). In a post-hoc analysis, we found that the likelihood of medications
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16 7 being restarted on discharge was not affected by whether or not a pharmacist was involved in the
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18 8 discharge medication reconciliation ($\chi^2=0.34$, $p=0.56$, data not shown). Of the 122 medications that
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20 9 remained discontinued at the time of discharge, we were able to assess the status of 36 medications (16
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22 10 patients) at 3-months post-discharge because both the patient and the medication was covered by the
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24 11 Ontario Drug Benefit (ODB) program, and the patient neither died nor transferred to a PCU during the
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26 12 admission or the follow-up period. The ODB records revealed that 29/36 (81%) remained discontinued.
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28 13 We could not assess the status of the remaining medications either because the patient had died or
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30 14 been transferred to an inpatient palliative care unit (5 patients, 23 medications), or the medication or
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32 15 patient was not covered by this plan (41 medications), or the medication was for hospital use only and
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34 16 would not have been expected to be used post-discharge (2 medications). Using ODB cost data and
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36 17 assuming that prescriptions required one refill in the 100 days post-discharge, we found that the total
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38 18 direct cost of these stopped medications was \$1508.47, or \$94.28 per 100 patient-days. Of the 13
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40 19 medications added, 6 were stopped prior to discharge. There were 6 of these medications prescribed on
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42 20 discharge (1 medication was taken by a patient who died during admission) and of these, 3 were taken
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44 21 by patients who either died or transferred to a PCU within 3 months post-discharge, therefore we could
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46 22 not assess the status of these medications. The remaining 3 were not filled according to the ODB record.
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52 23 The medication changes made in response to the MERA intervention were compared with
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54 24 medication changes made on the two non-MERA comparison CTUs for 51 consecutive patients admitted
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1 over the same study period who met our inclusion criteria (Table 1). There was no difference between
2 the two groups in the number of medication discontinuations that would have been recommended by
3 the MERA algorithm (3.7 vs. 3.8, $p=0.95$), but significantly more of these medications were actually
4 stopped in the intervention group (3.1 vs. 0.9, $p<0.001$; Table 2). Using a multivariable linear regression
5 analysis including treatment group (MERA vs. non-MERA comparison), age, sex, inclusion criterion, and
6 number of baseline medications, we found that both the treatment group ($p<0.001$) and number of
7 baseline medications ($p<0.001$) were associated with the number of medications stopped. Within the
8 MERA intervention group, the number of medications discontinued was not influenced by the main
9 inclusion criterion or whether or not a Palliative Care team was previously involved in the patient's care
10 (Table 2). In a multivariable linear regression analysis that included each of the domains of the BMQ, the
11 total ESAS score, the number of "severe" symptoms (>6) on the ESAS, and the Clinical Frailty Score, only
12 the BMQ-General domain was significantly associated with the number of medications discontinued
13 ($p=0.02$, data not shown).

14 We were able to administer a follow-up questionnaire to 41 patients or SDMs after the
15 recommendations were discussed with them (Supplementary Figure 1). A majority reported being
16 comfortable with starting (11/14, 79%) and stopping (33/38, 87%) medications as recommended by the
17 MERA team, and only a very small number found the experience stressful (5%) or confusing (11%).
18 Thirty-seven (92%) reported being "glad" that the MERA team reviewed their medications.

19 We administered a follow-up survey to the members of the medical team who participated in
20 the MERA meetings, obtaining 16 responses (response rate of 53%). Respondents reported that
21 medication rationalization was a good idea (100%), that it was easy to discuss MERA recommendations
22 with patients (87%), and that "MERA meetings were a good use of my time" (94%). No respondent felt
23 that it was difficult to attend the MERA meetings or that the meetings were too long, or that the MERA
24 team's involvement negatively affected their own relationship with the patient or SDM.

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45 2 *Discussion.*
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7 3 In this single-centre study, we pilot-tested an innovative interprofessional medication-focused
8 4 intervention aimed at medication rationalization (MERA), including both deprescribing of harmful or
9 5 nonbeneficial medications and addition of comfort medications for inpatients with a limited life
10 6 expectancy due to serious illness, advanced co-morbidities or frailty. We found that the MERA
11 7 intervention met or exceeded all pilot objectives; it was feasible and possibly effective for reducing
12 8 medication use and costs in both the short and long term; it was efficient and acceptable for the
13 9 admitting team; and it was satisfactory to the patient and family. We also learned lessons to improve
14 10 the scalability and effectiveness of MERA in a larger, multicentre study.

15 11 In our study population of elderly, frail or seriously ill inpatients, we found that virtually every
16 12 patient was taking multiple medications that were either unnecessary or potentially harmful. Up to 40%
17 13 of frail elderly patients are prescribed medications that are potentially inappropriate for them according
18 14 to guidelines¹³, and up to 30% of hospital admissions for patients over age 75 are medication-related; a
19 15 large proportion are preventable²⁹. Deprescribing interventions delivered on medical wards can be
20 16 effective¹⁹, but often patients are discharged on the same, if not more medications³⁰⁻³². We previously
21 17 found that even patients treated with a palliative intent in our institution received an average of 40
22 18 doses of non-comfort medications in the week prior to their death or transfer to a Palliative Care Unit⁴.
23 19 Although we found only a modest reduction in direct medication costs in our population of patients
24 20 nearing the end of life, other studies have shown the large potential financial costs of inappropriate
25 21 prescription on a population scale^{15,16}, and medication costs are often partially borne by patients
26 22 themselves.

27 23 Our participants were comfortable stopping medications if their medical team felt it was
28 24 possible, and virtually all were grateful that the MERA team reviewed their medications. Previous

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3 1 deprescribing interventions have sometimes had little or no effect³³, and there are multiple factors that
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5 2 shape both prescriber³⁴ and patient³⁵ barriers to deprescribing including complexity and time
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7 3 limitations, an underappreciation of the scale of polypharmacy-related harms, the increasing intensity of
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9 4 medical care in general, the fear of precipitating an acute event, and the conceptual difficulty involved in
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11 5 balancing risks and benefits^{3,13}. Only 21% of the *Choosing Wisely* campaign's current recommendations
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13 6 refer to stopping specific medications³⁶. Physicians may also hesitate to label a medication as "low
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15 7 value" for a patient³⁶, especially when that medication may have been prescribed by another physician
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17 8 and appears to be well-tolerated¹³. And even patients who dislike taking medications may be upset by
18
19 9 the implication that they are too sick or too close to death to gain any benefit from them³⁵. The MERA
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21 10 intervention used an innovative, pharmacist-led approach that appeared to be reassuring to patients,
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23 11 SDMs and health care professionals alike. Notably, the effectiveness of the MERA approach was seen
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25 12 broadly, regardless of the patient's views towards their medications, their symptom burden, their
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27 13 degree of frailty, age or diagnosis. It was also equally effective in patients already seen by a Palliative
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29 14 Care consultant, and the comparison with non-MERA CTUs suggests that MERA provides a benefit not
30
31 15 seen in "routine" interprofessional care.

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37 16 Although our limited follow-up data suggested that the effect of MERA was durable, there were
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39 17 a substantial number of medications restarted at discharge. These medications may have been restarted
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41 18 deliberately, or they may have been accidentally restarted due to poor communication at the time of
42
43 19 medication reconciliation. Our Medication Reconciliation Program uses multiple sources of information,
44
45 20 but our discharge forms are electronically prepopulated and can prompt providers to restart
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47 21 discontinued medications in error, as has been shown by Stockton et al³⁷. To improve effectiveness,
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49 22 rationalization and reconciliation will need to be better integrated. Garfinkel and Mangin tested a
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51 23 similar intervention in community-dwelling seniors (who do not experience transfers of care shortly
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1 after the intervention), and they reported that 81% of their discontinuations remained effective after a
2 mean follow-up of 19 months³⁸.

3 Strengths of this study include the collection of multiple perspectives (patient, SDM, and
4 medical team) and dimensions (e.g. symptom burden, function, medication changes, and views on
5 medications and deprescribing) to study a novel, interdisciplinary intervention to address a common
6 problem in the seriously ill and frail elderly. Limitations include the fact that it was a single centre, non-
7 randomized pilot study involving a dedicated, independent team, which precludes broad interpretation
8 of the effectiveness of the MERA intervention. Our follow-up data was limited to medications covered
9 by the ODB program, without quality of life measures. The enrolment rate of 53% is typical for studies of
10 palliative-relevant topics³⁹, but it raises concerns about a selection bias as patients or SDMs who
11 enrolled in this study may have been particularly keen to stop their medications, although the BMQ and
12 PATD results suggest that this was not the case. However, our comparison group was identified
13 retrospectively without being enrolled and randomized; they may not have accepted MERA
14 recommendations as readily as our enrolled patients did. Admitting team members who did not
15 complete the follow-up survey may not have shared the enthusiasm for MERA shown by those who did
16 respond. Our cost data included only the costs of the medications that were stopped; the cost of the
17 MERA team itself (e.g. the time taken to prepare reports) was not captured. Finally, an intervention of
18 this nature involves medical, social and ethical considerations that may not be captured by quantitative
19 methods; our qualitative results will be presented separately.

20 In conclusion, we found that the MERA intervention was feasible, acceptable, efficient, and
21 possibly effective for changing medication use among seriously ill and/or frail elderly inpatients in a
22 single-centre pilot study. Future studies will explore the possibility of automating the MERA approach to
23 improve scalability, better integrating MERA with medication reconciliation, and testing this approach in
24 other care settings.

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45 2 *Acknowledgments.*
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16 12 Authorship contributions: RW, SP, KB and JD conceived and designed the study. RW, SP, KB, PB, EK, CK
17 13 and JD were involved in data collection. All authors were involved in data analysis and interpretation. JD,
18 14 RW, SP, KB and PW were involved in drafting the manuscript. All authors were involved in revising the
19 15 manuscript and approved the final version submitted.

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- 1 Legends.
- 2 Figure 1. Patient enrolment CONSORT flow diagram.
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- 4 Figure 2. Flowchart of medication recommendations and changes.
- 5
- 6 Table 1. Demographics and baseline characteristics of intervention group.
- 7
- 8 Table 2. Differences in medication discontinuation among groups and subgroups.
- 9
- 10 Table 3. Most common medications recommended to be stopped by the MERA Team.
- 11
- 12 Supplementary Table 1. Patient baseline symptom and perception data
- 13
- 14 Supplementary Figure 1. Patient perceptions of medication rationalization.
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Title.

A pilot study of a MEducation RAationalization (MERA) Intervention.

Running Title.

MEducation RAationalization (MERA).

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Key Points:

- An interprofessional, pharmacist-led team was effective for rationalizing the medications prescribed to seriously ill and elderly medical inpatients.
- Our MEducation RAationalization (MERA) approach was highly acceptable to patients, caregivers and staff alike, and played a role currently unfilled by other members of the care team.
- Scalability and effectiveness of the MERA approach may be improved through automation and integration with medication reconciliation programs.

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8 **1 Abstract.**
9

10 2 Background: Many seriously ill and frail inpatients receive potentially inappropriate or harmful
11 3 medications, and do not receive medications for symptoms of advanced illness. We developed and
12 4 piloted an interprofessional medication rationalization (MERA) approach to deprescribing inappropriate
13 5 medications and prescribing appropriate comfort medications.

14 6 Methods: Single centre pilot study of inpatients at risk of 6-month mortality from advanced age or
15 7 morbidity. The MERA team reviewed medications and made recommendations based on guidelines. We
16 8 measured endpoints for feasibility, acceptability, efficiency, and effectiveness.

17 9 Results: We enrolled 61 of 1125 (53.48%) eligible patients with a mean age (SD) of 79.6 (11.7). Patients
18 10 were taking an average (SD) of 11.5 (5.2) medications prior to admission, and had an average of 2.2
19 11 symptoms with >6/10 severity on the Edmonton Symptom Assessment System. The MERA team
20 12 recommended 263 medication changes, of which 237 (90%) were accepted by both the medical team
21 13 and the patient. MERA recommendations resulted in the discontinuation of 162 medications (mean 3.1
22 14 per patient), dose changes for 48 medications (mean 0.9 per patient), and the addition of 13
23 15 medications (mean 0.2 per patient). Patients who received the MERA intervention stopped significantly
24 16 more inappropriate medications than similar retrospective ~~control~~ non-MERA comparison patients (3.1
25 17 vs. 0.9 medications per patient, $p < 0.01$). The MERA approach was highly acceptable to patients and
26 18 medical team members.

27 19 Interpretation: The MERA intervention is feasible, acceptable, efficient, and possibly effective for
28 20 changing medication use among seriously ill and frail elderly inpatients. Scalability and effectiveness
29 21 may be improved through automation and integration with medication reconciliation programs.

30 22
31 23 Key Words.
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1 Deprescriptions; Potentially Inappropriate Medication List; Palliative Care; Patient Comfort; Quality

2 | Improvem~~ent~~³; Pilot Study

3 | *Introduction.*

4 Polypharmacy (the concomitant use of 5 or more medications) is present in more than half of the
 5 seriously ill and frail elderly^{1,2} and is associated with medication errors, drug interactions, adverse drug
 6 reactions and nonadherence³. Even as patients approach death, they are often prescribed a substantial
 7 number of non-comfort medications that are likely inappropriate and burdensome to patients and
 8 healthcare providers alike⁴. At the same time, many dying patients are not given comfort medications
 9 ~~(e.g. opioids)~~⁵, suggesting that the problem is not simply overtreatment but a mismatch between care
 10 and values.

11 In order to promote “~~deprescrib~~^{ing}tion”, different organizations have published lists and criteria for
 12 medications that are potentially inappropriate in older adults⁶⁻⁸. Palliative Care (PC) practitioners have
 13 also developed lists of medications with questionable benefit in patients with end-stage or terminal
 14 illnesses^{4,9-12}; for example, preventive medications with only long-term benefits. Yet there are many
 15 barriers to ~~deprescription~~^{deprescribing}^{3,13} and to providing comfort-oriented medications ~~(e.g.~~
 16 ~~opioids)~~¹⁴, even if these would appear to be rational choices for a patient nearing the end of life.

17 An effort to “~~rationalize~~” medications in the seriously ill and frail elderly, by deprescribing
 18 inappropriate medications and prescribing appropriate comfort medications, may simultaneously
 19 improve care while reducing costs^{15,16}. ~~Deprescription~~^{Deprescribing} has been studied extensively in the
 20 general medical population¹⁷⁻¹⁹, but there is little published research on this approach in patients
 21 nearing the end of life²⁰. Other medication-focused quality improvement initiatives have ~~improved~~
 22 ~~patient safety and reduced costs~~^{been broadly implemented}, such as Antibiotic Stewardship²¹ and
 23 Medication Reconciliation²², ~~although they may not always improve patient care~~^{23,24}. In this study, we
 24 sought to ~~apply a similar model by~~ develop^{ing} and pilot^{ing} a MEdication RAtionalization (MERA) team

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8 1 that would systematically rationalize medications for seriously ill and frail elderly patients admitted to a
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10 2 medical ward.

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14 4 *Methods.*

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17 6 *Design.*

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19 7 We conducted a Pilot study using a mixed-methods triangulation design (convergence model) in two
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21 8 populations (Patients/Substitute Decision-Makers (SDM) and Healthcare Providers). We are presenting
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23 9 the quantitative results in this report.

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26 11 *Participants.*

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28 12 1. Patients. Inclusion Criteria: We enrolled Seriously ill or frail elderly patients admitted to the General
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30 13 Internal Medicine ward, at elevated risk of 6-month mortality or ICU-Intensive Care Unit admission
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32 14 according to published criteria²⁵ (Appendix G), or followed by the PC service. Exclusion Criteria
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34 15 included r-Refusal of consent to participate, or refusal by attending physician or delegate to enrol
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36 16 that particular patient. If the patient was not capable of providing consent, we approached their SDM
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38 17 to offer enrolment.

39 18 2. Healthcare Team Members. Inclusion Criteria for the follow-up survey and qualitative components:
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41 19 We offered enrolment to any Any consenting physician, medical trainee, or pharmacist members of
42
43 20 General Internal Medicine Clinical Teaching Units (CTU)); or any physician or pharmacist members
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45 21 of the MERA team were also offered participation in the qualitative component of the study.
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47 22 Exclusion Criteria included r-Refusal of consent to participate.

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49 24 *Setting/Duration.*

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1 The intervention was delivered on two of six General Internal Medicine CTUs at Toronto General
2 Hospital between August and December 2015, and we screened the medical record of every patient
3 admitted to those CTUs over that period to look for eligible patients. Screening took place during
4 weekdays for any patient admitted in the previous 72 hours. We also collected medication data
5 retrospectively on a ~~control-comparison~~ group consisting of consecutive eligible patients admitted
6 concurrently to two other CTUs where the MERA intervention was not delivered. A description of the
7 units is provided in *Appendix A*.

8 9 *Intervention.*

10 The study coordinator screened the charts of newly admitted patients each day on the General Internal
11 Medicine wards to identify patients who met inclusion criteria, obtained informed consent to
12 participate, collected demographic and clinical data (including the Clinical Frailty Score), administered
13 baseline questionnaires to the patient or SDM, and prepared a list of their current medications for the
14 MERA team. A MERA physician and ~~or~~ pharmacist reviewed this information in the context of the
15 patient's clinical history, symptoms and medications, and made recommendations to stop, start, or
16 change doses of specific medications using a guideline-based algorithm (described in *Appendix B*). Any
17 disagreements about recommendations were resolved by consensus within the team. The study
18 coordinator then arranged a meeting between the CTU attending physician (or delegate), CTU clinical
19 pharmacist, and a physician and/or pharmacist from the MERA team to review the recommendations
20 and discuss the potential need for additional symptomatic medication (e.g. opioids). If the admitting
21 team disagreed with the rationale behind any MERA recommendation, the recommendation was
22 dropped and not presented to the patient or family member.

23 A summary of the medication recommendations was then discussed with the patient or SDM by
24 a member of the MERA team. Medication changes were only made with the consent of the patient or

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8 1 SDM. A written summary report of all medication changes made including rationale was provided to the
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10 2 patient or SDM. Note that all patients admitted to our facility undergo both admission and discharge
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12 3 medication reconciliation; the discharge reconciliation does not always involve a pharmacist.
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15 5 *Endpoints and Analysis*

16 6 Our baseline data included demographic data and other pertinent information; the Patient Attitudes
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18 7 Towards Deprescribing (PATD) questionnaire, a validated 15-item exploratory measure of acceptance of
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20 8 ~~deprescription~~ deprescribing²⁶; the Beliefs about Medicines Questionnaire (BMQ), a validated 17-item
21
22 9 questionnaire assessing beliefs about the necessity, toxicity and overuse of medications²⁷ (*Appendix C*);
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24 10 and the Edmonton Symptom Assessment System-revised²⁸ (ESAS). We collected pilot endpoints to
25
26 11 evaluate the feasibility, acceptability, time efficiency, and effect of MERA (justification in *Appendix D*),
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28 12 and we analyzed medication use 3 months post-discharge using the Ontario Drug Benefit (ODB) program
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30 13 database (which would have information for many medications taken by participants over age 65). Our
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32 14 co-primary outcomes were the enrolment rate and the acceptability of the MERA intervention to
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34 15 patients/SDMs.

35 16 Data were analyzed descriptively for most outcomes. Demographic comparisons between the
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37 17 intervention and ~~control~~ non-MERA comparison groups were made using a t-test for continuous
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39 18 variables and chi-square test for categorical variables. Comparisons of numbers of medications
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41 19 prescribed, recommended discontinuations, and accepted discontinuations between ~~control~~ non-MERA
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43 20 comparison and interventions groups were made using a Mann-Whitney U test as the data were non-
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45 21 parametric. Comparisons involving more than 2 categorical predictor variables were made using a
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47 22 Kruskal Wallis ANOVA. Multivariable linear regression was used to measure the ~~correlation~~ association
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49 23 between demographic and baseline data and the number of medications discontinued. This study was
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51 24 approved by the Research Ethics Board at our facility (REB# 15-8840-A).

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2 *Results.*
3 Overall, we enrolled 61 of the 1215 (48.53%) eligible patients admitted during the study period (Figure
4 1). For eight patients, the MERA team made recommendations to the treating team but these could not
5 be discussed with the patient or SDM prior to the death or discharge of the patient. These patients were
6 excluded from the analysis of effect and acceptability to patients/SDMs. Participant demographics are
7 presented in Table 1.

8 Baseline patient perception and symptom data are provided in Supplementary Table 1. Taken
9 together, the BMQ scores indicate that participants generally believed that their medications were
10 necessary (but this belief was not strong), and they did not have strong concerns about harm and
11 overuse (more detailed explanation provided in *Appendix E*). The PATD questionnaire indicated that
12 participants generally felt that they were taking a large number of medications (61%) and only 29 (55%)
13 felt that their medications were necessary. There was a strong willingness to stop one or more
14 medications (91%) or take additional medications (68%) if suggested by a physician. Participants were
15 comfortable with the idea of a pharmacist stopping a medication, provided that their physician was
16 informed (75%), and there was a strong preference for a face-to-face encounter to follow-up any
17 decision to stop a medication (66%). Average patient symptom severity scores on the ESAS-r were in the
18 low to moderate range (1.3-5.2), but each patient had an average of 2.1 symptom scores greater than 6
19 (severe).

20 The median (range) duration of MERA meetings with the admitting team was 7 minutes (1-
21 12) lasted an average of 6.7 minutes, and the MERA team recommended a total of 263 medication
22 changes, affecting 51/53 (96%) enrolled patients (Figure 2). Of the 201 recommendations to stop
23 medications, the medical team accepted 176 (88%) and the patient/SDM accepted 162, for a combined
24 acceptance rate of 81%. Sixty-one of 62(98%) recommendations to change doses/frequencies or add

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9 1 medications were accepted by both the medical team and the patient/SDM, for an overall
10 2 recommendation acceptance rate of 223/263 (85%). MERA recommendations resulted in the
11 3 discontinuation of a mean (SD) of 3.1(2.6) medications, dose changes in 0.9 (1.5) medications, and the
12 4 addition of 0.2 (0.5) medications per patient (Table 2). The most common recommended
13 5 discontinuations were vitamins/minerals, lipid lowering agents, homeopathic/herbal supplements,
14 6 proton pump inhibitors, and docusate (Table 3). These five medications/classes accounted for 55% of all
15 7 recommended discontinuations. The medications added were opioids (3), mirtazapine (3), inhaled
16 8 bronchodilators (2), non-opioid analgesics (2), metoclopramide (1), rivaroxaban (1), and paroxetine (1).

17 9 Of the 162 medications that were stopped, 40 (25%) were restarted during hospitalization or at
18 10 the time of discharge (Figure 2). In a post-hoc analysis, we found that the likelihood of medications
19 11 being restarted on discharge was not affected by whether or not a pharmacist was involved in the
20 12 discharge medication reconciliation ($\chi^2=0.34$, $p=0.56$, data not shown). Of the 122 medications that
21 13 remained discontinued at the time of discharge, we were able to assess the status of 36 medications (16
22 14 patients) at 3-months post-discharge because both the patient and the medication was covered by the
23 15 Ontario Drug Benefit (ODB) program, and the patient neither died nor transferred to a PCU during the
24 16 admission or the follow-up period. The ODB records revealed that 29/36 (81%) remained discontinued.
25 17 We could not assess the status of the remaining medications either because the patient had died or
26 18 been transferred to an inpatient palliative care unit (5 patients, 23 medications), or the medication or
27 19 patient was not covered by this plan (41 medications), or the medication was for hospital use only and
28 20 would not have been expected to be used post-discharge (2 medications). Using ODB cost data and
29 21 assuming that prescriptions required one refill in the 100 days post-discharge, we found that the total
30 22 direct cost of these stopped medications was \$1508.47, or \$94.28 per 100 patient-days. Of the 13
31 23 medications added, 6 were stopped prior to discharge. There were 6 of these medications prescribed on
32 24 discharge (1 medication was taken by a patient who died during admission) and of these, 3 were taken

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1 by patients who either died or transferred to a PCU within 3 months post-discharge, therefore we could
2 not assess the status of these medications. The remaining 3 were not filled according to the ODB record.

3 The medication changes made in response to the MERA intervention were compared with
4 medication changes made on the two ~~control~~non-MERA comparison CTUs for 51 consecutive patients
5 admitted over the same study period who met our inclusion criteria (Table 1). There was no difference
6 between the two groups in the number of medication discontinuations that would have been
7 recommended by the MERA algorithm (3.7 vs. 3.8, $p=0.95$), but significantly more of these medications
8 were actually stopped in the intervention group (3.1 vs. 0.9, $p<0.001$; Table 2). Using a multivariable
9 linear regression analysis including treatment group (MERA vs. ~~control~~non-MERA comparison), age, sex,
10 inclusion criterion, and number of baseline medications, we found that both the treatment group
11 ($p<0.001$) and number of baseline medications ($p<0.001$) were ~~correlated~~associated with the number of
12 medications stopped. Within the MERA intervention group, the number of medications discontinued
13 was not influenced by the main inclusion criterion or whether or not a Palliative Care team was
14 previously involved in the patient's care (Table 2). In a multivariable linear regression analysis that
15 included each of the domains of the BMQ, the total ESAS score, the number of "severe" symptoms (>6)
16 on the ESAS, and the Clinical Frailty Score, only the BMQ-General domain was significantly ~~correlated~~
17 associated with the number of medications discontinued ($p=0.02$, data not shown).

18 We were able to administer a follow-up questionnaire to 41 patients or SDMs after the
19 recommendations were discussed with them (Supplementary Figure 1). A ~~large~~ majority reported being
20 comfortable with starting (11/14, 79%) and stopping (33/38, 87%) medications as recommended by the
21 MERA team, and only a very small number found the experience stressful (5%) or confusing (11%).
22 Thirty-seven (92%) reported being "glad" that the MERA team reviewed their medications.

23 We administered a follow-up survey to the members of the medical team who participated in
24 the MERA meetings, obtaining 16 responses (response rate of 53%). Respondents reported that

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8 1 medication rationalization was a good idea (100%), that it was easy to discuss MERA recommendations
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10 2 with patients (87%), and that “MERA meetings were a good use of my time” (94%). No respondent felt
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12 3 that it was difficult to attend the MERA meetings or that the meetings were too long, or that the MERA
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14 4 team’s involvement negatively affected their own relationship with the patient or SDM.
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17 6 *Discussion.*

19 7 In this single-centre study, we pilot-tested an innovative interprofessional medication-focused
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21 8 intervention aimed at medication rationalization (MERA), including both ~~deprescription~~deprescribing of
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23 9 harmful or nonbeneficial medications and addition of ~~symptom-focused~~comfort medications for
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25 10 inpatients with a limited life expectancy due to serious illness, advanced co-morbidities or frailty. We
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27 11 found that the MERA intervention met or exceeded all pilot objectives; it was feasible and possibly
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29 12 effective for reducing medication use and costs in both the short and long term; it was efficient and
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31 13 acceptable for the admitting team; and it was satisfactory to the patient and family. We also learned
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33 14 lessons to improve the scalability and effectiveness of MERA in a larger, multicentre study.

34 15 In our study population of elderly, frail or seriously ill inpatients, we found that virtually every
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36 16 patient was taking multiple medications that were either unnecessary or potentially harmful. Up to 40%
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38 17 of frail elderly patients are prescribed medications that are potentially inappropriate for them according
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40 18 to guidelines¹³, and up to 30% of hospital admissions for patients over age 75 are medication-related; a
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42 19 large proportion are preventable²⁹. ~~Deprescription~~Deprescribing interventions delivered on medical
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44 20 wards can be effective¹⁹, but often patients are discharged on the same, if not more medications³⁰⁻³².
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46 21 We previously found that even patients treated with a palliative intent in our institution received an
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48 22 average of 40 doses of non-comfort medications in the week prior to their death or transfer to a
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50 23 Palliative Care Unit⁴. Although we found only a modest reduction in direct medication costs in our
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52 24 population of patients nearing the end of life, other studies have shown the large potential financial
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1 costs of inappropriate prescription on a population scale^{15,16}, and medication costs are often partially
2 borne by patients themselves.

3 Our participants were comfortable stopping medications if their medical team felt it was
4 possible, and virtually all were grateful that the MERA team reviewed their medications. Previous
5 ~~deprescription~~~~deprescribing~~ interventions have sometimes had little or no effect³³, and there are
6 multiple factors that shape both prescriber³⁴ and patient³⁵ barriers to ~~deprescription~~~~deprescribing~~
7 including complexity and time limitations, an underappreciation of the scale of polypharmacy-related
8 harms, the increasing intensity of medical care in general, the fear of precipitating an acute event, and
9 the conceptual difficulty involved in balancing risks and benefits^{3,13}. Only 21% of the *Choosing Wisely*
10 campaign's current recommendations refer to stopping specific medications³⁶. Physicians may also
11 hesitate to label a medication as "low value" for a patient³⁶, especially when that medication may have
12 been prescribed by another physician and appears to be well-tolerated¹³. And even patients who dislike
13 taking medications may be upset by the implication that they are too sick or too close to death to gain
14 any benefit from them³⁵. The MERA intervention used an innovative, pharmacist-led approach that
15 appeared to be reassuring to patients, SDMs and health care professionals alike. Notably, the
16 effectiveness of the MERA approach was seen broadly, regardless of the patient's views towards their
17 medications, their symptom burden, their degree of frailty, age or diagnosis. It was also equally effective
18 in patients already seen by a Palliative Care consultant, and the comparison with non-MERA
19 ~~CTU~~~~controls~~ suggests that MERA provides a benefit not seen in "routine" interprofessional care.

20 Although our limited follow-up data suggested that the effect of MERA was durable, there were
21 a substantial number of medications restarted at discharge. These medications may have been restarted
22 deliberately, or they may have been accidentally restarted due to poor communication at the time of
23 medication reconciliation. Our Medication Reconciliation Program uses multiple sources of information,
24 but our discharge forms are electronically prepopulated and can prompt providers to restart

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9 1 ~~discontinued medications in error, as~~ sometimes the person completing a patient's discharge
10 2 ~~reconciliation may be unable to distinguish between medications stopped deliberately and those~~
11 3 ~~stopped accidentally~~ has been shown by Stockton et al³⁷. To improve effectiveness, rationalization and
12 4 reconciliation will need to be better integrated. Garfinkel and Mangin tested a similar intervention in
13 5 community-dwelling seniors (who do not experience transfers of care shortly after the intervention),
14 6 and they reported that 81% of their discontinuations remained effective after a mean follow-up of 19
15 7 months³⁸.

16 8 Strengths of this study include the collection of multiple perspectives (patient, SDM, and
17 9 medical team) and dimensions (e.g. symptom burden, function, medication changes, and views on
18 10 medications and ~~deprescription~~ ~~deprescribing~~) to study a novel, interdisciplinary intervention to address
19 11 a common problem in the seriously ill and frail elderly. Limitations include the fact that it was a single
20 12 centre, non-randomized pilot study involving a dedicated, independent team, which precludes broad
21 13 interpretation of the effectiveness of the MERA intervention. Our follow-up data was limited to
22 14 medications covered by the ODB program, without quality of life measures. The enrolment rate of 53%
23 15 is typical for studies of palliative-relevant topics³⁹, but it raises concerns about a ~~There may also be a~~
24 16 selection bias as patients or SDMs who enrolled in this study may have been particularly keen to stop
25 17 their medications, although the BMQ and PATD results suggest that this was not the case. However, our
26 18 comparison group was identified retrospectively without being enrolled and randomized; they may not
27 19 have accepted MERA recommendations as readily as our enrolled patients did. Admitting team
28 20 members who did not complete the follow-up survey may not have shared the enthusiasm for MERA
29 21 shown by those who did respond. Our cost data included only the costs of the medications that were
30 22 stopped; the cost of the MERA team itself (e.g. the time taken to prepare reports) was not captured.
31 23 Finally, an intervention of this nature involves medical, social and ethical considerations that may not be
32 24 captured by quantitative methods; our qualitative results will be presented separately.

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1 In conclusion, we found that the MERA intervention was feasible, acceptable, efficient, and
2 **possibly** effective for changing medication use among seriously ill and/or frail elderly inpatients in a
3 single-centre pilot study. Future studies will explore the possibility of automating the MERA approach to
4 improve scalability, better integrating MERA with medication reconciliation, and testing this approach in
5 other care settings.

6 *Acknowledgments.*

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15 of interest to declare.

16 Authorship contributions: RW, SP, KB and JD conceived and designed the study. RW, SP, KB, PB, EK, CK
17 and JD were involved in data collection. All authors were involved in data analysis and interpretation. JD,
18 RW, SP, KB and PW were involved in drafting the manuscript. All authors were involved in revising the
19 manuscript and approved the final version submitted.

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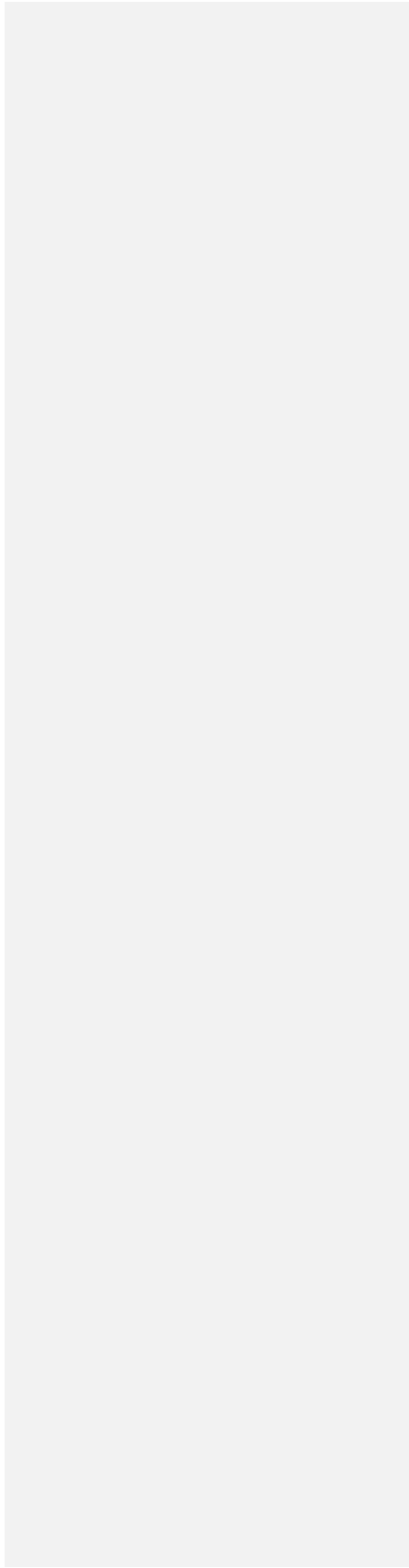
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- 1 Legends.
- 2 Figure 1. Patient enrolment CONSORT flow diagram.
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- 4 Figure 2. Flowchart of medication recommendations and changes.
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- 6 Table 1. Demographics and baseline characteristics of intervention group.
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- 8 Table 2. Differences in medication discontinuation among groups and subgroups.
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- 10 Table 3. Most common medications recommended to be stopped by the MERA Team.
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- 12 Supplementary Table 1. Patient baseline symptom and perception data
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- 14 Supplementary Figure 1. Patient perceptions of medication rationalization.
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Confidential



1 *Appendix A. Description of study setting.*

2 The General Internal Medicine service at Toronto General Hospital includes 6 Clinical Teaching Units
 3 (CTUs), which are non-geographical teams spread out over multiple wards. Four of these teams include
 4 an attending physician, undergraduate and postgraduate medical trainees, a pharmacist, and other
 5 allied health care professionals (including, social workers, occupational therapists and physiotherapists).
 6 Since the MERA intervention is delivered at the level of the team, we selected two of these four teams
 7 randomly to receive the intervention, while two were used for the control patients (to minimize the risk
 8 of contamination). Nurses care for patients across teams on the wards, but other team members
 9 typically do not, limiting the opportunity for contamination.

10 The entire service comprises 75 physical inpatient beds, although actual patient numbers may
 11 often exceed this number. Individual teams are responsible for between 15-25 patients, and admit and
 12 discharge approximately 1-4 patients per day.

13 *Appendix B. Medication Recommendations and the MERA Algorithm.*

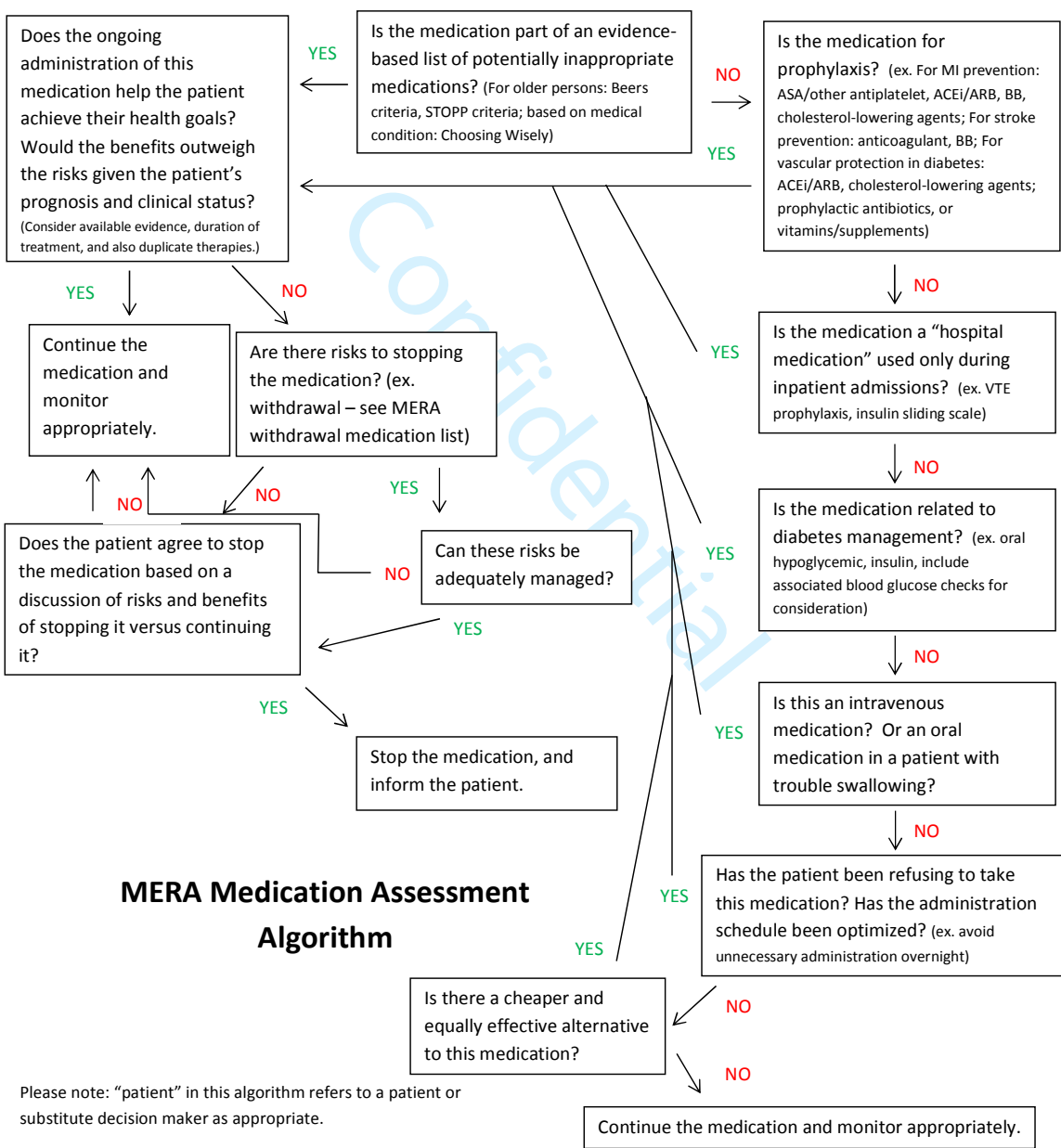
14 Three pharmacists involved in this project (RW, SP and KB) assembled a table of medication-related
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 17 column, to allow the reader to rapidly review all recommendations for any given medication. An
 18 additional column was added for “MERA guidelines”, which included recommendations based on
 19 common practice for patients with a limited life expectancy that were not covered in the other
 20 guidelines (expressed in the algorithm below; e.g. discontinuing oral hypoglycemic agents and
 21 medications taken only for prevention such as ACE inhibitor for vascular protection in diabetes or
 22 prophylactic antibiotics, optimizing medication route and schedule (changing intravenous medications
 23 to oral medications, or stopping oral medications in patients having trouble swallowing, minimizing
 24 number of administration times, adjusting timing of medications to allow uninterrupted sleep)). Where
 25 appropriate, the algorithm also included recommendations to wean some medications rather than stop
 26 them abruptly (e.g. benzodiazepines). The full document is over 47 pages long but we provide a sample:
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Medication/Class	STOPP	Beers	Choosing Wisely	Choosing Wisely Canada	MERA
Proton Pump Inhibitors	Do not use for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated)	--	Don't maintain long term Proton Pump Inhibitor (PPI) therapy for gastrointestinal symptoms without an attempt to stop/reduce PPI at least once per year in most patients.	For pharmacological treatment of patients with gastroesophageal reflux disease (GERD), long-term acid suppression therapy (proton pump inhibitors or histamine2 receptor antagonists) should be titrated to the lowest effective dose needed to achieve therapeutic goals.	--

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					OR Don't prescribe medications for stress ulcer prophylaxis to medical inpatients unless at high risk for GI complications.
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Appendix C. The Beliefs about Medications Questionnaire.

1 The Beliefs about Medications Questionnaire (BMQ) produces numerical scores for four different
 2 domains of perception about medication use. Note that higher scores indicate negative beliefs for only
 3 three out of four domains).

- 4 ○ Specific Necessity- a scale of 5-25 where high scores indicate stronger beliefs in the necessity and
 5 efficacy of medications prescribed for the patient; a previous report found that a general medical
 6 population had a mean score of ~20 in this domain³¹.
- 7 ○ Specific Concerns- a scale of 5-25 where higher scores indicate higher concern about potential
 8 adverse effects of medications prescribed for the patient.
- 9 ○ General Overuse- a scale of 3-15 where high scores indicate strong beliefs that medications are
 10 overused by doctors.
- 11 ○ General Harm- a scale of 4-20 where high scores indicate strong beliefs that medications are
 12 “harmful, “addictive” and/or “poisons”.

14 Appendix D. Explanation and justification of pilot endpoints.

15 For feasibility, we aimed to enrol 50 patients over a 6-month period, achieve an enrolment rate
 16 of >50%, and keep MERA meetings with the medicine teams less than 30 minutes in duration. For
 17 acceptability, we aimed to have >75% of the CTU team members agree that the MERA meetings were a
 18 good use of time on a post-study survey administered at the end of the team members’ rotation on the
 19 CTU (Appendix F), and a similarly high rate of satisfaction among patients and SDMs with the MERA
 20 experience. Our co-primary outcomes were the enrolment rate and the acceptability of the MERA
 21 intervention to patients/SDMs. To determine effect, we measured the number of recommendations
 22 made, and the proportion that resulted in prescription changes initially, at discharge, and 3 months
 23 following discharge using the Ontario Drug Benefit database (when available). We compared these
 24 results to medication changes made to 51 consecutive patients who met eligibility criteria on two CTUs
 25 that were not part of the MERA pilot (control group). We also calculated the direct medication costs of
 26 the medications stopped by the MERA team during the inpatient admission and follow-up periods. Cost
 27 per unit was obtained from the ODB Formulary 42nd edition, and this was used to calculate cost savings
 28 during the inpatient admission by calculating the daily medication cost from the date of the MERA
 29 meeting until the date of discharge (or of transfer or death as applicable). Of the 122 medications that
 30 remained discontinued at the time of discharge, cost data was available from the Ontario Drug Benefit
 31 (ODB) program for 50 of them, and we used this to calculate the costs saved during the hospital
 32 admission to be \$161.09, or \$0.02 per patient-day. Of the 13 medications added, 6 were stopped prior
 33 to discharge. Cost data was available from ODB for the remaining 7 medications, and we used this to
 34 calculate costs added during the hospital admission to be \$14.17 or \$0.10 per patient-day. During the
 35 follow-up period, the same unit costs were used, and an 8% markup, \$8.83 dispensing fee, and \$6.11 co-
 36 payment was added to each medication (as per ODB Formulary 42nd edition), assuming it was dispensed
 37 once during the 100 day period. Costs were only included for patients who continued to fill medications
 38 during the entire 100 day period, according to the ODB record. Patients who did not, for example
 39 because they died or went to a PCU during the follow-up period, were not included, as the date of
 40 death/date of admission could not be confirmed. Medications considered to be for hospital use only (1
 41 for VTE prophylaxis and 1 for CIWA protocol) were removed from the analysis, as they would not have
 42 been expected to continue post-discharge.

44 Appendix E. Explanation of results from Beliefs about Medications Questionnaire (BMQ).

45 The BMQ revealed a mean Specific-Necessity subscale score of 18.5, which indicates an average score of
 46 3.7 on each 5-point Likert question (where 3 indicates uncertainty and 4 indicates agreement, higher
 47 scores indicate a belief that the patient’s current medications are necessary). The other subscales
 48 (measuring concerns, overuse and harm) revealed average scores ranging from 2.6 to 3.1 on each

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1 question (where 2 indicates disagreement and 3 indicates uncertainty, and higher scores indicate
2 concerns about medications).

3 4 5 6 Appendix F. Admitting Team Member Follow-up Questionnaire.

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9 1. Approximately how often did you attend MERA meetings?

10 -Always/almost always

11 -Often (~75%)

12 -Sometimes (~50%)

13 -Rarely (~25%)

14 -Never/almost never

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17 2. On average, how long did the MERA meetings last?

18 ->60 minutes

19 -45-60 minutes

20 -30-45 minutes

21 -15-30 minutes

22 -<15 minutes

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25 3. Please rate your agreement with the following statements.

26 [Each was given a 5-point Likert scale ranging from “Strongly disagree” to “Strongly agree”

27 -I think that medication rationalization is a good idea.

28 -I found it difficult to attend the MERA meetings.

29 -I found that the MERA meetings were too long.

30 -I found it easy to discuss the recommendations that came from the MERA meeting with the patient or
31 substitute decision-maker.

32 -I found that substitute decision-makers were receptive to the recommendations of the MERA team.

33 -I think that the MERA meetings were a good use of my time.

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36 4. Overall, how did the involvement of the MERA team affect your relationship with patients involved in
37 the study?

38 -The MERA team's involvement greatly improved my relationship with the patients.

39 -The MERA team's involvement slightly improved my relationship with the patients.

40 -The MERA team's involvement did not affect my relationship with the patients.

41 -The MERA team's involvement slightly worsened my relationship with the patients.

42 -The MERA team's involvement greatly worsened my relationship with the patients.

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45 5. Overall, how did the involvement of the MERA team affect your relationship with substitute
46 decision-makers (SDMs) involved in the study?

47 -The MERA team's involvement greatly improved my relationship with the SDMs.

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54 Appendix G. The CARENET Criteria for elevated risk of death in the next 6 months.

55 We enrolled medical inpatients with:

- 56 • Age >80

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- Age 55 plus one of:
 - Chronic obstructive lung disease, with at least 2 of these 4 conditions: baseline Paco2 of at least 45 mm Hg; cor pulmonale; an episode of respiratory failure during the past year; forced expiratory volume in 1 second of 0.75 L or less
 - Congestive heart failure, with New York Heart Association class IV symptoms or a left-ventricular ejection fraction measured at 25% or less
 - Cirrhosis, confirmed by imaging studies or documentation of esophageal varices, and any of hepatic coma, Child’s class C liver disease or Child’s class B liver disease with gastrointestinal bleeding
 - Cancer, diagnosed as metastatic cancer or stage IV lymphoma

Confidential

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9 **Appendix A. Description of study setting.**

10 The General Internal Medicine service at Toronto General Hospital includes 6 Clinical Teaching Units
11 (CTUs), which are non-geographical teams spread out over multiple wards. Four of these teams include
12 an attending physician, undergraduate and postgraduate medical trainees, a pharmacist, and other
13 allied health care professionals (including, social workers, occupational therapists and physiotherapists).
14 Since the MERA intervention is delivered at the level of the team, we selected two of these four teams
15 randomly to receive the intervention, while two were used for the control patients (to minimize the risk
16 of contamination). Nurses care for patients across teams on the wards, but other team members
17 typically do not, limiting the opportunity for contamination.-

18 The entire service comprises 75 physical inpatient beds, although actual patient numbers may
19 often exceed this number. Individual teams are responsible for between 15-25 patients, and admit and
20 discharge approximately 1-4 patients per day.

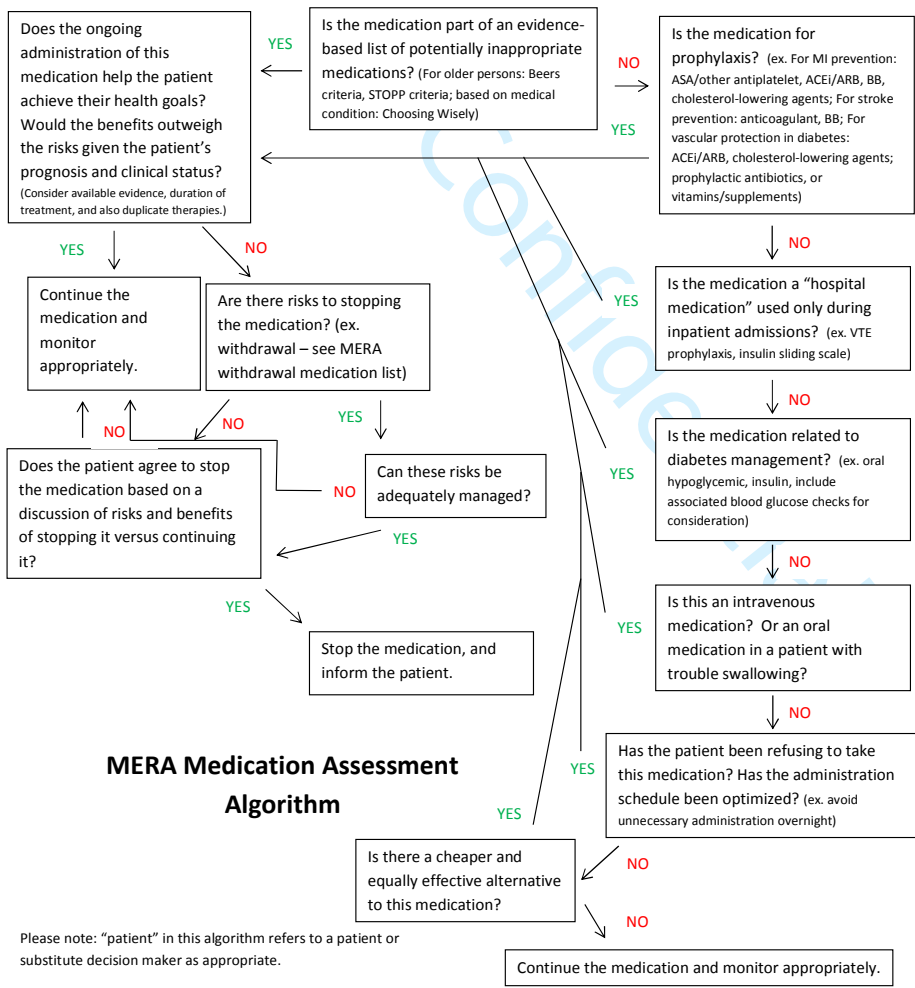
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28 guidelines (expressed in the algorithm below; e.g. discontinuing oral hypoglycemic agents and
29 medications taken only for prevention such as ACE inhibitor for vascular protection in diabetes or
30 prophylactic antibiotics, optimizing medication route and schedule (changing intravenous medications
31 to oral medications, or stopping oral medications in patients having trouble swallowing, minimizing
32 number of administration times, adjusting timing of medications to allow uninterrupted sleep)). Where
33 appropriate, the algorithm also included recommendations to wean some medications rather than stop
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Medication/Class	STOPP	Beers	Choosing Wisely	Choosing Wisely Canada	MERA
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				OR Don't prescribe medications for stress ulcer prophylaxis to medical inpatients unless at high risk for GI complications.
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Appendix C. The Beliefs about Medications Questionnaire.

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The Beliefs about Medications Questionnaire (BMQ) produces numerical scores for four different domains of perception about medication use. Note that higher scores indicate negative beliefs for only three out of four domains).

- Specific Necessity- a scale of 5-25 where high scores indicate stronger beliefs in the necessity and efficacy of medications prescribed for the patient; a previous report found that a general medical population had a mean score of ~20 in this domain³¹.
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Appendix D. Explanation and justification of pilot endpoints.

For feasibility ~~and acceptability~~, we aimed to enrol 50 patients over a 6-month period, ~~and~~ achieve an enrolment rate of >50%. ~~For time efficiency and seamlessness, we aimed to~~ keep MERA meetings with the medicine teams less than 30 minutes in duration. ~~hold them during their daily afternoon meeting times, For acceptability, we aimed to have and have~~ >75% of the CTU team members agree that the MERA meetings were a good use of time on a post-study survey administered at the end of the team members' rotation on the CTU (Appendix F), and a similarly high rate of satisfaction among patients and SDMs with the MERA experience. Our co-primary outcomes were the enrolment rate and the acceptability of the MERA intervention to patients/SDMs. To determine effect, we measured the number of recommendations made, and the proportion that resulted in prescription changes initially, at discharge, and 3 months following discharge using the Ontario Drug Benefit database (when available). We compared these results to medication changes made to 51 consecutive patients who met eligibility criteria on two CTUs that were not part of the MERA pilot (control group). We also calculated the direct medication costs of the medications stopped by the MERA team during the inpatient admission and follow-up periods. Cost per unit was obtained from the ODB Formulary 42nd edition, and this was used to calculate cost savings during the inpatient admission by calculating the daily medication cost from the date of the MERA meeting until the date of discharge (or of transfer or death as applicable). Of the 122 medications that remained discontinued at the time of discharge, cost data was available from the Ontario Drug Benefit (ODB) program for 50 of them, and we used this to calculate the costs saved during the hospital admission to be \$161.09, or \$0.02 per patient-day. Of the 13 medications added, 6 were stopped prior to discharge. Cost data was available from ODB for the remaining 7 medications, and we used this to calculate costs added during the hospital admission to be \$14.17 or \$0.10 per patient-day. During the follow-up period, the same unit costs were used, and an 8% markup, \$8.83 dispensing fee, and \$6.11 co-payment was added to each medication (as per ODB Formulary 42nd edition), assuming it was dispensed once during the 100 day period. Costs were only included for patients who continued to fill medications during the entire 100 day period, according to the ODB record. Patients who did not, for example because they died or went to a PCU during the follow-up period, were not included, as the date of death/date of admission could not be confirmed. Medications considered to be for hospital use only (1 for VTE prophylaxis and 1 for CIWA protocol) were removed from the analysis, as they would not have been expected to continue post-discharge.

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Appendix F. Admitting Team Member Follow-up Questionnaire.

1. Approximately how often did you attend MERA meetings?

- Always/almost always
- Often (~75%)
- Sometimes (~50%)
- Rarely (~25%)
- Never/almost never

2. On average, how long did the MERA meetings last?

- >60 minutes
- 45-60 minutes
- 30-45 minutes
- 15-30 minutes
- <15 minutes

3. Please rate your agreement with the following statements.

[Each was given a 5-point Likert scale ranging from "Strongly disagree" to "Strongly agree"]

- I think that medication rationalization is a good idea.
- I found it difficult to attend the MERA meetings.
- I found that the MERA meetings were too long.
- I found it easy to discuss the recommendations that came from the MERA meeting with the patient or substitute decision-maker.
- I found that substitute decision-makers were receptive to the recommendations of the MERA team.
- I think that the MERA meetings were a good use of my time.

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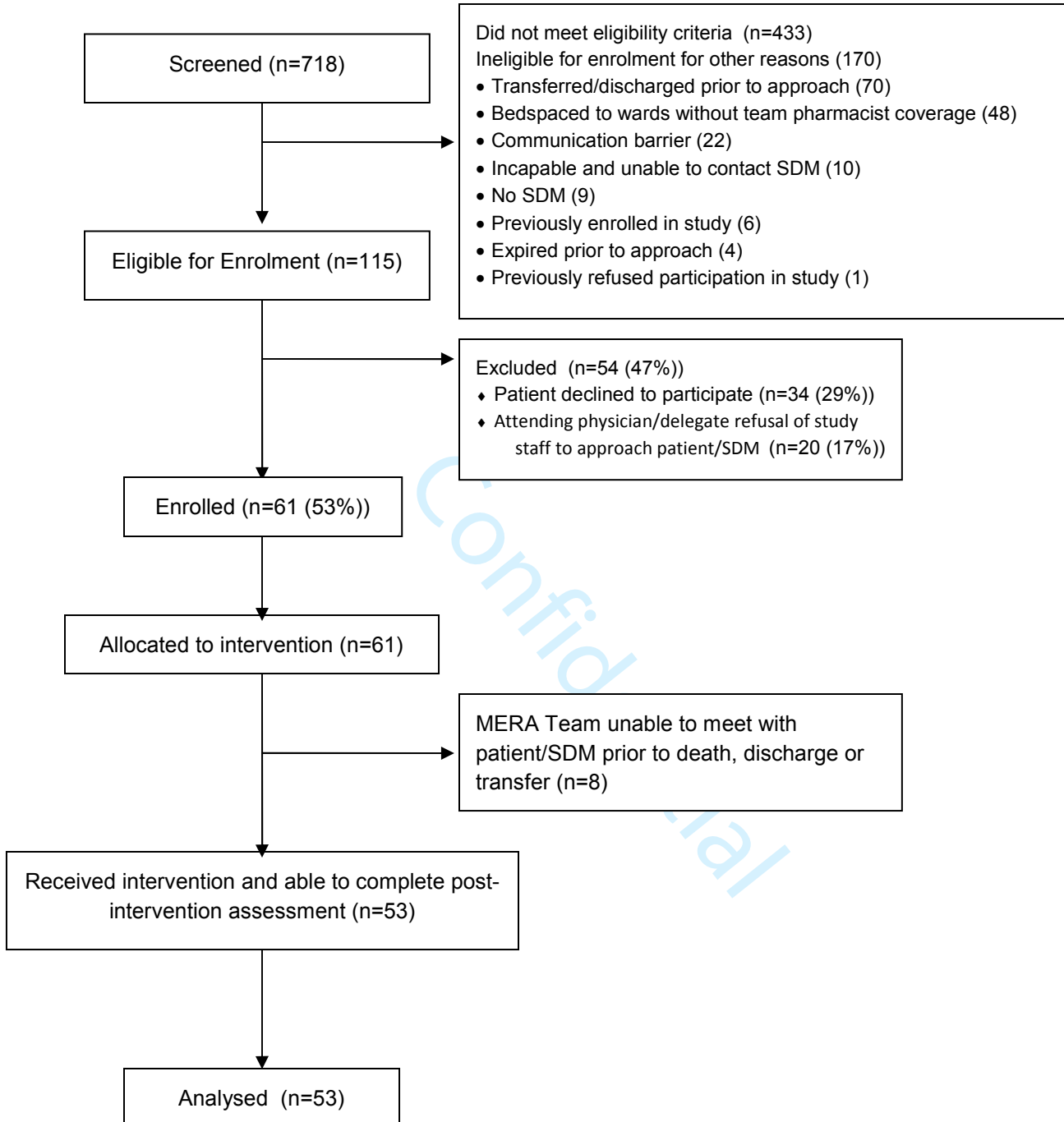


Table 1. Demographics and baseline characteristics of intervention and comparison group

<u>Demographic</u>	<u>Intervention Group (n=53)</u>	<u>Non-MERA Comparison Group (n=51)</u>	<u>P value for difference between intervention and comparison groups</u>
Mean Age (SD)	79.6 (11.7)	79.2 (13.4)	0.86*
Male gender (%)	30 (57)	19 (37)	0.048**
Mean hospital length of stay (SD)	10.6 (8.4)	7.7 (17.0)	0.27*
Admission Diagnosis, n (%)			
Cancer	10 (19)	10 (20)	
Cardiovascular (e.g. Stroke, myocardial infarction)	6 (11)	9(18)	
Respiratory (e.g. COPD exacerbation, pneumonia)	12 (23)	7(14)	
Gastrointestinal (e.g. gastrointestinal bleed, cirrhosis)	9 (17)	6 (12)	
Other (e.g. failure to cope)	16 (30)	19 (37)	
Main Criterion for Inclusion, n (%)			0.64**
Age >80	22 (42)	23 (45)	
Metastatic Cancer	20 (38)	21 (41)	
End-Stage Organ Failure	11 (21)	7 (14)	
Medications at the time of enrolment (intervention) or day #3 of admission (comparison) (SD)	13.3 (6.1)	10.9 (4.5)	0.03***
Clinical Frailty Score, n (%)			
1-3	21 (40)	N/A	
4-5	18 (35)	N/A	
6-8	13 (25)	N/A	
Followed by a Palliative Care consultant prior to MERA intervention	12 (23)	N/A	

SD- Standard Deviation; COPD- Chronic Obstructive Pulmonary Disease

*t-test

**Chi-square test

***Mann-Whitney U test

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*t-test

**Chi-square test

***Mann-Whitney U test

Table 2. Differences in medication discontinuation among groups and subgroups..

<u>Variable</u>	<u>Mean number of medication discontinuations (SD)</u>	<u>p-value for difference</u>
MERA Intervention Group	3.1 (2.6)	<0.001*
Non-MERA Comparison Group	0.9 (1.5)	
Within Intervention Group		
Main Inclusion Criterion		0.6**
Age >80	3.0 (3.1)	
Metastatic Cancer	2.8 (1.7)	
End-stage organ failure	3.6 (2.9)	
Role of PC		0.36**
Followed by PC Specialist	4.0 (2.8)	
Never followed by PC Specialist	2.8 (2.3)	
PC Consultation suggested by MERA but refused by admitting team or patient	2.8 (3.3)	

PC- Palliative Care; MERA- Medication Rationalization

*Mann-Whitney U test

**Kruskal-Wallis ANOVA

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PC Consultation suggested by MERA but refused by admitting team or patient	2.8 (3.3)	

PC- Palliative Care; MERA- MEducation RAationalization

*Mann-Whitney U test

**Kruskal-Wallis ANOVA

Table 3. Most common medications recommended to be stopped by the MERA Team.

<u>MERA Medication Class</u>	<u>Number of times MERA team recommended discontinuation (% of all recommended discontinuations), n=201</u>	<u>Number of patients in whom medication class was recommended to be stopped (% of all patients enrolled), n=53</u>
Vitamins/Minerals	55 (27%)	28 (53%)
Lipid Lowering Agents	20 (10%)	20 (38%)
Homeopathic/Herbal Supplements	14 (7%)	6 (11%)
Proton Pump Inhibitors	13 (6%)	13 (25%)
Docusate	8 (4%)	8 (15%)
Antiplatelets	7 (3%)	7 (13%)
Benzodiazepines	6 (3%)	6 (11%)
Bisphosphonates (oral)	5 (2%)	5 (9%)
Dihydropyridine calcium channel blockers	5 (2%)	5 (9%)
Opioids	5 (2%)	5 (9%)
Acetaminophen	4 (2%)	4 (8%)
Iron (oral)	4 (2%)	4 (8%)
Nonbenzodiazepine hypnotics	4 (2%)	4 (8%)
Thiazide diuretics	4 (2%)	4 (8%)

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