A pilot study of a MEdication RAtionalization (MERA) Intervention.

Journal:	*CMAJ Open*
Manuscript ID	CMAJOpen-2017-0134.R1
Manuscript Type:	Other
Date Submitted by the Author:	17-Jan-2018
Complete List of Authors:	Whitty, Rachel; University Health Network, Pharmacy Porter, Sandra; University Health Network, Pharmacy Battu, Kiran; University Health Network, Pharmacy Bhatt, Pranjal; University Health Network, Pharmacy Koo, Ellen; University Health Network, Medicine Kalocsai, Csilla; Centre for Addiction and Mental Health Wu, Peter; Department of Medicine, University of Toronto Delicaet, Kendra; University Health Network, Centre for Innovation in Complex Care Bogoch, Isaac; University Health Network, Infectious Diseases and Internal Medicine Wu, Robert; University Health Network, Department of Medicine Downar, James; University of Toronto, Medicine
Keywords:	Drugs and therapeutics, Geriatric medicine, Internal medicine, Palliative medicine, Pharmacology and toxicology
More Detailed Keywords:	Deprescriptions; Potentially Inappropriate Medication List; Palliative Care; Patient Comfort; Quality Improvement; Pilot Study
Abstract:	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. 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. 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

	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. 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.

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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4	
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)	

Continued on next page

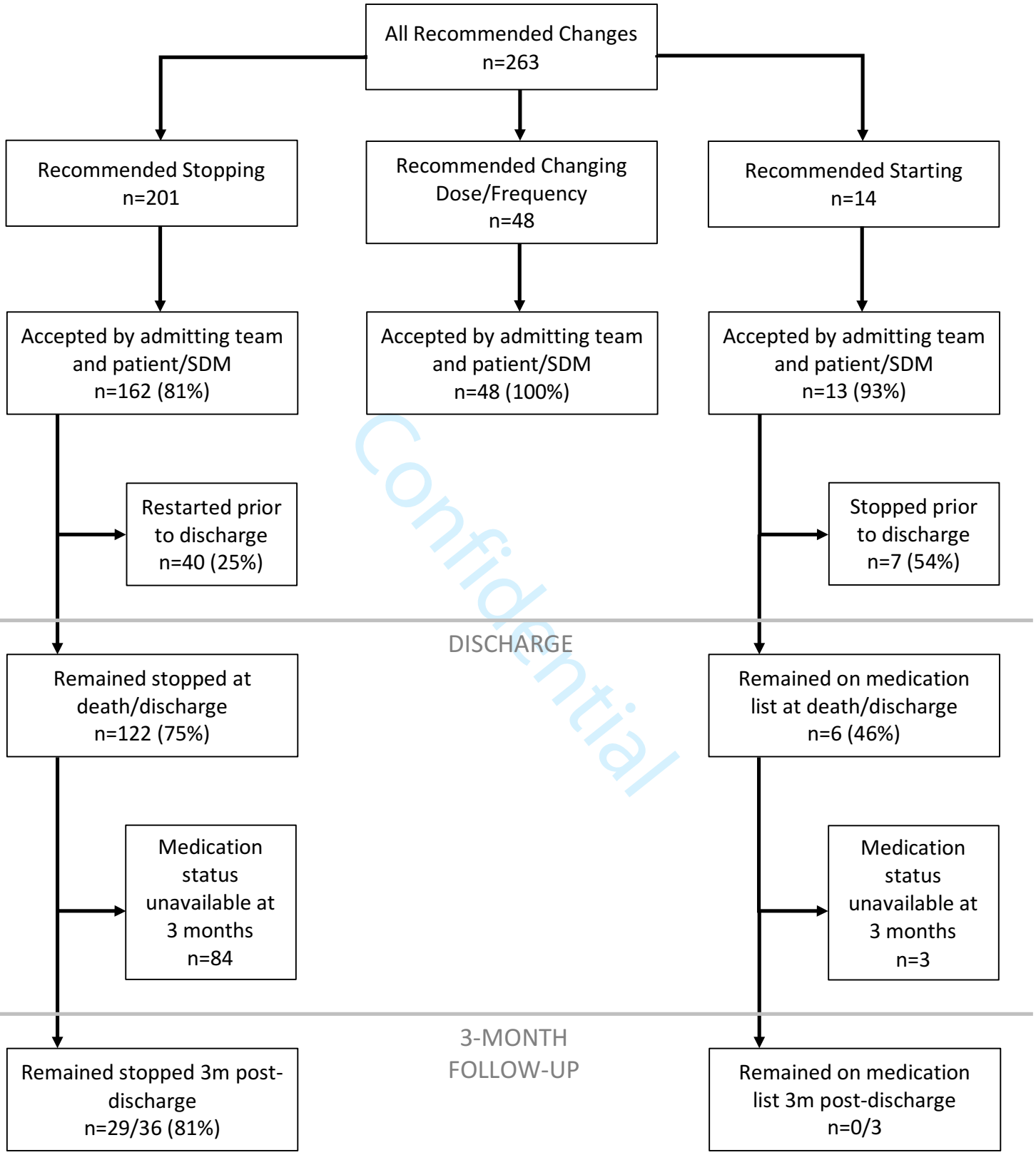
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	--
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Page 7-8, Fig 2
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*Page 7-8,* *Fig 2*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	--
		Cross-sectional study—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	--

Continued on next page

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.



Title.
A pilot study of a MEdication RAtionalization (MERA) Intervention.

Running Title.
MEdication RAtionalization (MERA).

Authors.
1. Rachel Whitty, BScPhm, RPh
2. Sandra Porter, BScPhm, RPh
3. Kiran Battu, BScPhm, RPh
4. Pranjal Bhatt, Pharm D.
5. Ellen Koo, MSc.
6. Csilla Kalocsai, PhD
7. Peter Wu, MD, MSc
8. Kendra Delicaet, MA
9. Isaac I.Bogoch, MD, MS
10. Robert Wu, MD, MSc
11. James Downar, MD, MHSc (bioethics)**

** Corresponding Author.
200 Elizabeth St. 11PMB-195, Toronto, ON, M5G 2C4
james.downar@utoronto.ca f. 416-340-3170

Abstract Word Count: 248
Word Count: 2795

Key Points:

- An interprofessional, pharmacist-led team was effective for rationalizing the medications prescribed to seriously ill and elderly medical inpatients.
- 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.
- Scalability and effectiveness of the MERA approach may be improved through automation and integration with medication reconciliation programs.

Abstract.

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.

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.

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 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.

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.

Key Words.

Deprescriptions; Potentially Inappropriate Medication List; Palliative Care; Patient Comfort; Quality Improvem3ent; Pilot Study

Introduction.

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

An effort to rationalize medications in the seriously ill and frail elderly, by deprescribing inappropriate medications and prescribing appropriate comfort medications, may simultaneously improve care while reducing costs[15,16]. Deprescribing has been studied extensively in the general medical population[17-19], but there is little published research on this approach in patients nearing the end of life[20]. Other medication-focused quality improvement initiatives have been broadly implemented, such as Antibiotic Stewardship[21] and Medication Reconciliation[22], although they may not always improve patient care[23,24]. In this study, we sought to develop and pilot a MEdication RAtionalization (MERA) team that would systematically rationalize medications for seriously ill and frail elderly patients admitted to a medical ward.

Methods.

Design.

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

Participants.

1. Patients. Inclusion Criteria: We enrolled seriously ill or frail elderly patients admitted to the General Internal Medicine ward, at elevated risk of 6-month mortality or Intensive Care Unit admission according to published criteria[25] (Appendix G), or followed by the PC service. Exclusion Criteria included refusal of consent to participate, or refusal by attending physician or delegate to enrol that particular patient. If the patient was not capable of providing consent, we approached their SDM to offer enrolment.
2. Healthcare Team Members. Inclusion Criteria for the follow-up survey and qualitative components: We offered enrolment to any consenting physician, medical trainee, or pharmacist members of General Internal Medicine Clinical Teaching Units (CTU). Physician or pharmacist members of the MERA team were also offered participation in the qualitative component of the study. Exclusion Criteria included refusal of consent to participate.

Setting/Duration.

The intervention was delivered on two of six General Internal Medicine CTUs at Toronto General Hospital between August and December 2015, and we screened the medical record of every patient admitted to those CTUs over that period to look for eligible patients. Screening took place during weekdays for any patient admitted in the previous 72 hours. We also collected medication data

retrospectively on a comparison group consisting of consecutive eligible patients admitted concurrently to two other CTUs where the MERA intervention was not delivered. A description of the units is provided in *Appendix A*.

Intervention.

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

A summary of the medication recommendations was then discussed with the patient or SDM by a member of the MERA team. Medication changes were only made with the consent of the patient or SDM. A written summary report of all medication changes made including rationale was provided to the patient or SDM. Note that all patients admitted to our facility undergo both admission and discharge medication reconciliation; the discharge reconciliation does not always involve a pharmacist.

Endpoints and Analysis

Our baseline data included demographic data and other pertinent information; the Patient Attitudes Towards Deprescribing (PATD) questionnaire, a validated 15-item exploratory measure of acceptance of deprescribing[26]; the Beliefs about Medicines Questionnaire (BMQ), a validated 17-item questionnaire assessing beliefs about the necessity, toxicity and overuse of medications[27] (*Appendix C*); and the Edmonton Symptom Assessment System-revised[28] (ESAS). We collected pilot endpoints to evaluate the feasibility, acceptability, time efficiency, and effect of MERA (justification in *Appendix D*), and we analyzed medication use 3 months post-discharge using the Ontario Drug Benefit (ODB) program database (which would have information for many medications taken by participants over age 65). Our co-primary outcomes were the enrolment rate and the acceptability of the MERA intervention to patients/SDMs.

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

Results.

Overall, we enrolled 61 of the 115 (53%) eligible patients admitted during the study period (Figure 1). For eight patients, the MERA team made recommendations to the treating team but these could not be

discussed with the patient or SDM prior to the death or discharge of the patient. These patients were excluded from the analysis of effect and acceptability to patients/SDMs. Participant demographics are presented in Table 1.

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

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

homeopathic/herbal supplements, proton pump inhibitors, and docusate (Table 3). These five medications/classes accounted for 55% of all recommended discontinuations. The medications added were opioids (3), mirtazapine (3), inhaled bronchodilators (2), non-opioid analgesics (2), metoclopramide (1), rivaroxaban (1), and paroxetine (1).

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

The medication changes made in response to the MERA intervention were compared with medication changes made on the two non-MERA comparison CTUs for 51 consecutive patients admitted

over the same study period who met our inclusion criteria (Table 1). There was no difference between the two groups in the number of medication discontinuations that would have been recommended by the MERA algorithm (3.7 vs. 3.8, p=0.95), but significantly more of these medications were actually stopped in the intervention group (3.1 vs. 0.9, p<0.001; Table 2). Using a multivariable linear regression analysis including treatment group (MERA vs. non-MERA comparison), age, sex, inclusion criterion, and number of baseline medications, we found that both the treatment group (p<0.001) and number of baseline medications (p<0.001) were associated with the number of medications stopped. Within the MERA intervention group, the number of medications discontinued was not influenced by the main inclusion criterion or whether or not a Palliative Care team was previously involved in the patient's care (Table 2). In a multivariable linear regression analysis that included each of the domains of the BMQ, the total ESAS score, the number of "severe" symptoms (>6) on the ESAS, and the Clinical Frailty Score, only the BMQ-General domain was significantly associated with the number of medications discontinued (p=0.02, data not shown).

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

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

Discussion.

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

In our study population of elderly, frail or seriously ill inpatients, we found that virtually every patient was taking multiple medications that were either unnecessary or potentially harmful. Up to 40% of frail elderly patients are prescribed medications that are potentially inappropriate for them according to guidelines[13], and up to 30% of hospital admissions for patients over age 75 are medication-related; a large proportion are preventable[29]. Deprescribing interventions delivered on medical wards can be effective[19], but often patients are discharged on the same, if not more medications[30-32]. We previously found that even patients treated with a palliative intent in our institution received an average of 40 doses of non-comfort medications in the week prior to their death or transfer to a Palliative Care Unit[4]. Although we found only a modest reduction in direct medication costs in our population of patients nearing the end of life, other studies have shown the large potential financial costs of inappropriate prescription on a population scale[15,16], and medication costs are often partially borne by patients themselves.

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

deprescribing interventions have sometimes had little or no effect[33], and there are multiple factors that shape both prescriber[34] and patient[35] barriers to deprescribing including complexity and time limitations, an underappreciation of the scale of polypharmacy-related harms, the increasing intensity of medical care in general, the fear of precipitating an acute event, and the conceptual difficulty involved in balancing risks and benefits[3,13]. Only 21% of the *Choosing Wisely* campaign's current recommendations refer to stopping specific medications[36]. Physicians may also hesitate to label a medication as "low value" for a patient[36], especially when that medication may have been prescribed by another physician and appears to be well-tolerated[13]. And even patients who dislike taking medications may be upset by the implication that they are too sick or too close to death to gain any benefit from them[35]. The MERA intervention used an innovative, pharmacist-led approach that appeared to be reassuring to patients, SDMs and health care professionals alike. Notably, the effectiveness of the MERA approach was seen broadly, regardless of the patient's views towards their medications, their symptom burden, their degree of frailty, age or diagnosis. It was also equally effective in patients already seen by a Palliative Care consultant, and the comparison with non-MERA CTUs suggests that MERA provides a benefit not seen in "routine" interprofessional care.

Although our limited follow-up data suggested that the effect of MERA was durable, there were a substantial number of medications restarted at discharge. These medications may have been restarted deliberately, or they may have been accidentally restarted due to poor communication at the time of medication reconciliation. Our Medication Reconciliation Program uses multiple sources of information, but our discharge forms are electronically prepopulated and can prompt providers to restart discontinued medications in error, as has been shown by Stockton et al[37]. To improve effectiveness, rationalization and reconciliation will need to be better integrated. Garfinkel and Mangin tested a similar intervention in community-dwelling seniors (who do not experience transfers of care shortly

after the intervention), and they reported that 81% of their discontinuations remained effective after a mean follow-up of 19 months[38].

Strengths of this study include the collection of multiple perspectives (patient, SDM, and medical team) and dimensions (e.g. symptom burden, function, medication changes, and views on medications and deprescribing) to study a novel, interdisciplinary intervention to address a common problem in the seriously ill and frail elderly. Limitations include the fact that it was a single centre, non-randomized pilot study involving a dedicated, independent team, which precludes broad interpretation of the effectiveness of the MERA intervention. Our follow-up data was limited to medications covered by the ODB program, without quality of life measures. The enrolment rate of 53% is typical for studies of palliative-relevant topics[39], but it raises concerns about a selection bias as patients or SDMs who enrolled in this study may have been particularly keen to stop their medications, although the BMQ and PATD results suggest that this was not the case. However, our comparison group was identified retrospectively without being enrolled and randomized; they may not have accepted MERA recommendations as readily as our enrolled patients did. Admitting team members who did not complete the follow-up survey may not have shared the enthusiasm for MERA shown by those who did respond. Our cost data included only the costs of the medications that were stopped; the cost of the MERA team itself (e.g. the time taken to prepare reports) was not captured. Finally, an intervention of this nature involves medical, social and ethical considerations that may not be captured by quantitative methods; our qualitative results will be presented separately.

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

Acknowledgments.

This study was funded by a Catalyst Grant (CAT 2014-29) from the Canadian Frailty Network (a National Centre of Excellence), with additional funding from the Toronto General/Toronto Western Hospital Foundation. We would like to thank the University Health Network Pharmacy Department for contributing in-kind support to ensure the success of this project. None of the funders or in-kind contributors had any role in the design or interpretation of the study, or in the preparation of the manuscript.

Disclosures: JD has received speaker fees and Honoraria from Boehringer-Ingelheim (Canada), Medtronic Inc., and Novartis for reasons unrelated to this study. None of the authors have any conflicts of interest to declare.

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

References.

1. Kuijpers MA, van Marum RJ, Egberts AC, Jansen PA, Group OS. Relationship between polypharmacy and underprescribing. *Br J Clin Pharmacol.* 2008;65(1):130-133.
2. Linton A, Garber M, Fagan NK, Peterson MR. Examination of multiple medication use among TRICARE beneficiaries aged 65 years and older. *J Manag Care Pharm.* 2007;13(2):155-162.
3. Farrell B, Shamji S, Monahan A, Merkley VF. Clinical vignettes to help you deprescribe medications in elderly patients: Introduction to the polypharmacy case series. *Canadian family physician Medecin de famille canadien.* 2013;59(12):1257-1258, 1263-1254.
4. Ma G, Downar J. Noncomfort Medication Use in Acute Care Inpatients Comanaged by Palliative Care Specialists Near the End of Life: A Cohort Study. *The American journal of hospice & palliative care.* 2013.

5. Downar J, Rodin D, Barua R, et al. Rapid response teams, do not resuscitate orders, and potential opportunities to improve end-of-life care: a multicentre retrospective study. *J Crit Care.* 2013;28(4):498-503.
6. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2012;60(4):616-631.
7. O'Connor MN, Gallagher P, O'Mahony D. Inappropriate Prescribing Criteria, Detection and Prevention. *Drugs Aging.* 2012;29(6):437-452.
8. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther.* 2008;46(2):72-83.
9. Currow DC, Stevenson JP, Abernethy AP, Plummer J, Shelby-James TM. Prescribing in palliative care as death approaches. *J Am Geriatr Soc.* 2007;55(4):590-595.
10. Riechelmann RP, Krzyzanowska MK, Zimmermann C. Futile medication use in terminally ill cancer patients. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* 2009;17(6):745-748.
11. Fede A, Miranda M, Antonangelo D, et al. Use of unnecessary medications by patients with advanced cancer: cross-sectional survey. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* 2011;19(9):1313-1318.
12. Néron A. Table 31.1 – Classification of drugs according to medical necessity at end of life. . In: Care HPSIGiP, ed. *Care Beyond Cure: Management of Pain and Other Symptoms, 4th Edition*. 4th ed: Association des pharmaciens des etablissements de sante du Quebec,
Sandoz; 2009.
13. Scott IA, Anderson K, Freeman CR, Stowasser DA. First do no harm: a real need to deprescribe in older patients. *The Medical journal of Australia.* 2014;201(7):390-392.
14. Berterame S, Erthal J, Thomas J, et al. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. *Lancet.* 2016;387(10028):1644-1656.
15. Pellegrin KL, Krenk L, Oakes SJ, et al. Reductions in Medication-Related Hospitalizations in Older Adults with Medication Management by Hospital and Community Pharmacists: A Quasi-Experimental Study. *J Am Geriatr Soc.* 2017;65(1):212-219.
16. Gillespie U, Alassaad A, Henrohn D, et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. *Arch Intern Med.* 2009;169(9):894-900.
17. Kaboli PJ, Hoth AB, McClimon BJ, Schnipper JL. Clinical pharmacists and inpatient medical care: a systematic review. *Arch Intern Med.* 2006;166(9):955-964.
18. Potter K, Flicker L, Page A, Etherton-Beer C. Deprescribing in Frail Older People: A Randomised Controlled Trial. *PLoS One.* 2016;11(3):e0149984.
19. McKean M, Pillans P, Scott IA. A medication review and deprescribing method for hospitalised older patients receiving multiple medications. *Intern Med J.* 2016;46(1):35-42.
20. Tjia J, Velten SJ, Parsons C, Valluri S, Briesacher BA. Studies to reduce unnecessary medication use in frail older adults: a systematic review. *Drugs Aging.* 2013;30(5):285-307.

21. Dellit TH, Owens RC, McGowan JE, Jr., et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2007;44(2):159-177.
22. Medication Reconciliation. http://www.saferhealthcarenow.ca/EN/Interventions/medrec/Pages/default.aspx. Accessed October 20th, 2014, 2014.
23. Mueller SK, Sponsler KC, Kripalani S, Schnipper JL. Hospital-based medication reconciliation practices: a systematic review. *Arch Intern Med.* 2012;172(14):1057-1069.
24. Kwan JL, Lo L, Sampson M, Shojania KG. Medication reconciliation during transitions of care as a patient safety strategy: a systematic review. *Ann Intern Med.* 2013;158(5 Pt 2):397-403.
25. Heyland DK, Dodek P, Rocker G, et al. What matters most in end-of-life care: perceptions of seriously ill patients and their family members. *CMAJ.* 2006;174(5):627-633.
26. Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD. Development and validation of the patients' attitudes towards deprescribing (PATD) questionnaire. *Int J Clin Pharm.* 2013;35(1):51-56.
27. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. *Psychol Health.* 1999;14:24.
28. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *Journal of Palliative Care.* 1991;7(2):6-9.
29. Runciman WB, Roughead EE, Semple SJ, Adams RJ. Adverse drug events and medication errors in Australia. *Int J Qual Health Care.* 2003;15 Suppl 1:i49-59.
30. Hubbard RE, Peel NM, Scott IA, et al. Polypharmacy among inpatients aged 70 years or older in Australia. *Med J Aust.* 2015;202(7):373-377.
31. Betteridge TM, Frampton CM, Jardine DL. Polypharmacy--we make it worse! A cross-sectional study from an acute admissions unit. *Intern Med J.* 2012;42(2):208-211.
32. Poudel A, Peel NM, Nissen L, Mitchell C, Gray LC, Hubbard RE. Potentially inappropriate prescribing in older patients discharged from acute care hospitals to residential aged care facilities. *Ann Pharmacother.* 2014;48(11):1425-1433.
33. Williams ME, Pulliam CC, Hunter R, et al. The short-term effect of interdisciplinary medication review on function and cost in ambulatory elderly people. *J Am Geriatr Soc.* 2004;52(1):93-98.
34. Anderson K, Stowasser D, Freeman C, Scott I. Prescriber barriers and enablers to minimising potentially inappropriate medications in adults: a systematic review and thematic synthesis. *BMJ Open.* 2014;4(12):e006544.
35. Reeve E, To J, Hendrix I, Shakib S, Roberts MS, Wiese MD. Patient barriers to and enablers of deprescribing: a systematic review. *Drugs Aging.* 2013;30(10):793-807.
36. Morden NE, Colla CH, Sequist TD, Rosenthal MB. Choosing Wisely - The Politics and Economics of Labeling Low-Value Services. *N Engl J Med.* 2014;370(7):589-592.

37. Stockton KR, Wickham ME, Lai S, et al. Incidence of clinically relevant medication errors in the era of electronically prepopulated medication reconciliation forms: a retrospective chart review. *CMAJ Open.* 2017;5(2):E345-E353.
38. Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. *Arch Intern Med.* 2010;170(18):1648-1654.
39. Heyland DK, Barwich D, Pichora D, et al. Failure to Engage Hospitalized Elderly Patients and Their Families in Advance Care Planning. *JAMA Intern Med.* 2013:1-10.

Legends.

Figure 1. Patient enrolment CONSORT flow diagram.

Figure 2. Flowchart of medication recommendations and changes.

Table 1. Demographics and baseline characteristics of intervention group.

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

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

Supplementary Table 1. Patient baseline symptom and perception data

Supplementary Figure 1. Patient perceptions of medication rationalization.

Title.
A pilot study of a MEdication RAtionalization (MERA) Intervention.

Running Title.
MEdication RAtionalization (MERA).

Authors.
1. Rachel Whitty, BScPhm, RPh
2. Sandra Porter, BScPhm, RPh
3. Kiran Battu, BScPhm, RPh
4. Pranjal Bhatt, Pharm D.
5. Ellen Koo, MSc.
6. Csilla Kalocsai, PhD
7. Peter Wu, MD, MSc
8. Kendra Delicaet, MA
9. Isaac I.Bogoch, MD, MS
10. Robert Wu, MD, MSc
11. James Downar, MD, MHSc (bioethics)**

** Corresponding Author.
200 Elizabeth St. 11PMB-195, Toronto, ON, M5G 2C4
james.downar@utoronto.ca f. 416-340-3170

Abstract Word Count: 248
Word Count: 2795

Key Points:

- An interprofessional, pharmacist-led team was effective for rationalizing the medications prescribed to seriously ill and elderly medical inpatients.
- 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.
- Scalability and effectiveness of the MERA approach may be improved through automation and integration with medication reconciliation programs.

Abstract.

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.

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.

Results: We enrolled 61 of 112~~2~~5 (5348~~8~~%) 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 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 ~~control~~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.

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.

Key Words.

Deprescriptions; Potentially Inappropriate Medication List; Palliative Care; Patient Comfort; Quality Improvem3ent; Pilot Study

Introduction.

Polypharmacy (the concomitant use of 5 or more medications) is present in more than half of the seriously ill and frail elderly[1,2] and is associated with medication errors, drug interactions, adverse drug reactions and nonadherence[3]. Even as patients approach death, they are often prescribed a substantial number of non-comfort medications that are likely inappropriate and burdensome to patients and healthcare providers alike[4]. At the same time, many dying patients are not given comfort medications (e.g. opioids)[5], suggesting that the problem is not simply overtreatment but a mismatch between care and values.

In order to promote ~~"~~deprescribing~~ption"~~, different organizations have published lists and criteria for medications that are potentially inappropriate in older adults[6-8]. Palliative Care (PC) practitioners have also developed lists of medications with questionable benefit in patients with end-stage or terminal illnesses[4,9-12]; for example, preventive medications with only long-term benefits. Yet there are many barriers to ~~deprescription~~deprescribing[3,13] and to providing comfort-oriented medications (e.g. opioids)[14], even if these would appear to be rational choices for a patient nearing the end of life.

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

Formatted: Indent: First line: 0"

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

Methods.

Design.

We conducted a ~~P~~pilot study using a mixed-methods triangulation design (convergence model) in two populations (Patients/Substitute Decision-Makers (SDM) and Healthcare Providers). We are presenting the quantitative results in this report.

Participants.

1. Patients. Inclusion Criteria: We enrolled ~~S~~seriously ill or frail elderly patients admitted to the General Internal Medicine ward, at elevated risk of 6-month mortality or ~~ICU~~ Intensive Care Unit admission according to published criteria[25] (Appendix G), or followed by the PC service. Exclusion Criteria included ~~: R~~refusal of consent to participate, or refusal by attending physician or delegate to enrol that particular patient. If the patient was not capable of providing consent, we approached their SDM to offer enrolment.
2. Healthcare Team Members. Inclusion Criteria for the follow-up survey and qualitative components: We offered enrolment to any ~~Any~~ consenting physician, medical trainee, or pharmacist members of General Internal Medicine Clinical Teaching Units (CTU). ~~); or any p~~Physician or pharmacist members of the MERA team were also offered participation in the qualitative component of the study. Exclusion Criteria included r~~: R~~efusal of consent to participate.

Setting/Duration.

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

Intervention.

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

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

Formatted: Indent: First line: 0.5"

SDM. A written summary report of all medication changes made including rationale was provided to the patient or SDM. Note that all patients admitted to our facility undergo both admission and discharge medication reconciliation; the discharge reconciliation does not always involve a pharmacist.

Endpoints and Analysis

Our baseline data included demographic data and other pertinent information; the Patient Attitudes Towards Deprescribing (PATD) questionnaire, a validated 15-item exploratory measure of acceptance of ~~deprescription~~deprescribing[26]; the Beliefs about Medicines Questionnaire (BMQ), a validated 17-item questionnaire assessing beliefs about the necessity, toxicity and overuse of medications[27] (*Appendix C*); and the Edmonton Symptom Assessment System-revised[28] (ESAS). We collected pilot endpoints to evaluate the feasibility, acceptability, time efficiency, and effect of MERA (justification in *Appendix D*), and we analyzed medication use 3 months post-discharge using the Ontario Drug Benefit (ODB) program database (which would have information for many medications taken by participants over age 65). Our co-primary outcomes were the enrolment rate and the acceptability of the MERA intervention to patients/SDMs.

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

Results.

Overall, we enrolled 61 of the 1~~2~~15 (~~48~~53%) eligible patients admitted during the study period (Figure 1). For eight patients, the MERA team made recommendations to the treating team but these could not be discussed with the patient or SDM prior to the death or discharge of the patient. These patients were excluded from the analysis of effect and acceptability to patients/SDMs. Participant demographics are presented in Table 1.

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

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

Comment [JD1]: Need range

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

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

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

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

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

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

medication rationalization was a good idea (100%), that it was easy to discuss MERA recommendations with patients (87%), and that "MERA meetings were a good use of my time" (94%). No respondent felt that it was difficult to attend the MERA meetings or that the meetings were too long, or that the MERA team's involvement negatively affected their own relationship with the patient or SDM.

Discussion.

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

In our study population of elderly, frail or seriously ill inpatients, we found that virtually every patient was taking multiple medications that were either unnecessary or potentially harmful. Up to 40% of frail elderly patients are prescribed medications that are potentially inappropriate for them according to guidelines[13], and up to 30% of hospital admissions for patients over age 75 are medication-related; a large proportion are preventable[29]. ~~Deprescription~~Deprescribing interventions delivered on medical wards can be effective[19], but often patients are discharged on the same, if not more medications[30-32]. We previously found that even patients treated with a palliative intent in our institution received an average of 40 doses of non-comfort medications in the week prior to their death or transfer to a Palliative Care Unit[4]. Although we found only a modest reduction in direct medication costs in our population of patients nearing the end of life, other studies have shown the large potential financial

costs of inappropriate prescription on a population scale[15,16], and medication costs are often partially borne by patients themselves.

Our participants were comfortable stopping medications if their medical team felt it was possible, and virtually all were grateful that the MERA team reviewed their medications. Previous ~~deprescription~~deprescribing interventions have sometimes had little or no effect[33], and there are multiple factors that shape both prescriber[34] and patient[35] barriers to ~~deprescription~~deprescribing including complexity and time limitations, an underappreciation of the scale of polypharmacy-related harms, the increasing intensity of medical care in general, the fear of precipitating an acute event, and the conceptual difficulty involved in balancing risks and benefits[3,13]. Only 21% of the *Choosing Wisely* campaign's current recommendations refer to stopping specific medications[36]. Physicians may also hesitate to label a medication as "low value" for a patient[36], especially when that medication may have been prescribed by another physician and appears to be well-tolerated[13]. And even patients who dislike taking medications may be upset by the implication that they are too sick or too close to death to gain any benefit from them[35]. The MERA intervention used an innovative, pharmacist-led approach that appeared to be reassuring to patients, SDMs and health care professionals alike. Notably, the effectiveness of the MERA approach was seen broadly, regardless of the patient's views towards their medications, their symptom burden, their degree of frailty, age or diagnosis. It was also equally effective in patients already seen by a Palliative Care consultant, and the comparison with non-MERA CTUs~~controls~~ suggests that MERA provides a benefit not seen in "routine" interprofessional care.

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

discontinued medications in error, as~~sometimes the person completing a patient's discharge reconciliation may be unable to distinguish between medications stopped deliberately and those stopped accidentally~~ has been shown by Stockton et al[37]. To improve effectiveness, rationalization and reconciliation will need to be better integrated. Garfinkel and Mangin tested a similar intervention in community-dwelling seniors (who do not experience transfers of care shortly after the intervention), and they reported that 81% of their discontinuations remained effective after a mean follow-up of 19 months[38].

Strengths of this study include the collection of multiple perspectives (patient, SDM, and medical team) and dimensions (e.g. symptom burden, function, medication changes, and views on medications and ~~deprescription~~deprescribing) to study a novel, interdisciplinary intervention to address a common problem in the seriously ill and frail elderly. Limitations include the fact that it was a single centre, non-randomized pilot study involving a dedicated, independent team, which precludes broad interpretation of the effectiveness of the MERA intervention. Our follow-up data was limited to medications covered by the ODB program, without quality of life measures. The enrolment rate of 53% is typical for studies of palliative-relevant topics[39], but it raises concerns about a ~~There may also be a~~ selection bias as patients or SDMs who enrolled in this study may have been particularly keen to stop their medications, although the BMQ and PATD results suggest that this was not the case. However, our comparison group was identified retrospectively without being enrolled and randomized; they may not have accepted MERA recommendations as readily as our enrolled patients did. Admitting team members who did not complete the follow-up survey may not have shared the enthusiasm for MERA shown by those who did respond. Our cost data included only the costs of the medications that were stopped; the cost of the MERA team itself (e.g. the time taken to prepare reports) was not captured. Finally, an intervention of this nature involves medical, social and ethical considerations that may not be captured by quantitative methods; our qualitative results will be presented separately.

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

Acknowledgments.

This study was funded by a Catalyst Grant (CAT 2014-29) from the Canadian Frailty Network (a National Centre of Excellence), with additional funding from the Toronto General/Toronto Western Hospital Foundation. We would like to thank the University Health Network Pharmacy Department for contributing in-kind support to ensure the success of this project. None of the funders or in-kind contributors had any role in the design or interpretation of the study, or in the preparation of the manuscript.

Disclosures: JD has received speaker fees and Honoraria from Boehringer-Ingelheim (Canada), Medtronic Inc., and Novartis for reasons unrelated to this study. None of the authors have any conflicts of interest to declare.

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

References.

1. Kuijpers MA, van Marum RJ, Egberts AC, Jansen PA, Group OS. Relationship between polypharmacy and underprescribing. *Br J Clin Pharmacol.* 2008;65(1):130-133.

2. Linton A, Garber M, Fagan NK, Peterson MR. Examination of multiple medication use among TRICARE beneficiaries aged 65 years and older. *J Manag Care Pharm.* 2007;13(2):155-162.
3. Farrell B, Shamji S, Monahan A, Merkley VF. Clinical vignettes to help you deprescribe medications in elderly patients: Introduction to the polypharmacy case series. *Canadian family physician Medecin de famille canadien.* 2013;59(12):1257-1258, 1263-1254.
4. Ma G, Downar J. Noncomfort Medication Use in Acute Care Inpatients Comanaged by Palliative Care Specialists Near the End of Life: A Cohort Study. *The American journal of hospice & palliative care.* 2013.
5. Downar J, Rodin D, Barua R, et al. Rapid response teams, do not resuscitate orders, and potential opportunities to improve end-of-life care: a multicentre retrospective study. *J Crit Care.* 2013;28(4):498-503.
6. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2012;60(4):616-631.
7. O'Connor MN, Gallagher P, O'Mahony D. Inappropriate Prescribing Criteria, Detection and Prevention. *Drugs Aging.* 2012;29(6):437-452.
8. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther.* 2008;46(2):72-83.
9. Currow DC, Stevenson JP, Abernethy AP, Plummer J, Shelby-James TM. Prescribing in palliative care as death approaches. *J Am Geriatr Soc.* 2007;55(4):590-595.
10. Riechelmann RP, Krzyzanowska MK, Zimmermann C. Futile medication use in terminally ill cancer patients. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* 2009;17(6):745-748.
11. Fede A, Miranda M, Antonangelo D, et al. Use of unnecessary medications by patients with advanced cancer: cross-sectional survey. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* 2011;19(9):1313-1318.
12. Néron A. Table 31.1 – Classification of drugs according to medical necessity at end of life. . In: Care HPSIGiP, ed. *Care Beyond Cure: Management of Pain and Other Symptoms, 4th Edition*. 4th ed: Association des pharmaciens des etablissements de sante du Quebec,
Sandoz; 2009.
13. Scott IA, Anderson K, Freeman CR, Stowasser DA. First do no harm: a real need to deprescribe in older patients. *The Medical journal of Australia.* 2014;201(7):390-392.
14. Berterame S, Erthal J, Thomas J, et al. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. *Lancet.* 2016;387(10028):1644-1656.
15. Pellegrin KL, Krenk L, Oakes SJ, et al. Reductions in Medication-Related Hospitalizations in Older Adults with Medication Management by Hospital and Community Pharmacists: A Quasi-Experimental Study. *J Am Geriatr Soc.* 2017;65(1):212-219.
16. Gillespie U, Alassaad A, Henrohn D, et al. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. *Arch Intern Med.* 2009;169(9):894-900.
17. Kaboli PJ, Hoth AB, McClimon BJ, Schnipper JL. Clinical pharmacists and inpatient medical care: a systematic review. *Arch Intern Med.* 2006;166(9):955-964.

18. Potter K, Flicker L, Page A, Etherton-Beer C. Deprescribing in Frail Older People: A Randomised Controlled Trial. *PLoS One.* 2016;11(3):e0149984.
19. McKean M, Pillans P, Scott IA. A medication review and deprescribing method for hospitalised older patients receiving multiple medications. *Intern Med J.* 2016;46(1):35-42.
20. Tjia J, Velten SJ, Parsons C, Valluri S, Briesacher BA. Studies to reduce unnecessary medication use in frail older adults: a systematic review. *Drugs Aging.* 2013;30(5):285-307.
21. Dellit TH, Owens RC, McGowan JE, Jr., et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2007;44(2):159-177.
22. Medication Reconciliation. http://www.saferhealthcarenow.ca/EN/Interventions/medrec/Pages/default.aspx. Accessed October 20th, 2014, 2014.
23. Mueller SK, Sponsler KC, Kripalani S, Schnipper JL. Hospital-based medication reconciliation practices: a systematic review. *Arch Intern Med.* 2012;172(14):1057-1069.
24. Kwan JL, Lo L, Sampson M, Shojania KG. Medication reconciliation during transitions of care as a patient safety strategy: a systematic review. *Ann Intern Med.* 2013;158(5 Pt 2):397-403.
25. Heyland DK, Dodek P, Rocker G, et al. What matters most in end-of-life care: perceptions of seriously ill patients and their family members. *CMAJ.* 2006;174(5):627-633.
26. Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD. Development and validation of the patients' attitudes towards deprescribing (PATD) questionnaire. *Int J Clin Pharm.* 2013;35(1):51-56.
27. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. *Psychol Health.* 1999;14:24.
28. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *Journal of Palliative Care.* 1991;7(2):6-9.
29. Runciman WB, Roughead EE, Semple SJ, Adams RJ. Adverse drug events and medication errors in Australia. *Int J Qual Health Care.* 2003;15 Suppl 1:i49-59.
30. Hubbard RE, Peel NM, Scott IA, et al. Polypharmacy among inpatients aged 70 years or older in Australia. *Med J Aust.* 2015;202(7):373-377.
31. Betteridge TM, Frampton CM, Jardine DL. Polypharmacy--we make it worse! A cross-sectional study from an acute admissions unit. *Intern Med J.* 2012;42(2):208-211.
32. Poudel A, Peel NM, Nissen L, Mitchell C, Gray LC, Hubbard RE. Potentially inappropriate prescribing in older patients discharged from acute care hospitals to residential aged care facilities. *Ann Pharmacother.* 2014;48(11):1425-1433.
33. Williams ME, Pulliam CC, Hunter R, et al. The short-term effect of interdisciplinary medication review on function and cost in ambulatory elderly people. *J Am Geriatr Soc.* 2004;52(1):93-98.

34. Anderson K, Stowasser D, Freeman C, Scott I. Prescriber barriers and enablers to minimising potentially inappropriate medications in adults: a systematic review and thematic synthesis. *BMJ Open.* 2014;4(12):e006544.
35. Reeve E, To J, Hendrix I, Shakib S, Roberts MS, Wiese MD. Patient barriers to and enablers of deprescribing: a systematic review. *Drugs Aging.* 2013;30(10):793-807.
36. Morden NE, Colla CH, Sequist TD, Rosenthal MB. Choosing Wisely - The Politics and Economics of Labeling Low-Value Services. *N Engl J Med.* 2014;370(7):589-592.
37. Stockton KR, Wickham ME, Lai S, et al. Incidence of clinically relevant medication errors in the era of electronically prepopulated medication reconciliation forms: a retrospective chart review. *CMAJ Open.* 2017;5(2):E345-E353.
38. Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. *Arch Intern Med.* 2010;170(18):1648-1654.
39. Heyland DK, Barwich D, Pichora D, et al. Failure to Engage Hospitalized Elderly Patients and Their Families in Advance Care Planning. *JAMA Intern Med.* 2013:1-10.

Legends.

Figure 1. Patient enrolment CONSORT flow diagram.

Figure 2. Flowchart of medication recommendations and changes.

Table 1. Demographics and baseline characteristics of intervention group.

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

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

Supplementary Table 1. Patient baseline symptom and perception data

Supplementary Figure 1. Patient perceptions of medication rationalization.

Appendix A. Description of study setting.

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

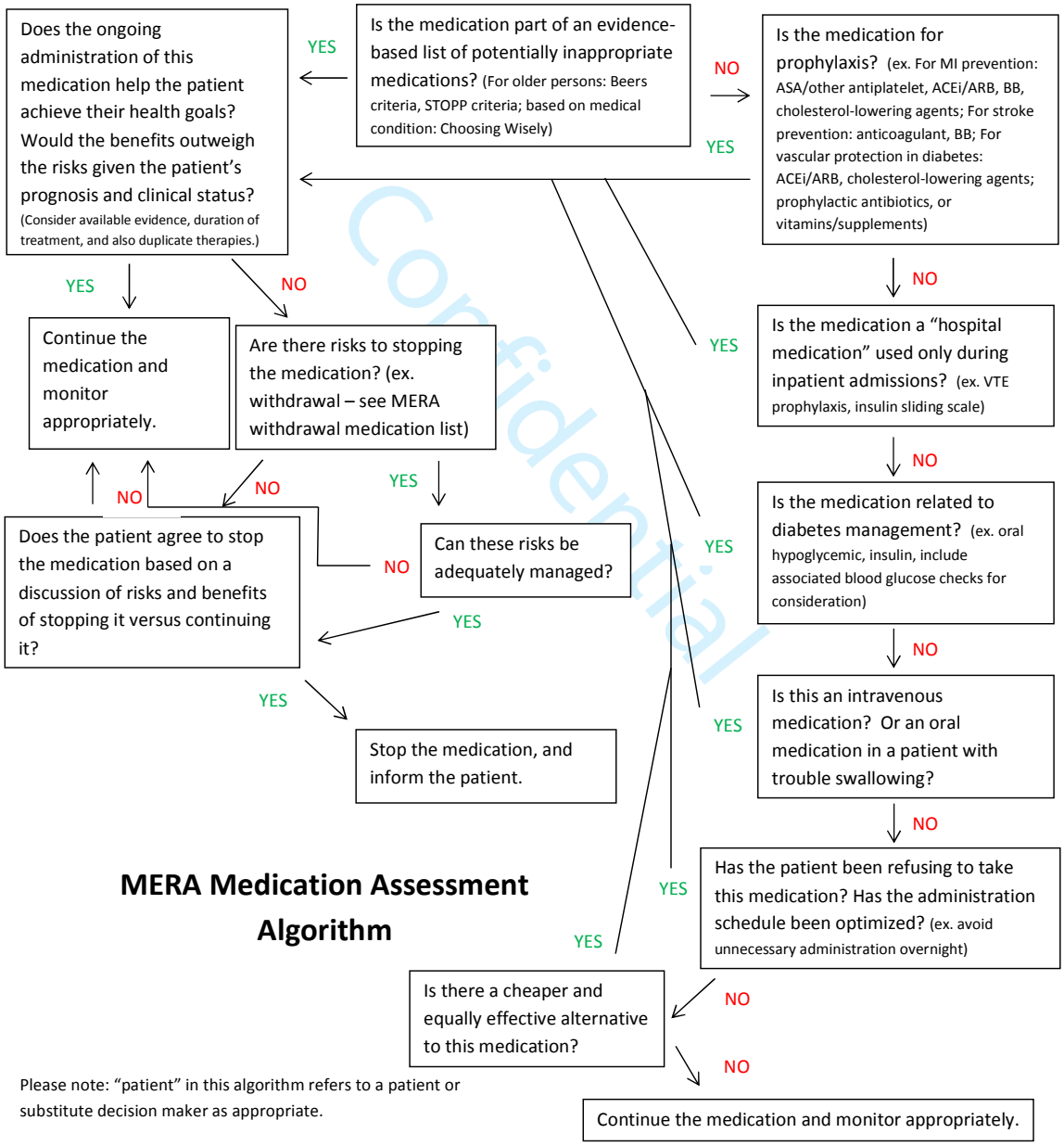
The entire service comprises 75 physical inpatient beds, although actual patient numbers may often exceed this number. Individual teams are responsible for between 15-25 patients, and admit and discharge approximately 1-4 patients per day.

Appendix B. Medication Recommendations and the MERA Algorithm.

Three pharmacists involved in this project (RW, SP and KB) assembled a table of medication-related recommendations from the STOPP guidelines[8], Beers criteria[6], Choosing Wisely[29], and Choosing Wisely Canada[30]. This table was organized with each medication or class in a row, and each guideline in a column, to allow the reader to rapidly review all recommendations for any given medication. An additional column was added for "MERA guidelines", which included recommendations based on common practice for patients with a limited life expectancy that were not covered in the other guidelines (expressed in the algorithm below; e.g. discontinuing oral hypoglycemic agents and medications taken only for prevention such as ACE inhibitor for vascular protection in diabetes or prophylactic antibiotics, optimizing medication route and schedule (changing intravenous medications to oral medications, or stopping oral medications in patients having trouble swallowing, minimizing number of administration times, adjusting timing of medications to allow uninterrupted sleep)).Where appropriate, the algorithm also included recommendations to wean some medications rather than stop them abruptly (e.g. benzodiazepines). The full document is over 47 pages long but we provide a sample:

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.	--

				OR Don't prescribe medications for stress ulcer prophylaxis to medical inpatients unless at high risk for GI complications.	



Appendix C. The Beliefs about Medications Questionnaire.

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 domain[31].
- Specific Concerns- a scale of 5-25 where higher scores indicate higher concern about potential adverse effects of medications prescribed for the patient.
- General Overuse- a scale of 3-15 where high scores indicate strong beliefs that medications are overused by doctors.
- General Harm- a scale of 4-20 where high scores indicate strong beliefs that medications are "harmful, "addictive" and/or "poisons".

Appendix D. Explanation and justification of pilot endpoints.

For feasibility, we aimed to enrol 50 patients over a 6-month period, achieve an enrolment rate of >50%, and keep MERA meetings with the medicine teams less than 30 minutes in duration. For acceptability, we aimed to 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.

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

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

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

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.

4. Overall, how did the involvement of the MERA team affect your relationship with patients involved in the study?
-The MERA team's involvement greatly improved my relationship with the patients.
-The MERA team's involvement slightly improved my relationship with the patients.
-The MERA team's involvement did not affect my relationship with the patients.
-The MERA team's involvement slightly worsened my relationship with the patients.
-The MERA team's involvement greatly worsened my relationship with the patients.

5. Overall, how did the involvement of the MERA team affect your relationship with substitute decision-makers (SDMs) involved in the study?
-The MERA team's involvement greatly improved my relationship with the SDMs.
-The MERA team's involvement slightly improved my relationship with the SDMs.
-The MERA team's involvement did not affect my relationship with the SDMs.
-The MERA team's involvement slightly worsened my relationship with the SDMs.
-The MERA team's involvement greatly worsened my relationship with the SDMs

Appendix G. The CARENET Criteria for elevated risk of death in the next 6 months.
We enrolled medical inpatients with:

- Age >80

- 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

Appendix A. Description of study setting.

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

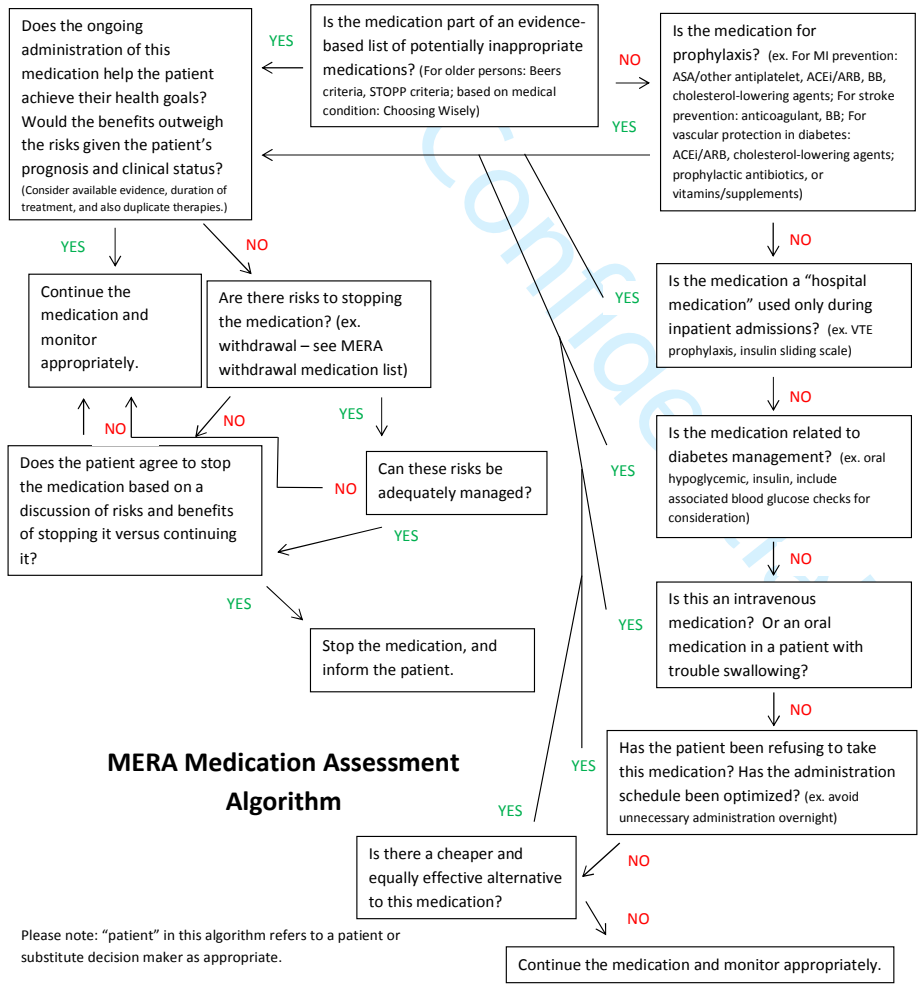
The entire service comprises 75 physical inpatient beds, although actual patient numbers may often exceed this number. Individual teams are responsible for between 15-25 patients, and admit and discharge approximately 1-4 patients per day.

Appendix B. Medication Recommendations and the ~~The~~ MERA Algorithm.

Three pharmacists involved in this project (RW, SP and KB) assembled a table of medication-related recommendations from the STOPP guidelines[8], Beers criteria[6], Choosing Wisely[29], and Choosing Wisely Canada[30]. This table was organized with each medication or class in a row, and each guideline in a column, to allow the reader to rapidly review all recommendations for any given medication. An additional column was added for "MERA guidelines", which included recommendations based on common practice for patients with a limited life expectancy that were not covered in the other guidelines (expressed in the algorithm below; e.g. discontinuing oral hypoglycemic agents and medications taken only for prevention such as ACE inhibitor for vascular protection in diabetes or prophylactic antibiotics, optimizing medication route and schedule (changing intravenous medications to oral medications, or stopping oral medications in patients having trouble swallowing, minimizing number of administration times, adjusting timing of medications to allow uninterrupted sleep)).Where appropriate, the algorithm also included recommendations to wean some medications rather than stop them abruptly (e.g. benzodiazepines). The full document is over 47 pages long but we provide a sample:

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.	--

				OR Don't prescribe medications for stress ulcer prophylaxis to medical inpatients unless at high risk for GI complications.	



Appendix C. The Beliefs about Medications Questionnaire.

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 domain[31].
- Specific Concerns- a scale of 5-25 where higher scores indicate higher concern about potential adverse effects of medications prescribed for the patient.
- General Overuse- a scale of 3-15 where high scores indicate strong beliefs that medications are overused by doctors.
- General Harm- a scale of 4-20 where high scores indicate strong beliefs that medications are "harmful, "addictive" and/or "poisons".

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~~and 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.

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

The BMQ revealed a mean Specific-Necessity subscale score of 18.5, which indicates an average score of 3.7 on each 5-point Likert question (where 3 indicates uncertainty and 4 indicates agreement, higher scores indicate a belief that the patient's current medications are necessary). The other subscales

(measuring concerns, overuse and harm) revealed average scores ranging from 2.6 to 3.1 on each question (where 2 indicates disagreement and 3 indicates uncertainty, and higher scores indicate concerns about medications).

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.

4. Overall, how did the involvement of the MERA team affect your relationship with patients involved in the study?
-The MERA team's involvement greatly improved my relationship with the patients.
-The MERA team's involvement slightly improved my relationship with the patients.
-The MERA team's involvement did not affect my relationship with the patients.
-The MERA team's involvement slightly worsened my relationship with the patients.
-The MERA team's involvement greatly worsened my relationship with the patients.

5. Overall, how did the involvement of the MERA team affect your relationship with substitute decision-makers (SDMs) involved in the study?
-The MERA team's involvement greatly improved my relationship with the SDMs.
-The MERA team's involvement slightly improved my relationship with the SDMs.
-The MERA team's involvement did not affect my relationship with the SDMs.
-The MERA team's involvement slightly worsened my relationship with the SDMs.
-The MERA team's involvement greatly worsened my relationship with the SDMs

Appendix G. The CARENET Criteria for elevated risk of death in the next 6 months.
We enrolled medical inpatients with:

Formatted: Font: 11 pt
Formatted: Font: Not Bold
Formatted: Font: Not Bold
Formatted: Font: Not Bold
Formatted: Font: Not Bold
Formatted: Font: Not Bold

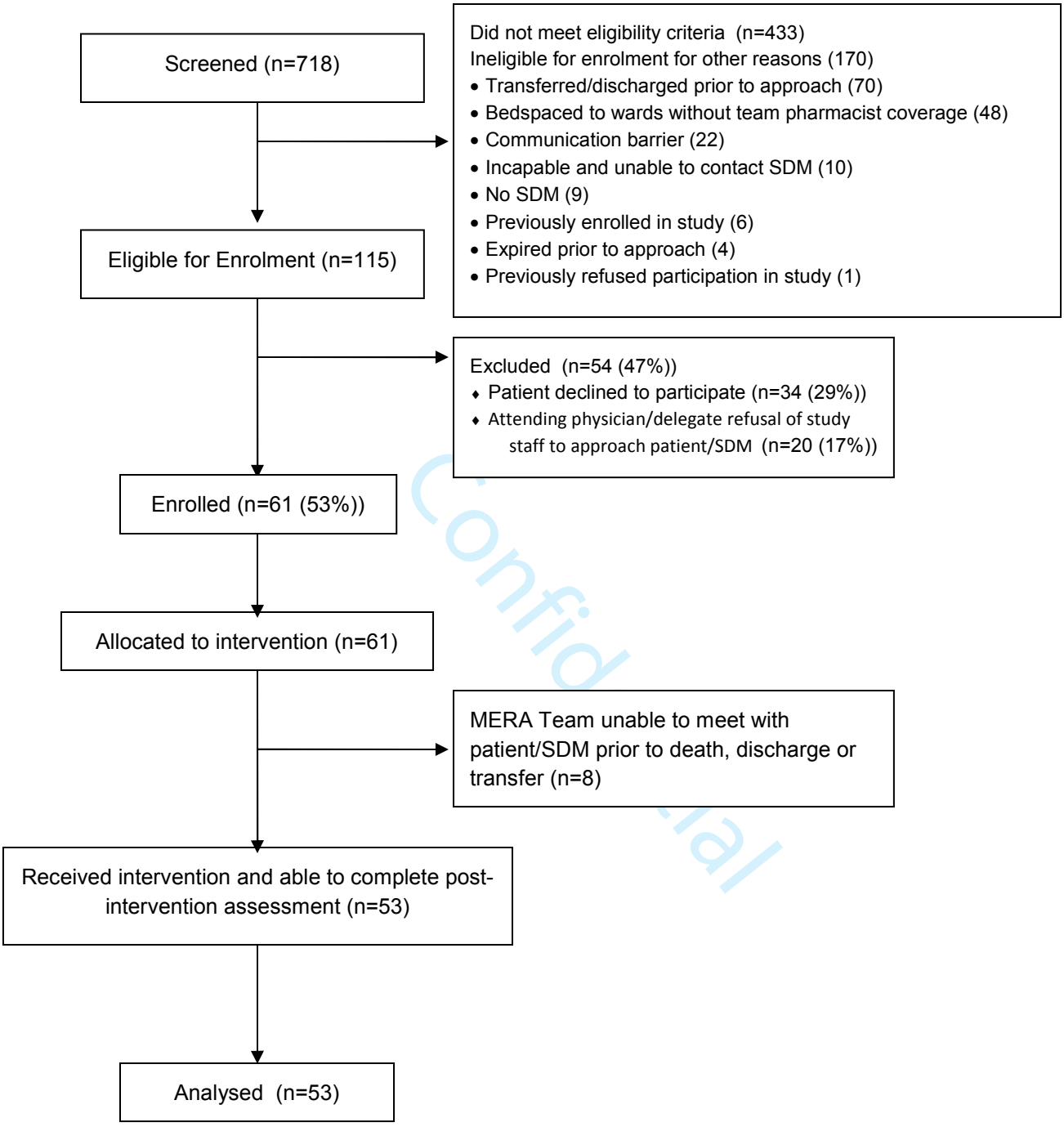


Table 1. Demographics and baseline characteristics of intervention and comparison group

Demographic	**Intervention Group (n=53)**	**Non-MERA Comparison Group (n=51)**	**P value for difference between intervention and comparison groups**
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

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

Demographic	**Intervention Group (n=53)**	**~~Control~~ Non-MERA Comparison Group (n=51)**	**P value for difference between intervention and ~~control~~ comparison groups**
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 (~~control~~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

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

Variable	**Mean number of medication discontinuations (SD)**	**p-value for difference**
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

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

Variable	**Mean number of medication discontinuations (SD)**	**p-value for difference**
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

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

MERA Medication Class	**Number of times MERA team recommended discontinuation (% of all recommended discontinuations), n=201**	**Number of patients in whom medication class was recommended to be stopped (% of all patients enrolled), n=53**
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%)