Improving **M**edication **P**rescribing-**R**elated **O**utcomes for **V**ulnerable **E**lderly **I**n **T**ransitions on **H**igh **R**isk **M**edications (**IMPROVE-IT HRM):** A Pilot Randomized Trial Protocol

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ABSTRACT

Rationale: Transitions in, through, and out of hospital define the highest risk periods for patient safety. Hospitalized senior high-cost health care users taking high risk medications, are a large group of patients, usually highly complex with polypharmacy, and at high risk of serious adverse medication events. We will assess whether an expert Clinical Pharmacology Toxicology (CPT) medication management intervention during hospitalization with follow-up post-discharge and communication with circle of care, is feasible and can decrease drug therapy problems amongst this group.
Design: Pragmatic pilot randomized trial at SJHH with 1:1 patient-level concealed randomization with blinded outcome assessment and data analysis.
Participants: Adults 65 years of age and older, admitted to Internal Medicine services for more than 2 days, who are high-cost users defined as at least one other hospitalization in the prior year, taking 5 or more chronic medications including at least one high risk medication.
Intervention: CPT consult service identifies medication target(s), completes consult, including priorities for improving prescribing negotiated with the patient, starts the care plan, ensures a detailed discharge medication reconciliation and circle-of-care communication, and sees the patient at least twice after hospital discharge via integrated virtual visits to consolidate the care plan in the community. Control group receives usual care as provided by admitting services.
Outcomes: Include a) Feasibility Outcomes and b) Clinical Outcomes including the number of drug therapy problems improved, medication appropriateness and safety, the quality and coordination of transitions in care, quality of life, and health care utilization and costs by 3-month follow-up.
Impact: If results support feasibility of ramp-up and promising clinical outcomes, a follow-up definitive trial will be organized using a developing national platform and medication appropriateness network.

RESEARCH QUESTION

Our detailed research question is *'In a randomized pilot trial, can an expert Clinical Pharmacology team coordinate and improve medication management during the very high-risk transition period from hospitalization through post-hospital discharge follow-up for senior high-cost users of healthcare taking high risk medications, meeting key feasibility outcomes while improving patient-important outcomes and health care costs sufficiently to warrant a large subsequent trial?'*

INTRODUCTION

Current systematic reviews of randomized trials to manage polypharmacy or to manage medications in hospital or in the transitions of care have been unable to demonstrate improvements in important clinical outcomes.[1-5] This is largely because a) the interventions have been led by providers without the requisite combination of diagnostic, therapeutic and risk management expertise or authority to make requisite changes, b) the intervention was not sufficiently concentrated (too short, incomplete or misdirected), c) the medication focus was misplaced (i.e., not high-risk medications, which are the most associated with adverse clinical outcomes) or the outcomes were overly focused on poor quality surrogates for clinical outcomes.

Because of the huge potential burden of harm and the number of affected vulnerable older adults in our population (details below), the value of more randomized trial inquiry is very high. There is enough suggestion of benefit from trials on prescribing appropriateness combined with the potential for major medication safety improvements,[4, 6-9] to support an expert intervention concentrated on the highest risk group as they transition through a very high-risk period targeting the highest risk medications. In addition, recent advances in digital health in Canada make it feasible for scarce clinical expertise to be concentrated on this high priority problem with robust communication systems that support patient consultation and follow-up to any part of country no matter how remote.

Medication Safety is an International Health Priority

In 2017, the World Health Organization (WHO) declared Medication Safety to be its current Global Patient Safety Challenge, with a specific focus on improving poor processes and procedures.[10] Their three categories for early priority action include high-risk situations (eg, hospitals and high alert medications), polypharmacy, and transitions of care. *We will address all three of these key categories in this project.*

High Risk Medication Safety Situations Are Known

Transitions in Care, particularly in and out of hospital and High Alert Medications, are two primary high risk situations referenced by WHO.[10] Even with evidence of under-detection, systematic reviews of the literature conclude that adverse drug events (ADEs) amongst older adults lead to approximately 1 in 10 hospitalizations.[11-13] Canada-wide data suggest that adverse drug-related hospital admissions are directly correlated with the number of medications taken concurrently, the number of prescribers involved, possibly the number of pharmacies used, and to hospitalization within the previous year.[14] In several studies, female sex was also a risk factor.

Once in hospital, patients (n=46,626) remain at high risk of ADEs, with a mean prevalence of 21.6% (SD 16.7,), 20.7% of these judged to be severe or life-threatening and 32.3% (SD 22.6%) judged to be preventable.[15] In addition to the risk factors above, a complex patient (several comorbidities with several provider experts involved) is significantly more likely to suffer adverse events in hospital.[16, 17] In Canada, medical and surgical services, because of the older age, high complexity and volume of patients seen, have the highest rates of adverse events overall.[16]

The period immediately following hospital discharge remains high risk with 37% of seniors sustaining

medication-related harm (81% serious) within 8 weeks.[18] In this systematic review, female sex was associated with medication-related harm.[18] This leads to frequent readmissions and high costs. The outcomes of ADEs included prolonged length of stay, frequent readmission, emotional trauma, high costs, and death.[16, 19, 20]

Polypharmacy and Potentially Inappropriate Prescribing (PIP) Are Important Signals

The term "polypharmacy" has multiple definitions, but the most common is the concurrent use of 5 or more medications daily by a single individual.[4] The prevalence of polypharmacy in Canada is very high amongst seniors, at approximately 66%, with 27% of these taking 10 or more medications concurrently, a situation we label major polypharmacy.[4, 21] While the number of medications used remains a useful signal, it is impossible to gauge the quality of medication regimens simply by the number of medications, as this does not account for the patient's main diagnosis, comorbidities, risk factors, past history of medication use, or the benefit-harm ratio of the drug for that patient. For example, an older patient with diabetes frequently requires two glucose lowering medications, a statin for cholesterol, and two to three medications for blood pressure, just to manage their high cardiovascular risk without treating their other health problems. Thus, the medication safety target is problematic polypharmacy as opposed to appropriate polypharmacy.[22]

Medications which frequently lead to harms outweighing benefit in certain situations are termed 'potentially inappropriate medications' (PIMs). PIMs that have been associated with ADEs have been grouped together in medication screening lists, with the most evidence-based being the **STOPP** criteria.[23] Randomized trials in Europe show that use of the STOPP criteria as a trigger for medication review for hospitalized seniors can improve the appropriateness of prescribing, reduce ADEs and reduce length of stay.[24, 25] A cross-Canada study found that nearly 40% of seniors fill a prescription for at least one PIM per year, with the highest rates in women > 85 years of age and the most common PIM drug category being sedative-hypnotic drugs.[26] The cost of these PIMS plus the cost of treating their adverse effects has been estimated to be more than $1.8 billion every year in Canada.[26]

Interventions Should be Focused on Priority Areas

A. Priority Medications

Although STOPP is an excellent screening tool, there are too many alerts (80 in current iteration) to feasibly apply in hospitalized patients where timely discharge is a high priority.[25] Analyses of Canadian and U.S. data on medication utilization and drug-related causes of hospitalization by our group and others, suggest recurring groups of very commonly, widely used medications as the main causes of drug-related hospitalizations.[14, 27, 28] These are all medication families with proven benefit of varying clinical importance but also clinically important harm when not managed expertly. Thus, these are medications that should trigger review of the entire medication regimen to consider improvements. We have labelled these the high risk medications (HRM):

i. Anticoagulants,
ii. Analgesics including Opioids, NSAIDs and Glucocorticoids,
iii. Antimicrobials,
iv. Antineoplastic agents,
v. Glucose-lowering drugs for diabetes,
vi. Cardiac drugs including Diuretics and Digoxin,
vii. Sedative-hypnotics including Benzodiazepine receptor antagonists,
viii. Antipsychotic agents

Further details are included in Appendix 1. In many cases, the high-risk medication itself (e.g., anticoagulant, glucocorticoid, glucose lowering medication, antineoplastic agent, etc) is required for the patient but the dose may require adjustment, a tapering regimen might be appropriate, or a review for potentially serious drug interactions or medication burden identifies another medication that can be removed to decrease the patient's

overall risk of medication-related harm. We have previously developed an 'Appropriateness of Prescribing Evaluation Questionnaire' that has become the standard, holistic, medication appropriateness assessment tool.[29,30] Our ongoing development work suggests that while optimization of the high risk medications is feasible, it also opens up other opportunities for important improvements in medication management, including removal of medications and supplements with no benefit or with possibility of contamination, or substitution of more cost-effective alternatives.

B. Priority Patients

So-called high cost users (HCUs) have been an international priority target for quality and cost of care improvements for years.[31] In a series of large population-based observational studies, we have shown that 5% of Ontarians generate 65% of the entire health care costs, approximately 70% of these are seniors (> 500,000), and these are complex patients with multiple hospital admissions, multiple providers, multiple diagnostic labels and problematic polypharmacy.[32-34] Use of high-risk medications is very prevalent in this population and strongly predictive of future healthcare utilization and mortality in a dose- and duration-dependent manner compared to non-users.[32-35]

C. Priority Situations

Senior HCUs taking high-risk medications who are transitioning in, through, and out of hospital are at very high risk of serious ADEs. Hospitalization is a double-edged sword in that it defines high risk situations but also houses the expertise required to effectively intervene. This opportunity to optimize medication regimens for these inpatients is widely underutilized worldwide, due to a) huge pressures to just deal with the main problem requiring admission and get the patient discharged as quickly as possible due to bed shortages and b) lack of expertise amongst general medicine and surgery admitting services to complete an expert medication assessment quickly. In preparation for this trial, we recently completed a chart review of 100 randomly selected senior HCUs who were admitted to a Hamilton hospital (mean age 82 years), and found the mean rate of potentially inappropriate medications to be 2.8 per person. Only 16.6% of these had been addressed by the time of discharge.[36]

Medication Safety Interventions Worth Evaluating

Two areas of innovation, heretofore not available for use in Canada, have matured sufficiently to be potentially effective, cost-effective, and highly feasible.

*A. Innovation in **Digital Health***

The ability to date of digital health solutions, including electronic health records (EHRs) to meet the demands and complexity of modern medicine has been underwhelming.[37] However, all patient safety leadership organizations including the Institute for Safe Medication Practices (ISMP), the Canadian Patient Safety Institute (CPSI), and the Agency for Health Care Research and Quality, agree that EHRs must be part of the medication safety solution, as system factors in addition to human factors, are always amongst the key root causes of adverse events. [38-40]

Epic is a world-leading EHR software. It has won the Best in KLAS award for healthcare software suites 8 years in a row and is the EHR for the 20 top hospitals and the 20 top graduate schools for medical research in the United States.[41, 42] St Joseph's Healthcare Hamilton is the first large academic hospital system in Canada to go live (in 2017) with a build called Dovetale-Epic.[43] This installation of Epic has led to rapid *innovation in both Clinical Care and in Research*.

Clinical Care advances relevant to this project include a) automated patient risk screening abilities, b) medication management alerts, c) improved physician- pharmacist communications, d) ability to easily maintain and connect an organized 'circle of care' for the patient (hospital and community providers, family, caregivers), and e) fully integrated telemedicine/telehealth compatible with a patient's smart phone which facilitates and documents 'virtual visit' follow-up in the patient's home. This technology extends the consultation reach of scarce, valuable specialties such as Clinical Pharmacology and Toxicology (CPT) to anywhere in Canada.

Research innovation includes novel major efficiencies in a) recruiting for trials, and b) quality and efficiency improvements in data collection and capture using secure transfer to industry-standard research data platforms (REDCap). Although a long time coming, EHRs have tremendous potential to improve the quality (richer data) while reducing the cost of RCTs.[44] Since virtually all of the leading medical centres for clinical care and research in the United States use Epic, and several large additional hospital installations are imminent in Canada, this project will serve as a prototype pilot for a very large international research network serving a population of more than 150 million people.

*B. Innovation in **Clinical Expertise***

Clinical Pharmacology and Toxicology (CPT) is one of the newest and smallest Royal College of Physicians - certified specialties in Canada. Its key mandate is improving the quality of drug therapy from bench to bedside to policy.[45] Hamilton's clinical pharmacologists who are also certified in Internal Medicine are unique in Canada in their ability and depth of experience in caring for complex elderly patients on multiple medications in need of evidence-informed review while in hospital and in follow-up. Their training and supervisory expertise has been recognized with multiple awards, and includes building capacity amongst trainees who will work elsewhere. In addition, the drug policy and formulary decision-making that is crucial to guiding cost-effective prescribing, is heavily influenced by CPT.

METHODS

Design

Pragmatic pilot randomized trial (RCT) at SJHH with 1:1 patient-level concealed-allocation randomization with blinded outcome assessment and data analysis. Randomization provides the highest quality methods to minimize bias, the pragmatic design ensures relevance to clinical practice essential for implementation, and a pilot RCT addresses feasibility of a large definitive subsequent RCT directly without waste of research dollars.[46, 47] A study flow diagram is shown below in Figure 1.

Participants

Adults over the age of 65 years who are admitted to Medicine services for more than 2 days, who are high cost users defined as at least one other hospitalization within the previous year, who are taking 5 or more chronic medications including at least one high risk medication and provide informed consent. It is estimated that at least ten patients daily meet these eligibility criteria.

Recruitment and Randomization

The Research Institute of St Joes Hamilton recently approved a policy that every patient admitted can be approached to participate in studies unless they decline (Access Research). Dovetale-Epic tracks this 'may approach/do not approach' status for each patient in real time. This effectively alleviates a barrier as the (usual) necessity of relying on the patient's core team to refer a potentially eligible patient is a major barrier to recruitment, simply due to distraction of the team with the clinical priorities.

We are working with the Dovetale team to have all potentially eligible patients screened for age, HCU status (defined as at least one previous admission in the prior year) and the presence of five or more chronic (not prn) medications with one or more high risk medication. Screen eligibility-positive patients will be posted to the current Clinical Pharmacology and Toxicology team's intake list. Once eligibility is confirmed, the ward pharmacist will ensure that an accurate BPMH (best possible medication history) is completed and documented appropriately in Dovetale-Epic. An accurate BPMH is critical for an accurate discharge medication reconciliation. Research staff will check with the most responsible physician (MRP) team regarding eligibility (this stage picks up on delirium and dementia, for example). The research team will then approach the patient to invite participation, introduce the study and complete the informed consent process which includes answering questions, completing a short Capacity to Consent questionnaire (Appendix 2), and Informed Consent document.[48]

Patients with cognitive impairment will not be excluded as they constitute a vulnerable group in need of

assistance, but they must have a primary caregiver who assists them with medications and who is willing to sign informed consent if the patient fails the Capacity to Consent questionnaire.[48] For this pilot trial, either the patient or caregiver must be fluent in English.

Patients will be randomly allocated to the intervention or control arms in a 1:1 ratio in permuted blocks using a statistician-formulated randomization schedule that will be available online 24/7.

A validated patient frailty index will be incorporated at baseline as a prognostic marker[49].

Intervention

Our intervention follows the general Innovative Practices framework recommended by Health Quality Ontario for Transitions between Hospital and Home, and uses the specific approach in Figure 2 .[50]

CPICS (Clinical Pharmacology Inpatient Consult Service) Notification

Randomization to the intervention arm will trigger a request for a CPT (Clinical Pharmacology & Toxicology) consult, using our Clinical Pharmacology Inpatient Consult Service (CPICS) workflow. The CPT team consists of a unique combination of expert Clinical Pharmacologists (Royal College physician specialist in patient assessment and diagnosis, drug therapy, adverse drug events, drug access, safe prescribing, cost-effective medication management) with additional expertise in evidence-based geriatric prescribing, multi-morbidity, and de-prescribing; medicine and pharmacy trainees; and a research assistant. There are fewer than 20 such CPT specialists in Canada, four of them located at SJHH with the largest cumulated experience of any medical centre at more than 90 physician-years.

Initial Consult

The initial CPT consult for each patient includes a comprehensive patient assessment including demographics, social situation, drug coverage insurance, functional status (activities of daily living, instrumental activities of daily living), cognition, frailty markers, level of caregiver involvement, past medical history and current problems, allergies and intolerances, detailed medication history including reminder aids and methods of accessing medication, physical exam and review of current and historical laboratory and diagnostic imaging results. These details are structured data items in EPIC behind a customized CPT consult, progress or discharge note structured template, which ensures consistency of intervention across the four consultants.

In addition, the CPT team will document a detailed ‘circle of care’ for each patient (their primary caregiver, hospital MRP team, family doctor, community physician specialists, community pharmacists and home care), and will identify all potential high-risk medications targets that the patient is taking or is due to resume post-hospitalization. Using patient preference elicitation methods and motivational interviewing, priorities for medication optimization will be negotiated.[51-56] Short patient infographics endorsed by the Canadian Medication Appropriateness and Deprescribing Network (CADeN) will be used as educational materials.

CPICS Follow-up

While the patient is still hospitalized, the high-risk medications care plan begins and the team ensures close communication with the MRP (Most Responsible Physician) admitting team, coordinates a detailed discharge medication reconciliation (documenting medication changes with rationale, formulating an accurate discharge prescription including rapid access to new medications), ensures circle-of-care communication and sees the patient via Virtual Visit twice in follow-up at 1 week and 1 month after hospital discharge to complete the care plan.

Control

These patients will receive usual care by their primary team. This means that the MRP team is responsible for coordinating medication management at discharge and post-hospital follow-up, as is currently practiced.

Outcomes

The Core Outcome Set for Interventions to Improve Polypharmacy in Older People was consulted to assist

with our selection of outcomes.[57] Core outcome sets are consensus-based guidelines from groups of clinicians, patients and methodologists on which outcomes with which metrics, are the most important to be measured in prospective studies.[58] In addition, we consulted other polypharmacy/deprescribing trials for recommended patient-important outcomes.[59-64]

For this pilot RCT, we will analyze outcomes according to a set of Primary and Secondary Outcomes. (see details in Table 1 and Table 2.)

Primary Outcomes. There are two types of primary outcomes that will be evaluated:

a) The *Primary Feasibility Outcomes* will be recruitment and retention rate for eligible patients, and the estimated resources required per patient to complete the main trial. We aim for at least 30% recruitment of those eligible, 90% retention of those recruited, and no more than $1500 per patient spent on running the pilot trial.

b) The *Primary Clinical Outcome* will be the number of drug therapy problems improved including the number of high-risk medications improved (for example, dose adjustment, discontinued, seriously interacting drugs removed) at 3 months post- hospital discharge end-study visit.

Secondary Outcomes:

a) The *Secondary Feasibility Outcomes* of CPT consultation include: CPICS recommendation acceptance by primary team and by patients, consult volume capacity, and potential to apply the intervention entirely through virtual visits.

b) *The Secondary Clinical/Patient-important outcomes* will include:

1. Other medication management outcomes (details in Table 1)
2. Adverse drug events using the standard definition of harm caused by use or inappropriate use of a drug, and including rating of preventability using the 'best practice'-based definition of Woo et al – inappropriate drug or dosage or route or frequency of a drug given the patient's age, diagnoses, weight, organ function; or administration of a drug for which the patient has a major allergy or intolerance; or inappropriate laboratory monitoring.[65] Specific rating of ADE will use the standard Leape and Bates scale: 6- definitely due to medication, 5- probably due to medication, 4- possibly due to medication, 3- possibly due to disease, 2- probably due to disease, 1- definitely due to disease.[66]
3. Medication errors – characterized as errors in prescription, dispensing, or administration using standard NCC-MERP definitions and classification.[67] A Medication Error is an error (of commission or omission) at any step along the pathway that begins with prescribing and ends with the patient taking or not taking the medication. [68]
4. Patient Problems with Medications: The COMPETE Medication Problems Questionnaire measures problems with medication access, handling, beliefs and adherence.[69]
5. Medication Knowledge Assessment: this will be assessed using the Medication Knowledge Assessment form, which tests knowledge of medication name, indication, dosage instructions, and precautions.[70]
6. Coordination and Continuity of Care: Adapted from Health Quality Ontario's draft guidance and a Rand instrument, the Coordination and Continuity of Care Questionnaire is designed to measure the quality of the transitional and follow-up care. We will focus on medication reconciliations and education, and circle of care communications.[71, 72]
7. Patient Quality of Life: The EQ-5D-5L is the 5-level classification system of the EQ-5D, a measure of health status from the EuroQol Group, which also contributes incremental utility values to the cost-effectiveness evaluation.[73] Using EQ-5D-5L, respondents are asked a short series of questions about mobility, self-care, usual activities, pain discomfort, and anxiety/ depression, as well as a summary visual analogue scale. This scale, which provides utility measurements, has been well validated for the Canadian population.[73-75] We will also use a 'condition-specific' QOL measure, the Medication-related Quality of Life measure which is designed for people with polypharmacy.[76]

8. Satisfaction with Care: Satisfaction reported by patients and by key health professionals is one of the recommended outcomes to report in medical research, as it may influence adherence.[77, 78] This outcome will be assessed by the Patient/Caregiver Study Satisfaction Survey and by the Provider Study Satisfaction Survey.[79]
9. Health Resource Utilization: This is a key outcome to determine cost-effectiveness and cost-utility which then determines whether health care systems might pay for this type of care.[80, 81] To improve accuracy and feasibility, we will estimate costs based on healthcare utilization, concentrating on Emergency Department visits, hospitalizations, unplanned physician visits and medication costs, including out-of-pocket medication costs in follow-up.[72, 81]. The analysis will follow the guidance of international and Canadian guidelines.[82, 83]

Outcomes will be collected through a mix of patient interview and chart review. The impact of sex, gender, age, social support, socioeconomic status, cognition, number of medications, and location of discharge, will be examined as potential interaction variables with the intervention and as predictors of outcomes. Sensitivity analyses will assist with determination of potential for cost-effectiveness of the intervention overall and in selected subgroups.

Geographic wards in the hospital allow for evaluation of the intra-cluster correlation (ICC), which based on past experience, we expect to be low. If ICC proves to be high, more complex cluster RCTs will be required. Additionally, barriers and facilitators to success of the primary outcomes, in terms of process and management issues will be evaluated. These will be used to determine whether a large definitive research study is likely to be feasible, taking into account the practical aspects of managing and funding the project.

Follow-up

Patients will be followed until three months post-hospital discharge or until death, whichever occurs first. The challenges and uncertainties posed by the COVID-19 pandemic have highlighted the role and importance of telemedicine, which this trial will utilize for patient follow-up visits. These visits will be conducted by videoconference via Dovetale-Epic or Ontario Telehealth Network, or by phone call, depending on the patient's digital technology capability.

Sample size

Our calculations, based on two independent study groups, measuring a continuous primary outcome, allowing a probability of a Type 1 error of 5%, suggest that to have 80% power to determine an improvement in number of drug therapy problems improved from 3 (Standard deviation 1.4) to 2.5, would require a total sample size of 248 or 124 per group.[84]. Since this is a pilot RCT, we will aim for 30 patients per group or 60 in total as this number is likely to provide adequate evidence regarding feasibility for ramp-up and actual sample size.

Allocation

Participants who meet all the inclusion/exclusion criteria at screening and have completed informed consent will be enrolled in the study, complete baseline assessments, then will be randomized via a computer-generated randomization sequence to one of the two study arms, intervention or control.
A statistician will prepare the randomization schedule.[85] The pilot is being carried out at a single site, although an eventual trial will be multicentre.[86] To restrict treatment group imbalance a maximal tolerable imbalance between treatment groups will be incorporated into the schedule.[87] The randomization schedule will be produced by a program written in R and implemented in REDCap where each patient's treatment assignment will be available on-line to the research staff only at the time of randomization. This process ensures allocation concealment, and randomization awareness where necessary, for example for the intervention staff.

Blinding

Since this is a pragmatic RCT, it will not be possible to completely blind patients or their providers, however outcome data collectors, adjudicators and statisticians will be blinded to group allocation until analysis is completed at the end of the study.

Data Collection Methods

Trained research staff will conduct the interviews with the patients or caregivers, entering data electronically on study laptops directly into REDCap case report forms. The participants' medical records will be reviewed to abstract data on baseline characteristics, medical history, and medication information. Strategies to promote participant retention and complete follow-up include reminding participants in advance of their end-of-study visit and communicating by email if email address is provided at baseline. Participants who drop out of the study will have their data to that point retained in the study, as approved by REB, to avoid bias. The reasons for study non-completion will be recorded.

Data Management

REDCap (Research Electronic Data Capture) is our study software platform – secure, web-based, providing interfaces for validated data capture, role-specific access, audit trails for tracking data manipulation and exports, automated export procedures to SAS and encrypted transmissions.[88, 89] Paper study documents including signed informed consent forms will be stored in our secure research office once they are scanned into REDCap study files. Regular data quality checks, such as automatic range checks, will be performed by the study team to identify data that appear inconsistent, incomplete, or inaccurate.

Patients are not identifiable in the project results database. The identifying information required for the clinical team to deliver the intervention is kept in a separate database. Access to the final dataset will be restricted to the core research team.

Statistical Analyses

The reporting of the results of this trial will follow the CONSORT extension for pilot trials.[90] We will use descriptive statistics for presentation of baseline variables and adequacy of follow-up. Feasibility analysis including recruitment rate (≥30% is considered success), participant retention rate (≥90% to end of study is considered success), study resource utilization required (less than CAD $1500 per patient recruited), management assessment, and scientific assessment, will be descriptive.

Analysis will use intention-to-treat methods with censoring only if the patient dies or drops out of the study with refusal of negotiated further assessments. A sensitivity analysis of the subgroup of patients who received all planned follow-up intervention calls and completed the end-study data collection (per protocol analysis), will be carried out. Research staff and statisticians will review outcome data and analysis blinded to group identification.

The primary clinical endpoint will be number of drug therapy problems improved including the number of high-risk medications improved, as measured by chi-squared and t-tests. Secondary endpoint analyses of the coordination and continuity of care, patient quality of life, medication knowledge, satisfaction with care (providers & patients), and resource utilization, will be analyzed using t-tests. The incidence of the adjudicated individual clinical events (all-cause hospitalizations and emergency department visits) will be analysed using the methods described above for drug therapy problems. Public unit costs from Ontario will be used to cost healthcare resource utilization collected as part of the trial. Using an area under the curve approach, quality adjusted life years (QALYs) will be determined by weighting the EQ-5D-5L health utility scores by time spent in health state. Costs and outcomes (i.e., QALYs, adverse clinical events) between the groups will be compared from a public payer perspective.

Given the short follow-up, low risk of the trial and pilot design, no interim analysis or imputation for missing data is planned. All statistical analyses will be performed using SAS V9.4 software (SAS Institute Inc., Cary, NC, USA).

Data Monitoring

Any serious adverse event will be reviewed by our Trial Steering Committee (TSC) within a week of detection, to discern any attribution to our procedures. If found to be due to our coordination procedures, the trial steering committee will recommend whether modifications are indicated. The TSC will be composed of individuals with expertise in clinical trials, chaired by the lead statistician, include the PI, the operational statistician plus a methodologist independent of the study team. Similarly, since this is a short pilot pragmatic RCT where no

harm is expected and adjustment of trial procedures may be necessary for feasibility, no formal external auditing of trial conduct is planned. There is no requirement for additional ancillary and post-trial care for those who might come to harm while in the trial, as usual medical care which covers this eventuality is already in place.

Privacy and Confidentiality

Study data will be entered into REDCap, which is a secure database, and access to REDCap will only be provided to approved research staff who are trained in general research guidelines (i.e. GCP, TCPS2, privacy tutorial). Patient identifiers will be stored in a separare REDCap folder with limited access. All data on the REDCap server is encrypted and all access is audited. A paper copy of the link between study ID and patient identifiers will be stored in a locked cabinet in a locked cabinet inside our locked research offices in the hospital, which is accessed only by our research staff. This link, both paper and electronic, will be destroyed at the end of the study. Any other hard copies of study related information (i.e. signed Informed Consent Forms), will be transported within SJHH by the research staff and stored in our secured offices. Patients will be assigned a study ID that will be recorded on their CRFs and no direct identifiers will be used on the Case Report Forms.

IMPACT OF RESEARCH

By using an integrated KT approach with clinicians, patients, researchers, drug policy advisors, information technology advisors, quality improvement advisors, and hospital and national medication safety administrators involved in the project from protocol to dissemination, we hope to strengthen and broaden the usual dissemination of research to practice and policy. However, this is a pilot study, so the main dissemination question will revolve around whether there is sufficient value to justify a larger, definitive clinical trial. Given the major improvements in research efficiency and international research product dissemination that EPIC affords us, we will be cultivating a Canadian EPIC-based research network amongst the impending participating hospitals.

ETHICS

The study has been approved (study #7598) by Hamilton Integrated Research Ethics Board. Significant protocol modifications will be proactively communicated to the research ethics boards through study amendments to obtain approval prior to the changes being implemented. Each modification will be assessed to determine whether it warrants communication with trial participants.

REFERENCES

1. Rankin A CC, Patterson SM, Kerse N, Cardwell CR, Bradley MC, et al. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev. 2018;9(9):CD008165.
2. Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. Cochrane Database Syst Rev. 2016;2:CD008986.
3. Redmond P, Grimes TC, McDonnell R, Boland F, Hughes C, Fahey T. Impact of medication reconciliation for improving transitions of care. Cochrane Database Syst Rev. 2018;8:CD010791.
4. Anderson LJ, Schnipper JL, Nuckols TK, Shane R, Sarkisian C, Le MM, et al. A systematic overview of systematic reviews evaluating interventions addressing polypharmacy. Am J Health Syst Pharm. 2019;76(21):1777-87.
5. Johansson T, Abuzahra ME, Keller S, Mann E, Faller B, Sommerauer C, et al. Impact of strategies to reduce polypharmacy on clinically relevant endpoints: a systematic review and meta-analysis. Br J Clin Pharmacol. 2016;82(2):532-48.
6. Gray SL, Hart LA, Perera S, Semla TP, Schmader KE, Hanlon JT. Meta-analysis of Interventions to Reduce Adverse Drug Reactions in Older Adults. J Am Geriatr Soc. 2018;66(2):282-8.
7. Le Berre M, Maimon G, Sourial N, Gueriton M, Vedel I. Impact of Transitional Care Services for Chronically Ill Older Patients: A Systematic Evidence Review. J Am Geriatr Soc. 2017;65(7):1597-608.
8. Kastner M, Cardoso R, Lai Y, Treister V, Hamid JS, Hayden L, et al. Effectiveness of interventions for managing multiple high-burden chronic diseases in older adults: a systematic review and meta-analysis. CMAJ. 2018;190(34):E1004-E12.
9. Ravn-Nielsen LV, Duckert ML, Lund ML, Henriksen JP, Nielsen ML, Eriksen CS, et al. Effect of an In-Hospital Multifaceted Clinical Pharmacist Intervention on the Risk of Readmission: A Randomized Clinical Trial. JAMA Intern Med. 2018;178(3):375-82.
10. WHO. Medication Without Harm: WHO; 2017 [Available from: https://www.who.int/initiatives/medication-without-harm.
11. Oscanoa TJ LF, Carvajal A. Hospital admissions due to adverse drug reactions in the elderly: A meta-analysis. Eur J Clin Pharmacol. 2017;6:759-70.
12. Alhawassi TM, Krass I, Bajorek BV, Pont LG. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. Clin Interv Aging. 2014;9:2079-86.
13. Hohl CM, de Lemos J, Abu Laban RB. Emergency hospitalizations for adverse drug events. N Engl J Med. 2012;366(9):858-9; author reply 9-60.
14. Canadian Institute for Health Information. Adverse Drug Reaction–Related Hospitalizations Among Seniors, 2006 to 2011: CIHI; 2013 [Available from: www.cihi.ca.
15. Laatikainen O, Miettunen J, Sneck S, Lehtiniemi H, Tenhunen O, Turpeinen M. The prevalence of medication-related adverse events in inpatients-a systematic review and meta-analysis. Eur J Clin Pharmacol. 2017;73(12):1539-49.
16. Chan B CD. Measuring Patient Harm in Canadian Hospitals. With What can be done to improve patient safety? : Canadian Institute for Health Information (CIHI); 2016 [Available from: www.cihi.ca.
17. Institue for Safe Medication Practices Canada. Ontario Hospital Critical Incidents Related to Medications or IV Fluids Analysis Report: October 2011 to December 2012: ISMP; 2013 [Available from: www.ismp-canada.org.
18. Parekh N, Ali K, Stevenson JM, Davies JG, Schiff R, Van der Cammen T, et al. Incidence and cost of medication harm in older adults following hospital discharge: a multicentre prospective study in the UK. Br J Clin Pharmacol. 2018;84(8):1789-97.
19. Amelung S, Meid AD, Nafe M, Thalheimer M, Hoppe-Tichy T, Haefeli WE, et al. Association of preventable adverse drug events with inpatients' length of stay-A propensity-matched cohort study. Int J Clin Pract. 2017;71(10).
20. Parameswaran Nair N, Chalmers L, Bereznicki BJ, Curtain CM, Bereznicki LR. Repeat Adverse Drug Reaction-Related Hospital Admissions in Elderly Australians: A Retrospective Study at the Royal Hobart Hospital. Drugs Aging. 2017;34(10):777-83.
21. Canadian Institute for Health Information. Drug Use Among Seniors on Public Drug Programs in

Canada 2012: CIHI; 2012 [Available from: www.cihi.ca.
22. Duerden M AT, Payne R. Polypharmacy and Medicines Optimisation: Making it Safe and Sound. UK: Kings Fund; 2013.
23. Hamilton H, Gallagher P, Ryan C, Byrne S, O'Mahony D. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. Arch Intern Med. 2011;171(11):1013-9.
24. Gallagher PF, O'Connor MN, O'Mahony D. Prevention of potentially inappropriate prescribing for elderly patients: a randomized controlled trial using STOPP/START criteria. Clin Pharmacol Ther. 2011;89(6):845-54.
25. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015;44(2):213-8.
26. Morgan SG, Hunt J, Rioux J, Proulx J, Weymann D, Tannenbaum C. Frequency and cost of potentially inappropriate prescribing for older adults: a cross-sectional study. CMAJ Open. 2016;4(2):E346-51.
27. Bayoumi I, Dolovich L, Hutchison B, Holbrook A. Medication-related emergency department visits and hospitalizations among older adults. Can Fam Physician. 2014;60(4):e217-22.
28. Budnitz DS, Shehab N, Lovegrove MC, Geller AI, Lind JN, Pollock DA. US Emergency Department Visits Attributed to Medication Harms, 2017-2019. JAMA. 2021;326(13):1299-309.
29. Holbrook A JV, Goldsmith CH, Shcherbatykh IY, COMPETE Investigators. A comprehensive appropriateness of prescribing questionnaire was validated by nominal consensus group. J Clin Epidemiol. 2007;10(60):1022-8.
30. Holbrook A KK, Troyan S, Goldmith C, Smiley T, Nabzdyk K. Measuring the appropriateness of prescribing. Can it be explicit and evidence-based? Can J Clin Pharmacol. 1999;6(44).
31. Lee JY, Muratov S, Tarride JE, Holbrook AM. Managing High-Cost Healthcare Users: The International Search for Effective Evidence-Supported Strategies. J Am Geriatr Soc. 2018;66(5):1002-8.
32. Lee J MS, Tarride J-E, Paterson JM, Thavorn K, Mbuagbaw L, Gomes T, Khuu W, Seow H, Thabane L, Holbrook A. Medication use and its impact on high-cost health care users among older adults: protocol for the population-based matched cohort HiCOSTT study. CMAJ Open. 2011;9(1):E44-52.
33. Muratov S LJ, Holbrook A, Paterson JM, Guertin JR, Mbuagbaw L, et al. Unplanned index hospital admissions among new older high-cost health care users in Ontario: a population-based matched cohort study. CMAJ Open. 2019;3(7):E537-E45.
34. Muratov S, Lee J, Holbrook A, Guertin JR, Mbuagbaw L, Paterson JM, et al. Incremental healthcare utilisation and costs among new senior high-cost users in Ontario, Canada: a retrospective matched cohort study. BMJ Open. 2019;9(10):e028637.
35. Lee J MS, Tarride J, Paterson J, Thavorn K, Mbuagbaw L, et al. Medication Predictors of High Cost Healthcare Use Among Older Adults. Canadian Association for Health Services and Policy Research (CAHSPR) Conference; May 29-31; Montreal, QC2018.
36. Sanh M HA, Macdonald P, Lee J. Potentially Inappropriate Prescribing in Hospitalized Older Adult High-Cost Health Care Users: A Pilot Study. The Canadian Journal of Hospital Pharmacy. 2022;75(3).
37. Zhao EJ. The future of electronic medical records in Canada. CMAJ. 2019;191(19):E542.
38. Agency for Healthcare Research and Quality. 10 Patient Safety Tips for Hospitals: Agency for Healthcare Research and Quality; 2018 [Available from: http://www.ahrq.gov/patients-consumers/diagnosis-treatment/hospitals-clinics/10-tips/index.html.
39. Canadian Patient Safety Institute (CPSI). Improving Medication Safety Canada: CPSI; 2021 [Available from: https://www.patientsafetyinstitute.ca/en/Topic/Pages/Improving-Medication-Safety.aspx.
40. Institue for Safe Medication Practices Canada. Electronic Prescribing in Primary Care: Effects on Medication Safety. Canada; 2018.
41. B M. Epic Systems lands Best in KLAS award 8th year in a row: Healthcare IT News; 2018 [Available from: https://www.healthcareitnews.com/news/epic-systems-lands-best-klas-award-8th-year- row.
42. EPIC [Internet]. 1979 [cited 2017]. Available from: https://www.epic.com/about.
43. Dovetale [Internet]. St. Joseph's Healthcare Hamilton. 2017.
44. Mc Cord KA HL. Using electronic health records for clinical trials: Where do we stand and where can we go? Canadian Medical Association Journal. 2019;5(191):E128-E33.

45. Royal College of Physicians and Surgeons of Canada. Clinical Pharmacology and Toxicology Competencies: The Royal College of Physicians and Surgeons of Canada; 2021 [Available from: file:///C:/Users/vtelford/Downloads/clinical-pharmacology-toxicology-competencies-e%20(1).pdf.
46. Thabane L, Hopewell S, Lancaster GA, Bond CM, Coleman CL, Campbell MJ, et al. Methods and processes for development of a CONSORT extension for reporting pilot randomized controlled trials. Pilot Feasibility Stud. 2016;2:25.
47. Thabane L, Lancaster G. A guide to the reporting of protocols of pilot and feasibility trials. Pilot Feasibility Stud. 2019;5:37.
48. COACHeD RCT Capacity to Consent Questionnaire [Internet]. MacSphere. 2021. Available from: http://hdl.handle.net/11375/27712.
49. Shears M, Takaoka A, Rochwerg B, Bagshaw SM, Johnstone J, Holding A, et al. Assessing frailty in the intensive care unit: A reliability and validity study. J Crit Care. 2018;45:197-203.
50. Health Quality Ontario. Transitions between Hospital and Home: HQO; 2022 [Available from: https://www.hqontario.ca/Quality-Improvement/Quality-Improvement-in-Action/Health-Links/Health-Links-Resources/Transitions-between-Hospital-and-Home.
51. Stacey D, Legare F, Lewis K, Barry MJ, Bennett CL, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2017;4:CD001431.
52. Fatima S, Holbrook A, Schulman S, Park S, Troyan S, Curnew G. Development and validation of a decision aid for choosing among antithrombotic agents for atrial fibrillation. Thromb Res. 2016;145:143-8.
53. Holbrook AM PE, Troyan SM, Nikitovic M, Crowther MA. Personalized benefit-harm information influences patient decisions regarding warfarin. Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique. 2013;20(3).
54. Hong C KS, Curnew G, Schulman S, Pullenayegum E, Holbrook A. Validation of a patient decision aid for choosing between dabigatran and warfarin for atrial fibrillation. Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique. 2013;20(3):e229-37.
55. Holbrook A, Labiris R, Goldsmith CH, Ota K, Harb S, Sebaldt RJ. Influence of decision aids on patient preferences for anticoagulant therapy: a randomized trial. CMAJ. 2007;176(11):1583-7.
56. Lundahl B, Moleni T, Burke BL, Butters R, Tollefson D, Butler C, et al. Motivational interviewing in medical care settings: a systematic review and meta-analysis of randomized controlled trials. Patient Educ Couns. 2013;93(2):157-68.
57. Rankin A CC, Ryan CI, Clyne B, Smith SM, Hughes CM. Core Outcome Set for Trials Aimed at Improving the Appropriateness of Polypharmacy in Older People in Primary Care. Journal of the American Geriatrics Society. 2018;66(6):1206-12.
58. Prinsen CA VS, Rose MR, Boers M, Tugwell P, Clarke M, et al. How to select outcome measurement instruments for outcomes included in a "Core Outcome Set" - A Practical Guidline. Trials. 2016;17(1).
59. McDonald EG, Wu PE, Rashidi B, Wilson MG, Bortolussi-Courval E, Atique A, et al. The MedSafer Study-Electronic Decision Support for Deprescribing in Hospitalized Older Adults: A Cluster Randomized Clinical Trial. JAMA Intern Med. 2022;182(3):265-73.
60. Mangin D, Lamarche L, Agarwal G, Banh HL, Dore Brown N, Cassels A, et al. Team approach to polypharmacy evaluation and reduction: study protocol for a randomized controlled trial. Trials. 2021;22(1):746.
61. Blum MR, Sallevelt B, Spinewine A, O'Mahony D, Moutzouri E, Feller M, et al. Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM): cluster randomised controlled trial. BMJ. 2021;374:n1585.
62. O'Mahony D, Gudmundsson A, Soiza RL, Petrovic M, Jose Cruz-Jentoft A, Cherubini A, et al. Prevention of adverse drug reactions in hospitalized older patients with multi-morbidity and polypharmacy: the SENATOR* randomized controlled clinical trial. Age Ageing. 2020;49(4):605-14.
63. Riceckert A RD, Altiner A, Drewelow E, Esmail A, Flamm M, Hann M, Johansson T, Klaassen-Mielke R, Kunnamo I, Loffler C, Piccoliori G, Sommerauer C, Trampisch U, Vogele A, Woodham A, Sonnichsen A. Use of an electronic decision support tool to reduce polypharmacy in elderly people with chronic diseases: cluster randomised controlled trial. BMJ. 2020;369:m1822.
64. Vasilevskis E SAS, Hollingsworth E K, Shotwell S, Kripalani S, Mixon A, Simmons S. Deprescribing

Medications Among Older Adults From End of Hospitalization Through Postacute Care: A Shed-MEDS Randomized Clinical Trial. JAMA Intern Med. 2023.
65. Woo SA, Cragg A, Wickham ME, Peddie D, Balka E, Scheuermeyer F, et al. Methods for evaluating adverse drug event preventability in emergency department patients. BMC Med Res Methodol. 2018;18(1):160.
66. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med. 1991;324(6):377-84.
67. National Coordinating Council for Medication Error Reporting and Prevention. About Medication Errors: MERP: National Coordinating Council for Medication Error Reporting and Prevention; 2020 [Available from: https://www.nccmerp.org/about-medication-errors.
68. Patient Safety Network. Patient Safety 101: Medication Errors and Adverse Drug Events Rockville, Maryland: Agency for Healthcare Research and Quality; 2019 [Available from: https://psnet.ahrq.gov/primer/medication-errors-and-adverse-drug-events.
69. Holbrook A, Pullenayegum E, Thabane L, Troyan S, Foster G, Keshavjee K, et al. Shared electronic vascular risk decision support in primary care: Computerization of Medical Practices for the Enhancement of Therapeutic Effectiveness (COMPETE III) randomized trial. Arch Intern Med. 2011;171(19):1736-44.
70. American Society on Aging and American Society of Consultant Pharmacists Foundation. Medication Knowledge Assessment: Adult Medication; 2012 [Available from: http://adultmeducation.com/AssessmentTools_2.html.
71. Ontario HQ. Transitions between Hospital and Home: Care for People of All Ages: HQO; 2020 [Available from: https://www.hqontario.ca/Portals/0/documents/evidence/quality-standards/qs-transitions-between-hospital-and-home-quality-standard-en.pdf.
72. Wenger NS, Roth CP, Shekelle P, Investigators A. Introduction to the assessing care of vulnerable elders-3 quality indicator measurement set. J Am Geriatr Soc. 2007;55 Suppl 2:S247-52.
73. Euroqol. EQ-5D Instruments: Euroqol; 2018 [Available from: https://euroqol.org/eq-5d-instruments/.
74. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.
75. Xie F, Pullenayegum E, Gaebel K, Bansback N, Bryan S, Ohinmaa A, et al. A Time Trade-off-derived Value Set of the EQ-5D-5L for Canada. Med Care. 2016;54(1):98-105.
76. Tseng HM, Lee CH, Chen YJ, Hsu HH, Huang LY, Huang JL. Developing a measure of medication-related quality of life for people with polypharmacy. Qual Life Res. 2016;25(5):1295-302.
77. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET Handbook: version 1.0. Trials. 2017;18(Suppl 3):280.
78. Perino AC, Shrader P, Turakhia MP, Ansell JE, Gersh BJ, Fonarow GC, et al. Comparison of Patient-Reported Care Satisfaction, Quality of Warfarin Therapy, and Outcomes of Atrial Fibrillation: Findings From the ORBIT - AF Registry. J Am Heart Assoc. 2019;8(9):e011205.
79. COACHeD RCT Additional Files 2021 (CCCQ, OAC Knowledge Test, Patient/Caregiver Study Satisfaction Survey) [Internet]. MacSphere, McMaster University. 2021. Available from: http://hdl.handle.net/11375/27213.
80. Carrasquillo O. Health Care Utilization. Encyclopedia of Behavioral Medicine. Gellman MD, Turner JR ed. New York: Springer; 2013. p. 909-10.
81. Canadian Agency for Drug and Technogolies in Health (CADTH). Canadian Agency for Drug and Technogolies in Health [Internet] Canada: Canadian Journal of Health Technologies; 2021 [Available from: https://www.cadth.ca/.
82. CADTH. Guidelines for the Economic Evaluation of Health Technologies: Canada. Ottawa, ON: CADTH; 2017.
83. Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, et al. Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. Value Health. 2015;18(2):161-72.
84. Statulator. Statulator - An Online Statistical Calculator (Sample Size Calculator for Comparing Two Independent Means): online; 2014 [Available from: http://statulator.com/SampleSize/ss2M.html.
85. LJ W. The Adaptive Biased Coin Design for Sequential Experiments. The Annals of Statistics.

1978;6(1):92-100.
86. Markaaryan T RW. Exact properties of Efron's biased coin randomization procedure. Ann Statist. 2010;38(3):1546-67.
87. Soares JF JWC. Some restricted randomization rules in sequential designs. Communications in Statistics. 1983;12(17):2017-34.
88. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
89. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.
90. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. Pilot Feasibility Stud. 2016;2:64.
91. Holbrook A VK, Yoo L, Troyan S, Schulman S, Douketis J, Thabane L, Giilck S, Koubaesh Y, Hyland S, Keshavjee K, Ho J, Tarride J-E, Ahemd A, Talman M, Leonard B, Ahemd K, Refai M, Siegal D. Coordination of Oral Anticoagulant Care at Hospital Discharge (COACHeD): Protocol for a Pilot Randomised Controlled Trial. Pilot Feasibility Stud. 2022;8(166).
92. Ross MCSB, Wu PE, Atique Md Candidate A, Papillon-Ferland L, Tamblyn R, Lee TC, et al. Adverse Drug Events in Older Adults: Review of Adjudication Methods in Deprescribing Studies. J Am Geriatr Soc. 2020;68(7):1594-602.

Figure 1. IMPROVE-IT HRM RCT Flow Diagram

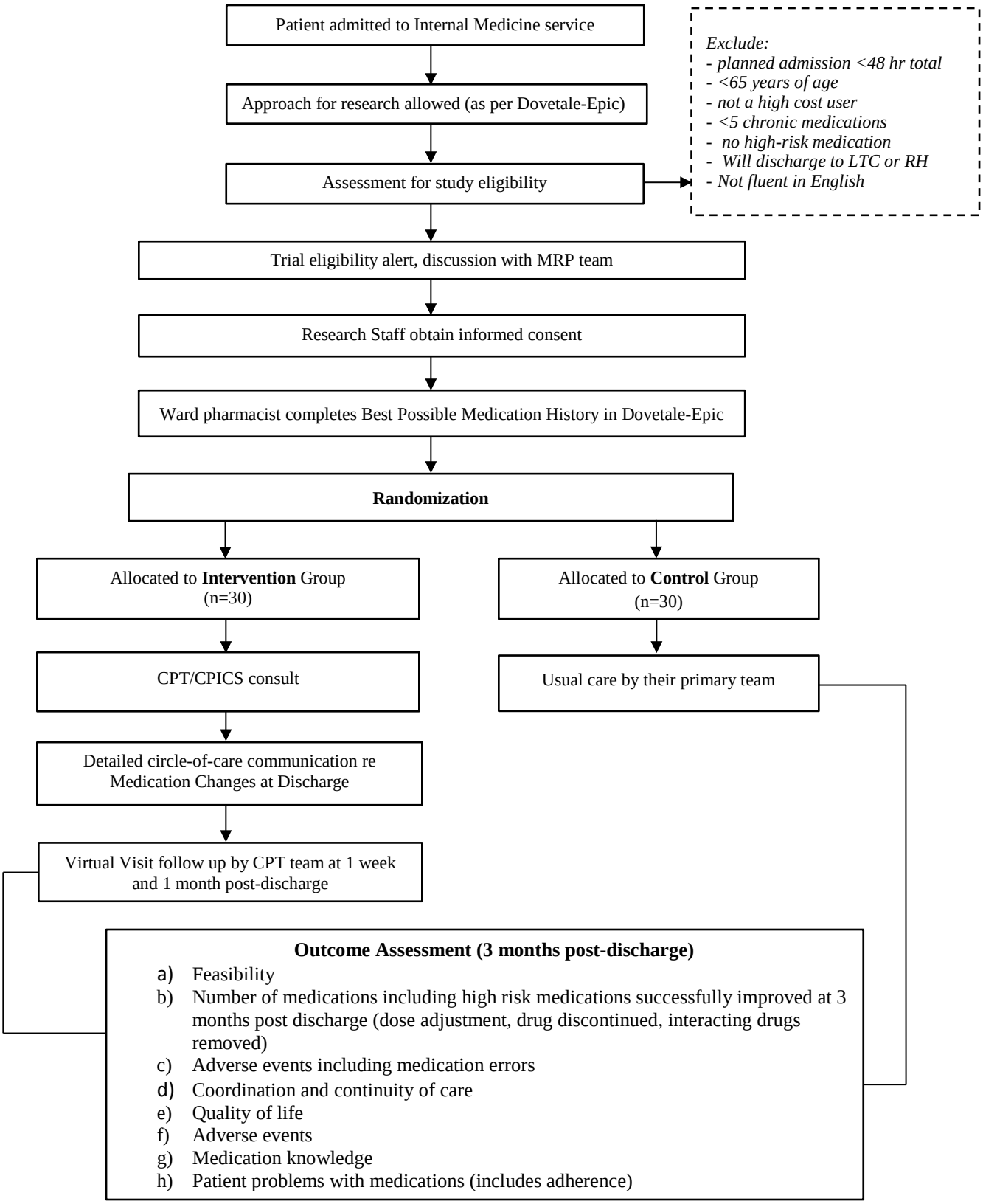

Figure 2. IMPROVE-IT HRM Clinical Approach

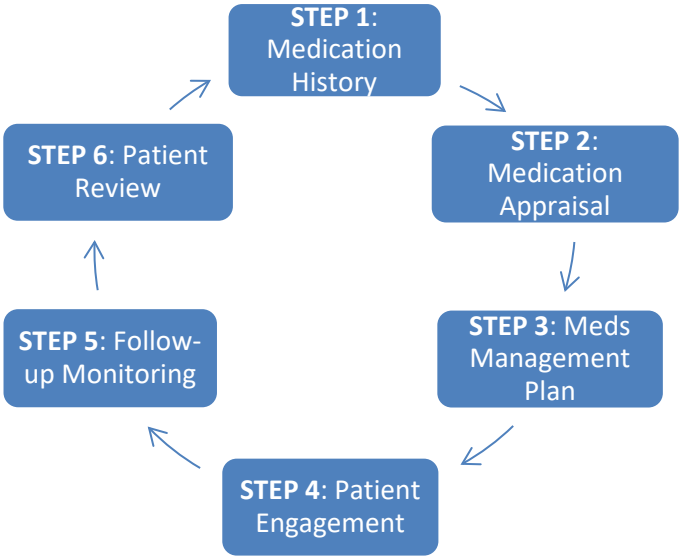

Table 1. IMPROVE-IT HRM OUTCOMES[29, 30, 57, 59, 60, 65, 68, 91, 92]

	Outcome
Feasibility	**1.** Participant recruitment rates
	2. Participant retention rate
	3. Trial resource utilization, costs
	4. Recommendation acceptance rates by MRP team
	5. Recommendation acceptance rates by patient
	6. Recommendation adherence rates by patient
	7. CPICS consultation volume capacity
	8. Potential to intervene entirely virtually (online)
Clinical	**1.** Medication Management Outcomes a) # drug therapy problems improved b) # High Risk medication problems improved c) # PIMs tapered or discontinued (using APEQ) d) # medications per patient end-study versus baseline
	2. Adverse drug events including adverse drug withdrawal event
	3. Medication Errors, including preventability
	4. Patient Problems with Medications Questionnaire (includes general adherence)
	5. Coordination and continuity of care
	6. Patient Quality of Life (EQ-5D-5L and Medication-related QOL)
	7. Patient Knowledge of Medications
	8. Satisfaction with Care (Patients and Providers)
	9. Health Resource Utilization, including Clinical events of death, ED visits, hospitalization or unplanned physician visits; medication costs, to estimate cost - effectiveness

* An Adverse drug event (ADE) is defined as "Harm caused by exposure to a drug" whereas an adverse drug reaction (ADR) is a subset of these events, where harm is caused by a drug under appropriate use (i.e. at usual doses) – adjudicated using Leape and Bates scale: 6- definitely due to medication, 5- probably due to medication, 4- possibly due to medication, 3- possibly due to disease, 2- probably due to disease, 1- definitely due to disease (5 and 6 considered ADE).[66] Medication Errors have been defined as an error (of commission or omission) at any step along the pathway that begins with prescribing and ends with the patient taking the medication.[66]

Table 2. IMPROVE-IT HRM Study Outcomes and Measures

Outcomes*		Criteria for success	Outcome Measure	Method of Analysis	When Assessed
A. Feasibility Outcomes					
A1. Primary feasibility outcomes	A1.1 Participant recruitment rates	≥ 30% of those eligible will be considered success	Percentage recruited and rate of recruitment (of those screened, of those eligible and of those approached).	Count of percentages over time	Baseline
	A1.2 Participant retention rate	≥ 90% is considered success	Primary: Percentage of those recruited (eligible and signed informed consent) who were alive at end of study**	Count of percentages over time	End of study
	A1.3 Intervention Adherence	≥ 90% is considered success	Percentage of those recruited who completed each phase of the study (baseline, virtual visits, end of study)	Count of percentages over time	End of study
	A1.4 Study Resource Utilization	< $1500 per patient recruited and completing the study	Study costs per patient recruited to end-follow-up	Cost of personnel, supplies, travel, etc. to run the study	End of study
A2. Secondary feasibility outcomes	A2.1 CPICS Recommendation Acceptance – Primary Team	≥ 50% medication recommendations	% CPICS recommendations per patient accepted (continued or implemented)	Count of percentages over time, Descriptive	End of study
	A2.2 CPICS Recommendation Acceptance – Patients	≥ 50% medication recommendations	% CPICS recommendations per patient that were followed by patient	Count of percentages over time, Descriptive	End of study

	A2.3 CPICS Recommendation Adherence – Patients	≥ 90% is considered success	% of intervention patients who follow CPICS recommendations throughout the study (virtual visits, end of study)	Count of percentages over time, Descriptive	Virtual Visits, End of Study
	A2.4 CPICS Consultation Volume Capacity	Number of eligible patients available to approach per week is > 3 per day	Volume of eligible patients available to approach per week	Count of percentages over time	Baseline
	A2.5 Potential to intervene entirely virtually	≥ 90% patients can be managed through follow-up entirely by virtual care platform	Number (%) patients entering follow-up who do not require an unscheduled in person visit Number of follow-up visits conducted using secure videoconference platform	Count of percentages over time, Descriptive Count of rates and percentages over time	End of study
B. Clinical Outcomes		**Hypothesis**			
B1. Primary clinical outcomes	B1.1 Drug Therapy Problems Improved	Intervention group will have more improved drug therapy problems compared to control group (e.g. dose adjusted, discontinued, interacting drugs removed)	Percentage of identified baseline drug therapy problems that have been improved by end of study	Count of percentages by end of study	End of study
B2 Secondary clinical outcomes	B2.1 Medication Management	Intervention will report better medication management	# medications adjusted throughout study; # medications remaining adjusted as per CPT recommendations end-study; # High Risk medications adjusted	T-tests	Baseline, Virtual Visits and End of Study

		throughout study; # High Risk medications remaining adjusted as per CPT recommendations end-study; # PIMs tapered or discontinued; # medications per patient end-study versus baseline		
B2.2 Adverse Drug Events	Intervention will have lower event rates than control	Event rate counts from end of study interviews using Leape and Bates scale	T-tests	End of study
B2.3 Coordination and continuity of care	Intervention will have higher ratings than control	Coordination and Continuity of Care Questionnaire	T-tests	End of study
B2.4 Patient quality of life	Intervention will improve more than control	EQ5D-5L and MedQOL - difference in mean change scores at the end of the study.	T-tests (scored in SAS)	Baseline and end of study
B2.5 Medication Knowledge – patient	Intervention will have higher scores than control	Medication Knowledge Assessment Form	T-tests	Baseline and end of study
B2.6 Patient Satisfaction with Care	Intervention will have higher scores than control	Patient Satisfaction Questionnaire	Descriptive analysis	End of study
B2.7 Provider Satisfaction with Care	Intervention will have higher scores than control	Physician, pharmacist Study Satisfaction Questionnaire	Descriptive analysis	End of study
B2.9 Patient Problems with Medications	Intervention will have fewer medication problems than control	COMPETE Medication Problems Questionnaire	T-tests	End of study

	B2.10 Medication Errors	Intervention will have fever medication errors	NCC-MERP definition	T-tests	End of study
	B2.11 Cost-effectiveness/Resource Utilization	Intervention will be cost-effective compared to control using a threshold of $50,000 per QALY.	Cost per adverse drug events avoided and cost per quality-adjusted life-years (QALYs)	Economic analysis	Based on EQ-5D-5L at baseline and 3-month follow-up, and adverse events at 3-month follow-up

**Include patients who are alive and those we were able to follow throughout the study, but may not complete the 3-month follow-up

Appendix 1. IMPROVE-IT HRM High-Risk Medications[27, 28]

Medication Families	Medications	ATC Codes
1. Anti-thrombotics	Warfarin	B01AA03
	Acenocoumarol	B01AA07
	Heparin	B01AB01
	Enoxaparin	B01AB05
	Nadroparin	B01AB06
	Tinzaparin	B01AB10
	Argatroban	B01AE03
	Bivalirudin	B01AE06
	Dabigatran etexilate	B01AE07
	Rivaroxaban	B01AF01
	Apixaban	B01AF02
	Edoxaban	B01AF03
	Fondaparinux	B01AX05
2. Analgesics		
2.1. Opioids	Morphine	N02AA01
	Hydromorphone	N02AA03
	Oxycodone	N02AA05
	Fentanyl	N02AB03
	Buprenorphine	N02AE01
	Butorphanol	N02AF01
	Nalbuphine	N02AF02
	Tramadol	N02AX02
	Tapentadol	N02AX06
	Codeine	R05DA04
	Hydrocodone	R05DA03
	Methadone	N07BC02
	Diamorphine	N07BC06
	Oxycodone and naloxone	N02AA55
	Codeine, combinations with psycholeptics	N02AA79
	Oxycodone and paracetamol	N02AJ17
	Oxycodone and acetylsalicylic acid	N02AJ18

	Codeine, combinations excl. psycholeptics	N02AA59
	Tramadol and paracetamol	N02AJ13
	Codeine and paracetamol	N02AJ06
	Hydrocodone	R05DA03
2.2. Glucocorticoids	Betamethasone	H02AB01
	Dexamethasone	H02AB02
	Methylprednisolone	H02AB04
	Prednisolone	H02AB06
	Prednisone	H02AB07
	Triamcinolone	H02AB08
	Hydrocortisone	H02AB09
	Cortisone	H02AB10
2.3. Colchicine (long term use)	Colchicine	M04AC01
3.	Doxycycline	J01AA02
	Tetracycline	J01AA07
	Minocycline	J01AA08
	Tigecycline	J01AA12
	Chloramphenicol	J01BA01
	Ampicillin	J01CA01
	Amoxicillin	J01CA04
	Amoxicillin and beta-lactamase inhibitor	J01CR02
	Piperacillin	J01CA12
	Piperacillin and beta-lactamase inhibitor	J01CR05
	Benzylpenicillin	J01CE01
	Phenoxymethylpenicillin	J01CE02
	Procaine benzylpenicillin	J01CE09
	Cloxacillin	J01CF02
	Oxacillin	J01CF04
	Cefalexin	J01DB01
	Cefalotin	J01DB03
	Cefazolin	J01DB04
	Cefadroxil	J01DB05
	Cefotaxime	J01DD01
	Ceftazidime	J01DD02

	Ceftriaxone	J01DD04
	Cefixime	J01DD08
	Cefepime	J01DE01
	Aztreonam	J01DF01
	Meropenem	J01DH02
	Ertapenem	J01DH03
	Ceftobiprole medocaril	J01DI01
	Trimethoprim	J01EA01
	Sulfamethizole	J01EB02
	Sulfapyridine	J01EB04
	Sulfamethoxazole and trimethoprim	J01EE01
	Sulfadiazine	J01EC02
	Erythromycin	J01FA01
	Spiramycin	J01FA02
	Clarithromycin	J01FA09
	Azithromycin	J01FA10
	Clindamycin	J01FF01
	Streptomycin	J01GA01
	Tobramycin	J01GB01
	Gentamicin	J01GB03
	Amikacin	J01GB06
	Ciprofloxacin	J01MA02
	Norfloxacin	J01MA06
	Levofloxacin	J01MA12
	Moxifloxacin	J01MA14
	Vancomycin	J01XA01
	Telavancin	J01XA03
	Dalbavancin	J01XA04
	Colistin	J01XB01
	Polymyxin B	J01XB02
	Metronidazole	J01XD01
	Nitrofurantoin	J01XE01
	Fosfomycin	J01XX01
	Spectinomycin	J01XX04
	Methenamine	J01XX05

	Linezolid	J01XX08
	Daptomycin	J01XX09
	Bacitracin	J01XX10
	Tedizolid	J01XX11
	Ceftolozane and beta-lactamase inhibitor	J01DI54
	Imipenem and cilastatin	J01DH51
	Lefamulin	J01XX12
	Amphotericin B	J02AA01
	Ketoconazole	J02AB02
	Fluconazole	J02AC01
	Itraconazole	J02AC02
	Voriconazole	J02AC03
	Posaconazole	J02AC04
	Isavuconazole	J02AC05
	Caspofungin	J02AX04
	Micafungin	J02AX05
	Anidulafungin	J02AX06
	Rifampicin	J04AB02
	Rifabutin	J04AB04
	Isoniazid	J04AC01
	Pyrazinamide	J04AK01
	Ethambutol	J04AK02
	Dapsone	J04BA02
	Acyclovir	J05AB01
	Ganciclovir	J05AB06
	Famciclovir	J05AB09
	Valaciclovir	J05AB11
	Cidofovir	J05AB12
	Valganciclovir	J05AB14
	Remdesivir	J05AB16
	Foscarnet	J05AD01
	Ritonavir	J05AE03
	Fosamprenavir	J05AE07
	Atazanavir	J05AE08
	Tipranavir	J05AE09

	Darunavir	J05AE10
	Nirmatrelvir and ritonavir	J05AE30
	Zidovudine	J05AF01
	Lamivudine	J05AF05
	Abacavir	J05AF06
	Tenofovir disoproxil	J05AF07
	Adefovir dipivoxil	J05AF08
	Entecavir	J05AF10
	Tenofovir alafenamide	J05AF13
	Nevirapine	J05AG01
	Efavirenz	J05AG03
	Etravirine	J05AG04
	Rilpivirine	J05AG05
	Doravirine	J05AG06
	Zanamivir	J05AH01
	Oseltamivir	J05AH02
	Raltegravir	J05AJ01
	Dolutegravir	J05AJ03
	Cabotegravir	J05AJ04
	Ribavirin	J05AP01
	Sofosbuvir	J05AP08
	Sofosbuvir and ledipasvir	J05AP51
	Sofosbuvir and velpatasvir	J05AP55
	Sofosbuvir, velpatasvir and voxilaprevir	J05AP56
	Glecaprevir and pibrentasvir	J05AP57
	Zidovudine and lamivudine	J05AR01
	Lamivudine and abacavir	J05AR02
	Tenofovir disoproxil and emtricitabine	J05AR03
	Zidovudine, lamivudine and nevirapine	J05AR05
	Emtricitabine, tenofovir disoproxil and efavirenz	J05AR06
	Emtricitabine, tenofovir disoproxil and rilpivirine	J05AR08
	Emtricitabine, tenofovir disoproxil, elvitegravir and cobicistat	J05AR09

	Lopinavir and ritonavir	J05AR10
	Lamivudine, abacavir and dolutegravir	J05AR13
	Darunavir and cobicistat	J05AR14
	Emtricitabine and tenofovir alafenamide	J05AR17
	Emtricitabine, tenofovir alafenamide, elvitegravir and cobicistat	J05AR18
	Emtricitabine, tenofovir alafenamide and rilpivirine	J05AR19
	Emtricitabine, tenofovir alafenamide and bictegravir	J05AR20
	Dolutegravir and rilpivirine	J05AR21
	Emtricitabine, tenofovir alafenamide, darunavir and cobicistat	J05AR22
	Lamivudine, tenofovir disoproxil and doravirine	J05AR24
	Lamivudine and dolutegravir	J05AR25
	Inosine pranobex	J05AX05
	Enfuvirtide	J05AX07
	Maraviroc	J05AX09
	Maribavir	J05AX10
	Letermovir	J05AX18
	Tecovirimat	J05AX24
	Baloxavir marboxil	J05AX25
	Fostemsavir	J05AX29
	Lenacapavir	J05AX31
4. Antineoplastics	Cyclophosphamide	L01AA01
	Chlorambucil	L01AA02
	Melphalan	L01AA03
	Chlormethine	L01AA05
	Ifosfamide	L01AA06
	Bendamustine	L01AA09
	Busulfan	L01AB01
	Treosulfan	L01AB02
	Thiotepa	L01AC01
	Carmustine	L01AD01

	Lomustine	L01AD02
	Temozolomide	L01AX03
	Dacarbazine	L01AX04
	Methotrexate	L01BA01
	Raltitrexed	L01BA03
	Pemetrexed	L01BA04
	Pralatrexate	L01BA05
	Mercaptopurine	L01BB02
	Tioguanine	L01BB03
	Cladribine	L01BB04
	Fludarabine	L01BB05
	Clofarabine	L01BB06
	Nelarabine	L01BB07
	Cytarabine	L01BC01
	Fluorouracil	L01BC02
	Gemcitabine	L01BC05
	Capecitabine	L01BC06
	Azacitidine	L01BC07
	Decitabine	L01BC08
	Vinblastine	L01CA01
	Vincristine	L01CA02
	Vindesine	L01CA03
	Vinorelbine	L01CA04
	Paclitaxel	L01CD01
	Docetaxel	L01CD02
	Cabazitaxel	L01CD04
	Topotecan	L01CE01
	Irinotecan	L01CE02
	Trabectedin	L01CX01
	Dactinomycin	L01DA01
	Doxorubicin	L01DB01
	Daunorubicin	L01DB02
	Epirubicin	L01DB03
	Idarubicin	L01DB06
	Mitoxantrone	L01DB07

	Bleomycin	L01DC01
	Mitomycin	L01DC03
	Imatinib	L01EA01
	Dasatinib	L01EA02
	Nilotinib	L01EA03
	Bosutinib	L01EA04
	Ponatinib	L01EA05
	Asciminib	L01EA06
	Gefitinib	L01EB01
	Erlotinib	L01EB02
	Afatinib	L01EB03
	Osimertinib	L01EB04
	Dacomitinib	L01EB07
	Vemurafenib	L01EC01
	Dabrafenib	L01EC02
	Encorafenib	L01EC03
	Crizotinib	L01ED01
	Ceritinib	L01ED02
	Alectinib	L01ED03
	Brigatinib	L01ED04
	Lorlatinib	L01ED05
	Trametinib	L01EE01
	Cobimetinib	L01EE02
	Binimetinib	L01EE03
	Selumetinib	L01EE04
	Palbociclib	L01EF01
	Ribociclib	L01EF02
	Abemaciclib	L01EF03
	Temsirolimus	L01EG01
	Everolimus	L01EG02
	Lapatinib	L01EH01
	Neratinib	L01EH02
	Tucatinib	L01EH03
	Ruxolitinib	L01EJ01
	Fedratinib	L01EJ02

	Axitinib	L01EK01
	Ibrutinib	L01EL01
	Acalabrutinib	L01EL02
	Zanubrutinib	L01EL03
	Idelalisib	L01EM01
	Alpelisib	L01EM03
	Erdafitinib	L01EN01
	Pemigatinib	L01EN02
	Infigratinib	L01EN03
	Sunitinib	L01EX01
	Sorafenib	L01EX02
	Pazopanib	L01EX03
	Vandetanib	L01EX04
	Regorafenib	L01EX05
	Cabozantinib	L01EX07
	Lenvatinib	L01EX08
	Nintedanib	L01EX09
	Midostaurin	L01EX10
	Larotrectinib	L01EX12
	Gilteritinib	L01EX13
	Entrectinib	L01EX14
	Capmatinib	L01EX17
	Ripretinib	L01EX19
	Tepotinib	L01EX21
	Selpercatinib	L01EX22
	Pralsetinib	L01EX23
	Rituximab	L01FA01
	Ofatumumab	L01FA02
	Obinutuzumab	L01FA03
	Inotuzumab ozogamicin	L01FB01
	Daratumumab	L01FC01
	Isatuximab	L01FC02
	Trastuzumab	L01FD01
	Pertuzumab	L01FD02
	Trastuzumab emtansine	L01FD03

	Trastuzumab deruxtecan	L01FD04
	Cetuximab	L01FE01
	Panitumumab	L01FE02
	Necitumumab	L01FE03
	Nivolumab	L01FF01
	Pembrolizumab	L01FF02
	Durvalumab	L01FF03
	Avelumab	L01FF04
	Atezolizumab	L01FF05
	Cemiplimab	L01FF06
	Dostarlimab	L01FF07
	Bevacizumab	L01FG01
	Ramucirumab	L01FG02
	Gemtuzumab ozogamicin	L01FX02
	Ipilimumab	L01FX04
	Brentuximab vedotin	L01FX05
	Dinutuximab	L01FX06
	Blinatumomab	L01FX07
	Elotuzumab	L01FX08
	Mogamulizumab	L01FX09
	Tafasitamab	L01FX12
	Enfortumab vedotin	L01FX13
	Polatuzumab vedotin	L01FX14
	Sacituzumab govitecan	L01FX17
	Amivantamab	L01FX18
	Cisplatin	L01XA01
	Carboplatin	L01XA02
	Oxaliplatin	L01XA03
	Procarbazine	L01XB01
	Porfimer sodium	L01XD01
	Methyl aminolevulinate	L01XD03
	Aminolevulinic acid	L01XD04
	Tretinoin	L01XF01
	Bortezomib	L01XG01
	Carfilzomib	L01XG02

	Ixazomib	L01XG03
	Vorinostat	L01XH01
	Romidepsin	L01XH02
	Vismodegib	L01XJ01
	Sonidegib	L01XJ02
	Glasdegib	L01XJ03
	Olaparib	L01XK01
	Niraparib	L01XK02
	Talazoparib	L01XK04
	Axicabtagene ciloleucel	L01XL03
	Tisagenlecleucel	L01XL04
	Brexucabtagene autoleucel	L01XL06
	Idecabtagene vicleucel	L01XL07
	Amsacrine	L01XX01
	Asparaginase	L01XX02
	Altretamine	L01XX03
	Hydroxycarbamide	L01XX05
	Pentostatin	L01XX08
	Estramustine	L01XX11
	Mitotane	L01XX23
	Pegaspargase	L01XX24
	Arsenic trioxide	L01XX27
	Anagrelide	L01XX35
	Eribulin	L01XX41
	Aflibercept	L01XX44
	Venetoclax	L01XX52
	Enasidenib	L01XX59
	Selinexor	L01XX66
	Lurbinectedin	L01XX69
	Sotorasib	L01XX73
	Belzutifan	L01XX74
	Tebentafusp	L01XX75
5. Glucose lowering/hypoglycemics	Glibenclamide	A10BB01
	Chlorpropamide	A10BB02
	Tolbutamide	A10BB03

	Gliclazide	A10BB09
	Glimepiride	A10BB12
	Acarbose	A10BF01
	Rosiglitazone	A10BG02
	Pioglitazone	A10BG03
	Sitagliptin	A10BH01
	Saxagliptin	A10BH03
	Alogliptin	A10BH04
	Linagliptin	A10BH05
	Liraglutide	A10BJ02
	Lixisenatide	A10BJ03
	Dulaglutide	A10BJ05
	Semaglutide	A10BJ06
	Dapagliflozin	A10BK01
	Canagliflozin	A10BK02
	Empagliflozin	A10BK03
	Repaglinide	A10BX02
	Tirzepatide	A10BX16
	Insulin human	A10AB01
	Insulin pork	A10AB03
	Insulin lispro	A10AB04
	Insulin aspart	A10AB05
	Insulin glulisine	A10AB06
	Insulin human (intermediate acting)	A10AC01
	Insulin pork (intermediate acting)	A10AC03
	Insulin human (long acting)	A10AD01
	Insulin lispro (long acting)	A10AD04
	Insulin aspart (long acting)	A10AD05
6. Hormone therapy		
6.1 Postmenopausal estrogen	Estradiol	G03CA03
	Estrone	G03CA07
	Dienestrol	G03CB01
	Tibolone	G03CX01
6.2. Androgens for menopause	Methyltestosterone	G03BA02
	Testosterone	G03BA03

7. Cardiac Medications		
7.1. Diuretics	Hydrochlorothiazide	C03AA03
	Chlorthalidone	C03BA04
	Metolazone	C03BA08
	Indapamide	C03BA11
	Furosemide	C03CA01
	Bumetanide	C03CA02
	Etacrynic acid	C03CC01
	Spironolactone	C03DA01
	Eplerenone	C03DA04
	Amiloride	C03DB01
	Tolvaptan	C03XA01
7.2. Digoxin	Digoxin	C01AA05
7.3. Amiodarone	Amiodarone	C01BD01
8. Sedatives and hypnotics		
8.2. BZRAs	Flurazepam	N05CD01
	Nitrazepam	N05CD02
	Triazolam	N05CD05
	Temazepam	N05CD07
	Midazolam	N05CD08
	Zopiclone	N05CF01
	Zolpidem	N05CF02
	Eszopiclone	N05CF04
	Clonazepam	N03AE01
	Alprazolam	N05BA12
	Diazepam	N05BA01
	Lorazepam	N05BA06
8.3. Sedating Antihistamines	Alimemazine	R06AD01
	Chlorpheniramine	R06AB04
	Cyproheptadine	R06AX02
	Hydroxyzine	N05BB01
	Ketotifen	R06AX17
	Promethazine	R06AD02

	Cetirizine	R06AE07
	Dimenhydrinate	R06AA11
	Diphenhydramine	R06AA02
9. Baclofen	Baclofen	M03BX01
10. Antipsychotics	Chlorpromazine	N05AA01
	Methotrimeprazine	N05AA02
	Fluphenazine	N05AB02
	Perphenazine	N05AB03
	Prochlorperazine	N05AB04
	Trifluoperazine	N05AB06
	Periciazine	N05AC01
	Haloperidol	N05AD01
	Ziprasidone	N05AE04
	Lurasidone	N05AE05
	Flupentixol	N05AF01
	Zuclopenthixol	N05AF05
	Pimozide	N05AG02
	Loxapine	N05AH01
	Clozapine	N05AH02
	Olanzapine	N05AH03
	Quetiapine	N05AH04
	Asenapine	N05AH05
	Risperidone	N05AX08
	Aripiprazole	N05AX12
	Paliperidone	N05AX13
	Cariprazine	N05AX15
	Brexpiprazole	N05AX16
11. Lithium	Lithium	N05AN01
12. Tricyclic antidepressants	Amitriptyline	N06AA09
	Desipramine	N06AA01
	Imipramine	N06AA02
	Clomipramine	N06AA04

	Trimipramine	N06AA06
	Nortriptyline	N06AA10
	Doxepin	N06AA12
13. Trazodone	Trazodone	N06AX05
14. Acetylcholinesterase inhibitors	Donepezil	N06DA02
	Rivastigmine	N06DA03
	Galantamine	N06DA04
	Neostigmine	N07AA01
	Pyridostigmine	N07AA02
15. Oxybutinin	Oxybutynin	G04BD04
16. GI Medications	Metoclopramide	A03FA01
	Domperidone	A03FA03
	Misoprostol	A02BB01
	Cimetidine	A02BA01
	Ranitidine	A02BA02
	Famotidine	A02BA03
	Nizatidine	A02BA04
	Omeprazole	A02BC01
	Pantoprazole	A02BC02
	Lansoprazole	A02BC03
	Rabeprazole	A02BC04
	Esomeprazole	A02BC05
	Dexlansoprazole	A02BC06
	Sucralfate	A02BX02
	Trimebutine	A03AA05
	Dicyclomine	A03AA07
	Glycopyrronium	A03AB02
	Papaverine	A03AD01
	Pinaverium	A03AX04
17. Other (quinine, supplements melatonin, etc)	Quinine	P01BC01
	Melatonin	N05CH01
18.		

Appendix 2. IMPROVE-IT HRM Capacity to Consent Questionnaire

IMPROVE-IT HRM Capacity to Consent

Record ID _____

This participant is not eligible. This form can only be completed for participants who meet the preliminary eligibility criteria.

Screening ID [screen_id]

Start time: _____

I will now ask you a few questions to make sure you understand the study.

Is this a research study or is it part of the regular treatment that the hospital provides?	◯ Regular treatment ◯ Research study
What is the purpose of the study that was just described to you? Interviewer: Allow patient to answer and prompt for additional answers as at least 2 responses are required.	◯ I don't know/ No clue ◯ Partial response regarding medication/treatment (without mention of medication management/coordinated care) ◯ *One of the field notes examples or similar* (*Coordinate care/communication from hospital to home *Improve medication safety or medication management *Better communication with my providers about my medications *Help prevent complications related to taking multiple medications *High-risk medications *Other reasonable response)

What aspects of the study described might encourage you to participate? Interviewer: Allow patient to answer and prompt for additional answers if required as at least 2 responses are required.	◯ I don't know ◯ Partial response regarding treatment, follow-up ◯ *At least one of the specific themes in field note examples, or similar* (*Medication review with the doctor or pharmacist *Help me understand what is going on with my medications *Avoid confusion about my medications when I get discharged back home *Get advice about my medications and have my questions answered *Better communication with my doctors and specialists, so that they understand what happened and what is going on with my medications *Other reasonable response)
Do you have to be in this study if you do not want to participate?	◯ Yes or don't know ◯ No
If you withdraw from this study, will you still be able to receive regular medical care?	◯ Yes ◯ No

Can you tell us a couple of things that you will be asked to do if you participate in the study?? Interviewer: Allow patient to answer and prompt for additional answers if required as at least 2 responses are required.	◯ I don't know/no correct response ◯ Only one of the below field note examples ◯ *At least two of the following field note examples or similar* (*Go through my medications with the doctor or pharmacist *Answer some questionnaires at the beginning of the study *Participate in phone visits with doctor/pharmacist about my medications at different time points *Answer questions at the end of study *Other reasonable response)
What might be some risks or downsides involved with participating in this study? Interviewer: Allow patient to answer and prompt for additional answers if required as at least 2 responses are required.	◯ I don't know ◯ Partial response with generalities (eg, 'waste of time', 'too many phone calls', etc ◯ *One of the themes listed in the field note or similar* (*Inconvenience or hassle of research coordinators phoning me at three different time points *Time commitment involved at the beginning or with the phone calls *Potential for privacy breach of my personal health information *Too many people involved in my care *Other reasonable response)
Can you describe some of the benefits that you may gain by participating in this study?? Interviewer: Allow patient to answer and prompt for additional answers if required as at least 2 responses are required.	◯ I don't know ◯ Partial response on only one of the themes listed in field notes ◯ *At least one of the field note examples or similar* (*Avoiding complications with my medications *Help from a doctor/pharmacist with managing my medications *Understanding my medications better *Getting advice on what to do after I go home from the hospital *Better communication with my doctors about what is going on with my medications *Other reasonable response)
Is it possible that being in this study will not have any benefit to you personally?	◯ No, or don't know ◯ Yes

Total score	_____ (Threshold to enroll: 12/18)

REDCap Form Completion Details	
Form entered and completed by:	◯ Victoria Telford ◯ Research Assistant
Date of Form Completion:	_____
Time form completed	_____