SUPPLEMENTAL ANALYSIS PLAN: MGB TRIAL PROTOCOL

Optimizing electronic health record prompts with behavioral economics to improve prescribing for older adults: **Replication trial at Mass General Brigham**

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Summary of Changes from Previous Version

Date of submission	Summary of Revisions Made	Rationale for modification	Approval date
April 14, 2025	Minor changes to outcomes and analysis descriptions based on inconsistencies in the protocol	Fixed typographical errors and inconsistencies across the protocol sections within the document	

1. Background and Rationale

The prescribing of inappropriate medications for older adults is extremely common in the United States, ranging from 12% in community settings to 40% of those who are institutionalized.[1-3] Benzodiazepines, anticholinergics, and sedative hypnotics are among the most commonly prescribed in circumstances that are inconsistent with practice guidelines.[3,4] While inappropriate prescribing increases the risk of adverse health consequences for all patients, older adults are particularly vulnerable.[2,5-7] Physicians' lack of awareness of alternatives, ambiguous practice guidelines, and perceived pressure of patients or caregivers are among the reasons why these drugs are used more than might be optimal.[2]

Reducing inappropriate use of these drugs may be achieved through decision support tools for physicians that are embedded in electronic health record (EHR) systems. While EHR strategies are widely used to support the informational needs of providers, these tools have demonstrated only modest effectiveness at improving prescribing.[8-13] The moderate effectiveness of current clinical decision support tools is thought to be largely due to what content they contain and the lack of provider-focused design principles being used to develop them.[14,15] Prior approaches have also been criticized for the sheer volume of alerts, the lack of clinical significance of the tools, and the poor/delayed timing of the clinical decision support (i.e., after the prescribing decision). Accordingly, the effectiveness of these tools could be enhanced by leveraging recently-gained insights from behavioral economics and other related sciences. Their application to EHRs has been limited, and they have not been used to reduce the prescribing of potentially harmful medications to older adults.

2. Study Aims

The overall goal of the proposed research is to evaluate whether EHR-based tools, optimized using behavioral science principles, reduce inappropriate prescribing among older adults. Our overall hypothesis is that thoughtful incorporation of behavioral principles into

EHRs will reduce inappropriate prescribing and adverse drug events among older adults compared to usual care.

The objectives and endpoints for the adaptive and replication trials are summarized below.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine whether EHR-tools designed using behavioral science principles are more effective than at reducing inappropriate prescribing of high-risk medications in older adults than standard EHR tools or usual care.	Composite of 1) discontinuation of high-risk medications (benzodiazepines, sedative hypnotics, or anticholinergicsor 2) ordering a gradual dose taper for one of these medications	These outcomes are rapidly measurable using EHR data alone and will provide evidence of provider behavior change.
Secondary		
To examine whether behavioral science-based EHR tools reduce cumulative prescribing of high-risk medications in older adults compared with usual care.	Quantity of high-risk medication prescribed, defined by number of pills and milligram equivalents of high-risk medications prescribed to patients in follow-up	These outcomes capture the extent to which high-risk medications are cumulatively prescribed to patients by all providers over the follow-up period.
Tertiary/Exploratory		
To evaluate whether behavioral science-based EHR tools reduce the risk of clinically-significant adverse drug events, falls, fractures, hospitalizations, or emergency room visits compared with usual care.	Rates of adverse drug events, falls, fractures, hospitalizations, and emergency room visits in follow-up; quantity of high-risk medications dispensed to patients in follow-up period	These outcomes measure clinical outcomes that are consequences of these high-risk medications, measured in medical and pharmacy administrative claims data.

3. Study Design

3.1 Study site

The replication trial will be conducted in outpatient primary care practices at Mass General Brigham (MGB), specifically Mass General Hospital. MGB has a fully functional EHR, EpicCare (www.epicsys.com), that supports computerized ordering of medications. MGB is comprised of 150 outpatient practices with over 1,800 physicians.

3.2 Overall design

We will conduct a parallel group trial at Mass General Brigham, specifically within MGH primary care practices. We hypothesize that these tools will reduce prescribing of high-risk medications (primary outcome), cumulative prescribing of high-risk medications (secondary outcome), and clinically-significant adverse drug events like sedation and confusion (tertiary outcome) compared with usual care.

3.2.1 Trial Design

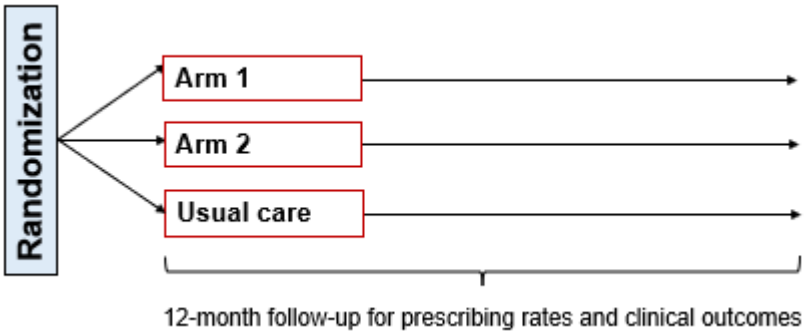
This trial is a cluster-randomized, NIH-defined Phase III pragmatic trial. The study statistician, in partnership with data analysts at MGB, will generate and implement the randomization scheme, with oversight by the Principal Investigators. All the study sites will be at MGH for this trial; we have received approval from leadership at MGH primary care practices and Digital Health eCare teams to conduct this trial. For study evaluation, data regarding patients' medical history, disease control, medication use, and healthcare utilization will be obtained from EHR data or administrative claims data. Any administrative claims data used for evaluation in this study will come directly from MGB in HIPAA-limited datasets through their risk-bearing contracts.

We will randomize primary care providers at MGH to one of the 2 most promising treatment arms identified in the prior adaptive randomized trial conducted at Atrius Health or usual care (described in further detail in 5.2). We expect to randomize approximately 200 providers. Providers randomized to one of the 2 selected treatment arms will receive an EHR tool to guide their care of eligible patients. We will randomize providers based on provider demographic characteristics, patient case-mix factors, and baseline rates of high-risk medication prescribing measured in EHR data.

Providers will be eligible if they prescribed a benzodiazepine, sedative hypnotic, or two distinct anticholinergics to at least one older adult in the 180 days prior to randomization. Providers will receive these EHR tools for their patients who meet the following criteria: 1) older adults (aged 65 years or more), and 2) who have been prescribed at least 90 pills of benzodiazepine or sedative hypnotic or have been prescribed at least one active orders of at least 90 pills of two different anticholinergics in the last 180 days. Follow-up will last 12 months. These patients will also be included in the analyses. The type and timing of EHR tool that the providers receive for these patients will vary based on their assigned intervention arm.

3.3 Study Schema

3.3.1 Mass General Brigham



3.4 Scientific rationale for study design

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

3.5 Justification for intervention

The focus areas for the EHR tools 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.[16-18] In specific, we plan to focus on the following therapeutic classes: (1) benzodiazepines; (2) sedative hypnotics (sleep medicines) and (3) anticholinergics. These classes were chosen because they all have established clinical guidelines recommending reductions in use, continue to be heavily over-prescribed, contribute significantly to poor clinical outcomes in older adults, and also have non-drug or less risky therapeutic alternatives. While prescribing non-drug options may be the optimal alternative to these potentially inappropriate medications, their adverse effects could also be attenuated by choosing alternative medications in a different drug class, lower doses of medication, or alternative, safer medications within the same drug class.

We have chosen to focus on key principles of behavioral economics and cognitive psychology to "nudge" providers to optimize prescribing, such as timing, salience, framing, simplification, pre-commitment, and boostering. These principles were selected based on their effectiveness in other settings[19-22], their applicability to the care of older adults, and their ability to be adapted to the EHR context.

3.6 End-of-study definition

The MGB trial will be completed 12 months after randomization. Providers and their eligible patients will be followed until the end of this follow-up date, or until censoring.

3.7 Data sources

We will use EHR data to implement the EHR tools, identify study subjects, track study progress, and evaluate the effect of the interventions. We will also use administrative claims data to evaluate tertiary outcomes among the subgroup of patients with claims data.

Data warehouses reside in an Oracle environment and consist of the Clarity and Payer databases. The Clarity database is a relational database that contains clinical and financial information from the Epic Suite of products; including the electronic medical record system, the

appointment scheduling system, the patient accounting system, and the master patient index (Identity). The various tables within the Clarity database are refreshed on a daily, weekly or monthly basis. At MGB, we will extract clinical information from the electronic medical record system via the Epic Enterprise Data Warehouse (EDW) or the Mass General Brigham Research Patient Data Registry (RPDR). Accessing the EDW in particular is necessary in order to adequately identify and link all eligible patients seen by the enrolled providers in our study and measure outcomes, which is not possible using other sources.

For the claims data, the Medicare claims data are being provided by the funder, the National Institute on Aging (NIA), through their partnership with Acumen and the established MedRIC (https://www.medric.info/data-enclave/data-pages/data). In order to obtain claims data from the funder, we will provide them with Medicare Beneficiary Identifier (MBI) for linked patients in our study. We are executing all appropriate data use agreements with the NIA and Acumen to receive these data.

3.8 Schedule of activities

Data collection	**MGB trial: Pre-randomization**	**MGB trial: Follow-up**
EHR review for provider eligibility	X	
Patient characteristics (Demographics, clinical characteristics)	X	
Provider characteristics (Demographics, patient case-mix)	X	
Benzodiazepine/sedative hypnotic prescribing		X
Benzodiazepine/sedative hypnotic dispensations		X
Anticholinergic prescribing/dispensations		X
Adverse drug events		X
Falls or fractures		X
Resource use (hospitalizations, ER visits)		X

4. Study Population

The study will intervene upon primary care providers (primary care provider designated physicians, nurse practitioners, physician assistants) and their patients in the outpatient practices of Mass General Hospital.

4.1 Inclusion Criteria

The subjects involved in this trial are providers from multiple clinical sites, all at Mass General Hospital. The target population of providers and the patients they treat is pragmatic and widely representative. Providers will be eligible if they treat older adult patients. Each study clinic has an EHR system in place. The inclusion criteria are limited to maximize generalizability in accordance with pragmatic trial principles by PRECIS-2 (PRagmatic Explanatory Continuum Indicator Summary).

Providers will be eligible if they:

- Are a primary care provider at Mass General Hospital, with a minimum clinical schedule of 2 sessions per week
- Prescribed a benzodiazepine, sedative hypnotic, or anticholinergic to at least one older adult in the 180 days prior to randomization

Patients will be included in the analysis if they:

- Are assigned to one of the randomized primary care providers (by MGB indicators)
- Are aged 65 years or more
- Have been prescribed at least 90 pills of benzodiazepine or sedative hypnotic or at least one active orders of at least 90 pills of two different anticholinergics in the prior 180 days

4.2 Exclusion Criteria

Patients not meeting the inclusion criteria above will not be included in the study. No other exclusion criteria will be used.

4.3 Recruitment and retention

4.3.1 Informed consent considerations

We have received a waiver of informed consent and HIPAA authorization for all physician-subjects and patient-subjects in this study. The goal of this project is to improve existing decision support to reduce the use of potentially dangerous medications in the elderly, consistent with numerous professional guidelines and quality metrics. Providers will retain oversight of their patients' care and will be able to make therapeutic choices based using their professional judgement. Patients will not receive any direct intervention as a result of their inclusion in the study.

4.3.2 Inclusivity of study subjects

Physician and patient subjects will be included based on their meeting eligibility criteria as part of routine care, and the study population will be highly inclusive. We expect these participants to cover a broad range of participants by gender and race/ethnicity. Given the minimal risk nature of the study, participants will not receive incentives, remuneration, or be required to provide informed consent.

5. Study Interventions

5.1 Therapeutic areas

The focus areas for the EHR tools 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.[4,23] In specific, we plan to focus on the following therapeutic

classes: (1) benzodiazepines; (2) sedative hypnotics (sleep medicines) and (3) anticholinergics.

5.2 Study interventions

Physicians in the replication trial randomized to one of the 2 active intervention arms will receive one of several possible enhanced EHR decision support to guide care. The type and timing of an alert will vary based on the intervention are outlined below. The two specific EHR tools for the replication trial at MGB was determined based on the adaptive randomized trial results:

Arm	Alert type	Open encounter	Follow-up booster	Pre-commitment
1	Enhanced	X	X	
2	Enhanced	X		X
Usual care	None			

Arms 1 through 2 are enhanced EHR tools to encourage the deprescribing of the medications under study. Physicians randomized to usual care will receive no intervention.

The central component of Arms 1 through 2 will be an enhanced EHR alert (known as a Best Practice Advisory [BPA]). The enhanced BPA will appear on each provider's EHR screen and will contain several standard components. The BPA will:

1. give providers information about why the medication is dangerous for their patient using the behavioral science principle of salience to make this information as impactful as possible;
2. include a set of tips to help providers discuss medication discontinuation with their patients;
3. ask providers to select an acknowledgment reason if they decided not to discontinue the medication;

4. include a SmartSet order set that will allow providers to order a gradual dose taper for their patient, which limits risks of withdrawal symptoms for the patients for benzodiazepines and sedative hypnotics, order alternative medications, place a referral to a behavioral health specialist, provide instructions on how to make lifestyle modifications to improve patient symptoms, and add customizable patient instructions for how to gradually taper off benzodiazepines and sedative hypnotics, as applicable.

We will also test several other modifications to this enhanced BPA. In specific, as outlined in the table above, we will add in a boostering option in the enhanced BPA in Arm 1, which is a provider-directed option for a follow-up in-basket message sent 4 weeks after the BPA is triggered. Arm 2 will test the use of a two-staged pre-commitment BPA in which the providers are prompted to discuss risks of these high-risk medications and share a handout about the risks with their patients, at their own discretion.

If patients are eligible for alerts to be fired for multiple therapeutic classes of interest (e.g., benzodiazepines and sedative hypnotics), the EHR tools will appear for both classes separately.

5.3 Measures to minimize bias: randomization and blinding

Providers will be randomized to treatment arms in equal proportions based on blocks. We will use provider-based cluster randomization to minimize the possibility of contamination in study interventions between practices and clinic staff. For the randomization, we will use stratified randomization based on clinic practice size and baseline rates of prescribing to reduce potential imbalances between the providers assigned to the treatment arms.

The providers will not be blinded to which arm they were assigned to, as blinding is the context of an intervention that is intended to motivate action will be infeasible. The study

analyst will generate and implement the randomization scheme, with oversight by the Principal Investigators. Investigators will be blinded to the treatment arms during interim and final analyses.

6. Study Assessments and Procedures

6.1 Baseline data

We will collect baseline data on patients and providers using extracted EHR data and/or administrative claims data as applicable for the study aim. This baseline data will be used to assess any potential imbalances in the characteristics of providers or patients despite randomization. The baseline data will include, but are not limited to: gender, baseline rates of prescribing, practice location, and patient case-mix. We will also collect patient data that include but are not limited to: sociodemographic data, medical history and comorbidities, baseline resource utilization in prior 12 months (i.e., number of visits), biometric values (e.g., serum creatinine, systolic/diastolic blood pressures).

6.2 Outcomes

The primary outcome will be a binary composite measure of a reduction in inappropriate prescribing, evaluated using EHR data. In specific, we will measure a composite of 1) discontinuation of high-risk medications (benzodiazepines, sedative hypnotics, or anticholinergics) defined by either: a) active discontinuation and no subsequent order or b) no order during follow-up or 2) ordering a gradual dose taper (for benzodiazepine or sedative hypnotics). Our primary analyses will be within patients who had a visit (telemedicine or in-person) with a study provider after randomization. If either of these actions is taken by providers for a specific patient at any point in the follow-up window, we will classify the patient as having had a reduction in inappropriate prescribing. If the patient has multiple therapeutic classes of interest (e.g., benzodiazepines and sedative hypnotics), we will classify patients with a reduction for any class as a “reduction” for the composite measure. We will also stratify

patients by their number of eligible therapeutic classes (i.e., one, two, or three classes) and analyze outcomes within these strata.

Secondary outcomes include the quantity of high-risk medication prescribed, defined by number of pills of high-risk medications (all three classes) prescribed to patients in the follow-up period and number of lorazepam milligram equivalents of benzodiazepines and sedative hypnotics to capture cumulative prescribing by all providers. As above, we will also stratify patients by their number of eligible therapeutic classes (i.e., one, two, or three classes) and analyze outcomes within these strata.

Tertiary outcomes will include the extent to which medications are filled and consumed by patients, as measured within the subgroup of patients with claims data. In specific, these outcomes will be conducted among the large subgroup of patients funded by Medicare, including pharmacy claims via the secure MedRIC data enclave. In particular, we will measure the quantity of high-risk medication dispensed, defined by number of milligram equivalents of high-risk medications filled by patients, in follow-up, using pharmacy claims data. Other tertiary outcomes will include the occurrence of clinically-significant adverse drug events, including but not limited to, sedation or cognitive impairment, and all-cause hospitalizations and falls or fractures, measured in administrative claims data. These clinical outcomes will be evaluated using validated and CMS-driven ICD-10-CM diagnosis and procedure-based algorithms applied to these patients' medical and pharmacy administrative claims data. Because the sensitivity of clinical outcomes in EHR systems is known to be low (e.g., because patients may seek subsequent care at other healthcare systems), using routinely-collected data from insurers overcomes this limitation.[24] We will also evaluate implementation of the intervention using structured deidentified data from the EHR about use of the EHR system, which will help inform how to scale the interventions (see Data to be collected form).

6.3 Adverse events and unanticipated problems

For provider-subjects, the EHR decision support designed for this trial is only meant to highlight information that could be useful in patient management and prescribing. Therefore, we do not anticipate any safety issues to arise with regards to provider-subjects who receive the electronic decision support, and the IRBs who have reviewed our prior proposals have agreed with this general approach.

For patient-subjects, we do not anticipate the occurrence of any adverse events as a result of providers receiving decision support aimed at reducing the use of potentially unsafe medications that already have established clinical guidelines advising against their use. The decision support provides resources to help patients safely discontinue the high-risk medications under study (e.g., providing tapering guidelines and facilitating the substitution of lower-risk therapies). There is a theoretical risk of precipitating withdrawal, but the risk is less than the continued risks of ongoing use of the drugs being addressed by the interventions.

We will ensure the safety of patient-subjects by leaving ultimate clinical decision-making in the hands of the evaluating provider who is in charge of caring for the patient. The study team will not be providing any direct care to patients, and all treatment decisions will ultimately be made by the patients' own medical teams. As a result, any adverse events will be handled in the course of regular clinical care. Further, to maximize the generalizability of the results and to avoid co-intervention, patients will not be required to have study-specific monitoring as part of the proposed pragmatic trials. Therefore, we do not plan to use any patient-directed prospective monitoring of Adverse Events (AEs) or Significant Adverse Events (SAEs) in this trial. An *Adverse Event (AE)* is defined as 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) are defined as 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, and is another condition which investigators judge to represent significant hazards.

However, our plan for data and safety monitoring does include multiple mechanisms to ensure minimal risk of participation in the trials. We will leverage an automatic adverse event reporting and review system to observe and monitor for any SAEs that do occur. In specific, providers report adverse events through an online reporting system. Any reports of deaths will be submitted to the NIA Program Officer and to the Data Safety Monitoring Board (DSMB) Chair or designated DSMB member within 24 hours. Any unanticipated SAEs deemed by the specialists and to be related to the intervention will be reported to the NIA PO and to the DSMB Chair or to the designated DSMB member 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 DSMB quarterly, unless otherwise requested by the DSMB or a Safety Officer.

7. Statistical Considerations

7.1 Statistical Hypotheses

Our null hypothesis will be that rates of provider prescribing (defined by evidence of a reduction in prescribing of high-risk medication) in the intervention arms will be no different than in the other arms, including the usual care arm.

7.2 Sample size determination

We should have >80% power to detect absolute differences of 10% or smaller in the reduction in prescribing between each intervention arms and usual care, assuming an intra-provider correlation of 0.1 (which is based on prior work including the Atrius trial) and a baseline rate of the primary outcome of 25% in the usual care arm. We plan to use Holm-Bonferroni correction to account for multiple testing between each of the intervention arms and usual care, but we will be powered even if using a Bonferroni correction. Our assumptions will also be robust to a slightly higher baseline rate of the primary outcome in the usual care arm. We should also be sufficiently powered to detect meaningful differences in the clinically significant adverse events.

7.3 Statistical analyses

7.3.1 Analysis of the primary endpoints

The unit of analysis is at the patient-level. All analyses will use intention-to-treat principles. We will use generalized estimating equations to adjust for clustering and repeated observations per provider to evaluate the effectiveness of the intervention arms versus usual care. For the inappropriate prescribing outcome, we will use a log link function and binary distributed errors. These models generate the estimated relative risks (RRs) with robust standard errors and are considered to be particularly appropriate when outcomes are common (e.g., incidences of ≥10%). Because this is a randomized trial, our primary analyses are

planned as unadjusted; however, in secondary analyses, we will adjust for patient age, race/ethnicity, and gender.

Given the nature of the data and how the outcomes are categorized, there will not be missing values for the primary endpoint, as the absence of action is classified as no action by the provider. For the primary analysis, we will include all eligible patients in the denominator who had at least one visit with their primary care provider. In secondary analyses, we will include all eligible patients of those primary care providers in the denominator, regardless of whether the patient visited the provider over the follow-up period.

7.3.2 Analysis of secondary endpoints

For the secondary outcome of cumulative medication prescribing, will use an identity link function and normally distributed errors within the generalized linear models. For tertiary adverse clinical outcomes and resource utilization outcomes, we will use a log link function and binary distributed errors. These models generate the estimated relative risks (RRs) with robust standard errors and are considered to be particularly appropriate when outcomes are common (e.g., incidences of ≥10%). For these outcomes from claims data, we will follow patients whose providers are randomized to the study from the time of randomization until they are censored due to lose of continuous enrollment in their health plan. Due to the nature of the randomization, we do not anticipate any systematic differences in the amount of follow-up time per arm but will account for any imbalances using inverse probability censoring weights.

Because this is a randomized trial, our primary analyses are planned as unadjusted; however, if there are strong patient-level predictors of the outcomes not balanced by stratified randomization, we will adjust for these. Given the nature of the data and how the outcomes are being measured, there should not be missing values. However, should there be sufficient missing data (e.g., >10%), we will use multiple imputation.[25]

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 EHR tools. For example, we will explore if certain types of providers (e.g., by specialty) were more likely to respond to the EHR tools or if there were observable differences in patients who were less likely to receive inappropriate medications, such as gender or race/ethnicity.

7.3.5 Exploratory analyses

In secondary analyses, we will control for potential confounders which will be measured using EHR data from structured fields and administrative claims data. These variables will include provider characteristics (such as specialty, age, and gender), patient characteristics (such as major comorbidities, race/ethnicity, and age), and practice characteristics (such as practice size).

8. Ethical and regulatory requirements

8.1 Ethical conduct

General oversight of the project by the principal investigators (Drs. Choudhry and Lauffenburger) will occur throughout the study period, including regular contact with practice managers and clinical leadership at each health center to obtain ongoing feedback. In addition, this protocol will undergo Institutional Review Board (IRB) evaluation by a centralized IRB for this multi-site clinical trial. Study data will be accessible at all times for the principal

investigators (Drs. Choudhry and Lauffenburger) 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.

First, the intervention aims to emphasize guideline-recommended information for providers to assist in their decision-making when caring for older patients. Second, all treatment decisions will ultimately be made by licensed health care providers. Finally, the intervention is specifically provider-focused and delivered in an electronic health record system using information already available to providers. We believe there is no more than minimal risk involved to the provider subjects, as the providers will simply be “nudged” to alter their behaviors towards guideline recommended care, as opposed to being forced to do so. All medical decisions are ultimately made by the provider. This trial will not interfere with the ordinary workings of the outpatient centers.

There is a small risk associated with altering medication prescribing behaviors, including allergic reactions or other adverse medication effects; however, these risks are no more than are encountered during routine clinical care and are less than patients would otherwise encounter if there were to receive the high-risk medications whose use the intervention seeks to reduce. In addition, these risks will be minimized in our protocol as we are relying on the provider to prescribe as they see best for their patient; the prescribing changes in the EHR tools are simply suggestions, not rigid rules for the providers. In addition, as described above, in the unexpected situation in which the EHR tools lead to worse prescribing decisions, we will discontinue those arms at the end of Stage 1.

The primary risk to patients will be privacy of health information. We will minimize the risk to privacy by taking appropriate steps to limit access to data to study investigators. Clinical

data on the care for patients will be retrieved from the electronic medical records and insurer administrative claims. The data extracts obtained from the electronic medical record are continuously used by clinical operations staff for quality assessment and improvement, and undergo routine, rigorous peer-review by experienced data analysts to ensure accuracy and completeness. Drs. Choudhry and Lauffenburger will work with the research project staff to ensure the accuracy of these data throughout the study period. For the purpose of conducting analyses of the study outcomes, this will involve creating scrambled patient and provider identifiers and sharing only limited Protected Health Information (PHI) with investigators for the purposes of analysis. All team members have received appropriate training in data privacy.

8.2 Informed consent

We will enroll provider-subjects based on their being employed by Mass General Brigham as an outpatient primary care provider. As with other minimal-risk, quality improvement studies we have performed that involve electronic alerts to providers, formal informed consent will not be sought. First, the nature of this quality improvement intervention involves testing EHR decision support directly for providers (using information already available to them and a similar infrastructure they use in the course of regular clinical care). Second, the ability to understand the true effect of the intervention as it is delivered in the real world would be difficult to ascertain if true informed consent was sought. Third, obtaining true informed consent would predictably reduce the number of patients participating in the study, especially those from unrepresented populations, and therefore undermine the generalizability of the study results, a foundational aspect of pragmatic clinical trial principles. Fourth, this approach has been approved by clinical leadership at the health organization. In our prior work at these institutions, we have received a waiver of informed consent from the IRBs of these organizations for similar interventions. We also request a HIPAA waiver of patient authorization

to access the administrative claims and EHR data necessary for outcome evaluation, as doing so would be impractical and infeasible to conduct the study.

While providers and patients will not be consented into the study, an organization-wide email will be circulated across MGH to inform providers of the launch of an intervention leveraging clinical decision support tools to support improved prescribing for older adults.

8.3 Confidentiality and privacy

To protect against the risk of inappropriate disclosure of personal health information, the study team will use limited PHI data for the purpose of analyzing the study. These analyses will be overseen and conducted by MGB investigators. These datasets will consist of pharmacy and medical claims, laboratory information, and structured information from the EHR. The only PHI that will be shared with the study investigators are dates (e.g., date of birth, admission/discharge dates, and dates of medication fills), zip code, and Medicare Beneficiary Identifier (MBI), which is necessary in order to access the Medicare administrative claims data for the outcome evaluation. Sharing this information will be necessary to assess the impact of the interventions.

The electronic data will be safeguarded by state-of-the-art security protocols. The facilities have 24-hour security and are protected by locked entrances. Both health systems have computer networks in place that employ up to date virus protection software and enable password-protected access only to study investigators. All data transfers between the organizations will be accomplished using secure file transfer protocols. 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 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.

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). 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 MGB Healthcare's 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

We plan to use a centralized Institutional Review Board (IRB) and a Data Safety Monitoring Board (DSMB) for all aspects of this research. We will also establish an independent data and safety monitoring board (DSMB) with experience in quality of care, patient safety, and biostatistics. The DSMB will act in an advisory capacity to monitor participant safety and evaluate the progress of the study, review procedures and management of the study. Drs. Choudhry and Lauffenburger are the PIs at MGB. The DSMB will consist of individuals with experience in quality of care, patient safety, and biostatistics. This committee will convene biannually and review data related to the study protocols and ensure protection of patient confidentiality and safety, as well as to monitor the quality of the data collected via the

study protocols on a semi-annual basis. We will also be in routine contact with clinical leadership to obtain any feedback from clinicians regarding the studies. Compliance of regulatory documents and study data accuracy and completeness will be maintained through an internal study team quality assurance process. At each meeting, the DSMB will make recommendations as to whether the studies should continue or if changes to the protocol are necessary for continuation. This trial will be registered with clinicaltrials.gov.

8.5 Benefit risk assessment

8.5.1 Known potential risks

There is a small risk associated with altering medication prescribing behaviors, including allergic reactions or other adverse medication effects; however, these risks are no more than are encountered during routine clinical care. In addition, these risks will be minimized in our protocol as we are relying on the provider to prescribe as they see best for their patient; the prescribing changes in the EHR tools are simply suggestions, not rigid rules for the providers. In the intervention arms, providers will be encouraged to follow national guidelines in the care of their patients and discontinue dangerous medications. It is recommended that some of these medications (benzodiazepines, sedative hypnotics) be discontinued through a gradual dose taper so as to avoid withdrawal symptoms, and suggested tapers will be provided as a solution within the EHR prompts. Another potential small risk to patients will be privacy of health information. We will minimize the risk to privacy by taking appropriate steps to limit access to data to study investigators. Clinical data on the care for patients will be retrieved from the electronic medical records and insurer administrative claims.

8.5.2 Known potential benefits

This study is designed to improve electronic health record prescribing tools for providers caring for older adults. Potential benefits for participants in this study include improved decision

support tools and guideline-concordant prescribing. The human subjects may benefit from discontinuing a dangerous drug that is not recommended for them. Additionally, the subjects and society may benefit in the future from accumulated knowledge that originates from this research. We will also produce several EHR tool deliverables for this work for the public, researchers, and policymakers, which will be shared as generalized knowledge.

8.5.3 Assessment of potential risks and benefits

The intervention aims to emphasize guideline-recommended information for providers to assist in their decision-making when caring for older patients. All treatment decisions will ultimately be made by licensed health care providers. The intervention is specifically provider-focused and delivered in an electronic health record system using information already available to providers. We believe there is no more than minimal risk involved to the provider subjects, as the providers will simply be “nudged” to alter their behaviors towards guideline recommended care, as opposed to being forced to do so. All medical decisions are ultimately made by the provider. This trial will not interfere with the ordinary workings of the outpatient centers.

The potential societal benefits outweigh the minimal risk, especially in light of multiple measures in place to protect confidentiality. The data extracts obtained from the electronic medical record and these claims are continuously used by clinical operations staff for quality assessment and improvement, and undergo routine, rigorous peer-review by experienced data analysts to ensure accuracy and completeness. For the purpose of conducting analyses of the study outcomes, this will involve creating scrambled patient and provider identifiers and sharing only limited Protected Health Information (PHI) with investigators for the purposes of analysis. Because our intervention encourages providers to discontinue dangerous medications in a way that prioritized patient safety and enables the provider to retain full decision-making power of the care of the patient, there is no more than minimal risk involved for our patient and physician-subjects.

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