CLINICAL TRIAL PROTOCOL

Novel application of simulation for providers to overcome decisional gaps in high-risk prescribing

National Clinical Trial (NCT) Identified Number: NCT04668248

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1. Background and Rationale

The overuse of medications with psychoactive properties such as antipsychotics, benzodiazepines, or sedative hypnotic “Z-drugs”, is extremely common in inpatient and acute care settings to manage delirium and agitation, despite the considerable risks associated with their use and guidelines that recommend their avoidance in older adults.[1-4] In addition to their short-term risks, many patients are discharged on these potentially inappropriate medications which leads to longer-term adverse consequences such as falls and cognitive decline.[5,6] While there are many contributors to the prescribing of these high-risk medications in the inpatient setting, provider-level barriers are thought to be central. These include clinical inertia (i.e., habits/culture of prescribing), perceived pressure from front-line nursing staff or patients and/or their caregivers, a lack of familiarity with a particular patient and fatigue.[7-9]

Unfortunately, efforts to address these barriers have been largely unsuccessful.[10-13] We hypothesize that this reflects inadequate addressing of the specific needs of complex and acutely-ill inpatients in stressful clinical situations by providers.

In stressful situations, people rely on automatic, quick, or even emotional thinking, sometimes referred to as “System 1” thinking and may make different decisions than they would if they were instead using controlled, slow or rational or “System 2” thought.[14-17] One example of a behavioral principle describing these differences is the “hot-cold” empathy gap which is based on the observation that when people are in rational or “cold” states, they incorrectly predict what their behavior will be during “hot states”.[18] Other related behavioral principles include those that describe deliberative versus impulsive thinking and have found similar gaps in behaviors when people are in different states.[19-21]

In the case of health care, the “empathy gap” has been thought to lead physicians to underestimate their actual prescribing of antibiotics or opioids when experiencing pressure to do so.[17] For the prescribing of potentially-inappropriate medications to acutely-ill inpatients, most interventions have focused on educating and training providers when they can access System 2 thinking mechanisms, and may not have adequately prepared them for making complex and urgent therapeutic decisions under System 1 conditions.[14,22]

Efforts to address decisional gaps between System 1 and System 2 thinking in other fields have involved role-playing or games to simulate System 2 thinking states, such as having participants

evaluate their cravings for tobacco during hot state and cold state sessions.[14,15,23,24] In clinical medicine, simulation has increasingly been used to help health care professionals, alone and in teams, practice how they would handle stressful situations such as cardiac arrest or emergent trauma situations in emergency rooms.[25-31] By extension, these approaches could help address decisional gaps for prescribing high-risk medications for older adults, thereby improving patient safety and welfare.

2. Study Aims

We propose a 2-phase project consisting of provider qualitative interviews and a 2-arm pilot randomized controlled pragmatic trial in which physicians in training (interns) caring for elderly inpatients are assigned to receive simulation training or an educational control. The main goal of this project is to improve patient safety.

The objectives and endpoints for the trial are summarized below.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine whether simulation-based training reduces the prescribing of high-risk medications to hospitalized older adults.	Number of high-risk medications doses prescribed per day to eligible patients assigned to intervention providers compared with control providers.	This outcome is measurable using electronic health record (EHR) data and will provide evidence of provider behavior change during the follow-up period.
Secondary		
To evaluate whether simulation-based training reduces the continued prescription for high-risk medication to hospitalized older adults at discharge.	Discharge medication order written for one of the eligible high-risk medications to eligible patients assigned to intervention providers versus control providers	This outcome is measurable using EHR data and will provide evidence of whether the intervention results in fewer high-risk medications for patients at discharge.
To determine whether there are impacts of simulation-based training on prescribing of other related medications.	Number of medication doses prescribed per day to eligible patients assigned to intervention providers versus control providers for opioids, trazodone, and melatonin	This outcome is measurable using EHR data and will provide evidence of whether there are spillover effects on other related medications.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To evaluate adoption and implementation outcomes for the intervention	Implementation outcomes informed by the Reach Effectiveness Adoption Implementation Maintenance (RE-AIM) framework: • Characteristics of consenting and non-consenting providers • Completion of the simulation training (intervention) or online educational training (control) • Feedback from and issues reported by providers about the intervention • Self-reported satisfaction with the intervention	These outcomes capture the extent to which the intervention could be replicated on a larger scale. This approach will provide valuable information regardless of the results of the trial, as evaluating implementation will enable us to explain why the intervention did not work, should that turn out to be the case. These outcomes are also easily measurable using baseline and endline (follow-up) questionnaires.

3. Study Design

3.1 Study site

Study participants will be providers recruited from the general medicine inpatient service at Brigham and Women's Hospital (BWH) and Brigham and Women's Faulkner Hospital (BWFH). BWH is part of Mass General Brigham (MGB), formerly known as Partners Healthcare, a large hospital system in Boston, MA, and are both staffed by the same general medicine service at the main BWH campus.

3.2 Overall design

We propose a 2-phase project consisting of provider qualitative interviews and a 2-arm pilot randomized controlled pragmatic trial in which physicians in training (interns) caring for elderly inpatients are assigned to receive simulation training or an educational control.

The first phase, qualitative interviews, are a separate aim from the pragmatic trial and have already been reviewed and approved by the MGB IRB and is governed under a separate protocol (MGB IRB: 2020P002467). This aim consists of brief virtual qualitative interviews with approximately 25 inpatient providers and allied team members (e.g., nurses or pharmacists) to elicit perspectives on prescribing of high-risk medications in the in-patients setting as well as simulation-based training. These interviews are being conducted virtually with providers at other MGB sites and former interns who are no longer part of the general medicine service to avoid contamination with the trial using an MGB-approved video platform. This aim is being used to inform the design of the simulation-based training intervention used

in Aim 2 (pragmatic trial). Providers are identified through referrals by clinicians and recent prescribing history and contacted through email invitation. They are providing verbal consent for their participation and receiving renumeration for their participation. **The remainder of this protocol is about the 2-arm pilot randomized trial.**

The 2-arm pilot randomized controlled trial will determine whether a newly-designed simulation-based training program for providers based on underlying principles of System 1 and System 2 thinking reduces prescribing of high-risk medications for hospitalized older adults versus control, with the ultimate goal of improving patient safety. We will also measure subsequent prescribing for patients cared for by other providers and other adoption and implementation outcomes to explore the extent to which the intervention could be used at scale.

BWH and BWFH uses 2-week service blocks for its inpatient general medicine evening coverage, and the service overall consists of 6 day and 8 evening (twilight) teams covering geographically distinct wards at 2 hospital sites with daily censuses of 15-20 patients. These teams typically consist of an attending, a resident, an intern (i.e., 1st year of residency), and medical students. There is no cross-coverage across teams. We will focus on interns from the “twilight” (i.e., evening) teams as they cover the shifts during which the high-risk medications of interest (specifically anti-psychotics, benzodiazepines, and sedative hypnotic “Z-drugs”) are typically first initiated and are also the first point of contact for nurses, pharmacists, and other physicians. Given their stage of training and the nature of their workflow, they are also most prone to make decisions using System 1 thinking.

At the beginning of each rotation, we will identify the interns assigned to the twilight teams (i.e., the primary prescriber and responding clinician on the general medicine service team). We will invite these interns to participate in the study via email invitation. Interns who consent will be randomized in a 1:1 ratio with a random number generator to one of 2 arms: (a) Arm 1: simulation intervention and (b) Arm 2: control (online education) intervention. The unit of randomization will therefore be the intern. Randomizing at the intern level will reduce the possibility of contamination across patients. Providers will receive $25 for completing the initial provider survey, $75 for completing the intervention or control assignment (e.g., simulation or online education training), and $50 for completing the endline (follow-up) questionnaire. Other ward staff will be blinded to arm assignment to the extent possible. Data analysts will be blinded to arm assignment. This is a highly feasible approach used by investigators conducting provider-facing intervention trials at BWH.

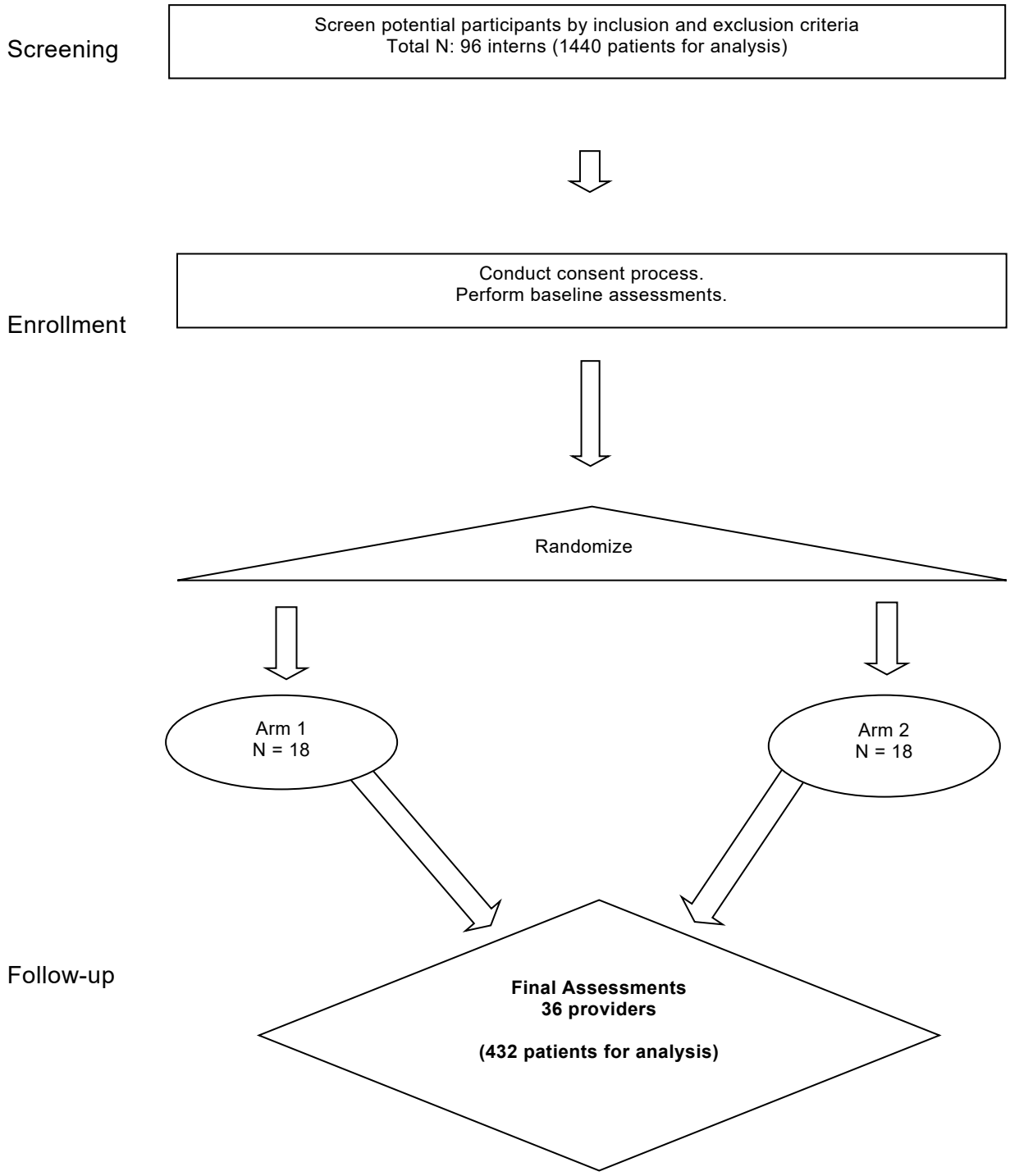
Providers assigned to the intervention arm will participate in a short simulation training at the beginning of their 2-week block (planned for their second day). The training will take place at the Neil and Elise Wallace STRATUS Center for Medical Simulation at Brigham and Women's Hospital and will follow all of their recommended and hospital-recommended practices on social distancing, including the learning limits. The training will also be led by Matthew DiFrancesco, hospitalist, Instructor in Medicine, and Assistant Director for Medicine at STRATUS. Based on discussion with Dr. DiFrancesco, the study team, and intern and resident interviews completed in the first phase, it is clear that in-person simulation will have be more effective at creating the stressful situations that could lead to inappropriate prescribing. Moreover, this approach has been used in numerous prior, unrelated trainings conducted by STRATUS and by the general medicine service.

Providers assigned to the control arm will receive online educational training about other poorly-prescribed medications, including albumin, transfusion, and blood product repletion guidelines. This information will be in the form of electronically-delivered links to information already housed and available at BWH, including reviewing BWH guidelines and literature about transfusion reactions. The interns will be asked to answer several clinical questions about optimal prescribing. Albumin and related products are also high-risk medications often overprescribed on twilight shifts. Receiving education about another high-risk medication will reduce contamination and allow the ability to measure outcomes to other high-risk medications.

Follow-up time for trial evaluation will begin on the day in which the interventions are delivered (planned for Day 2 of their service) and will continue until the end of their coverage block on the twilight team. The interventions in both arms will be delivered on the same day, so there will be equal follow-up time. Upon completion of the trial, we will evaluate outcomes, including prescribing and implementation outcomes, using structured EHR data on the patient-level and a follow-up survey of the interns at 2 weeks after randomization.

We believe that this is a minimal-risk study for several reasons. First, the goal of the study is to improve patient safety, by reducing the prescribing of high-risk medications in older adults in a way that is concordant with well-established clinical guidelines. Second, the intervention itself is a quality-improvement intervention, leveraging resources already available at BWH. Third, all prescribing decisions will be made by the patients' covering providers. Fourth, providers will provide consent for their participation and will not be required to participate. Finally, all patient-level outcomes will be evaluated only through structured EHR data, collected during routine care.

3.3 Study Schema



3.4 Scientific rationale for study design

The use of a randomized trial to evaluate the primary outcome and secondary clinical outcome is scientifically justified, as this design will be able to provide evidence of causality in the effectiveness of the tools on reducing prescribing. An observational study design, by contrast, would not provide the same degree of scientific rigor.

3.5 Justification for intervention

Simulation has increasingly been used to help health care professionals, alone and in teams, practice how they would handle stressful situations such as cardiac arrest or emergent trauma situations in emergency rooms. By extension, leveraging behavioral science principles within simulation to address decisional gaps in System 1 and System 2 thinking holds great promise for reducing for high-risk medications for older adults. Of note, the intervention in this study will be integrated in the intern schedule with minimal impact on workflow. We believe this is a minimal risk intervention overall, as providers could seek to ignore the simulation training and are ultimately responsible for making any prescribing decisions. Patients will not be specifically engaged as part of the trial, as any non-specific attention from the trial protocol in the control arm will undermine the ability to observe the effect of the intervention.

3.6 End-of-study definition

The trial will be completed 1 month after completing randomization. Providers and their eligible patients will be followed until the end of this follow-up date, or until censoring.

3.7 Data sources

Sources of research material, data that will be recorded, when data will be collected

We will use electronic health record (EHR) data to retrospectively identify eligible patients. Data regarding patients' medical history, disease control, medication use, and health care utilization will be obtained from EHR data (Epic). In specific we will extract clinical and financial information from the electronic medical record system (EpicCare), the patient accounting system (Resolute), the patient web portal and the master patient index (Identity). The various tables within these databases are refreshed on a daily, weekly or monthly basis. Data regarding intern scheduling and team assignments will be gathered from Amion®, the residency scheduling system. We will also gather information from provider surveys, one at baseline and one at the end of follow-up.

Linkages to subjects, access to subject identities

Individually-identifiable data are maintained for patient care purposes within the MGB network and are needed to identify patients for evaluation and to monitor care recommendations by providers. Without this linkage, we could not fulfill the study's objectives. To protect the confidentiality of these data, only the minimal necessary research staff will have access to personal identifiers. This will be necessary for linking data and contacting providers. After linkage is completed and study variables are created, all identifiable information will be deleted from the study database. All research staff are properly trained in research management and will be approved by the IRB. All personally identifiable health information will be kept under lock and key.

3.8 Schedule of activities

	Screening (7 days prior to rotation)	Randomization (2 days prior to rotation)	Day 2 of rotation	2-week follow-up
Review of general medical service schedule and outreach to eligible interns	X			
Completion of consent		X		
Completion of baseline questionnaire*		X		
Randomization		X		
Provision of interventions (simulation training and online education)			X	
Adverse event reporting measurement			X	X
Provision of endline (follow-up) questionnaire*				X
EHR and scheduling system data evaluation*				X

***Baseline Questionnaire (Providers):** Demographics (age, sex, race/ethnicity), 6-item State-Trait Anxiety Inventory[32], 8-item Physicians' Reaction to Uncertainty Stress from Uncertainty subscale

Endline Questionnaire (Providers): 6-item State-Trait Anxiety Inventory[32], 8-item Physicians' Reaction to Uncertainty Stress from Uncertainty subscale, Satisfaction with the interventions

EHR fields:

Baseline: Provider: Prior prescribing of high-risk medications; Eligible patients: Demographics (age, sex, race/ethnicity, insurance status), prior in-hospital use of one of the high-risk medications, admitted on one of the high-risk medications, hospitalization within last 30 days, total no. of home medications;

Follow-up: Prescribing of one of the high-risk medications, prescribing of albumin and other high-risk medications (e.g., opioids), discharge medication orders, administration of the one of the high-risk medications

Scheduling system (Amion®) fields:

Provider: Baseline; Prior inpatient service blocks (i.e., ICU service, ambulatory service), no. of months of internship, characteristics of the rest of the team (i.e., number of residents, seniority of attending, no. of other team members); Follow-up: Completion of simulation training, no. of days on twilight service

4. Study Population

The study will intervene upon physicians and their older adult patients admitted to the adult inpatient general internal medicine services at BWH and BWFH. We will focus on interns from the "twilight" (i.e., evening) teams as they cover the shifts during which the key high-risk medications of interest (specifically anti-psychotics, benzodiazepines, and sedative hypnotic "Z-drugs") are typically first initiated and are also the first point of contact for nurses, pharmacists, and other physicians. Given their stage of training and nature of their workflow, they are also most prone to make decisions using System 1 thinking. We plan to exclude patients for the purposes of analysis who were on the relevant high-risk medication of interest prior to admission. For example, patients who were admitted on a benzodiazepine will not be included in the benzodiazepine/sedative hypnotic analysis but will be included in the antipsychotic analysis. Benzodiazepines and sedative hypnotics will be considered interchangeable for this analysis, due to the fact that they have overlapping indications. We will conduct stratified analyses by whether patients by whether they had exposed to one of the high-risk medications during their present admission prior to being under the care of the consenting intern.

4.1 Inclusion Criteria

The study will include provider subjects for intervention and analysis and patient-subjects for analysis. The study criteria are defined below.

In order to be eligible to participate in this study, providers must meet all of the following criteria:

1. Intern practicing on the general internal medicine service at Brigham and Women's Hospital (including Faulkner)
2. Assigned to the "twilight" team
3. Consent to participate
4. Not previously identified for this study

Patients who meet the following criteria will be included in the analysis:

1. Adults ≥65 years

2. Admitted to the BWH/BWFH general medicine service under the care of one of the consenting interns (specifically, with the intern listed as the “Responding Clinician”)

4.2 Exclusion Criteria

Our study population will be restricted to adult subjects (≥65 years) who were not on the high-risk medication of interest before admission. The specific age range was selected because clinical guidelines for high-risk prescribing for the medications of interest are clearer for this age range, and because overprescribing is a well-documented issue in older patients. Patients who were previously on the medication of interest before their present admission will be excluded because of potential withdrawal concerns. To enhance generalizability, we will not apply any additional exclusion criteria.

4.3 Recruitment and retention

As described in Section 3.2, BWH uses 2-week service blocks for its inpatient general medicine evening (twilight) coverage, and at the beginning of each block, we will identify the interns assigned to twilight teams (i.e., the primary prescribers on the general medicine service team) one week prior to their service. We will focus on interns from the “twilight” (i.e., evening) teams as they cover the shifts during which the high-risk medications of interest (specifically anti-psychotics, benzodiazepines, and sedative hypnotic “Z-drugs”) are typically first initiated. In addition to being the least experienced physicians on the medical team, they are also the first and primary point of contact for nurses, pharmacists, and other physicians for these patients (i.e., the responding clinician). Their participation in twilight teams does not repeat once they have previously been assigned, so they cannot be re-randomized.

Over the 6-month window, at least 96 interns are expected to be eligible during the proposed 6-month recruitment window. Based on preliminary estimates and consultation with the general medicine service and chief residents, we expect that ≥40% of the interns will agree to participate and that therefore at least 36 interns will be included in the study. This rate is highly feasible based on feedback from the clinical leadership engaged in our study team.

Considering the number of potential eligible patients, these interns typically have daily census of 10-20 patients. Each patient is typically admitted for 3-5 days on each general medicine service, so interns typically care for approximately 40 unique patients during their time on the twilight team.

Based on preliminary estimates, ≥60% of their patients are older adults, and ≥50% will be naïve to either benzodiazepines/sedative hypnotics or antipsychotics. With 36 participating interns, we therefore expect that at least 430 unique patients will be included in the trial analyses (mean: 12 per intern).

We will provide compensation for participation in this trial, which will help ensure retention. Providers will receive $25 for completing the initial provider survey, $75 for completion of the simulation intervention or online educational training, and $50 for completing the follow-up questionnaire. Outside of the brief intervention itself and short baseline and endline (follow-up) questionnaires delivered electronically, there will otherwise be no action required by the participating interns. We have also engaged the chief medical residents in this project, which along with providing access to the scheduling system, will help us track their schedules and help ensure retention.

4.3.1 Inclusivity of study subjects

This study will be conducted on the adult inpatient general internal medicine services at Brigham and Women's Hospital (BWH), which serve a diverse range of patients. As such, we plan to include patients of all race/ethnicities in the analysis, regardless of their primary language. The specific age range (≥65 years) was selected because clinical guidelines for the prescribing of high-risk medications of interest are clearer for this age range, and because inappropriate prescribing of these medications is a well-documented issue in the older adult population. Based on the inclusion criteria, we expect that 59.2% of the trial patient participants will be female. In addition, we expect 84.6% will be white, 6.4% will be black or African American, 1.4% will be Hispanic/Latino, 4.2% will be biracial/other, and 3.1% will be Asian/Pacific Islander.

5. Study Interventions

5.1 Therapeutic areas

The focus areas for simulation training will be high-risk medications for older adults, which will be primarily drawn from the outpatient Choosing Wisely recommendations in geriatric medicine but are also informed by the Beers Criteria and other major clinical guidelines.[33,34] In specific, we plan to focus on the following therapeutic classes: (1) benzodiazepines; (2) sedative

hypnotics (sleep medicines) and (3) antipsychotics. We are also using albumin and blood products as a control, given that they are also high-risk and overprescribed, typically on twilight or evening shifts as patients are admitted to the hospital or are actively decompensating.

5.2 Study interventions

BWH uses 2-week service blocks for its inpatient general medicine evening (twilight) coverage. Prior to the beginning of each block, we will identify the interns assigned to twilight teams (i.e., the primary prescribers on the general medicine service team). We will invite these interns to participate in the study.

- Intervention: Providers in this arm will undergo simulation training at the onset of their 2-week block. The simulation will consist of a one-time, short immersive simulation session at the STRATUS Center for Medical Education at BWH (which is located within the hospital building). We plan to conduct this session with up to 4 interns at the same time, in accordance with social distancing practices at BWH. This simulation session will consist of 1 scenario with two parts of simulated patient experiences with expert facilitators in the simulated hospital rooms to help providers identify when they are in the hot state and their reactions, and work on improving communication skills, differential diagnoses, and alternative therapeutic options. These scenarios are intended to simulate both in-person and virtual interactions that are common in the inpatient setting. During these trainings, we will use behavioral principles like time pressure and increasing cognitive load to simulate a “hot state” environment. After the scenarios, the facilitator will perform a debriefing session for the interns, which will be used to complete the training.
- Control: Providers assigned to the control arm will receive online educational training about other poorly-prescribed medications, including albumin, transfusion, and blood product repletion guidelines. These treatments are often overprescribed on twilight shifts. Receiving education about another high-risk medication will reduce contamination and allow the ability to measure outcomes to other high-risk medications.

These interventions are described in further detail in the “Simulation Scenarios and Online Educational Training overview” document.

5.3 Measures to minimize bias: randomization and blinding

Interns who consent will be randomized in a 1:1 ratio to receive either intervention or control using a random number generator. We plan to conduct stratified randomization based on the service to which the intern is assigned to (GMS, ITU, or Faulkner).

The providers will not be blinded to which arm to which they were assigned, as blinding in the context of an intervention that is intended to motivate action will be infeasible. Physicians randomized to control will not have any way of accessing the intervention. Of note, once on a twilight team, interns are unlikely to rotate back onto a service, so contamination across arms should be minimal. Either way, if this does happen, they will not be re-randomized in the trial. Other ward staff and analysts will be blinded to arm assignment to the extent possible.

6. Study Assessments and Procedures

6.1 Baseline data

We will collect baseline data on providers using a brief baseline questionnaire at the time of consent as well as extracted EHR data and data from the Amion scheduling system. This baseline data will be used to assess any potential imbalances in the characteristics of providers despite randomization. The baseline data will include relevant demographic characteristics, such as age, sex, race/ethnicity, and number of months in training. Given the strong potential for characteristics of the study team to influence outcomes, despite randomization, we will also measure characteristics about the interns' team using the Amion scheduling system. Finally, we will also collect patient data from the EHR for eligible patients in follow-up (please see the footnote Section 3.8 for more detail).

6.2 Outcomes

The primary outcome will be measured on the patient-level as the number of high-risk medication doses prescribed per day to eligible patients beginning on the day the intervention arms are delivered to both arms until the end of follow-up. We will only measure doses ordered by the interns in the study. As described above, we will censor follow-up time on when patients transition from the intern's service, when the intern transitions off the twilight service, discharge, or in-hospital

death. The interventions in both arms will be delivered on the same day, so there will be no immortal time bias. Medications that are written pro re nata (PRN) will be treated the same as standing orders for the primary analysis. If patients are eligible to be measured for multiple medication classes (i.e., antipsychotics and benzodiazepines/sedative hypnotics), we will sum the medication doses across the classes.

In secondary analyses, we will only measure doses that are standing orders (i.e., not PRN doses) and doses that were actually administered to patients. We chose to measure this outcome on the patient-day level, because this would enable the fairest comparison between the arms, given that patients have variable lengths of stay and, as a result, the lengths of time under the interns' care. These data will be collected through structured EHR data from MGB paired with data collected from the scheduling system.

As secondary outcomes, we will measure whether patients are ultimately discharged on one of these medications and prescribing by the interns of other related medications such as opioids, trazodone, or melatonin, to measure spillover effects. We will also measure prescribing and monitoring of albumin and blood products. As above, if patients are not discharged within the timeframe for evaluation (i.e., are still admitted or experience in-hospital death), we will not include them in this analysis. We will also evaluate implementation outcomes informed by the RE-AIM framework. These implementation outcomes are: 1) Characteristics of consenting and non-consenting providers (measured by the Amion scheduling system), 2) Adoption: whether the simulation training was completed and whether the email with the online educational training was accessed/opened (measured by study staff), 3) Implementation: feedback and issues reported by the interns or study staff during the study (collected by study staff), and 4) Maintenance: reported satisfaction with the intervention and likelihood of incorporating insights into future practice (measured in the endline questionnaire).

6.3 Adverse events and unanticipated problems

Oversight:

Oversight of the pilot will be the responsibility of Drs. Lauffenburger and Choudhry, the Principal Investigators.

The co-leads and study investigators will meet on a regular basis throughout the study period and will be in direct contact with clinical leadership involved in the project to obtain ongoing feedback. In addition, the protocol will be overseen by the Institutional Review Board (IRB).

De-identified study data will be accessible at all times for the BWH PI and coinvestigators to review during the conduct of the trial and during the study analysis, if applicable. We will also ensure that all protocol deviations for the pilot study are reported to the NIH and the IRB according to the applicable regulatory requirements. Compliance of regulatory documents and study data accuracy and completeness will be maintained through an internal study team quality assurance process.

Definition:

Adverse Event (AE): Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

- Adverse Events will be classified using the following rating scales:
    - Severity: Mild, Moderate or Severe
        - Mild: Awareness of signs or symptoms but are easily tolerated
        - Moderate: Events introduce a low level of inconvenience or concern but may interfere with daily activities but are usually improved by simple therapeutic measures.
        - Severe: Events interrupt the participants' normal daily activities and generally require systemic drug therapy
    - Expectedness: Unexpected or Expected
        - Unexpected: nature or severity of the event is not consistent with the condition under study
        - Expected: event is known to be associated with the intervention or condition under study.

Serious Adverse Event (SAE): Any adverse event that:

• Results in death

• Is life threatening, or places the participant at immediate risk of death from the event as it occurred

- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

Determination:

Given the minimal risk nature of the study where the overall goal is to improve patient safety, the intervention is a quality improvement intervention, all prescribing decisions are made by providers who will provide consent, we do not anticipate any SAEs or AEs.

Reporting:

No SAEs or AEs are expected as part of this study, which aims to increase patient safety through the avoidance of high-risk medications. The study team will not be providing any direct care to patients and all treatment decisions will ultimately be made by the patients' medical teams at Brigham and Women's Hospital. While we will not be actively monitoring the occurrence of adverse events, which if done would require direct patient contact, detailed patient-level chart-reviews, and clinical assessments conducted by the study team, we anticipate that the study team will be informed of any AEs or SAEs that do occur through hospital safety reports.

If we become aware of any AEs or SAEs throughout the course of the study, we will collect this information. Any reports of deaths will be submitted to the NIA Program Officer and to the Safety Officer (SO) within 24 hours. Any unexpected SAEs will be reported to the NIA PO, SO and the IRB within 48 hours of the study's knowledge of the SAE. All other reported SAEs and AEs received by the study team will be reported to the NIA Program Officer and to the SO quarterly, unless otherwise requested by the Safety Officer or Roybal Center Program Data Safety Monitoring Board (DSMB).

7. Statistical Considerations

7.1 Statistical Hypotheses

Our null hypothesis will be that number of high-risk medication doses prescribed per day to eligible patients assigned to intervention providers will be no different than those in the control arm.

7.2 Sample size determination

As described in Section 4.3, we expect at least 36 interns to participate in the trial (18 per arm), and that at least 430 patients will be eligible for inclusion in the analysis, with approximately 3 eligible days per patient (i.e., 1290 patient-days of observations). With these estimates, we would have >80% power to detect a mean difference of 0.5 high-risk medication doses per patient-day in the intervention arm compared with the control arm, assuming a standard deviation of 1.1, power=0.8, alpha of 0.05 (two-sided), and patient correlation of 0.2, a conservative estimate.[13,35] We also assumed an average cluster size of 12 patients (and 36 patient-days) per provider based on preliminary estimates. As these data are intended to provide pilot data for larger evaluations, any positive signal from this pilot trial will help inform next steps.

7.3 Statistical analyses

7.3.1 Analysis of the primary endpoint

The unit of analysis is at the patient-level. We will evaluate the primary outcome using generalized estimating equations to adjust for physician-level clustering and multiple patient-day observations per physician using a log-link function, Poisson-distributed errors, and fixed effects for the treatment group and month of the year to account for seasonality. This approach will account for correlations between repeated measurements. Because this is a randomized trial, our primary analyses are planned as unadjusted; however, if there are strong predictors of the outcomes not balanced by stratified randomization, we will adjust for these in the primary analyses. We will conduct analyses using intention-to-treat principles. Given the nature of the data and how the outcomes are measured in EHR data, there will not be missing data for the primary outcome.

7.3.2 Analysis of secondary endpoints

We will use a similar approach for the secondary outcomes. For discharge medication orders (secondary outcome), we will also use generalized estimating equations that adjust for physician-level and patient-level clustering using a logit-link function, binary-distributed errors, and fixed effects for the treatment group and month of the year. For the outcomes measuring spillover

effects, the approach will be the same, except using a log-link function and Poisson-distributed errors. Given the nature of the data and how these outcomes are being measured primarily in EHR data, there should not be missing values. Because this is a randomized trial, our primary analyses are planned as unadjusted; however, if there are strong predictors of the outcomes not balanced by randomization, we will adjust for these in the primary analyses.

The implementation outcomes will be measured at the provider-level. The characteristics of consenting and non-consenting physicians will be measured descriptively, comparing the values using t-tests and chi-square tests or non-parametric analogs, as appropriate. Other implementation outcomes will be measured descriptively.

7.3.3 Baseline descriptive analyses

We will report the means and frequencies of pre-randomization variables separately for intervention and control subjects. Comparisons of these values will be performed using t-tests and chi square tests and their non-parametric analogs, as appropriate. The outcomes will be evaluated using intention-to-treat principles among all randomized patients.

7.3.4 Subgroup analyses

In subgroup analyses, we will explore whether there were any modifiers of the effects of the simulation-based intervention. For example, we will explore if the intervention effectiveness differed by month of the year, whether there were team-level differences, or if there were observable differences in patients who were less likely to receive high-risk medications, such as gender or race/ethnicity.

8. Ethical and regulatory requirements

8.1 Ethical conduct

General oversight of the project by the principal investigators (Drs. Lauffenburger and Choudhry) will occur throughout the study period, including regular contact with clinical leadership to obtain ongoing feedback. In addition, this protocol will be overseen by the MGB Institutional Review Board (IRB). Study data will be accessible at all times for the principal

investigators and co-investigators to review, if applicable. The principal investigators will review study conduct (e.g., protocol deviations) on a monthly basis. The principal investigators will also ensure that all protocol deviations for the trials are reported to the NIH and the IRB according to the applicable regulatory requirements.

We believe that the risks to participation for both sets of subjects (i.e. providers and patients) are no more than minimal for several reasons. We believe there is no more than minimal risk involved to the provider subjects, as the providers will simply undergo training to alter their behaviors towards guideline recommended care, as opposed to being forced to do so. The intervention is delivered as a simulation training that incorporates information already available to providers

In terms of patient-subjects, the intervention aims to emphasize guideline-recommended information for providers to assist in their decision-making when caring for older patients who have been admitted to the general medicine service. All treatment decisions will ultimately be made by licensed health care providers.

Patient data to inform the study and conduct evaluations will be drawn from EHR data maintained by the health systems. We will also safeguard any identifiable information in accordance with IRB practices, limit access to any information in accordance with IRB practices, limit access to the information to study investigators actively involved in the research who have all undergone human subjects research training, and destroy any data upon completion of the research. Finally, as is our routine practice, throughout this work, great care will be taken to ensure the confidentiality of all data and to protect the privacy of participants through translation of all potentially traceable identifiers into untraceable coded subject numbers.

8.2 Informed consent

Interns will be eligible if they are scheduled to work for one of the general medicine service wards during an evening block on one of the “twilight” teams.

We request a waiver of documentation of informed consent and will obtain e-consent without a signature requirement. We believe this waiver is justified for this study for several reasons. First, the subjects being intervened upon are physicians at BWH/BWFH and the study team will

not have any contact with patients. The proposed intervention being tested is very similar to existing quality improvement initiatives already offered at BWH and intends to evaluate interventions to encourage physicians to follow care processes based on widely-accepted clinical practice guidelines. The interventions involve providing them with tools to improve prescribing in accordance with these guidelines and they can ignore this guidance. Additionally, a formal written informed consent process would be infeasible for this study. Interns are busy and the components of this intervention are very familiar to them; therefore, the standard consent process would be burdensome and likely be a barrier to study enrollment. If we have difficulty recruiting sufficient interns for the study, and therefore unable to reach our sample size targets, our study will be insufficiently powered. Further, if we have highly self-selected sample, this can bias our results and make them less generalizable.

Instead, after reviewing the information sheet that we will electronically provide to potential participants and prior to their agreeing to participate, subjects will be invited to talk with the study team by phone or Zoom to address questions or concerns, and our contact information will be easily accessible for potential participants. For these reasons, we feel that a waiver of documentation of informed consent with the option for video or phone conversation for any questions or concerns would be the best consent process for this study. We also have approval from clinical leadership and chief residents for this approach. Finally, the surveys as part of this study take only 10-15 minutes, are all validated and widely used, and PCPs will be compensated for their time.

We will obtain e-consent with a waiver of written consent (signature) and waiver of documentation of informed consent for participation in the trial through e-consent documentation in REDCap, a secure HIPAA-compliant web-based platform hosted on our Mass General Brigham servers. Intern physician subjects will be invited to participate via email. The information sheet below will be attached to the email, and contains information about the study, their participation, and the names and contact information for study staff who can be reached for a phone or video conversation if they have any questions or concerns. We have received approval from clinical leadership for this approach. Interested intern physicians will be asked to click on a link in the email to open a secure RedCap survey. There, interns will again view an electronic copy of this information sheet. If the physician agrees to participate, he or she will click a button indicating “I agree”. E-consent documentation (without signature or documentation of written consent) will be captured in REDCap, which is a secure, HIPAA-compliant web-based platform hosted on the MGB servers. We will provide sufficient information to the prospective provider-

subjects about the nature of the study and their rights within the fact sheet, as well as provide contact information for study staff and IRB for any additional questions.

BWH study staff and data analysts will track any physician turnover in the study using the Amion electronic residency scheduling system and the paging directory. While minimal turnover before the end of the block is expected, we expect any turnover to bias the trial results towards the null. If providers wish to revoke their consent and no longer participate in the study, they will also be removed from the study.

We also request a waiver of patient informed consent and authorization for the collection of routinely-collected patient data for outcome evaluation, given the minimal risk nature of the study, as we have done in prior work. We believe this waiver is justified as investigators will have no direct patient contact and all prescribing decisions are made under the care of licensed physicians, including supervising residents and attending who are directing their care. Finally, the intervention is exclusively provider-facing with the underlying goal of promoting patient safety in accordance with clinical practice guidelines.

8.3 Confidentiality and privacy

We will enroll provider-subjects based on their being employed by MGB as interns. For the trial, we will seek informed consent from providers. We will also seek a HIPAA waiver of patient authorization to access the EHR data necessary for outcome evaluation.

To ensure the confidentiality and security of all data, the research team operates a secure, state-of-the-art computing facility housed at MGB's data center. The MGB data center is a secure facility that houses both computing environments as well as clinical systems and electronic medical records for several large hospitals in Eastern Massachusetts. Entry into the computer room requires staffed computer room security. The Division's computers are connected to the MGB networking backbone with 10 gigabit-per-second fiber links. Network security is overseen by electronic medical records systems to the research team's data. All data are transmitted to programmers' workstations in an encrypted state. Backups are created using 256-bit AES encryption, the current Department of Defense standard for data security, and are stored in a locked facility. The redundancy, extensive data power, and security of our computer facility confirm our capacity to collect and manage data and ensure confidentiality for all project participants.

We will also safeguard any identifiable information from the providers in accordance with IRB practices, limit access to any information in accordance with IRB practices, limit access to the information to study investigators actively involved in the research who have all undergone human subjects research training, and destroy any recordings from the qualitative interviews upon completion of the research.

All members of the research team have completed appropriate human subjects research training and patient privacy training related to the Health Insurance Portability and Accountability Act (HIPAA). The setup for analysis of these HIPAA-limited data will be exactly the same as all of the other IRB applications that our MGB research division submits for secondary use of data. In fact, we have an umbrella-approval place in place with the MGB IRB for using these types of HIPAA-limited data. All of the datasets, including limited PHI, will be stored only on secure servers at the MGB data center and will only be accessed by a limited number of individuals in the study team from this division who are all trained in data security and patient privacy.

8.4 Safety oversight

General oversight of this project by the BWH co-leads (Drs. Lauffenburger and Choudhry) will occur throughout the study period, including regular contact with clinical leadership of the general medicine service wards involved in the project to obtain ongoing feedback. In addition, this protocol will undergo Institutional Review Board (IRB) evaluation. Drs. Choudhry and Lauffenburger have previously overseen numerous large, multi-site pragmatic trials.

This study will include safety monitoring from both the Roybal Centers Program DSMB and an independent safety officer (SO) to perform data and safety monitoring activities. This SO will advise NIA Program staff and the PI regarding participant safety, study risks and benefits, scientific integrity, participant recruitment, and ethical conduct of the study. The SO will also provide the Program DSMB with periodic safety reports in a manner determined by the Program DSMB.

As directed by the NIA, the co-leads will appoint a licensed physician with relevant study and disease-specific expertise to serve as SO, submitted to the NIA PO for approval. The Program DSMB consists of members approved by the Director of NIA. Following approval, the SO and Program DSMB will receive a manual of operating procedures containing the study protocol and DSMP prior to study enrollment. The co-leads (Drs. Choudhry and Lauffenburger) have nominated

Gina Kruse, MD, MS, MPH, as the independent Safety Officer (SO), pending approval by the NIA PO, to act in an advisory capacity to the NIA PO and to evaluate the progress of the study.

8.5 Benefit risk assessment

8.5.1 Known potential risks

We believe there is no more than minimal risk involved to the provider subjects, as the providers will simply undergo training to alter their behaviors towards guideline recommended care, as opposed to being forced to do so. In terms of patient-subjects, all medical decisions are ultimately made by the provider. This trial will otherwise not interfere with the ordinary workings of the inpatient service.

8.5.2 Known potential benefits

Simulation training could help reduce high-risk prescribing in stressful situations as a way to improve patient safety. However, very few studies have evaluated the use of simulation training in the context of inpatient prescribing, and not in the context of bridging System 1 and System 2 prescribing behaviors. Thus, the research will have both immediate benefits for subjects enrolled in the study as well as for the larger population of older adults. We will also produce several deliverables for this work for the public, researchers, and policymakers, which will be shared as generalized knowledge. These deliverables include the results from the study and implementation toolkits. If effective, this intervention could be expanded to other high-risk prescribing situations.

8.5.3 Assessment of potential risks and benefits

We will enroll provider-subjects based on their being employed by MGB as interns. For the trial, we will seek informed consent. We will also receive a HIPAA waiver of patient authorization to access the EHR data necessary for outcome evaluation.

To protect against the risk of inappropriate disclosure of personal health information, the investigators at BWH will only access study data with encrypted identifiers. As described, all members of the research team have completed or will complete appropriate human subjects research training and patient privacy training related to the Health Insurance Portability and Accountability Act (HIPAA). We have a history of collaborative evaluations with delivery organizations that involves transfer of the minimum data necessary to complete rigorous evaluations, involving the use of encrypted identifiers to ensure patient confidentiality.

To ensure the confidentiality and security of all data, the research team operates a secure, state-of-the-art computing facility housed at MGB's data center.

We will also safeguard any identifiable information from the providers in accordance with IRB practices, limit access to any information in accordance with IRB practices, and limit access to the information to study investigators actively involved in the research who have all undergone human subjects research training.

For all of these reasons, we believe that this trial is a minimal risk trial and that we have the appropriate protections in place for all study subjects.

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