# Statistical Analysis Plan for

## A Technology-Driven Intervention to Improve Early Detection and Management of Cognitive Impairment (22-245)


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## LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| accrual period | time period when patients accrue into the study that begins at the same calendar time when the CI-CDS system is implemented in all clinics at a site and ends at a pre-determined calendar time |
| CDS | clinical decision support |
| CI | cognitive impairment |
| CI-CDS | cognitive impairment clinical decision support system |
| CONSORT | Consolidated Standards of Reporting Trials |
| DSMB | Data Safety Monitoring Board |
| ED | emergency department |
| EHR | electronic health record |
| EPIC | common EHR software system used by HealthPartners and other health systems to manage patient health records |
| GLM | generalized linear model |
| H<n> | Hypothesis <number> |
| ICC | intraclass correlation |
| ICD-10 | International Classification of Diseases, 10th Revision |
| index visit | first visit during the accrual period at a randomized clinic at which a patient meets all intervention eligibility criteria |
| intervention period | time period when the CI-CDS interface is operative in intervention clinics that begins at the same time as the accrual period and ends at a set calendar time |
| ITT | intent to treat |
| LMM | linear mixed model |
| MC-PLUS | algorithm developed in the R61 phase to identify patients at high risk of CI diagnosis |
| MCI | mild cognitive impairment |
| Mini-Cog | brief screening tool designed to help healthcare providers identify individuals who may have cognitive impairment |
| MMSE | Mini-Mental State Examination |
| MMM | Mayo Mini Mental |
| MoCA | Montreal Cognitive Assessment |
| NIH | National Institutes of Health |
| observation period | time period when patient outcome data accumulate that begins at the patient index visit and ends at the end of the intervention period |

| Abbreviation | Definition |
|---|---|
| OR | odds ratio |
| PCC | primary care clinician |
| PI | principal investigator |
| ROR | relative odds ratio |
| RR | risk ratio |
| SAP | Statistical Analysis Plan |
| SLUMS | St. Louis University Mental Status |
| UC | usual care |

# 1.0 INTRODUCTION

The Statistical Analysis Plan (SAP) for A Technology-Driven Intervention to Improve Early Detection and Management of Cognitive Impairment expands upon the statistical information presented in the protocol and describes all planned quantitative analyses for the primary, secondary and safety outcome measures.

The overarching aim of this study is to implement a clinical decision support (CDS) tool for identifying and managing cognitive impairment (CI) in a pragmatic clinic-randomized trial to evaluate its impact on CI detection, clinician perceptions and healthcare utilization among patients with elevated risk for CI in primary care clinics.

In the R61 phase of this study, our team developed and built the CI-CDS system that will make CI a priority to address at primary care office visits for patients with elevated risk for CI. The CI-CDS system is comprised of two interdependent processes that gather and assemble volumes of electronic health record (EHR) data to 1) offer clinicians tailored, point-of-care suggestions and tools for diagnosing and managing mild cognitive impairment (MCI) and dementia, and 2) estimate the likelihood of a future dementia diagnosis.

In this R33 phase of this study, we will conduct a pragmatic clinic-randomized trial to evaluate the effectiveness of the CI-CDS system in improving care for patients with elevated risk for CI by making it easier for clinicians to assess, diagnose, and manage cognitively impaired individuals. The study will randomize clinics to implement the CI-CDS system (CI-CDS) or to continue with usual care (UC). In the intervention clinics, the CI-CDS will use data stored in the EHR to identify patients with elevated risk for CI; assemble treatment recommendations tailored to each eligible patient's current needs; display these recommendations to primary care clinicians via the CI-CDS user interface; and store analytic data from all targeted visits. In UC clinics, the CI-CDS will run invisibly in the background to identify eligible patients, assemble tailored treatment recommendations, and store analytic data from all targeted visits, but will not display to clinicians or patients.

**The specific aims of the R33 phase of this trial are**: To evaluate the effect of the CI-CDS system on rates of CI detection, clinician confidence, and healthcare utilization costs in a pragmatic cluster-randomized trial of primary care clinics randomized to CI-CDS or UC.

**Primary Objective**: To evaluate the effect of the clinical decision support (CDS) tool for identifying and managing cognitive impairment (CI) on rates of CI detection in a pragmatic cluster-randomized trial of primary care clinics randomized to intervention (CI-CDS) or usual care (UC).

> **H1**: Patients with elevated CI risk at index visits in CI-CDS compared to UC clinics will have significantly higher rates of CI detection as indicated by EHR documentation of CI diagnosis in up to 24 months of follow up.

**Secondary Objectives**: To assess the extent to which the CI-CDS system increases clinician confidence in diagnosing and managing CI, or changes in healthcare utilization costs.

> **H2**: Clinicians at CI-CDS compared to UC clinics will have significantly more confidence in diagnosing and managing CI, as assessed through clinician surveys.
>
> **H3**: Among a subset of HealthPartners-insured patients with elevated CI risk at index visits, those at CI-CDS clinics will have significantly lower healthcare utilization costs

related to emergency room and inpatient visits in the follow-up period compared to similar patients at UC clinics.

Treatment effectiveness may vary as a function of contextual factors or patient characteristics. In secondary analyses, contextual factors and patient characteristics will be assessed for the extent to which the CI-CDS system is differentially effective (i.e., treatment heterogeneity) across patient subgroups, or relatedly, whether the CI-CDS intervention can reduce pre-intervention differences in CI care across patient characteristics.

# 2.0 STUDY DESIGN AND PROCEDURES

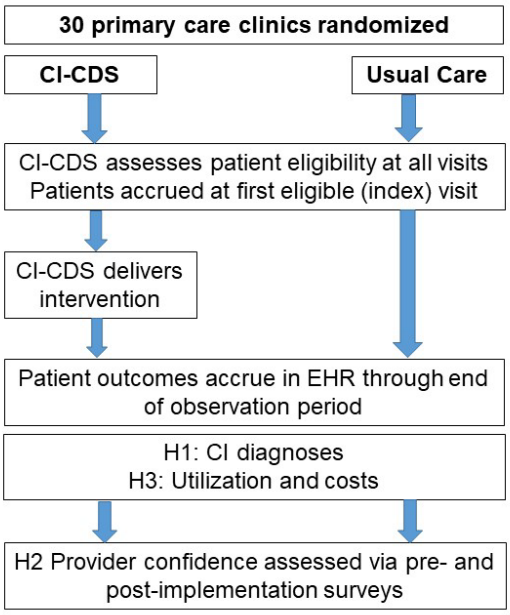
## 2.1 Study Design Overview

This large, unblinded, clinic-randomized pragmatic trial will evaluate the effectiveness of the CI-CDS system in improving care for patients with elevated risk for CI by making it easier for primary care clinicians to assess, diagnose, and manage individuals with CI. The study will be conducted in at least 30 HealthPartners primary care clinics, where at least 3000 patients with elevated risk for CI are estimated to receive care.

The CI-CDS software is a system level intervention comprised of 1) a passively operating web service that gathers, analyzes and retains information pertinent to every web service call, and 2) a user interface that presents a summary of algorithm results to front end users. The web service documents every web service call made by all front-end users in all participating locations so that data pertinent to all targeted visits from all eligible and accrued patients will be identically collected and available in both treatment arms. The user interface will function as the intervention delivery vehicle and therefore be operative only in intervention locations.

Clinics will be randomized equally to the CI-CDS or UC treatment group using simple randomization. CI-CDS clinics will fully implement the CI-CDS system. In these clinics, the CI-CDS will identify patients who are at high risk for CI; use data stored in the EHR for these patients to assemble treatment recommendations tailored to the current needs of each patient; display these recommendations via the CI-CDS user interface; and store analytic data from all targeted visits. UC clinics will silently implement the CI-CDS system at the same time as CI-CDS clinics so that it operates undetectably in the background. In these clinics, the CI-CDS will identify patients at high risk for CI, assemble treatment recommendations and store analytic data from all targeted visits.

The 12-month patient accrual period will begin at the same calendar time in all clinics when the CI-CDS system is implemented. The up to 24-month intervention period will begin in all clinics at the same time as the accrual period and is the time during which the CI-CDS interface will be operative in intervention clinics.




Each patient will accrue into the study at their index visit. The index visit is the first visit during the accrual period at a randomized clinic at which a patient meets all intervention eligibility criteria. The index visit date will mark the beginning of each accrued patient's observation period. Patients will have up to 24 months of observation period, and those with an index visit near the end of the accrual period will have an approximate 12-month observation period.

Following intent-to-treat (ITT) principles, all accrued patients will be attributed to the clinic at which their index visit took place, and to the treatment group to which their clinic is randomly assigned. Patients who have an index visit, and thus have accrued into the study, may have additional visits at randomized clinics prior to the end of the intervention period. The CI-CDS system is programmed to assess intervention eligibility at all visits at all randomized clinics in both treatment groups for the duration of the intervention period, and to display tailored CI-CDS for eligible post-index visits in CI-CDS clinics only.

In addition to the primary effectiveness trial, the CI-CDS system will be implemented and evaluated in a separate, independent health care system. The replication site study design will be similar in that up to 30 primary care clinics will be randomized to a CI-CDS or UC treatment group. The CI-CDS system will be fully implemented in CI-CDS clinics and partially implemented in UC clinics (i.e., working in the background to collect data but not visible to clinicians). Patients will accrue into the study at index visits over a 6-month accrual period, with an approximate 6-month observation period for the last accrued patient, resulting in a ~12-month intervention period.

Structural differences between the effectiveness and replication sites require that processes such as randomization, outcome measurement, and analysis be implemented differently at the replication relative to the effectiveness site. Information about these processes at the replication site will be provided in a site-specific supplemental analysis plan.

## 2.2 Randomization

Simple randomization will be carried out using SAS PROC PLAN to allocate clinics equally (1:1) to the CI-CDS (intervention) or UC (control) treatment arm. Because it is common for patients to see more than one clinician in a clinic location over time, and for clinicians within a clinic location to discuss aspects of care delivery with each other, the risk of intervention contamination within clinics is rather high. Randomizing by clinic rather than by PCC or patient will minimize risk of intervention contamination.

Each accrued patient will be assigned to the clinic in which his or her index visit takes place, and as such will be assigned to the treatment group to which their clinic was randomly assigned. Post-index visits may take place in the same or different clinics or treatment groups relative to

the index visit and may or may not be eligible for the CI-CDS to offer treatment recommendations. In keeping with an ITT principle, all index and post-index visits and outcome measures for each patient will be attributed to the treatment group assignment of the clinic where the index visit took place.

The nature of the intervention prevents study personnel, clinic leaders, or primary care clinicians from being blinded to the treatment group assignment of each clinic.

## 2.3 Study Eligibility

### 2.3.1 Primary Care Clinics

HealthPartners leaders have agreed to enroll at least 30 primary care clinics from the Twin Cities metropolitan area into this clinic-randomized effectiveness trial. The co-PIs will collaborate with HealthPartners leaders to identify specific clinics to enroll with the intention that study clinics are representative of primary care environments at this and other health systems. Clinics will be excluded from participation for reasons such as:

likely to close or transfer ownership during the study period;

planned leadership or operational transitions during the study period;

established CI workflow in place;

resident training facility;

involved in conflicting research;

few patients >= 65 years of age;

pilot location.

All potential study clinics are currently using a version of the CDS platform for non-CI-related clinical domains with high use rates.

### 2.3.2 Primary Care Clinicians

To be study-eligible, a primary care clinician must be a family physician, general internist, or adult-care non-obstetric nurse practitioner or physician assistant working at a randomized clinic. Eligible and non-eligible primary care clinicians practicing in clinics randomized to the intervention will be able to use the CI-CDS in their care of patients. Eligible primary care clinicians will be invited to complete pre-and post-implementation surveys assessing their comfort and confidence diagnosing and managing CI, perceived barriers to providing CI care (H2), and in intervention clinics, their perceptions of the CI-CDS.

### 2.3.3 Patients

The patient populations whose data will be included in the primary effectiveness analyses are the patients who have index visits at the CI-CDS and UC clinics during the accrual period. Patients will be automatically screened by the CI-CDS algorithms for intervention eligibility at all primary care visits at the randomized clinics during the intervention period. Patients who have a visit that meets the minimal intervention eligibility criteria during the accrual period will be considered accrued into the study.

Patients are accrued into the study upon completion of an index visit. The index visit is the first visit during the accrual period at which all of the following intervention eligibility criteria are met on the visit date:

- Primary care office visit at a randomized clinic during the accrual period, and
- Patient is age 65 or over, and
- Patient has no CI diagnosis documented in the EHR prior to the visit (ICD-10 codes F01-F03, G30, G31.0, G31.2, G31.83; or F06.7, G31.84), and
- Patient has elevated risk of CI
    - Any abnormal score on a comprehensive cognitive assessment (MoCA, MMSE, Mayo Mini Mental, or SLUMS) in the prior 18 months, or
    - MiniCog score <3 in the prior 18 months and there is no evidence of a subsequent comprehensive cognitive assessment (MoCA, MMSE, MMM, SLUMS), or
    - Risk of a dementia diagnosis in the next 3 years >=15% as calculated by the algorithm developed in the R61 phase

Any of the following exclusion criteria will prevent a visit from being intervention eligible, and therefore not considered for index visit status:

- Patient has received active parenteral chemotherapy within the last year
- Patient has stage 4 or equivalent cancer diagnosis
- Patient is enrolled in hospice care or palliative care programs

All accrued patients who meet these minimal eligibility criteria, except those who have opted out of research participation, will be included in the ITT primary study analyses to maximize the generalizability of study results. As this is a pragmatic clinic-randomized trial, patients on exclusion lists will have been assessed for intervention eligibility, and the CI-CDS intervention may have been delivered during a visit to a randomized clinic. All data from each patient (e.g., outcome measures) will be attributed to the treatment group assignment of the clinic where the index visit took place.

All accrued patients, including those who have opted out of research participation, will be included in the safety analyses to ensure a complete accounting of all documented safety events.

All women and members of racial or ethnic minority groups and their subpopulations who meet the above eligibility criteria will be included in accordance with the National Institutes of Health (NIH) Policy on Inclusion of Women and Minorities as Participants in Research Involving Human Subjects.

### 2.3.4 Eligibility Assessment

All primary care visits that take place at all randomized clinics after the CI-CDS system is implemented will be screened for intervention eligibility. Each time the vitals tab of the EPIC electronic health record (EHR) interface is closed (e.g., during the rooming process of nearly all primary care visits) the web service is programmed to automatically run a series of algorithms. The data elements needed to execute these algorithms, including eligibility algorithms, are gathered from EPIC and sent to the web service. The eligibility algorithms confirm that the person is age-eligible, search for prior cognitive screening and assessment data, run the algorithm to estimate risk of CI, and confirm that the patient does not already have a diagnosis of CI and that none of the exclusion criteria apply. They automatically and passively assess each web service call for CI-CDS eligibility without awareness or involvement of a front-end user. The platform additionally documents all eligibility assessments (i.e., eligible and ineligible) so that the characteristics of visits and patients screened for eligibility can be quantified as each

eligibility criterion is applied. This process results in eligibility being assessed and documented consistently for all patients at all randomized study clinics. Patients will be accrued into the study on the date of their first visit during the accrual period that meets all intervention eligibility criteria (i.e., index visit), and followed for the duration of the observation period.

When a patient is deemed eligible for CI-CDS content, a second set of algorithms use up to 5 years of clinical information stored in the EHR to assemble the intervention content (treatment recommendations) that should be presented to the clinician. Display rules determine whether the visit is occurring in a clinic randomized to present the intervention content to the clinician (i.e., CI-CDS) or not (i.e., UC). Trace data documenting the results of each of these sets of algorithms are stored in the web service. The study team retrospectively extracts the trace data from the web service to know how many index visits or intervention-eligible visits have occurred and with how many patients, and to know the content assembled for each of these visits.

## 2.4 Study Measures and outcome definitions

### 2.4.1 H1 outcome (primary): CI detection

The primary study outcome is CI detection. CI detection will be a binary outcome calculated from EHR data that is present if an ICD-10 diagnostic code for CI (dementia or mild cognitive impairment [MCI]) is documented at an outpatient or inpatient encounter, or added to the problem list, between the index visit and the end of the observation period, inclusive. The diagnostic codes that will denote CI detection will be the same as those used in determining eligibility (section 2.3.3). The data elements needed to calculate this outcome will be extracted at the conclusion of the observation period from the EHR of patients in the ITT population. It is hypothesized that patients in CI-CDS clinics will be more likely to have CI detected than patients in UC clinics.

### 2.4.2 H2 outcome (secondary): Clinician confidence

#### 2.4.2.1 Clinician confidence definitions

Clinician confidence in diagnosing CI will be measured by a single survey item (How confident are you in your ability to diagnose cognitive impairment, including mild cognitive impairment or dementia?), followed by 5 items asking about confidence with specific components or steps of diagnosis (e.g., confidence conducting a cognitive assessment using tools like the MoCA, or distinguishing between types of dementia).

Confidence in managing CI care will be measured similarly. An overall confidence item (How confident are you in your ability to manage care for patients with cognitive impairment?) will be followed by 9 items addressing confidence in conducting specific care management activities (e.g., providing pharmacological treatment, accessing patient education materials).

The response options for all clinician confidence items will be a 4-point rating scale (not at all, a little, moderately, or very confident). Responses may be dichotomized prior to analysis (e.g., moderately or very vs. little or not at all).

#### 2.4.2.2 Clinician survey administration

All eligible primary care clinicians practicing in all randomized study clinics will be invited to complete a pre-implementation PCC survey prior to clinician training on CI-CDS or its implementation in study clinics. Similarly, all primary care clinicians practicing in all randomized clinics approximately 8 months after CI-CDS implementation will be invited to complete a post-implementation PCC survey. The invitation to complete the post-implementation survey will not depend on having practiced at the clinic prior to CI-CDS implementation or upon completion of

the pre-implementation PCC survey. PCCs will be assigned to their primary clinic location and its randomized treatment group.

Invitations to complete each survey will be emailed to clinicians with a personalized link for completing the survey online. Reminder emails will be sent to clinicians who do not respond. An electronic gift card will be offered as a thank you for completing each survey.

Both surveys will include items to measure clinician confidence in diagnosing and managing care for CI as well as other barriers related to CI care and diagnosis. The post-implementation surveys emailed to clinicians who practice at CI-CDS clinics will include items regarding their use and satisfaction with the CI-CDS.

### 2.4.3 H3 outcomes (secondary): Cost and utilization

Indicators of any use (utilization) of emergency department (ED), inpatient or both facility types between 365 days prior to the index visit and during the observation period, inclusive, will be calculated from data extracted from insurance claims databases. Additionally, the combined costs of ED and inpatient care delivered will be extracted as paid amounts for facility and professional services on ED and inpatient days. The data elements needed to calculate this outcome will be extracted at the conclusion of the observation period from insurance claims databases among ITT patients who have HealthPartners insurance.

### 2.4.4 Pre-index characteristics

The index visit functions as a baseline to the extent that patients will be described / stratified according to characteristics that were documented at the beginning of the index visit, prior to potential intervention exposure. Patient information documented in the EHR or health plan claims databases on or prior to the index visit will be used to describe pre-intervention patient characteristics (e.g., age on index date, sex, risk of CI diagnosis at index visit), organize patients into groups to assess treatment heterogeneity (e.g., insurance status) or calculate pre-index values (e.g., healthcare utilization in pre-index year). All metrics needed for baseline characterization or reference are either already available in historical databases or will be documented in the course of care delivery. None will be assessed solely for research purposes.

### 2.4.5 Use of EHR and administrative data sources

Outcomes that assess clinical effectiveness, cost, utilization and safety will be calculated using data extracted from EHR and administrative data sources maintained by HealthPartners. By using these data sources, outcomes can be ascertained identically for all accrued patients in all randomized clinics. Also, documentation will occur in the course of delivering health care or administering health insurance (cost outcomes) so that records should be reasonably accurate and complete with minimal (and randomly) missing information. When care is delivered outside the HealthPartners care system, health care claims can document their occurrence for patients who are also health plan members. Missing information due to events for which patients do not seek care or care that escapes documentation in the EHR or claims will be assumed to occur equally across treatment groups.

## 3.0 ANALYSIS PLAN

### 3.1 Reporting and descriptive analyses

The number of patients accrued into the study will be monitored over the course of the accrual period by treatment arm, clinic and key patient characteristics (e.g., age, reason for eligibility). The number of index visits in CI-CDS clinics when a front-end user opens the CI-CDS interface

or prints CI-CDS content will also be monitored. Anomalous accrual counts or use rates will prompt investigation to ensure proper algorithm function.

Demographic and clinical patient characteristics that were available in the EHR at or prior to the index visit will be summarized for all patients in the ITT population, overall and by treatment arm. Patient characteristics related to the risk of CI or its diagnosis (e.g., age, sex, comorbidities) that are imbalanced across treatment arms may be considered for inclusion as covariates in secondary analyses. Pre-intervention characteristics will also be used as moderators in planned heterogeneity of treatment analyses.

Intervention exposure will be quantified by counting CI-CDS eligible visits through the end of each patient's observation period, and documenting CI-CDS use at those visits. Eligibility and exposure will be calculated and summarized, overall and by treatment arm.

A flow diagram will be assembled that follows the recommendations put forth in the extended Consolidated Standards of Reporting Trials (CONSORT) statement that applies to cluster randomized trials. The CONSORT figure will summarize the number of clinics and patients screened for eligibility and reasons for ineligibility; the allocation of clinics and patients to treatment arm; the range of patients per clinic by arm; intervention exposure at index and post-index visits by arm; and analyzed sample size with reasons for exclusions by arm.

### 3.2 Primary effectiveness analysis

The H1 effectiveness analyses – comparing likelihood of CI recognition across treatment arms – will be carried out using the ITT sample data: patients accrued from CI-CDS and UC clinics who are at elevated risk for CI but without a CI diagnosis prior to their index visit and not on a research exclusion list. Descriptive statistics will be used to characterize, overall and by treatment arm, the proportion of ITT sample patients who have CI recognized during the observation period, the time elapsed between study accrual and recognition and the clinic intraclass correlation in CI recognition. H1 will be tested using a generalized linear mixed model (LMM) to account for clustering within randomized clinics and normalize the binary outcome via a distribution-appropriate link function (e.g., logit, log). The model will include fixed effects for clinic-randomized treatment group and any patient covariates (e.g., age , sex, predicted risk score) and a random clinic intercept:

$$\text{logit}(\text{diagnosis}_{ji}) = \gamma_{00} + \gamma_{10}\text{CI-CDS}_j + \gamma_{0*}(\text{pt covars})_{ji} + [v_j], \qquad \text{where j=clinic, i=patient.}$$

Parameter $\gamma_{10}$ is expected to be positive and statistically significant, indicating that patients in clinics randomly assigned to CI-CDS are more likely to receive a CI diagnosis in the observation period than patients in UC clinics. Model-estimated outcomes will be calculated by treatment group, and the treatment effect will be presented as an odds ratio (OR, or risk ratio [RR]) and its 95% confidence interval.

A secondary model will add a fixed coefficient that represents time elapsed between the index visit and the first EHR-documented CI diagnosis, or zero for those lacking a CI diagnosis, and the interaction between treatment group and time. The time covariate will be coded as (days since index)/365 so that it quantifies the predicted annual change in CI diagnosis rates. The time parameter is expected to be near zero and not statistically significant. Should the time elapsed between index and CI diagnosis differ by treatment group, log (observation time) may be included as an offset in the primary analysis.

## 3.3 Secondary analyses

### 3.3.1 Clinician confidence (H2).

The H2 analyses, comparing clinician confidence following CI-CDS implementation to pre-implementation by treatment arm, will be carried out using all available data from PCCs who responded to either survey. Descriptive statistics will be used to characterize PCC respondents, assess the distributional properties of items from which the H2 outcomes (i.e., confidence in diagnosing and in managing CI) will be calculated and estimate clinic and PCC intraclass correlations. The distributional properties of the confidence ratings will inform how to specify the distribution and link functions for these variables (e.g., normal-identity, binomial-logit). Because ratings are unlikely to approximate a normal distribution, the anticipated H2 models are generalized LMMs to account for repeated ratings from PCCs and a link to normalize the binary outcomes:

$$\text{logit}(\text{confidence}_{it}) = \gamma_{00} + \gamma_{10}\text{CI-CDS}_i + \gamma_{01}\text{post-CI-CDS}_{it} + \gamma_{11}\text{CI-CDS}_i*\text{post-CI-CDS}_{it} + [v_i], \quad \text{where i=PCC, t=survey time.}$$

Parameter $\gamma_{11}$ is expected to be positive and statistically significant, indicating more increase in confidence from pre- to post-CI-CDS implementation among PCCs at CI-CDS clinics relative to PCCs at UC clinics. Model-estimated outcomes will be calculated by treatment group and time. Change in confidence will be presented within each treatment group as an OR or RR and 95% CI. The relative OR (i.e., ROR = $OR_{CI\text{-}CDS}$ / $OR_{UC}$) and its 95% confidence interval will estimate the difference across treatment arms in change in confidence.

### 3.3.2 Cost and utilization (H3).

The H3 cost analyses – comparing healthcare utilization costs related to emergency room and inpatient visits in the observation period by treatment arm – will be carried out using data from the subset of ITT patients who have HealthPartners insurance. Descriptive statistics will be used to compare the characteristics of patients by insurance status and treatment arm, and to summarize utilization (e.g., proportion of patients with a post-index inpatient stay) and cost (e.g., median cost of ED visits) outcomes overall and by treatment arm. Secondary H3 analyses may be conditioned on pre-index patient characteristics that differ by treatment arm.

H3 predicts that patients accrued from CI-CDS clinics will have lower post-index health care utilization costs related to emergency room and inpatient visits, relative to those accrued from UC clinics. Anticipating a zero-mass of patients with no emergency department or inpatient costs, we will employ a 2-part model to test H3[1]. In the first part, the probability that patients will experience one or more emergency department visits or inpatient stays will be assessed using logistic regression in the same form as was used for H1. The second part will employ a generalized linear model (GLM)[2, 3] allowing clustering by clinic and controlling for demographics and baseline risk. Such analyses often specify a gamma distribution for health care expenditures with a log link function of the explanatory variables. We will choose the distribution family based upon the data using a modified Park test and choose the link function using a Box-Cox test[4]. If we observe a statistically significant difference in emergency department and inpatient costs in the CI-CDS group, we will use similar methods to assess whether total costs of care, including all outpatient care and pharmacy, are also lower.

## 3.4 Heterogeneity of treatment effects

Treatment effectiveness may vary as a function of patient characteristics. Secondary H1 analyses will add fixed parameters to the H1 model that assess pre-index patient characteristics (e.g., pre-intervention CI risk), comorbidities (e.g., mental illness, substance use) and utilization

(e.g., number of specialty care visits) as main effects and in interaction with the CI-CDS indicator to assess whether the CI-CDS intervention is differentially effective (i.e., treatment heterogeneity) across patient subgroups, or relatedly, whether the CI-CDS intervention can reduce pre-intervention differences in CI care. Model-estimated treatment effects will be calculated within patient subgroups for the sake of description, and the interaction effect (ROR and 95% CI) interpreted if the omnibus interaction with treatment arm is statistically significant.

# 4.0 SAFETY MONITORING

## 4.1 Safety population

The safety population will consist of all study accrued patients, including those on research exclusions lists. Like the ITT population, patients will be assigned to the clinic at which their index visit took place, and to the treatment arm to which their clinic was randomized.

## 4.2 Safety events

Safety events will be monitored via passive surveillance of EHR and administrative data sources maintained by the health system, and state mortality data, for all safety population patients. Benefits to this approach are that safety events can be ascertained identically for all accrued patients in all randomized clinics. Documentation will occur while delivering health care or administering health insurance so that records should be reasonably accurate and complete with minimal and randomly missing information. When care for safety events is delivered outside the care system, health care claims can document their occurrence for patients who are also health plan members. Missing information due to events for which patients do not seek care or care that escapes documentation in the EHR or claims will be assumed to occur equally across treatment groups.

We will monitor emergency department (ED) visits, hospitalizations, suicide attempts, and deaths as safety events among all accrued patients from one year prior to their index visit through the end of the observation period. ED and hospital encounter dates, and suicide attempt and self-harm diagnosis code dates, will be used to determine whether safety events occurred pre- (365 to 1 days prior to index) or post-index (on the index visit date through the lesser of date of death or observation period end).

## 4.3 Safety reporting

A report will be prepared by the study statisticians and provided to the Data Safety Monitoring Board (DSMB) at a frequency determined by the DSMB. The report will provide information regarding patient accrual, intervention delivery and safety events. Patient accrual will be tracked through monthly and cumulative counts of actual and expected counts of index visits. Pre-randomization clinic characteristics and patient characteristics as of index visit date will be provided overall and by treatment group. CI-CDS use will be tracked monthly and cumulatively by treatment arm to monitor intervention adherence (intervention clinics) and check for contamination (control clinics).

The following metrics will be calculated for each safety event: total number of events, allowing multiple per patient; proportion of accrued patients with at least one event; and event rate in patient-years. Each of these metrics will be compared across treatment arms and two time periods (post-index vs. 1 year pre-index). Data from the pre-index year will provide baseline information about the prevalence of each safety event prior to potential CI-CDS intervention exposure. Post- and pre-index rates will be compared to identify differential changes in safety event rates.

As safety events will be summarized by treatment arm using EHR and administrative data, it is not feasible to assess relationship to the study intervention, per se. Instead, the study team and DSMB will evaluate safety data at an interval determined by the DSMB to evaluate differences in safety event rates across treatment arms.

# 5.0 DATA QUALITY AND MISSINGNESS

## 5.1 Person-based missingness

Patients whose data will be used for the primary and secondary effectiveness analyses will not be consented and are unlikely to be aware that their data are being used for this research. Only patients who have requested that their data not be used for research and appear on opt out lists will be excluded. Very few patients have made such a request. For these reasons we expect person-based missingness to be extremely rare.

## 5.2 Event-based missingness

Outcomes that assess clinical effectiveness, cost, utilization and safety will be calculated using data extracted from EHR and administrative data sources maintained by HealthPartners. As such, these outcomes will be ascertained identically for all accrued patients in all randomized clinics. Documentation of these outcomes will have occurred in the course of delivering health care (clinical, utilization outcomes) or administering health insurance (cost outcomes) so that records should be reasonably accurate and complete with minimal and randomly missing information. The absence of documentation of an event is virtually always due to it not having taken place. Truly missing field-based observations (e.g., CI diagnosis assigned, documentation not found) will be extremely rare, undetectable and assumed to occur at random. When care is delivered outside the HealthPartners care system, health care claims can document their occurrence for patients who are also HealthPartners insurance members. Missing information due to events for which patients do not seek care or care that escapes documentation in the EHR or claims will be assumed to occur equally across treatment groups. The estimation techniques used in the planned random coefficient models readily accommodate structural variation across observations in the amount of data present (e.g., patients per clinic) and lead to unbiased parameter estimates and accurate standard errors when data are missing at random.

## 5.3 Data security and quality

The CI-CDS itself will house the algorithms, communicate with and display within the EHR, and store data required to assess study objectives in a secure analytic database at HealthPartners Institute. These data, supplemented by EPIC Clarity and administrative claims data, will be used to assess CI-CDS use rates, diagnosis of CI, and hospitalizations and emergency department visits. Data collected from the primary care clinicians via surveys will be similarly housed on secure servers at HealthPartners Institute.

As this study is conducted as a pragmatic clinical trial, with CI-CDS being suggested to primary care clinicians in the course of usual care, the training and quality control metrics typically found in traditional randomized trials do not apply. Primary care clinicians will receive training on use of the CI-CDS, and print rates will be monitored and communicated to clinicians, as noted above.

# 6.0 SAMPLE SIZE AND POWER

The primary hypothesis test will compare patients in CI-CDS clinics to those in UC clinics on the likelihood that CI is diagnosed during the observation period. We conducted a power analysis to estimate the minimum detectable rate of new CI diagnoses given ranges of assumptions about

analytic sample sizes, proportions of patients currently meeting outcome criteria, and clinic intraclass correlation ($ICC_{clin}$).

We used data accrued into the CI-CDS system during the R61 silent pilot to identify patients who met intervention eligibility criteria at clinic visits (section 2.3.3). Based on the pilot CI-CDS data, we estimated that, on average, about n=100 patients in each of at least 30 clinics will likely have an index visit over the course of a 12-month accrual period.

An EHR-based cohort that consisted of patients who were age >=65 and had a primary care visit between September 2021 and August 2022 was assembled to provide estimates of CI diagnosis rates in primary care clinics that were candidates for randomization. The proportion of patients who had at least one CI diagnosis code at an encounter or listed on their active problem list during the 12-month period was 2.3% among all patients in the cohort, and 15.1% among those who had a MiniCog<3 during the period. The power analysis will assume that 8-16% of study accrued patients in UC clinics will have CI recognized between their index visit and end of their observation period.

There was substantial variation across primary care clinics in the proportion of patients with CI recognized as an encounter diagnosis or on their active problem list at the time of their 2021-2022 primary care visit. Among all patients, $ICC_{clin}$=0.03, and among those with MiniCog<3, $ICC_{clin}$=0.04. The power analysis will assume $ICC_{clin}$=0.03-0.05.

**Table 1.** Minimum detectable rates of CI diagnosis in CI-CDS clinics assuming n=100 accrued patients per clinic, 30-38 clinics, $ICC_{clin}$ = 0.03-0.05 and UC diagnosis rates = 8-16%.

| | | UC diagnoses (%) | | |
|---|---|---|---|---|
| clinics | $ICC_{clin}$ | 8% | 12% | 16% |
| 30 | 0.03 | 14.4 | 19.4 | 24.2 |
| | 0.04 | 15.3 | 20.4 | 25.2 |
| | 0.05 | 16.1 | 21.3 | **26.2** |
| 34 | 0.03 | 14.0 | 18.9 | 23.6 |
| | 0.04 | 14.8 | ***19.8*** | 24.6 |
| | 0.05 | 15.5 | 20.6 | 25.5 |
| 38 | 0.03 | **13.6** | 18.5 | 23.2 |
| | 0.04 | 14.4 | 19.4 | 24.1 |
| | 0.05 | 15.1 | 20.1 | 24.9 |

Based on these data-informed estimates, we used the following assumptions regarding the primary effectiveness study for the power analysis: 30, 34 or 38 clinics randomly assigned 1:1 to CI-CDS or UC, n=100 patients per clinic, $ICC_{clin}$=(0.03, 0.04, 0.05) and diagnosis rates = (8%, 12%, 16%) in UC clinics. The correlated sample size estimate, N, was divided by the design effect (deff; 1+(n-1)*ICC) to estimate an effective independent patient sample size (i.e., Neff=N/deff). The power analysis (power=0.80, $\alpha_2$=0.05) estimated the minimum detectable CI-CDS CI diagnosis rate from a single binary predictor in a logistic regression model using the downwardly adjusted effective sample size[5].

Given the median assumptions for number of randomized clinics, $ICC_{clin}$ and CI diagnosis rate, the study is powered to detect a diagnosis rate of 19.8% in CI-CDS clinics relative to 12% in UC clinics (Table 1). The absolute increase in diagnosis rates ranges from 5.6% (38 clinics, $ICC_{clin}$=0.03, 8%) to 10.2% (30 clinics, $ICC_{clin}$=0.05, 16%) across the range of these assumptions.

## 7.0 UPDATES TO THE STATISTICAL ANALYSIS PLAN

| ***SAP Version*** | ***Date of Approval*** | ***Summary of Changes*** |
|---|---|---|
| *1.0* | *7/25/2025* | *NA* |

## 8.0 REFERENCES


1. Duan N, et al., *Choosing between the sample-selection model and the multi-part model.* Journal of Business and Economic Statistics, 1984: p. 3
2. Blough, D., C. Madden, and M. Hornbrook, *Modeling risk using generalized linear models.* J Health Econ, 1999. 18(2): p. 153-71.
3. Manning, W.G. and J. Mullahy, *Estimating log models: to transform or not to transform?* J Health Econ, 2001. 20(4): p. 461-94
4. Park R.E., *Estimation with heteroscedastic error terms.* 1966. Econometrica(4): p. 888.
5. PASS 2024 Power Analysis and Sample Size Software (2024). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.