STATISTICAL ANALYSIS PLAN (SAP)

High-Risk Polypharmacy: Reducing High-Risk Geriatric Polypharmacy via EHR Nudges

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List of Abbreviations

Abbreviation	Definition
ADE	Adverse drug event
EHR	Electronic health record
HRPP	High risk polypharmacy
NM	Northwestern Medicine
NSAID	Nonsteroidal anti-inflammatory drug
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
UPMC	University of Pittsburgh Medical Center; affiliated with the University of Pittsburgh Schools of the Health Sciences

STATISTICAL ANALYSIS PLAN (SAP)

High-Risk Polypharmacy: Reducing High-Risk Geriatric Polypharmacy via EHR Nudges

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1. INTRODUCTION

This document outlines the proposed analyses for the High-Risk Polypharmacy (HRPP) clinical trial, which aims to compare the effectiveness of two types of clinical decision support tools (commitment and justification nudges) to reduce high-risk prescribing and adverse events in older patients who take high risk combinations of drugs (high-risk polypharmacy). Inappropriate polypharmacy, defined as the administration of more drugs than clinically necessary, is highly prevalent among geriatric patients in the United States. Polypharmacy is associated with adverse drug reactions, drug interactions, medication nonadherence, adverse events such as falls and mortality, and higher costs of care. We plan to conduct a four-arm, pragmatic, 2x2 factorial cluster randomized controlled trial with equal allocation (1:1:1:1 clinics) in adult patients aged 65 years or older who have polypharmacy (use five or more systemic prescription medications) seen at participating clinics at two health systems: Northwestern Medicine (NM) and University of Pittsburgh Medical Center (UPMC). The purpose of this document is to provide details regarding the statistical analysis plan (SAP) for this study.

Study Aims

The overarching study aims are as follows:

Aim 1: To evaluate the effects of an EHR-based commitment nudge, a justification nudge, and the combination of both nudges on a composite measure of high-risk polypharmacy via a pragmatic randomized controlled trial. *We will use cluster randomization in which primary care clinics are randomized to receive 0, 1, or 2 nudges using a factorial design. The nudges will run for 18 months, followed by 12 months of observation to assess persistence of effects*.

We hypothesize that the intervention will decrease polypharmacy, may decrease emergency care and hospitalizations, and improve the care of older adults.

After the 18-month intervention period, we will collect efficacy outcomes for an additional 12 months. We hypothesize that any observed differences in the trajectories of the rates of HRPP present at the end of the intervention period between active intervention groups and control will diminish during the 12-month follow-up period, and that the decline in effect will be greater for the single intervention group than the dual intervention group. This dissipation of effects is expected, although it may occur quite slowly because medication changes are fairly infrequent.

Exploratory Aim 1: We will perform sub-group analysis to examine patients with and without dementia or mild cognitive impairment. We also plan to conduct pre-specified sub-group analyses to examine whether the effects of the interventions differ by age category, sex, race, ethnicity, and degree of polypharmacy.

We hypothesize that the interventions' effects may be stronger among patients with dementia or mild cognitive impairment, the very elderly, and those with more extensive polypharmacy.

Exploratory Aim 2: To qualitatively and quantitatively assess clinician experiences with the EHR-based nudges, including their acceptability and effects on workflow. *At the conclusion of the intervention period, we will perform semi-structured interviews and field a clinician survey*.

This SAP will focus on the details of the analyses for Aim 1 and Exploratory Aim 1; we reserve details of the exploration of clinician experiences (Exploratory Aim 2) for future work.

Study time points include baseline assessment of clinics (to evaluate annual performance for use in constrained randomization), a 12-month historical baseline period, an 18-month active intervention period, and a 12-month post-intervention period (to evaluate persistence of effects).

2. STUDY OUTCOMES

In the sections below, we include the relevant specific field names for variables within the study database as of the time of SAP creation. These are indicated by square brackets, and include: composite_HRPP_numerator, composite_HRPP_denominator, prop_demential, fall_cndtn_rx_num, fall_cndtn_rx_deno, fall_rx_rx_num, fall_rx_rx_deno, hf_thia_num, hf_thia_deno, hf_nsaid_num, hf_nsaid_deno, hf_ccb_num, hf_ccb_deno, ckd_gly_num, ckd_gly_deno, ckd_nsaid_num, and ckd_nsaid_deno. All primary, secondary, and safety outcomes are produced from data abstracted from the EHR at each participating health system. The primary, and secondary outcomes were developed and piloted in the initial R21 study [R21AG057396].[1]

Primary Outcome

The primary effectiveness outcome is an indicator of an HRPP Composite Outcome [HRPP], which is experiencing one or more of the drug-conditions or drug-drug combinations listed in the HRPP Component Measures occurring in an eligible patient determined by an examination of the EHR active medication list and EHR-recorded discrete diagnoses. Eligible patients are age 65 years and older, prescribed five or more systemic medications in the outpatient setting and have a qualifying visit with a participating primary care clinician. Each of the seven components of the HRPP composite is defined under "Secondary Outcomes." Eligible patients (the denominator for the primary outcome) will have been seen at a participating clinic by a participating clinician for an in-person or telehealth visit in the prior 365 days, be age 65 years or older at the beginning of the 365 days look-back period, and have 5 or more qualifying medications on the active medication list at the time of the outcome assessment. This variable will be calculated on a monthly basis using the preceding 365 days of data.

Secondary Outcomes

Each individual measure component of the composite is a secondary outcome. The individual components of the HRPP Composite will use the same general eligibility criteria as the primary

outcome along with component-specific denominator criteria. A brief description of the components of the HRPP composite outcomes is included in **Table 1**, with detailed descriptions for abstraction of data components from the EHR available in Section 10 below.

Table 1. Overview of Components of the HRPP Composite Outcome	
Measure	Brief Description
Fall condition-drug interaction	≥1 active prescription for eligible fall risk medications (Opioids are not included)
Fall drug-drug interaction	≥ 3 active prescriptions for eligible fall risk mediations
Heart failure-thiazolidinedione interaction	Among those with HF, ≥1 active prescription for eligible thiazolidinedione medications
Heart failure-NSAID interaction	Among those with HF, ≥ 1 active prescription for eligible NSAIDs
Heart failure with reduced ejection fraction-non-dihydropyridine calcium channel blocker interaction	Among those with HFrEF (EF < 40%), ≥ 1 active prescription for eligible CCB medications
CKD-glyburide/glimepiride interaction	Among those with CKD, ≥ 1 active prescription for eligible glyburide-containing medications
CKD-NSAID interaction	Among those with CKD, ≥ 1 active prescription for eligible NSAIDs
Note: Prescriptions are active medications on the “medication list” available through the EHR.	

Additional secondary outcome measures are: (1) emergency department visits per patient—all cause, (2) emergency department visits per patient---potentially adverse drug event-specific, (3) hospital admissions per patient—all cause, and (4) hospital admissions per patient—potentially adverse drug event specific. Denominators for these secondary outcomes will be the same as for the primary HRPP composite. We will report the denominator and numerator counts in the month prior to the intervention beginning and during the last month of the active intervention, as well as a rate per 10,000 patients per year for these measures in each study arm.

Emergency department visits and hospitalizations will be assessed by queries of the NM or UMPC electronic medical records and will only include visits occurring within these health systems. Potentially adverse drug event-specific emergency visit and hospitalizations will be identified by the ICD-10 codes listed in Table 2.

Table 2. Diagnosis Criteria for Potentially ADE-Specific ED Visits and Hospitalizations	
ADE	ICD-10 values
Fall	W00-W19 and all sub-codes [all categories of falls] S72.0 and all sub-codes [fracture of head and neck of femur] S72.1 and all sub-codes [pertrochanteric fracture] S72.2 and all sub-codes [subtrochanteric fracture of femur]
Acute kidney injury	N17 and all sub-codes [acute kidney injury (nontraumatic)], N19 [unspecified kidney failure]

Hypoglycemia	E16.0, E16.1, E16.2 [hypoglycemia codes], E13.64 and all subcodes [DM2 with hypoglycemia], E10.64 and all subcodes [DM1 with hypoglycemia], T38.3 and all subcodes [poisoning by, adverse effect of, and underdosing of insulin and oral hypoglycemic drugs]
Fluid retention and heart failure exacerbation	I50.21 [acute systolic heart failure], I50.23 [acute on chronic systolic heart failure], I50.31 [acute diastolic heart failure], I50.33 [acute on chronic diastolic heart failure], I50.41 [acute combined systolic and diastolic heart failure], I50.43 [acute on chronic combined systolic and diastolic heart failure], I50.811 [acute right heart failure], I50.813 [acute on chronic right heart failure], J81.0 [acute pulmonary edema]

Safety Outcomes

Described below are the safety measures that we will assess during this trial using EHR data. We will conduct clinician chart review for events possibly or probably related to the clinical decision support interventions. We will report the denominator and numerator counts in the month prior to the intervention beginning and during the last month of the active intervention, as well as a rate per 10,000 patients per year for all safety measures in each study arm. These represent unlikely but conceivable adverse consequences of discontinuing or reducing the high-risk medications targeted by the nudges. Patients will be considered eligible for the denominator of a safety measure if they met that specific drug-condition or drug-drug high-risk polypharmacy criteria during the 365 days prior to the safety assessment period. We will collect safety assessments by quarter. For example, patients who met the safety-measure-specific high-risk polypharmacy criteria at any time from 1/1/2023 to 12/31/2023 would be in the denominator of patients assessed for the safety outcome from 1/1/2024 through 3/31/2024. We will also investigate all clinician-reported adverse events or unanticipated problems for all study clinical decision support (CDS).

1. **Safety measure for discontinuing or reducing benzodiazepines and anticonvulsants: hospitalization or emergency department (ED) visit for seizure.** Event is the occurrence of a hospitalization or ED visit for seizure, detected through a query of the Northwestern and UPMC EDWs. The denominator for this measure is all patients who met criteria for fall condition-drug interaction or fall drug-drug interaction with a benzodiazepine or anticonvulsant medication on the active medication list during the 365 days prior to the safety assessment period.
2. **Safety measure for discontinuing or reducing tricyclic antidepressants, gabapentinoids, serotonin and norepinephrine reuptake inhibitors, opioids, and NSAIDs: hospitalization or ED visit for pain.** Event is the occurrence of a hospitalization or ED visit for pain, detected through a query of the Northwestern and UPMC EDWs. The denominator for this measure is all patients who met criteria for fall condition-drug interaction or fall drug-drug interaction with a tricyclic antidepressant, gabapentinoid, SNRI or opioid on the active medication list or the CKD-NSAID interaction or Heart failure-NSAID interaction with an NSAID on the active medication list during the 365 days prior to the safety assessment period.
3. **Safety measure for discontinuing or reducing tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors: hospitalization or ED visit for depression or suicidality.** Event is the

occurrence of a hospitalization or ED visit for depression or suicidality, detected through a query of the Northwestern and UPMC EDWs. The denominator for this measure is all patients who met criteria for fall condition-drug interaction or fall drug-drug interaction with a tricyclic antidepressant, SNRIor SSRI on the active medication list during the 365 days prior to the safety assessment period.

4. **Safety measure for discontinuing or reducing benzodiazepines, serotonin and norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors: hospitalization or ED visit for anxiety.** Event is the occurrence of a hospitalization or ED visit for anxiety, detected through a query of the Northwestern and UPMC EDWs. The denominator for this measure is all patients who met criteria for fall condition-drug interaction or fall drug-drug interaction with a benzodiazepine, SNRI, or SSRI on the active medication list during the 365 days prior to the safety assessment period.
5. **Safety measure for discontinuing or reducing benzodiazepines and Z-drugs (GABA receptor modulators): hospitalization or ED visit for sedative withdrawal.** Event is the occurrence of a hospitalization or ED visit for withdrawal from sedative, hypnotic, or anxiolytic drug, detected through a query of the Northwestern and UPMC EDWs. The denominator for this measure is all patients who met criteria for fall condition-drug interaction or fall drug-drug interaction with a benzodiazepine or Z-drug on the active medication list during the 365 days prior to the safety assessment period.
6. **Safety measure for discontinuing or reducing opioids: hospitalization or ED visit for opioid withdrawal.** Event is the occurrence of a hospitalization or ED visit for opioid withdrawal, detected through a query of the Northwestern and UPMC EDWs. The denominator for this measure is all patients who met criteria for fall condition-drug interaction or fall drug-drug interaction with an opioid drug on the active medication list during the 365 days prior to the safety assessment period.
7. **Safety measure for discontinuing or reducing antipsychotics: hospitalization or ED visit for behavioral disturbance in dementia or psychosis.** Event is the occurrence of a hospitalization or ED visit for dementia with behavioral disturbance, or psychosis detected through a query of the Northwestern and UPMC EDWs. The denominator for this measure is all patients who met criteria for fall condition-drug interaction or fall drug-drug interaction with an antipsychotic drug on the active medication list during the 365 days prior to the safety assessment period.
8. **Safety measure for discontinuing or reducing glyburide, glimepiride, and thiazolidinediones: hospitalization or ED visit for hyperglycemia.** Event is the occurrence of a hospitalization or ED visit for hyperglycemia detected through a query of the Northwestern and UPMC EDWs. The denominator for this measure is all patients for who met criteria for CKD-glyburide/glimepiride interaction with glyburide or glimepiride, on the active medication list at the time of the event or in the year preceding the event or heart failure-thiazolidinedione interaction with a thiazolidinedione on the active medication list during the 365 days prior to the safety assessment period.
9. **Safety measure for discontinuing or reducing non-dihydropyridine calcium channel blockers: hospitalization or ED visit for tachycardia (other than ventricular) or hypertensive emergency.** Event is the occurrence of a hospitalization or ED visit for tachycardia (other than ventricular), detected through a query of the Northwestern and UPMC EDWs. The denominator for this measure is all patients who met criteria for heart failure with reduced ejection fraction-non-dihydropyridine calcium channel blocker interaction - with a non-dihydropyridine calcium channel blocker on the active medication list during the 365 days prior to the safety assessment period.

10. **Clinician reported adverse events/unanticipated problems.** At any time, participating clinicians can report an adverse event or unanticipated problem potentially related to study participation.

We will assess additional exploratory and safety outcomes, as recommended by the Data Safety Monitoring Board (DSMB), on an as-needed basis.

3. PATIENT AND CLINICIAN DEMOGRAPHICS AND CLINIC-LEVEL BASELINE ASSESSMENT

The following are specific patient and clinician demographics and clinic-level baseline assessments of interest for analyses. Primary analyses will adjust for fixed clinic-level covariates included in the constrained randomization procedure (detailed in Section 5 of this SAP). We plan to report marginal intervention effect estimates after adjustment for said covariates, regardless of significance.

Clinic-level Baseline Assessments

1) Practice region: At NM (NMG – Central; NMG – North; RMG); At UPMC these will be split into six existing administrative groups or consolidated into larger groups if some units have small numbers of practices.

2) Number of clinicians attributed to each participating clinic. A clinician is attributed to a clinic based on where they provide the plurality of their patient care.

3) Number of patients eligible for the composite HRPP outcome (detailed in “Primary Outcome” above) in the 12-month baseline period

4) Rate per 100 eligible patients of the composite HRPP outcome (detailed in “Primary Outcome” above) in the 12-month baseline period

Data to calculate 2-4 were abstracted from the EHR at NM on 5/25/2023 for the period 4/1/2022 – 3/31/2023 and will be abstracted from the EHR at UPMC later in 2023 [date to be included in subsequent version] for the same period.

Patient Demographics

Additional patient demographics of interest, abstracted from the EHR, will be used to describe the patient population and conduct subgroup analyses. These include:

1) Sex

2) Age

3) Race

4) Ethnicity

5) Presence or absence of dementia diagnosis, or diagnosis of mild cognitive impairment (defined using ICD-10 codes)

Clinician Demographics

The following clinician demographics, obtained from the two health systems or from public facing websites, will be used to describe the clinicians and to conduct pre-specified subgroup analyses:

1) Sex

2) Year of graduation

3) Specialty

DATA STORAGE

Data will be collected and managed using a variety of tools. For NM data abstracted from the EHR (baseline clinic-level characteristics, patient-level demographics, and patient-level outcomes) will be housed in the secured file server hosted by Feinberg School of Medicine (FSM) at Northwestern University (NU) in the excel format. For the UPMC data, the limited data set will be securely transferred to the secured FSM file server at NU for the analysis.

Clinician survey data will be collected and managed using Research Electronic Data Capture (REDCap) housed at Northwestern University's Clinical and Translational Sciences Institute (CTSA), NUCATS. REDCap is a secure, web-based application designed for research studies that provides an intuitive interface for validated data entry, audit trails for tracking data manipulation and export procedures, and automated export procedures for seamless data downloads to common statistical packages, and procedures for importing data from external sources.[2] Refer to the study Data Management and Sharing Plan (DMSP) for details.

4. RANDOMIZATION METHODS

This study uses a 2 x 2 factorial cluster-randomized design with equal allocation (1:1:1:1) across study arms. We will use a modified constrained randomization process, stratified by healthcare system (NM and UPMC), to randomize practices and maintain exchangeability between clinics assigned to each study arm. The clinic-specific characteristics include 1) baseline primary outcome performance, 2) size of eligible patient population at baseline, 3) number of clinicians attributed to the clinic, and 4) region within the health system (as detailed in Section 3). Participating clinics will then be randomized to 1 of 4 study arms:

- The 'control' arm of study will not receive any interventions other than the invitation to a brief educational module
- The 'Commitment' nudge plus brief educational module,
- The 'Justification' nudge plus brief educational module, or
- The Commitment and Justification nudges ('Both' nudges) plus brief educational module.

The study interventions will be delivered to clinicians based on their primary practices (i.e., the practices where they provide the majority plurality of their patient care), with clinical decision support keyed to the clinicians' EHR identifiers.

We will use a modification of the methodology proposed in Siddique et al. (2023) [under review] to implement the constrained randomization algorithm. First, the study statistician (Dr. Petito) will generate possible 1:1:1:1 randomization schemes. Since there are many ways to randomize the participating practices into 4 groups, the study statistician will create 100,000 possible

sequences. Second, the balance of the four prespecified variables (which were “constrained” upon) will then be evaluated in the 100,000 possibilities. Schemes will be deemed candidate schemes if they had “adequate balance,” adapting the minimal sufficient balance approach. For the three continuous variables, the balance metric will be the total inverse variance weighted Euclidean distances in each study arm, summed across clusters. We then will call a candidate scheme ‘adequately balanced’ if the balance metric was in the top 5% of all candidates. Then we will further restrict the space of candidate schemes to allow no more than a difference of one clinic across each arm for each category of the “region” variable. Last, the final sequence will be selected from the candidate schemes (which were adequately balanced) at random with equal probability.

As the inverse variance weighted balance metric is dependent on the normality of the continuous variables included in the constrained randomization, pre-randomization analysis will include visual inspection of the empirical distribution of each of the three continuous variables. If they are not normally distributed, a natural log transformation will be considered.

The study statistician (Dr. Petito) will generate the final study randomization sequence after setting a seed number to ensure reproducibility, separately for each study site. The study statistical analyst (Ms. Lee) will upload a “Production” randomization list into REDCap for use when deploying the baseline and follow-up clinician surveys. The randomization lists will be housed on Northwestern University’s “FSMResFiles” with restricted access so only the statistical team (Dr. Petito, Ms. Lee) can access. This is an unblinded pragmatic trial, so the clinics and attributed clinicians will be aware of the intervention they receive.

Randomization occurred in June 8, 2023 at NM and will occur later in 2023 at UPMC [date to be included in subsequent version of this document].

5. STATISTICAL METHODS

Descriptive statistics will summarize participant demographics and baseline clinical outcomes overall and across arms: proportion (percentages) for categorical variables; mean (± standard deviation) for continuous variables; and median (interquartile range) for skewed or count variables. Analyses in general will employ normal theory methods and residual diagnostics will evaluate validity of assumptions; where appropriate (i.e., in the event of low cell counts for categorical data or questions of normality), transformation of variables, nonparametric methods, or exact tests may be employed. All primary effectiveness and safety analyses will be pre-specified as outlined in this SAP, and deviations from planned analyses will be labeled as such in any reports or dissemination materials.

The primary and secondary outcome analyses will assume a two-sided 5% type I error rate. We will employ a Bonferroni correction for multiple hypothesis tests, as each intervention arm (justification, commitment, both) will be compared to the same control group. Thus, all reported “95% confidence intervals” will correspond to an alpha of 0.017 (0.05 / 3) and be calculated as 98.3% confidence intervals. Safety outcome analyses will not be Bonferroni-corrected.

<u>Planned Primary, Secondary, and Safety Analyses</u>

To test our hypotheses that the ‘commitment’, ‘justification’, and ‘both’ interventions are effective at reducing the composite HRPP outcome, we will employ a mixed-effects hierarchical logistic regression model to estimate the adjusted marginal effect over time of each intervention on the

binary outcome. Fixed effects will include intervention assignment (indicator for each of the 3 active intervention arms), time period (historical baseline versus intervention period), time period interacted with intervention assignment, time (continuous, linear), and a 3-way interaction term between time period, intervention, and time (continuous). The coefficient on the 3-way interaction terms will represent whether the log-odds of the monthly rate of change in the primary outcome differs between intervention and control patients during the intervention period. Clinicians will be included as random effects. To isolate the effect of the intervention on the primary outcome, we will also include fixed effects for the clinic-level variables included in the constrained randomization procedure.

The primary outcome will be examined in the following pre-specified subgroups:

- Sex
- Race: Asian, Black/African-American, White, American Indian/Alaskan Native, Native Hawaiian/Other Pacific Islander, multiracial/other, unknown
- Ethnicity: Hispanic or Latino vs not
- Dementia or mild cognitive impairment present vs absent
- Age categories: 65-74, 75-84, 85+
- Polypharmacy (number of systemic prescription meds): 5-9, 10-14, 15+

The secondary and safety outcomes will be examined in a similar fashion. If they are sufficiently rare (for example, no events in a given month), model convergence may become an issue. First, we plan to expand the measurement period from monthly to quarterly, and fit the same model on a coarser time scale. If that fails, we will abandon the time-varying aspect of the analysis and do one pull for the historical baseline period and one pull for the intervention period. This corresponds to a comparison of mean outcomes during entirety of the historical baseline and active intervention periods. The mixed effects logistic regression model would then be run without including continuous time, only an indicator for active intervention. If that still fails to converge, we will exclude the random effects for providers and use a fixed effects logistic regression model.

6. ANALYTIC DATASET

Analyses will be conducted in an intention-to-treat dataset, whereby all clinics with data at baseline will be included in analyses according to the study arm to which they were randomized, regardless of adherence to the study protocol (e.g. regardless of whether the clinical decision support fired appropriately). Clinicians will be attributed to the clinic at which they spent the most time during the most recent 6-month clinic-level baseline assessment period. Patients will be attributed to clinicians as indicated by the study outcome (Section 2). There are no planned per protocol analyses.

We do not anticipate missing data, as clinics can only leave the study if 1) leadership withdraws consent; 2) the clinic closes or leaves the health system altogether; or 3) all clinicians attributed to a given clinic at baseline leave the health system after the baseline assessment period. Clinicians who leave the health system before the end of the study period (and their attributed patients) will contribute data in measurement periods when they were working at the health system. Clinicians who join a participating clinic at the health system after the historical baseline period will not contribute data to the study.

7. POWER AND SAMPLE SIZE CONSIDERATIONS

As the two health systems included in this study, NM and UPMC, have a fixed number of clinics participating (and therefore clinicians and their patients), power calculations focused on our power to detect a range of clinically meaningful risk reductions in the primary outcome for a given number of clinics/clinicians/patients.

For illustrative purposes, we present power calculations for the primary outcome: the rate of HRPP among patients aged 65 years or greater. Preliminary data from Northwestern indicate that 6,256 of 55,000 (11%) patients aged 65 years or older taking at least 5 medications who attended at least one face-to-face visit with their primary care physician between January 1, 2017 and December 31, 2018 met one or more criteria for HRPP. We therefore assumed that between 10% and 14% of patients aged 65 years or greater will be classified as having HRPP at baseline. NM includes 60 primary care clinics with approximately 392 clinicians who empanel 55,000 adult patients aged 65 years or greater who are taking at least 5 medications. The UPMC system looks similar, with an estimated 90 primary care clinics with approximately 400 clinicians who empanel 105,000 older adult patients expected to meet eligibility criteria. To be conservative, our power calculation was designed with 37 clinics in each arm encompassing 37,000 unique patients. Assuming 100% clinician participation at both sites, clinic-level ICC of 0.017 (empirically derived from Northwestern data), and Bonferroni multiple-comparison corrections for 3 comparisons (each active treatment arm to control), we calculated the following levels of power for 2-tailed tests at the 0.05 level of significance for 5-, 4-, and 3-absolute percentage point reductions in the primary outcome (**Table 3**).

Table 3. Statistical Power for Bonferroni-Corrected Comparisons Between Trial Study Arms

	Absolute risk reduction of 5 percentage points			Absolute risk reduction of 4 percentage points			Absolute risk reduction of 3 percentage points		
Baseline event rate	10%	12%	14%	10%	12%	14%	10%	12%	14%
Corresponding relative risk	0.50	0.58	0.64	0.60	0.67	0.71	0.70	0.75	0.79
Power for 3 comparisons	>99%	99%	98%	99%	97%	94%	86%	77%	70%

8. TECHNICAL DETAILS

This SAP is subject to version control, and we anticipate modifications to analytic plans. Any changes will be documented herein. These changes may be due to assumption violations, logistical issues, unexpected empirical distributions of study outcomes, or a combination thereof. In these cases, the SAP will be updated accordingly. All analyses will be performed via SAS version 9.4 or higher (The SAS Institute; Cary, NC) or R version 4.3.0 or higher (The R Foundation for Statistical Computing platform). Table and figure formatting and style may be dictated by mode of dissemination or specific target journal(s) for results dissemination.

Summary of updates:

[To be included in future versions]

9. TIMELINE FOR ANALYSES

As this is a low-risk clinical trial, the SAP does not include any formal interim statistical analyses involving hypothesis testing or any pre-specified stopping criteria for effectiveness or futility on primary or secondary outcomes. Interim reports to the study team and data and safety monitoring board (DSM) will consist of process measures such as missing values (clinicians leaving the health system) and simple descriptive statistics on primary and safety outcomes of interest, NOT stratified by study arm. Quality control and assurance for primary, secondary, and safety outcomes will be conducted on a quarterly basis.

We foresee the DSMB requiring specific data listings or summarizations, but these will be specified at the time of the relevant DSMB meeting(s). At DSMB meetings, study outcomes stratified by study arm may be presented in a closed session to the DSMB members, study statistician (Dr. Petito), and study statistical analyst (Ms. Lee); the DSMB members will be un-blinded upon request.

To preserve the integrity of the study, no formal final statistical analyses will occur until the REDCap database has been locked and all queries/discrepancies resolved; the date of database lock will be documented.

10. HHRP MEASURE SPECIFICATIONS DEFINITIONS

Measure	Denominator	Numerator
Fall condition-drug interaction	All patients aged ≥65 years on the year prior to measurement date AND had at least one qualifying face-to-face or telehealth office visit (s) during one year prior to measurement date AND Alive AND total active medications[1] ≥5 AND have ≥1 fall marker[2] within the past 2 years	≥ 1 active eligible fall risk medication(s) (Opioids are not included as a criterion for fall condition-drug interaction)
Fall drug-drug interaction	all patients aged ≥65 years on the year prior to measurement date AND had at least one qualifying face-to-face or telehealth office visit(s) during one year prior to measurement date AND Alive AND total active medications[1] ≥ 5	≥ 3 active eligible fall risk mediations
HF-thiazolidinedione interaction	all patients aged ≥ 65 years on the year prior to measurement date AND had at least one qualifying face-to-face or telehealth office visit(s) during one year prior to measurement date AND Alive AND total active medications[1] ≥ 5 AND have ≥ 1 HF marker[3] within the past 2 years	≥1 active eligible thiazolidinedione medication(s)
HF-NSAID interaction	all patients aged ≥ 65 years on the year prior to measurement date AND	≥ 1 active eligible NSAID medication(s)

	had at least one qualifying face-to-face or telehealth office visit(s) during one year prior to measurement date AND Alive AND total active medications[1] ≥ 5 AND have ≥ 1 CHF marker[3] within the past 2 years	
HF-non-dihydropyridine calcium channel blocker interaction	all patients aged ≥ 65 years on the year prior to measurement date AND had at least one qualifying face-to-face or telehealth office visit(s) during one year prior to measurement date AND Alive AND total active medications[1] ≥ 5 AND have ≥ 1 CHFlowEF marker[4] within the past 2 years	≥ 1 active eligible CCB medication(s)
CKD-glyburide/glimepiride interaction	all patients aged ≥ 65 years on the year prior to measurement date AND had at least one qualifying face-to-face or telehealth office visit(s) during one year prior to measurement date AND Alive AND total active medications[1] ≥ 5 AND have most-recent eGFR[5] < 60 within the past 2 years	≥ 1 active eligible glyburide-containing medication(s)
CKD-NSAID interaction	all patients aged ≥ 65 years on the year prior to measurement date AND had at least one qualifying face-to-face or telehealth office visit(s) during one year prior to measurement date AND Alive AND total active medications[1] ≥ 5 AND have most-recent eGFR[5] < 30 within the past 2 years	≥ 1 active eligible NSAID medication(s)
Primary Composite Measure: Experiencing any of the 7 component measures	Met at least one of the above criteria	Experienced at least one of the above criteria

Footnotes

1. Logic to count total active medications
   - Include only medications with ROUTE = (oral, buccal, sublingual, or transdermal)
   - de-duplicate the resulting current medication list using the field “simple_generic_name” as the basis of deduplication. Discard any entries that do not have a “simple_generic_name” value

2. Fall marker

Variable	Values
ICD-10*	W00-W19 and all sub-codes [all categories of falls] S72.0 and all sub-codes [fracture of head and neck of femur] S72.1 and all sub-codes [pertrochanteric fracture] S72.2 and all sub-codes [subtrochanteric fracture of femur]
Fall risk screening marker	Health system variable to indicate a patient responded affirmatively to a fall risk screening questionnaire.

3. Heart Failure marker

Variable	Values
ICD-10	I25.5 and all sub-codes [ischemic cardiomyopathy] I42 and all sub-codes [cardiomyopathy] I43 and all sub-codes [cardiomyopathy in other diseases] I50 and all sub-codes except I50.8 (and all subcodes) [heart failure, excluding right heart failure]

4. Heart Failure low ejection fraction marker

Variable	Values
ICD-10	I50 and all sub-codes **except I50.3 (and all subcodes) and I50.8 (and all subcodes)** [heart failure, excluding CHF with preserved EF and right heart failure] I42 and all sub-codes [cardiomyopathy] I43 and all sub-codes [cardiomyopathy in other diseases] I25.5 and all sub-codes [ischemic cardiomyopathy]

5. Dementia or mild cognitive impairment

Variable	Values				
ICD-10	F03.90	G30.0	G31.09	G31.83	F01.51
	F02.80	G30.1	G31.1	G31.84	
	F02.81	G30.8	G31.2	G31.85	
	F03.90	G30.9	G31.81	G31.89	
	F03.91	G31.01	G31.82	F01.50	

6. eGFR (estimated glomerular filtration rate): mL/min/1.73m^2 from CKD-EPI Creatinine Equation 2021[3]

$$eGFR = 142 \times min\left(\frac{S_{cr}}{K}, 1\right)^{\alpha} \times max\left(\frac{S_{cr}}{K}, 1\right)^{-1.2} \times 0.9938^{Age} \times \beta,$$

where:

S_{cr} (Standardized serum creatinine) = mg/dL

K = 0.7 if female or 0.9 if male

α = -0.241 if female or -0.302 if male

β = 1.012 if female or 1 if male

REFERENCES

1. Persell SD, Brown T, Doctor JN, Fox CR, Goldstein NJ, Handler SM, Hanlon JT, Lee JY, Linder JA, Meeker D, Rowe TA, Sullivan MD, Friedberg MW. Development of high-risk geriatric polypharmacy electronic clinical quality measures and a pilot test of EHR-nudges based on these measures. J Gen Intern Med. 2022;37(11):2777-2785
2. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009 Apr;42(2):377-81. doi: 10.1016/j.jbi.2008.08.010. Epub 2008 Sep 30. PMID: 18929686; PMCID: PMC2700030.
3. National Kidney Foundation. https://www.kidney.org/professionals/kdoqi/gfr_calculator/formula. Accessed 9/25/23.