Clinical Interventional Study Protocol

A TECHNOLOGY-DRIVEN INTERVENTION TO IMPROVE EARLY DETECTION AND MANAGEMENT OF COGNITIVE IMPAIRMENT

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SUMMARY OF CHANGES

Summary of Changes from Protocol Version 4 dated July 17, 2023
to Protocol Version 5 dated May 08, 2025

Page #, Section #	Change Description	Rationale/Justification
Title page, footer, table of contents	Updated date and version number	New protocol submitted
Pg 7	Clarification on intervention/observation period length for HealthPartners	Changed paragraph to state “up to 24 month intervention period” to be consistent with the language in paragraph immediately following
Pg 7: Replication	Update on intervention/observation period length for OCHIN	The observation period length has changed to approximately 6 months due to some delays in go-live at OCHIN.
Pg 15	Clarification on chart audit procedures	Clarification in language regarding chart audit procedures to state that we will be pulling data related to completion of assessments in the accrued population as one aspect of the chart audit, and then manually auditing charts of 50-100 patients in each group to assess the presence of care plans.
Pg 28: OCHIN Appendix	Updated study roster to match the OCHIN study personnel document previously submitted	No new personnel were added to OCHIN’s study team beyond what was documented in the OCHIN study personnel documented dated 10/16/2024. Table was updated so that the protocol matched what was in this document.

PRÉCIS

Study Title

A Technology-Driven Intervention to Improve Early Detection and Management of Cognitive Impairment

Objectives

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).

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.

Design and Outcomes

This pragmatic clinic-randomized 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 randomize clinics 1:1 to continue with UC or to deploy the CI-CDS intervention.

The primary outcome is CI detection, defined as an ICD-10 diagnostic code for CI (dementia or mild cognitive impairment [MCI]) documented at outpatient or inpatient encounters or added to the problem list during the observation period among patients with elevated risk for CI.

Secondary outcomes are clinician-reported confidence in CI care management, assessed via pre-/post-surveys, and health care utilization among patients with HealthPartners insurance.

Interventions and Duration

The CI-CDS user interface will alert primary care clinicians when patients are at elevated risk for CI, prompting diagnostic screening exams, and, if indicated, CI diagnoses, quick orders (e.g., referrals, procedures, lab assessments, medications), patient education materials (e.g., diagnoses, legal documents, community resources), and CI management (e.g., diagnostic assessments, lab values, medications). The intervention will be active at HealthPartners for two years.

Sample Size and Population

Eligible patients are primary care patients $\geq$65 years of age with no CI diagnosis at the time of an index visit at a randomized clinic and have elevated risk of CI. Elevated risk is 1) an abnormal score on any comprehensive cognitive assessment; 2) a positive screen (MiniCog score <3) with no follow-up comprehensive cognitive assessment; or 3) >=15% risk of a CI diagnosis in the next 3 years as estimated by the MC-PLUS algorithm developed in the R61 phase. Preliminary data suggest at least 3000 patients at randomized HealthPartners primary care clinics will meet eligibility criteria over a 1-year accrual period.

STUDY TEAM ROSTER

Investigator	Role	Contact Information	Main responsibility/Key Roles
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STUDY OBJECTIVES

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. The CI algorithms extract and process clinical data elements (e.g., medications, diagnoses, laboratory values, screening results) from up to 5 years prior to provide clinicians with suggested actions to take during visits with patients at risk for CI that are informed by comprehensive, up to date information. The MC-PLUS prediction model gathers data from EHR sources beyond screening results (e.g., utilization patterns, laboratory testing history, diagnosis history from the prior 2 years) to accurately estimate 3-year risk of a dementia diagnosis. The CI algorithms and MC-PLUS were added to an existing successful web-based CDS platform that is seamlessly integrated in the HealthPartners EHR, resulting in the CI-CDS system. CI-CDS was developed and implemented in partnership with primary care leadership to ensure seamless integration with primary care workflows and inclusion of preferred instruments, materials, and care recommendations. Our team also successfully designed and piloted a survey of primary care clinicians during the R61 phase to identify clinician-reported barriers to diagnosing cognitive impairment and managing care, as well as the potential utility of a system such as CI-CDS. These survey findings are summarized in Section 15.3.

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.

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.

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.

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 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.

In addition to hypothesizing that the CI-CDS will increase the likelihood that CI is recognized among accrued patients in the intervention clinics, we will assess the extent to which the CI-CDS system increases the likelihood that clinicians more actively take appropriate clinical actions to manage patients with CI or elevated risk for CI.

One mechanism by which the CI-CDS system is thought to be effective in encouraging clinicians to take more action is by reducing perceived barriers to CI care. We will explore this possibility by surveying clinicians from CI-CDS clinics about how useful or accessible they found the CI-CDS system, and the extent to which the system supported them in their intentions to treat patients with CI or elevated risk of CI. We will also assess clinician attitudes and perceptions of control, perceived norms, and barriers to CI care among clinicians in CI-CDS relative to UC clinics.

Treatment effectiveness may vary as a function of contextual factors or patient characteristics. Qualitative semi-structured interviews will be conducted with newly diagnosed patient/care partner dyads to explore perspectives on experience with the assessment and diagnosis process as well as preparedness for subsequent management. Learnings will be used to inform future implementation and to design extensions of the CI-CDS related to disease management. 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 disparities in CI care.

1. BACKGROUND AND RATIONALE

1.1 Background on Condition, Disease, or Other Primary Study Focus

Cognitive impairment (CI) is an urgent global health problem affecting more than 47 million people.[1] The prevalence of Alzheimer's disease (AD) and related dementias (ADRD) is expected to triple by 2050 at an annual estimated cost of $818 billion.[2, 3] While CI is generally not curable, many interventions can transform the lives of people with CI and their families through maximizing cognition, decreasing distress associated with symptoms and crises, educating patients and caregivers and improving quality of life, but timely diagnosis is essential for these interventions.[1] In addition, family members and caregivers report a lower quality of life and have higher rates of medical problems, depression, anxiety and work absence.[4-6] Unfortunately, the diagnosis of CI is often not made until the disease is well advanced and the patient is in crisis, resulting in poor quality of life for both the individuals with CI and their relatives.[4, 7-9] In fact, most people with CI and their families are relieved when a diagnosis is finally made, and most people report wanting to be told if they were thought to have CI.[10] The problem is compounded by a care delivery system that is already stressed, with competing demands and limited access to specialists.[11] Primary care clinicians often lack the confidence or time to evaluate CI, tending instead to refer to specialists, even though many patients do not follow through with such referrals.[12-14] Aside from time and reimbursement, other commonly reported barriers to CI diagnosis and care include a lack of consensus for what constitutes adequate evaluation, which assessment tools to use, what type of brain imaging is most appropriate, and when referrals to specialists are indicated. [15-17] Given these ambiguities, it is not surprising that many clinicians report they would be moderately to extremely likely to treat more patients with CI rather than referring them to specialists if decision support tools were available.

1.2 Study Rationale

Barriers to CI Detection and Care: The United States Preventive Service Task Force does not recommend for or against CI screening due to insufficient evidence that screening leads to benefits for patients and caregivers.[16] In the absence of universal screening, most clinicians rely on case finding based on observed behaviors or concerns raised at the time of encounters.[18] To assess for CI, there are over 22 cognitive screening tests available.[19-21] The MiniCog is an example of a simple and brief cognitive screening tool, with sensitivity ranging between 76-100% in different study settings and specificity ranging between 27-85%.[22, 23] However, there is evidence that screening alone is insufficient to alter patterns of clinician practice for subsequent CI detection, evaluation, referrals, or treatments for CI. For example, relevant physician action only occurred in 17% of patients with a positive MiniCog screen in primary care.[24] Similarly, in our health system, there were no documented clinical actions in two-thirds of patients with a positive MiniCog screen completed at Annual Medicare Wellness (AMW) exams and neurology visits.[25] Reported primary care barriers to CI care management include lack of perceived control over diagnosis and care, inadequate time, difficulty accessing specialists, low reimbursement, difficulties connecting with social services, and need for clinical decision support (CDS).[12, 13, 26] Many clinicians rely solely on history and routine examination to make the diagnosis without using standardized CI testing, even though only 4% of clinicians said testing would not be of value.[27] If decision support tools were available, the features they said they would value most were choice of screening assessment, guiding the diagnostic process, and guidance for patient management and ongoing care.[27] Current EHR systems do not actively give clinicians many tools for CI diagnosis and care management. A CDS system that could selectively alert clinicians as to when cognitive assessments are warranted, along with CDS recommendations and tools to guide them, could lead to greater clinician confidence to assess, diagnose and manage CI and could address some of the time barriers.

Our previous work developing and implementing CDS to improve care outcomes is guided by Wagner's well-vetted and much-used Chronic Care Model, which posits that optimal care occurs when a "prepared practice team" encounters an activated patient.[28] It is no surprise that Wagner suggests that innovative use of information systems are foundational elements of successful care.[29, 30] Without, the complexity required to deliver evidence-based and appropriate CI (or other chronic disease) care in a timely way is an almost superhuman task.[31, 32] CI-CDS can prepare the clinician for the visit and present a set of evidence-based options related to CI diagnosis and care, thus promoting shared decision making and patient-centered care.[33]

How a Machine Learning Approach Could Help Overcome Barriers: The MiniCog is a 3-minute screening instrument with fairly high rates of false positives (specificity of 27-85%).[16, 22] If the MiniCog is positive, more detailed testing is recommended to assess potential CI, provide more information about affected cognitive functions, and to establish a basis for tracking change with tools such as the Montreal Cognitive Assessment (MoCA), Mini Mental Status Exam (MMSE), or the St. Louis University Mental Status Examination (SLUMS).[24, 34, 35] Longitudinal testing can provide insight in some circumstances, with rates of declines on some of these tests predictive of AD or MCI.[36] Prediction models using machine learning have been advocated as a way to more accurately predict risk. One newer prediction model, called eRADAR, with good discrimination (C statistic = 0.78, 95% CI: 0.76-0.81) and validation (C = 0.81, 95% CI: 0.78-0.84), was developed using a prospective cohort of research participants undergoing standardized cognitive testing every 2 years. It predicted undiagnosed dementia from available EHR data on the research cohort diagnosed with

dementia.[37] In our application, we suggested that a prediction model using CI screening data in combination with EHR data, developed and validated in a cohort of patients from a primary care setting, could have even greater predictive accuracy. Furthermore, while the eRADAR model predicts incident undiagnosed dementia in a research population, there may be additional clinical value to detecting future risk of being diagnosed with dementia in real world settings. In the R61 phase of this study, we developed and tested a prediction model for CI that attained a similar predictive value (C statistic = .80, 95% CI: .79, .81) as the eRADAR in adults in primary care settings. The MC-PLUS model estimates risk of dementia diagnosis in 3 years at a single visit using commonly available EHR data and requiring no prior cognitive screening.

Components of Evidence-Based CI Management for Developing CDS Content: Despite the lack of a "one-size fits all" approach to CI management, there is broad consensus and solid evidence that multidomain assessment and management are needed for optimal management of CI over time. These include:

1. **Diagnostic Assessments:** A cognitive history with input from a knowledgeable independent source is key to identifying and diagnosing CI. In addition, the American Academy of Neurology recommends routine neuroimaging as part of all workups for CI.[38] MRI is often preferred because of greater sensitivity and ability to differentiate dementia subtypes, such as vascular dementia.[39, 40] Other assessments routinely recommended to search for possible confounding problems, well within the score of primary care practice, include medication review for cognition-impairing medications and nutritional, endocrine, and metabolic disorders that can contribute to CI.[1]

2. **Needs Assessment:** A needs assessment can identify cognitive, emotional, psychological, and social needs as well as safety risks that if addressed can enable patients to have more autonomy and maximize potential for remaining in the community for as long as possible.[41, 42] Risks may include medication noncompliance, fall, fire, driving safety, and vulnerability to financial scams.[41] Driving safety is often one of the most contentious and difficult challenges for both clinicians and caregivers, and many clinicians need to be made aware of resources available to address this effectively.[43]

3. **Caregiver and/or proxy identification:** It is helpful for patients to choose a proxy or someone who can enact pre-specified wishes or choices consistent with their values while they retain some ability to consider future scenarios.[44, 45] In addition, keeping an updated release of information on file is recommended.

4. **Medications for cognition and affective, psychotic or behavioral symptoms:** Cognition enhancing medications may be helpful in mild to moderate dementia when tolerated and potentially improve everyday functioning.[46] Depression, apathy, anxiety, and sleep disturbances are very common.[47] Psychotic symptoms [48] such as delusions and visual hallucinations (most common in Lewy body dementia) occur in about 18% of patients with dementia.[49, 50] Use of antipsychotic medications aren't generally recommended for non-distressing symptoms that can be managed with caregiver education or other classes of medications.[51] Agitation and behavioral disturbance are also common, complicate family care, [52-54] and can increase the cost of care by 12%.[55] Measures to address them such as caregiver education and behavioral management training along with careful prescribing of medications, if systematically implemented, can mitigate the higher costs associated with behavioral disturbances.[55] Management can include coaching caregivers', communication skills,

use of antidepressants, or interventions to increase pleasant activities or social engagement.[1, 47] [56-59]

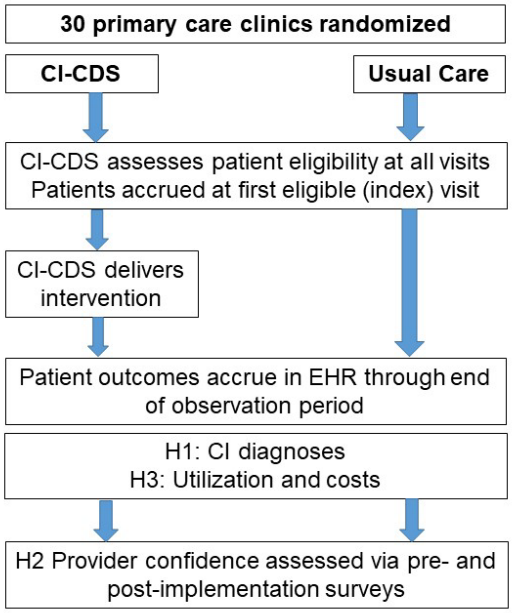
5. **Support for caregivers:** Family caregivers are the most important resource for many patients living with CI. Family caregivers suffer more often from depression, anxiety, work absence, and lower quality of life.[5, 6, 60] Care should be directed to support the needs of both patients and caregivers.

Features of Successful CDS: In reports issued 25 years ago, the Institute of Medicine asserted that EHR technology would lead to substantial improvements in quality of medical care in America.[61, 62] Since that time, private and public investments in EHR systems have totaled hundreds of billions of dollars, with most CDS interventions until very recently unable to demonstrate improvements in chronic disease outcomes other than process measures.[63-71] Much of what has been learned in the last 25 years about how to implement effective CDS in primary care settings for chronic diseases, such as diabetes and hypertension, can inform the design, implementation, and maintenance of CDS systems designed to address the complexity of CI care. The CDS platform we developed (prior to inclusion of CI-CDS) was informed by extensive input from primary care clinicians who would be users of the technology and by our careful analysis of numerous antecedent failed CDS efforts to improve chronic disease care in primary care settings.[63, 65, 66, 72-75] We deduced from this analysis that a CDS strategy must have the following key features in order to be successful: (a) CDS must be available in real-time at the point of care and be based on all available clinical data;[71] (b) CDS must be sophisticated and not limited to general prompts or reminders;[63, 66, 76] (c) CDS must be integrated into the routine workflow of the primary care clinician and use rooming staff and nurses to the fullest extent possible; (d) CDS should be provided to both patients and clinicians and implemented in a way that engages patients and caregivers and promotes shared decision-making;[77-79] (e) CDS must increase clinician efficiency and save them clicks or time; (f) CDS use must be sustained at high rates to affect clinical outcomes. High CDS use is achieved through clinic staff training, ongoing communication, and feedback to care teams on their use rates.

2. STUDY DESIGN

This pragmatic clinic-randomized 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 clinicians to assess, diagnose, and manage cognitively impaired individuals. 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.

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. 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. Following intent-to-treat principles, all eligible patients will be attributed to the treatment group to which their clinic is randomly assigned.



The 12-month patient accrual period will begin at the same calendar time in all clinics when the CI-CDS system is implemented; full implementation in CI-CDS clinics and partial implementation in UC clinics. The up to 24-month intervention period will begin in all clinics at the same time as the accrual period..

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 with an index visit near the beginning of the accrual period will have up to a 24-month observation period, and those with an index visit near the end of the accrual period will have an approximate 12-month observation period.

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 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.

Replication: In addition to the primary effectiveness trial, the CI-CDS system will be implemented and evaluated at OCHIN, a network of safety net health centers clinics across the country. organized under a 501(c)(3) designation. Across the country, OCHIN's highly customized, centrally hosted EpicCare ambulatory system EHR is used in a broad network of primary care safety net settings including Federally Qualified Health Centers (FQHCs) and FQHC lookalikes, rural health centers (RHCs), school-based health centers, and county health departments. The replication site study design will be similar in that service areas with constituent primary care clinics will be randomized equally to a CI-CDS or UC treatment group. The CI-CDS system will be fully implemented in CI-CDS clinics and silently 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 approximately 6-month observation period for the last accrued patient, resulting in an ~12-month intervention period. See replication site-specific protocol details in **Section 15.5**.

3. SELECTION AND ENROLLMENT OF PARTICIPANTS

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 that are likely to close or transfer ownership during the study period will be excluded from participation. All study clinics are currently using a version of the CDS platform for non-CI-related clinical domains with high use rates.

The co-PIs will collaborate with the replication Lead Co-Investigator to identify candidate clinics to enroll with the intention that they be representative of primary care environments at the replication site and other health systems. The replication site team will collaborate with health system leaders to identify the specific clinics to enroll. Replication site clinics are also using a version of the CDS platform for non-CI-related clinical domains.

Definitions

Intervention Period
- CI-CDS implementation date through a predetermined time at which the interface will be turned off in the intervention clinics

Accrual Period
- CI-CDS implementation date through a predetermined time at which no more people will be included in the analytic sample

Index Visit
- Varies by patient
- First visit during accrual period at which the CI-CDS identifies that the patient is study eligible
- Patient is accrued into study at index visit

Observation Period
- Varies by patient
- Index visit date through a predetermined time at which outcome data will no longer be accumulated

Primary care clinicians. All primary care clinicians practicing in clinics randomized to the intervention will be able to use the CI-CDS in their care of patients. To be study-eligible, a primary care clinician must be a family physician, general internist, or adult-care non-obstetric nurse practitioner (NP) or physician assistant (PA) working at a randomized clinic. 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. The clinician survey process will not be implemented at the replication site.

Patients. The study populations whose data will be included in the primary effectiveness analyses and in the replication analyses are the patients who have index visits at the CI-CDS and UC clinics during the accrual period at the primary and replication sites. 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 and included in the analyses to maximize generalizability.

3.1 Inclusion Criteria

Patients are accrued into the study upon completion of an index visit. All of the following intervention eligibility criteria must be met on the visit date for the visit to be an index visit:

- 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, and
- Patient has
    - Any abnormal score on a comprehensive cognitive assessment (MoCA, MMSE 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, SLUMS), or
    - No cognitive assessment in the past 18 months and risk of a dementia diagnosis in the next 3 years >=15% as calculated by the MC-PLUS algorithm developed in the R61 phase, and
- First visit during the accrual period at which all prior inclusion criteria are met.

3.2 Exclusion Criteria

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 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.

3.3 Study Enrollment Procedures

All primary care visits that take place at the randomized clinics after the CI-CDS system is implemented will be screened for intervention eligibility. The web platform in which the CI-CDS is housed is programmed to assess whether CDS content should be displayed each time the vitals section of the EHR is closed by extracting data elements from the EHR and supplying them to algorithms that assess eligibility. For the CI-CDS, this means that the algorithms run in all randomized clinics at all primary care visits. They confirm that the person is age-eligible, search for prior cognitive screening and assessment data, run the MC-PLUS 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. In short, intervention eligibility is systematically assessed at all visits with all patients at the randomized clinics where CI-CDS is running. The platform 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. 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.

We have received a waiver of informed consent for patients from the HealthPartners Institute Institutional Review Board (IRB) because the study is minimal or less than minimal risk compared to the risk associated with any primary care encounter. This was similarly granted for the R61 Phase. The evidence-based care recommendations in the CI-CDS intervention are from national guidelines and approved by primary and neurology care delivery leadership. Moreover, this pragmatic intervention could not be conducted if written informed consent were required to be obtained in the context of busy community-based primary care clinic environments. Note that patients who have requested non-participation in research studies will be excluded from all analyses.

Primary care clinicians in the intervention clinics will be encouraged but not required to use the CI-CDS with eligible patients, so that the decision to use or not use CI-CDS at a given clinical encounter is up to the clinician. All primary care clinicians at the primary site will be asked to consent to and complete pre-and post-implementation surveys and may receive modest compensation for completing these surveys. We have received a waiver of written informed consent for clinicians from the IRB for the intervention because (a) the CI-CDS is based on current national standards of CI identification and management and does not make any treatment recommendations that are not accepted as community standard of care, and (b) consenting clinicians would compromise the external validity of the study by introducing selection effects. Measures to protect the privacy of clinicians participating in this study are described further below.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The CI-CDS system 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 automatically triggered web service call made in all randomized clinics so that data pertinent to all visits from all intervention eligible and accrued patients will be identically collected and available across treatment groups. The user interface will function as the intervention delivery vehicle and be operative only in intervention clinics. The CI-CDS system will therefore operate passively in all randomized clinics, but the user interface will only be turned on in clinics that are randomly assigned to the CI-CDS group.

The CI-CDS system will be implemented in all randomized clinics to use data stored in the EHR to invisibly identify visits that are eligible for the CI-CDS intervention, assemble treatment recommendations tailored to the needs of each patient at eligible visits and store analytic data from all visits. In clinics randomized to the intervention group, the CI-CDS will display the treatment recommendations to primary care clinicians and document clinician actions via the CI-CDS user interface. The CI-CDS user interface will be disabled in clinics randomized to the control group.

The CI-CDS system is programmed to support primary care clinicians in assessing patients with elevated risk for CI and then diagnosing and managing care for patients with CI. The CI-CDS user interface will provide updated clinical recommendations at primary care encounters for patients with elevated CI risk or with a CI diagnosis. The interface will enable the user to administer diagnostic screening exams (e.g., Montreal Cognitive Assessment (MoCA), Patient Health Questionnaire (PHQ-9)), place quick orders (e.g., referrals, procedures, lab assessments, medications), accurately diagnose CI, provide patient education materials (e.g.,

diagnoses, legal documents, community resources), and manage CI (e.g., visualize trends in screening exams, lab values, medications). See Section 15.4 for more detailed content information. This approach presents patients and their primary care clinicians multiple encounter opportunities to consider an evolving array of timely, evidence-based treatment options to improve CI care. Operationally, implementing CI-CDS at clinics requires a series of distinct steps:

Step 1: Data Exchange. The EHR securely exchanges data with the web service at every encounter of adult patients aged 65 or older and is currently triggered by blood pressure entry at CI-CDS and UC clinics. Several measures are in place to ensure security of protected health information. Data transfer to the web service uses a Simple Object Access Protocol (SOAP) with Secure Sockets Layer (SSL) encryption over a Hypertext Transfer Protocol Secure (HTTPS) computer network. There is a double firewall in the web service; once data flows through the initial web service firewall, the data crosses another firewall into a new secure pathway that also employs SOAP, SSL, and HTTPS for processing. The data are sent through a batch server for more efficient processing, all within the double firewall web service. A unique study ID unrelated to subject-specific information is assigned at the index visit, saved in the EHR, and exchanged with the web service at subsequent encounters. Limited data is saved in an analytic data set for study purposes using the study ID to reduce the risk of breach of confidentiality.

Step 2: Algorithm Driven Assessment. The web service will use EHR data and the MC-PLUS prediction tool to identify individuals with elevated CI risk at primary care encounters and to create a flag which is returned to the EHR for use in a “best practice alert” (BPA) pop up to rooming staff. The algorithms will also identify patients with CI who have outstanding care opportunities even if they are not eligible for inclusion in the primary analyses. The data is run through coded algorithms within the web service to determine the content of clinical care suggestions that will be displayed in engagement tools for step 3 and to inform the content within the online CDS interface, outlined in Section 15.4.

Step 3: Patient/Caregiver and Clinician Engagement at Primary Care Office Visits. At visits with patients with elevated CI risk or with identified CI-related care opportunities, the rooming staff receives an immediate BPA to print CDS engagement materials. Using this sequence of steps successfully implemented in previous studies, the rooming staff will print the materials from a link on the BPA and give the lay version to the patient/caregiver to review while waiting for the clinician. A professional version is provided to the clinician to review before entering the exam room. This approach has been well-liked by our clinicians to help them be prepared to engage patients in their care needs before the clinician-patient interaction.

Step 4. Online CDS for Clinicians with More Detail and Tools to Promote Efficiency. Clinicians can opt to view CDS and more detailed materials and tools online through an activity that is seamlessly integrated into the EHR and can be viewed in real time for any patient at any time they choose. Newer EHR features make it easier for the web-based application to be interactive with the end user. As the user interacts with the CDS interface, a summary is generated that captures patient CI risk or diagnosis, results of additional assessments completed, and actions recommended. This summary can then be copy and pasted into the clinician’s progress note. Our team includes very experienced EPIC programmers employed by our research institute who take full advantage of new functionality as it becomes available to make the CI-CDS interface and interactive features as efficient as possible for clinicians.

5.2 Handling of Study Interventions

The CI algorithms that reside in the CI-CDS system consistently and universally assess automatically generated web calls for intervention eligibility. When a patient is deemed eligible for CI-CDS content, the 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., intervention) or not (i.e., control). Trace data documenting the results of each of these sets of algorithms are stored in the web service. The study team retrospectively extract 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.

The study team is responsible for developing and testing the CI-CDS system algorithms. Once programmed, though, all intervention delivery activities are managed by the CI-CDS system algorithms with no involvement from the study team. The CI-CDS system is an intervention that supports clinicians by efficiently aggregating and processing a broad spectrum of patient-focused data and then offering the clinician guideline-based recommendations based on those data. The clinicians, who are not part of the study team, have discretion with respect to whether and how much of the presented information to act on or share with the patient.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

As this pragmatic trial occurs in primary care clinics, and the intervention is provided in addition to any patient's routine care, any and all medications and other treatments and interventions ordered by a patient's routine care providers are allowed in the course of this trial.

5.3.2 Required Interventions

There are no required concomitant interventions in this clinic-based pragmatic trial.

5.3.3 Prohibited Interventions

There are no prohibited interventions in this clinic-based pragmatic trial.

5.4 Adherence Assessment

Clinician training. All clinician and staff training activities will be conducted collaboratively with quality improvement leaders at participating health systems through webinar training sessions for CI-CDS clinic staff, including clinicians, nurses, and rooming staff. The training will focus on the workflow, scripting when CI engagement tools are introduced to patients or caregivers, and the CI-CDS features and content. The training will emphasize that the CI-CDS is meant to supplement, not replace clinical care, and that primary care clinicians should use their clinical judgement to use the tool or follow its treatment suggestions. Training will be brief (about 50 minutes) and modeled after successful training programs conducted in our previous CDS studies. The webinar will be taped and available online for asynchronous viewing, and written materials will also be available. We will also provide information about the study and interventions regularly in our online newsletters and communications. Rooming staff printing

procedures for CDS tools are incorporated into the standard care model process that is part of all new staff training with periodic refreshers to existing staff.

Tracking CI-CDS use. Multiple processes are measured and tracked throughout the intervention period to assess CDS use as described by elements in the NIH Treatment Fidelity framework including delivery, receipt and enactment of intervention dose and content.[80] Print rates by rooming staff will be measured, grouped by clinic and clinician, and reported monthly to clinic leadership. The goal of printing the patient and clinician engagement materials will be set at ≥70% of targeted encounters. Using this strategy, we have maintained print rates for the existing CDS engagement interfaces at over 75% for many without financial incentives. We chose 70% as the target use rate given that at any given encounter, there may be more pressing issues or psychosocial factors that should be addressed instead, such as an acute care issue or death of a spouse, and clinicians are to use their clinical judgement about when use of the CI-CDS is appropriate. If necessary, supplemental communication and training will be provided to clinics and/or clinicians who have low print rates relative to other clinics or clinicians. We will also track clinician use of online CDS features by monitoring click rates on tools, quick orders, and educational materials. However, as clinicians are encouraged to use their clinical judgement to determine when and how to use the CI-CDS tool, we will not be providing clinic- or clinician-level feedback on click rates.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

All patient-focused data used to evaluate the effectiveness of the CI-CDS system on primary and secondary outcomes will derive from the CI-CDS system itself (e.g., eligibility criteria at index visit), the EHR (e.g., CI diagnosis, patient characteristics at index visit) or health care claims databases (e.g., paid amounts for emergency room visits or inpatient stays). There is no scheduled prospective data collection directly from accrued patients. Rather, data elements that document the process, outcomes and costs of care delivery will be recorded in these electronic resources as care is delivered to patients, with the timing of care delivery driven by clinician and patient judgment. This clinic-based pragmatic trial will not direct the timing, manner or amount of care delivered to any accrued patient according to a pre-defined schedule.

6.2 Description of Evaluations

6.2.1 Screening

The CI-CDS system is programmed to evaluate intervention eligibility each time a web service call is made from a randomized clinic during the accrual and intervention periods. Eligibility screening will therefore be consistently carried out and thoroughly documented for all patient visits as part of routine care at all randomized clinics. All primary care visits during the accrual period may be characterized with respect to basic patient demographics (e.g., age, sex, racial/ethnic group) and all eligibility criteria. Eligibility criteria are automatically extracted from the EHR when rooming staff enter a measured blood pressure into the EHR and the result of eligibility assessment is documented in less than one second. We have received a waiver of consent for use of the CI-CDS during clinical care because the CDS is consistent with recommended care guidelines and because conduct of the study would not be feasible without this waiver of consent.

6.2.2 Patient accrual and index visit assessment

Index visit

All primary care visits at randomized clinics during the accrual period will be assessed for intervention eligibility. Patients may be screened for eligibility more than once during this time period. The first visit at which the CI-CDS algorithms determine that a patient is intervention-eligible during their clinic's accrual period will be denoted as the patient's index visit. The patient will be accrued into the study at the index visit. 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.

Index Assessment

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., race / ethnic group, 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 for solely for research purposes.

Randomization

The primary effectiveness trial and the study at the replication site are both cluster-randomized pragmatic trials. Accrued patients will be assigned to the randomly assigned treatment group (CI-CDS, UC) of the clinic at which their index visit takes place.

6.2.3 Follow-up Visits

There is no study-determined visit schedule. Patient visits with their primary care clinicians in randomized clinics will take place on a frequency determined by the patient and clinician, without any interference from the study team. Primary care visits that take place at any clinic, randomized or non-randomized, after the index visit and prior to the end of the observation period will be denoted as post-index visits. All index and post-index visits will be documented in the EHR so that data documented from each may be extracted and assembled into an analytic dataset.

6.2.4 Completion/Final Evaluation

There is no study-determined visit schedule, and therefore no predetermined final visit. All documentation of care delivery in the EHR or claims database between each patient's index visit and the end of the observation period will be considered for inclusion in analyses, as appropriate.

6.2.5 Clinician surveys

As part of the R61 phase, primary care clinicians who practice in our 3 pilot clinics completed baseline surveys. Results of that survey are summarized in Section 15.3.

In the R33 phase, a baseline clinician survey conducted at HealthPartners (the primary effectiveness site) will serve as a pre-implementation assessment of clinician self-reports of

confidence and management of CI. A post-implementation clinician survey will be fielded 9-12 months after CI-CDS is implemented. Following extensive prior experience, HealthPartners Institute's Center for Evaluation and Survey Research (CESR) will field surveys using an initial leadership-endorsed invitation email to all practicing clinicians in the randomized clinics followed by as many as seven reminder emails over two months. Using this approach and modest monetary incentives, we expect clinician response rates of 60%.[81]

6.2.6 Chart audits

We will replicate procedures described in previous publications to measure rates of actions such as completion of cognitive assessments, orders for neuroimaging, referrals for neurocognitive testing, specialists, and orders for medications in the accrued population.[25] We will also audit the charts of 50-100 patients each in the CI-CDS and UC treatment groups, until saturation is reached. Chart audits are an important supplement to the EHR-based data to the extent that some clinician actions are difficult to obtain from fixed data fields in the EHR, including the presence and quality of care plans, caregiver identification, release of information authorization completion, and individualized recommendations for managing potentially distressful symptoms and safety issues.

6.2.7 Patient / caregiver dyad interviews

We will conduct semi-structured interviews with patient/caregiver dyads from randomized study clinics who are at elevated risk, recently screened, or newly diagnosed with CI to explore their experiences with screening, assessment, or diagnosis as well as their perceived preparedness for subsequent disease management. We will recruit study-accrued patients with recent study-eligible primary care index encounters to participate in the interviews. Following best-practice in qualitative data collection methods,[82] approximately twenty dyads will be recruited to participate. Interview guides will be designed in close partnership with qualitative and clinical experts to elicit rich qualitative patient and caregiver perspectives. A semi-structured design approach will be used consisting of 4-7 open-ended root questions each followed by a set of open-ended probes. Interviewers are trained and experienced in qualitative data collection within the health system setting. Interviewers will receive additional study-specific training related to CI care and the CI-CDS intervention. Practice interviews and on-going supervision will be conducted to ensure consistent, valuable data are collected. Detailed field notes will be collected using REDCap and, with permission, interviews will be recorded and transcribed. A thematic content analysis will be designed using combined inductive and deductive approaches to explore the perceived impact of clinic experience on addressed/unaddressed concerns, and resulting benefit/distress from screening, feelings about preparedness for future decisions, support, and distress. Learnings will be used to understand patient experience and inform future implementation and to design extensions of the CI-CDS related to disease management.

7. SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

This pragmatic trial introduces the CI-CDS system as an intervention delivery tool to clinics randomized to an intervention treatment group, where it provides data-informed clinical decision support to clinicians as an adjunct to the usual care they provide at primary care visits. The CI-CDS system is designed to facilitate the provision of accepted standards of care.

With this work, we are not attempting to change the standard of care for managing patients with CI in primary care, but rather are attempting to help clinicians achieve this standard of care in CI management such as through screening patients for CI or recognizing CI in the EHR. Primary care clinicians will be trained that, as with other clinical decision tools, the CI-CDS system is meant to supplement but not supersede clinical judgment. Clinicians will be able to choose to follow or to not follow the guidance of the CDS at any given time for any given patient.

Clinicians will be asked to use the Feedback Tab within the tool to let the study team know of questions or potential errors in the CDS. Additionally, clinicians will be trained to let the research team know via the Feedback Tab when their clinical judgment is inconsistent with the CDS. This feedback will be monitored by the treatment team and the CDS algorithms adjusted if indicated.

Actions suggested by the CI-CDS system are consistent with standard care for patients who meet intervention eligibility criteria, and therefore are unlikely to pose specific risks to their safety beyond those inherent to primary care. As such, we will not be monitoring safety events specific to the CI-CDS intervention or the content it delivers. Similarly, the intervention does not involve laboratory measures beyond those assessed in usual primary care, and as such we do not specify laboratory safety parameters. We will monitor emergency department visits, hospitalizations, suicide attempts, and deaths as safety events among all accrued patients from prior to their index visit through the end of the observation period although these events are unlikely to be related to the intervention.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

We propose to use passive surveillance of EHR and administrative data sources to monitor the occurrence of safety events. Benefits to this approach are that safety events can be ascertained identically for all accrued patients in all randomized clinics. Documentation will occur in the course of 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 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.

7.3 Clinician Feedback and Safety Events

7.3.1 Clinician Feedback

This intervention is being delivered by way of CDS prompts to influence clinician actions to incorporate evidence-based best practice standards related to CI. Prior to implementation, we will train all intervention clinicians and their rooming staff on the importance of helping us identify any clinician-identified safety events or near-misses that may be related to the EHR or CI-CDS. We will systematically educate them in identification of potential safety events and near-misses and informing us of these events via use of the Feedback Tab in the CDS or email. We will also ask clinicians to notify us of any clinical situations where their clinical judgment differs from the CI-CDS.

Use of the Feedback Tab will automatically generate an email that is sent to study team members, including investigators and programmers. The study team will then discuss this

feedback and any necessary actions, and reply to the clinician to answer the question, discuss steps taken to address the issue, or gather additional information if needed to further trouble-shoot. Clinicians will be asked to submit feedback any time their clinical judgment is inconsistent with the CDS tool. Additionally, the emails of study investigators will be listed in the training materials for clinicians, and clinicians will be encouraged to contact the study team directly with any questions or concerns if they would rather not use the Feedback Tab in the CI-CDS. This feedback will be provided to the DSMB at a frequency determined by the DSMB.

7.3.2 Safety events

Adverse Event (AE):

As this is a minimal risk study, with the CI-CDS intervention layered on top of usual care, adverse events will not be collected in the context of this trial.

Safety Events:

- emergency department visits
- hospitalizations
- suicide attempts
- death

We will extract data from the EHR and administrative databases to monitor safety events that occurred from 1 year prior to each accrued patient's index visit date through the end of the observation period. The following activities will be carried out at a frequency determined by the DSMB. The study statistician will assemble the random, unique study identifier and index visit date for all accrued patients. A study programmer will extract data elements needed to characterize the patient sample and to quantify rates of emergency department visits, hospitalizations, suicide attempts, and deaths. State preliminary manner of death data are sent to HealthPartners monthly, with a lag of about a month; these data and final adjudicated cause of death data are incorporated into HealthPartners databases upon receipt. The statistician will assemble a safety report and provide it to the co-PIs, OCHIN Lead Co-Investigator and the DSMB.

The DSMB 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 index visit date patient characteristics will be provided overall and by treatment group within site. CI-CDS use will be tracked monthly and cumulatively by treatment arm within site 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 the event rate in patient-years. Each metric for each event will be compared between the treatment groups (intervention vs. control) and over time (post-index vs. 1 year pre-index). Data from the year prior to each patient's index visit will provide baseline data regarding the prevalence of each safety event. Post-index data will be compared to baseline data by treatment group 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 groups.

7.3.3 Follow-up for Safety Events

As safety events will be assessed retrospectively via EHR and administrative data and given that the study team does not interact directly with patients (but instead they are treated by their primary care clinicians), the study team will not be providing follow-up for safety events. Instead, we can presume that the primary care clinicians and other medical professionals who are providing the patients' clinical care will manage these events.

7.4 Safety Monitoring

This study will be monitored by an NIA-appointed Data and Safety Monitoring Board (DSMB). Tables will summarize, within site and by blinded treatment group, (a) metrics pertaining to patient accrual; (b) performance of the CI-CDS system; (c) pre-randomization clinic characteristics and index visit patient characteristics; and (d) safety measures. Reports will be provided to the DSMB at a frequency the DSMB requests. The DSMB will provide an opinion on whether there is support for continuation of the trial, evidence that study procedures should be changed, or evidence that the trial should be halted for any reason, such as the safety of study participants, the efficacy of the treatment under study or inadequate trial performance.

8 INTERVENTION DISCONTINUATION

Once randomized, all primary care clinics are anticipated to remain enrolled for the duration of the study. All accrued patients will be followed for the duration of the observation period (i.e., end of study) unless they die or leave the care system. Patients who have opted out of research will be excluded from all analyses.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

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 at least 30 primary care clinics randomized to CI-CDS or 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.

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 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.

The primary effectiveness study is a pragmatic clinic-randomized trial that will assess the effectiveness of the CI-CDS system to impact outcomes that are important to patients, clinicians, and health system. This trial will be followed by a replication study in up to 30 randomized clinics in a separate health care system (replication site). The minimal eligibility criteria at the clinic and patient level help ensure that the results of these assessments will be generalizable to a range of clinical settings and patients. The intervention, the CI-CDS system, will be operating in live, primary care settings. At the end of the replication site intervention period, the study team will work with replication site leadership to transition the CI-CDS system from an experimental technology to the system-wide standard of care if so desired by leadership. The transition is readily accomplished by enabling user interface functionality in clinics that had been randomized to the UC group and by adding new clinic locations to the CI-CDS algorithms.

9.2 Sample Size and Randomization

9.2.1 Treatment Assignment Procedures

Clinics will be randomized 1:1 to CI-CDS or UC using simple randomization. Randomizing by clinic rather than clinician or patient is the most effective way to minimize risk of intervention contamination. Patients tend to receive most of their care over time at a single clinic, and clinicians tend to practice at a single clinic, so it is reasonable to assert that the risk of intervention contamination across clinics is low. However, it is common for patients to see more than one clinician in a clinic location over time. Randomizing by clinician is not preferable because it would increase the number of patients with multiple visits during the intervention period who would be exposed to both treatment groups over the course of these visits. Repeated use of the CI-CDS system may alter practice patterns so that clinicians may diagnose and manage care for patients with CI in the absence of prompts provided by the CDS. Randomizing by patients is not preferable because it would result in care for UC patients that was contaminated by changes in clinician practice patterns.

Each 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 intent-to-treat 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.

9.2.2 Sample Size Justification

The primary hypothesis test will compare patients in CI-CDS clinics to patients 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 silent pilot phase from the R61 to identify patients who met intervention eligibility criteria at clinic visits (sections 4.1, 4.2). Based on the pilot CI-CDS data, we estimate that, on average, about n=100 patients in each of at least 30 clinics will likely have an index visit in 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. There was substantial variation in CI recognition among all patients, ICC_{clin}=0.03, and among those with MiniCog<3, ICC_{clin}=0.04.

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 equivalent independent patient sample size (i.e., Neff=N/deff). The power analysis (power=0.80, α_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 independent sample size estimate.[84]

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

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.

Table 2. Minimum detectable rates of CI diagnosis in replication site CI-CDS clinics assuming n=60 accrued patients per clinic, 22-30 clinics, ICC_{clin} = 0.03-0.05 and UC diagnosis rates = 4-12%.

		UC diagnoses (%)		
clinics	ICC_{clin}	4%	8%	12%
22	0.03	10.7	16.4	21.6
	0.04	11.6	17.4	22.7
	0.05	12.4	18.3	23.7
26	0.03	10.0	15.6	20.7
	0.04	10.8	*16.5*	21.7
	0.05	11.5	17.4	22.6
30	0.03	9.5	15.0	20.1
	0.04	10.2	15.8	21.0
	0.05	10.9	16.6	21.8

A comparable power analysis was conducted for the replication site analysis of CI diagnosis rates among patients in CI-CDS relative to UC clinics. Assumptions about the number of randomized clinics (22, 26, 30), patients per clinic (n=60) and CI diagnosis rate (4%, 8%, 12%) were changed to acknowledge the likely smaller sample size and shorter observation period relative to the primary effectiveness site. 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 16.5% in CI-CDS clinics relative to 8% in UC clinics (Table 2). The absolute increase in diagnosis rates ranges from 5.5% (30 clinics, ICC_{clin}=0.03, 4%) to 9.7% (22 clinics, ICC_{clin}=0.05, 12%) across the range of these assumptions.

9.3 Interim analyses and Stopping Rules

There are no plans to conduct an interim analysis. The study team will collaborate with the DSMB to define thresholds at which differential rates of safety events by treatment group warrant consideration of suspending patient accrual or modifying intervention delivery.

9.4 Outcomes

9.4.1 Primary outcome

The primary outcome will be CI detection (H1). CI detection will be a binary outcome calculated from EHR data and defined as occurring when an ICD-10 diagnostic code for CI is documented at outpatient or inpatient encounters, or added to the problem list, between the index visit date and the end of the observation period, inclusive.

9.4.2 Secondary outcomes

A secondary outcome will be clinician-reported confidence in management of CI care (H2). The pre-and post-implementation clinician surveys in both study arms will include a series of Likert-scale survey items based on previous literature to assess confidence to correctly assess and diagnose CI.[14, 27] Items will ask about confidence in diagnosis and management of CI care generally and will include items about specific elements such as conducting appropriate testing and patient and care partner education. Items will be analyzed individually, and composite measures of confidence will be considered.

Another secondary outcome will be health care utilization among accrued patients with HealthPartners insurance (H3). Indicators of any use of emergency room (ER), inpatient or both facility types between the index visit and of the observation period, inclusive, will be calculated from data extracted from insurance claims databases. Additionally, the combined costs of ER and inpatient care delivered will be extracted as paid amounts for facility and professional services on ER and inpatient days.

Patient and clinician characteristics that could moderate the effectiveness of the CI-CDS system on these primary and secondary outcomes will also be extracted from the EHR and clinician surveys. EHR-based data include patient encounters (number and type), demographics (e.g., age, gender, race, ethnicity), social determinants of health (e.g., insurer, area deprivation index score for home address, median education for Census tract of home address, country of origin, need for interpreter) and comorbidities present at index (e.g., diabetes, cardiovascular disease, mental illnesses, substance use). Potential clinician moderators include clinician self-reported years in practice, sex, provider type and specialty.

The effectiveness of the CI-CDS system on several exploratory outcomes will also be assessed. These exploratory outcomes include clinical actions documented in patient charts or the EHR (e.g., referrals to community resources; documentation of care plans, release of information, caregiver identification or recommendations for managing stressful symptoms or safety); clinician attitudes (e.g., perceived control, attitudes about CI, perceived norms) or perceptions of CI-CDS (e.g., usefulness, intentions to treat patients with CI) reported in the post-implementation clinician survey; and patient or caregiver experiences discussed in the patient/caregiver dyad interviews about assessment for CI (e.g., addressed or unaddressed concerns about memory; benefit or harm of screening; feelings of preparedness, support, distress among newly diagnosed patients).

We will use the CI-CDS metadata (e.g., display, print, click rates for CI-CDS features or patient educational or resource materials) and the EHR (e.g., Quick Orders for cognitive assessment, labs, brain imaging, referrals, medications for cognition benefits or symptom management) to track clinician use of the CI-CDS system and compliance with suggested actions.

9.5 Data Analyses

9.5.1 Primary analysis

The H1 sample will consist of primary effectiveness site patients accrued from the CI-CDS and UC clinics who are at elevated risk for CI but without a CI diagnosis at index. The primary outcome is defined as at least one CI diagnostic code or CI diagnosis entry on the problem list at any time between the index visit and the end of the observation period (at least 12 and up to 24 months post-index), inclusive. 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). Clinic-randomized treatment group and any patient covariates (e.g., age at index visit, sex, MC-PLUS risk score at index visit) will be treated as fixed effects.

Descriptive statistics will be calculated on all pre-intervention patient variables across all accrued patients, by treatment group and by clinic to ensure that key patient characteristics related to the risk of CI or its diagnosis (i.e., age, sex, comorbidities) are balanced across treatment arms. Imbalanced patient characteristics will be considered for inclusion as covariates in the primary analyses.

For H1, we will fit a generalized LMM in which the binary post-index CI diagnosis outcome will be predicted via a link function from fixed effects for the clinic-randomized predictor, γ_{10}, and patient covariates, γ_{0*}, and a random clinic intercept, v_j, such as:

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

Parameter γ_{10} is expected to be positive and statistically significant, indicating that accrued 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, accounting for fixed effects and random clinic variation.

In a second model, we 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.

This same analytic approach will be used to estimate the CI-CDS system treatment effect at the replication site. There are no plans for a pooled analysis across the primary effectiveness and replication sites, nor to implement alpha-sparing techniques. The determination of CI-CDS effectiveness will rest on the results of the primary analysis at the effectiveness site.

9.5.2 Secondary analyses

Treatment effectiveness may vary as a function of contextual factors or patient characteristics.

Secondary H1 analyses will add fixed parameters to the H1 model that assess contextual factors (e.g., area deprivation index score for home address, median education for Census tract of home address) or patient characteristics (e.g., socioeconomic status, gender, pre-intervention CI risk) 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 disparities in CI care.

9.5.3. Secondary outcomes

H2 predicts that clinicians practicing in CI-CDS relative to UC clinics will report more post-implementation confidence in diagnosing and managing CI. We will also use a LMM approach for the H2 analyses. The distributional properties of the confidence and management composites calculated from post-implementation clinician survey data will inform how to specify the distribution and link functions for these variables (e.g., normal-identity, Poisson-log, binomial-logit, binomial-log, multinomial-cumulative logit). The fixed CI-CDS parameter and random clinic intercept from the H1 model will be retained, and a fixed parameter for the outcome value reported in the pre-implementation clinician survey will be added. Exploratory analyses will assess whether the relationship between CI-CDS and either of these outcomes is more pronounced among clinician subgroups (e.g., clinician type).

H3 predicts that patients accrued from CI-CDS clinics will have lower post-index health care utilization. Anticipating a zero-mass of patients with no emergency department or inpatient costs, we will employ a 2-part model to test H3.[86] 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)[87, 88] 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.[89] If we observe a statistically significant reduction 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.

Analyses of secondary and exploratory patient outcomes will also follow the same analytic approach as the H1 model with appropriate modifications to the link function and error distribution.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

We expect person-based missingness to be extremely rare. Patients are unlikely to be aware that their data are being used for this research. They will not be consented and are unlikely to request that their data be excluded from analyses. Only patients who have requested that their data not be used for research and appear on site-maintained opt out lists will be excluded.

The primary data source for hypotheses 1 and 3 and the safety analyses will be EHR- and claims-based data repositories maintained by HealthPartners. The stored EHR data elements

required for calculating the primary and secondary outcomes are extracted from live production tables. Medical care costs for H3 will come from administrative claims systems that are relied upon for reimbursement of medical care services. The absence of documentation of a care process, vital sign, or medication should not be interpreted as a missing value but rather as indicative of a care process or test not having been performed or medication not prescribed within the health system. Likewise, absence of utilization indicated by billing claims almost always indicates that the utilization (such as a hospitalization) did not occur. Truly missing field-based observations (e.g., CI diagnosis assigned, action not observed) will be extremely rare, undetectable, and assumed to be missing at random. The primary data source for H2 is a survey developed during the R61 phase. The survey will be administered and data stored securely using RedCap.

10.1.1 Missing Data

Data elements required for calculating the primary outcomes are extracted from EHR production tables. The absence of documentation of a care process, vital sign, or medication should not be interpreted as a missing value but rather as indicative of a care process or test not having been performed or medication not prescribed within the health system. Truly missing observations (e.g. value not available) will be extremely rare, undetectable and assumed to be missing at random. The estimation techniques used in 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.

10.2 Data Management

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 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.

10.3 Quality Assurance

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.

10.4 Protocol Deviations

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence.

Additionally, the Co-PIs are responsible for reviewing the IRB of record's definition of a protocol deviation or violation and understanding which events need to be reported.

10.5 Monitoring

All protocol deviations will be monitored for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial. The Co-PIs will be responsible for developing corrective action plans for both major and minor deviations as appropriate. Those corrective action plans may be reviewed/approved by the Co-PIs with overall approval by the IRB of record. All protocol deviations will be recorded in password protected project folders at HealthPartners Institute.

10.6 Regulatory Files

The regulatory files will contain all required regulatory documents, study-specific documents, and important communications.

10.7 Reporting to Sponsor

The lead investigators agree to submit accurate, complete, legible, and timely reports to the Sponsor, as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the trial or increase risk to study participants. Safety reporting will occur as previously described.

10.8 Audits

The Lead Investigator and authorized staff from the NIA CTN (the study sponsor); NIA's contracted agents, monitors or auditors; and other agencies such as the HHS, the OHRP and the IRB of record may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

10.9 Study Documentation

Each participating site will maintain appropriate study documentation (including medical and research records) for this trial, in compliance with ICH E6 R2 and regulatory and institutional requirements for the protection of confidentiality of participants.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

Prior to initiating the study, participating site investigators will obtain written IRB approval from the IRB to conduct the study at their respective sites, which will include approval of the study protocol. If changes to the study protocol become necessary, protocol amendments will be submitted in writing by the investigators for IRB approval prior to implementation. In addition, IRBs will approve recruitment materials, and any materials given to the participant, and any

changes made to these documents throughout study implementation. Unanticipated problems involving risk to study participants will be promptly reported to and reviewed by the IRB of record, according to its usual procedures.

HealthPartners will serve as the primary effectiveness study site, and as such, the HealthPartners IRB will serve as the central IRB for this study. The replication site will cede to the HealthPartners IRB and enter into reliance/authorization agreements. The HealthPartners IRB will provide study oversight in accordance with 45 CFR 46. HealthPartners IRB will follow written procedures for reporting its findings and actions to appropriate officials at each participating institution. Of note, it is possible a partner site may meet Exception Criteria to the NIH sIRB (single IRB) Policy and may not utilize the IRB of Record.

11.2 Informed Consent Forms

As this study aims to help clinicians achieve accepted standards of care for cognitive impairment, we have received a waiver of consent for clinicians and patients in this study. Patients and clinicians will be consented to participate in any surveys or interviews. The consent process will be IRB approved. We will request a waiver of documentation of consent as described in Section 15.2.

11.3 Participant Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor and funding agency, and will be maintained in accordance with all applicable federal regulations and/or state laws and regulations. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team.

All research activities will be conducted in as private a setting as possible.

Participant records will be held confidential using study codes for identifying participants, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. At the end of the study, all records will continue to be kept in a secure location for as long a period as required by state or federal law (whichever is longer).

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. ETHICAL CONSIDERATIONS

12.1 Statement of Compliance

This study will be conducted in accordance with the current version of the protocol, in full conformity with the ethical principles outlined in the Declaration of Helsinki, the Protection of Human Subjects described in the International Council for Harmonisation (ICH) GCP Guidelines, applicable United States Code of Federal Regulations (CFR), the NIA Terms and Conditions of Award, and all other applicable state, local and federal regulatory requirements.

The Co-PIs will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the Sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

12.2 Investigator Assurances

Each site must file (or have previously filed) a Federalwide Assurance (FWA) with the HHS Office for Human Research Protection (OHRP) setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects in alignment with 45 CFR 46, Subpart A, with documentation sent to NIA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103).

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will complete annual institutional financial disclosure requirements.

12.3 Inclusion of Women and Minorities

All patients aged 65 and older, inclusive, who are determined by the CI-CDS algorithms to be at high risk for CI and who meet all other protocol-defined eligibility criteria will be included in the study, regardless of sex or racial/ethnic group. Patients who have opted out of research will be excluded from analyses. All clinicians in randomized clinics will be included in the study, regardless of sex or racial/ethnic group.

12.4 Prisoner Certification

As per 45 CFR 46 Subpart C, there are additional protections pertaining to prisoners as study participants. A prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Due to the nature of the CI-CDS, a prisoner certificate is not applicable to this data collection. Patient participants who meet the OHRP definition of “prisoner” will be ineligible for participation in any surveys.

13. COMMITTEES

Committee	Role
Steering Committee	• Set strategic direction of project • Monitor project process and plans • Advocate for project across wider organization • Prioritize and reprioritize project deliverables

AI Team	• Development of MC-PLUS prediction model • Testing of prediction model • Validation of prediction model
Technical Team	• CDS algorithm development • Web/EPIC development
Dementia Expert Panel	• Contribute expertise in cognitive disorders and MiniCog testing • Contribute expertise in care processes improvements • Contribute expertise in machine learning
Data Collection and Analysis	• Analyze date from pilot and final intervention • Dissemination of results through publications and presentations

14. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Co-PIs.

15. SUPPLEMENTS / APPENDICES

15.1 Procedures schedule

In this pragmatic clinical trial, patients will receive care as part of their usual primary care. Clinic visits will be scheduled at a frequency determined by the patient with his or her primary care clinician. As such, there is not a specified procedures schedule. However, the timeline for the R33 Phase of this trial is below:

Phase	**R61**								**R33**											
	Year 1				**Year 2**				**Year 3**				**Year 4**				**Year 5**			
Quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Phase 1: Planning, Pilot, Validation																				
Machine Learning Analysis & Refinement																				
CDS & EHR Tool Development																				
Pilot and Revise CI-CDS																				
Phase 2: Implementation																				
CDS revisions; provider baseline survey; clinic randomization & training																				
Patient Accrual for Primary Effectiveness Site																				
Observation Period for Primary Effectiveness Site																				
Patient Accrual for Replication Site																				
Observation Period for Replication Site																				
Intervention fidelity monitoring; maintenance																				
Phase 2: Analysis, Reporting, Dissemination																				

Analysis preparation																			
Main outcome, disparities, & secondary analysis																			
Manuscript and conference dissemination																			

15.2 Informed Consent Document

As noted above, we have requested and been granted a waiver of consent for use of the CI-CDS in clinical care in both the R61 and R33 phases of this study. Reasons for requesting a waiver of consent include:

a) All treatment options identified by the CDS intervention are U.S. Food and Drug Administration-approved and evidence-based, as specified in the regional and national clinical practice guidelines. No care is advocated that is not evidence-based. The care conforms to current standards of care and does not represent any additional risk to patients beyond the routine risk that all patients assume whenever they have contact with the medical care system. The CDS system has been used in several previous randomized clinical trials with DSMB monitoring that revealed no safety concerns.
b) At clinic training sessions and on printed/electronically displayed decision support tools, we emphasize that it is inappropriate for a clinician to follow suggested treatment options without further checking the clinical status of a given patient. A disclaimer on the CDS says that treatment options are based only on electronically available data and are not intended to be a substitute for clinical judgment.
c) It would be impractical to consent patients (due to large numbers of patients) and impossible to answer the primary research questions (due to selection effects related to consent) if written informed consent of all patients were required.
d) The CDS platform upon which the CI-CDS intervention is based is supported by the care system's leadership, implemented with their collaboration and support, and embedded in the care process at the clinic and department level. Therefore, the CDS platform itself is part of routine care, and is accessible to all clinicians, with use of the CDS tool indicating implied consent.

A waiver of documentation of consent is being requested for surveys of providers and dyad interviews.

A general script for conversations with patients and care partners for interviews is as follows:

First, let me to go over some details about the study with you. If you have questions at any point as we go through the information, please feel free to interrupt me so that I can answer your questions. Once we are done, I will ask if you are still willing to participate in this interview.

In this study, we want to learn more about the assessments and diagnosis you received for cognitive impairment and to see how prepared you feel for the disease management. We expect up to 20 dyads (pairs of patients and care partners) to participate.

As a subject, you will participate in a telephone interview that will take about 20 minutes. We will schedule the interview for a time that works for you.

There are no anticipated physical risks to you related to this study. Some questions may make you uncomfortable, but you can skip any questions that you do not want to answer.

There is no cost for you to participate. If you complete the telephone interview, we will send you a $10 Amazon.com Gift Card.

Your study records will be kept confidential.

You do not have to be in this study. If you start the study, you may stop at any time. Your decision to participate will not affect the care provided by your clinic, your insurance coverage, or your relationship with your health care providers.

15.2.2 Survey Invitation and Consent for Primary Care Clinicians

An email invitation will be sent to clinicians to participate in the survey like this:

Our primary care clinics are collaborating with HealthPartners Institute on a short survey to better understand the experience of clinicians in detecting and diagnosing cognitive impairment.

You will soon receive an email from CIwizard@HealthPartners.com with a link to an online survey. Please take 10 minutes of your time to complete this confidential survey. If you choose to participate, you will receive a $100 Amazon.com Gift Card* after you complete the survey.

Your privacy is important to HealthPartners, and your name will not be associated with your responses. The results will go to HealthPartners Institute's central survey center and will only be reported to HealthPartners leadership in aggregate to ensure confidentiality. However, the center will be tracking who responds so they can provide follow-up reminder emails since it is important that we hear from as many providers as possible.

Thank you in advance for your participation; your feedback is greatly appreciated.

15.3 Summary Results of Primary Care Clinician Pilot Surveys

A survey to identify clinician-reported barriers to diagnosing cognitive impairment and managing care was designed following best practices in survey methods. The survey was designed to be completed in 10 minutes or less and included 30 items aligned with the Capability, Opportunity, Motivation – Behavior (COM-B) and Technology Acceptance Model (TAM) theoretical frameworks. These surveys were successfully fielded at all 3 of the clinics recruited to participate in the pilot. Prior to initiating the pilot intervention (clinician training and providing access to the clinical decision support tool), 25 eligible primary care clinicians were identified. All were in family practice or internal medicine departments and 68% had an MD or DO (as opposed to nurse practitioner or physician assistant degrees). With permission from clinic leaders, all clinicians were emailed a survey invitation from the study principal investigators offering an optional opportunity to participate. In total, 14 clinicians completed the survey (response rate of 56%) and were given a $100 gift card as a thank you for their time. Responding clinicians were primarily female (54%), white (92%), 40 years of age or younger (62%), had practiced for 10 years or less (62%), and saw patients in the clinic at least 4 days a week (86%).

Barriers to assessing and diagnosing cognitive impairment were identified across clinician motivation to diagnose and their social and environmental opportunity to diagnose. There were no substantial ceiling effects in these items, with all having opportunity for improvement with intervention. All clinicians reported time in visits and usability of EHR as at least somewhat of a barrier to diagnosing. The majority of clinicians also identified lacking confidence in diagnosing, perceiving patients as resistant to assessments, lacking access to care partners in visits, and lacking standard workflows for assessment and reimbursement. The least commonly reported barriers were lack of financial reimbursement and concerns about the reliability of cognitive screenings conducted.

Table 2. Clinician-report barriers to assessing and diagnosing cognitive impairment, N=14 clinicians.

	%
Motivation to Diagnose	
Beliefs about Capability to Diagnose/Confidence in…	
Diagnosing overall, without referral to specialist	57% a little or not at all confident
Understanding brief cognitive screening results	29% a little or not at all confident
Conducting comprehensive cognitive assessments	29% a little or not at all confident
Knowing labs or imagining needed	29% a little or not at all confident
Distinguishing types of dementia	71% a little or not at all confident
Having conversations with patients about new diagnoses	50% a little or not at all confident
Beliefs about Consequences of Diagnosing	
Patients will not benefit from diagnosis because no effective treatments	21% somewhat or strongly agree
Opportunity to Diagnose	
Social Influences on Diagnosing	
Patients are resistant to cognitive assessments	57% somewhat or strongly agree
Brief cognitive screenings conducted in my clinic are reliable	21% somewhat or strongly disagree
Lack of care partner availability at visits	71% moderate or large barrier
Environmental Influences on Diagnosing	
Standard workflows for abnormal screenings exist in my clinic	57% somewhat or strongly disagree
Lack of reimbursement for assessment and diagnosis	14% moderate or large barrier
Lack of time in visits for assessment and diagnosis	100% moderate or large barrier
Usability of EHR for Diagnosing	
EHR alerts make it easier to recognize cognitive impairment risk	100% somewhat or strongly disagree
EHR tools make it easier to assess and diagnose cognitive impairment	64% somewhat or strongly disagree

Similarly, barriers to managing care for dementia were also identified across clinician motivation and social and environmental opportunity. Again, no ceiling effects existed with all items allowing opportunity to improve. All or most clinicians reported a lack of confidence in managing various parts of dementia care, lack of access to care partners, lack of time in visits and limited usability of EHR to manage care for those with dementia. Only 14% (n=2 clinicians) reported lack of reimbursement as a moderate or large barrier to providing dementia care management.

Table 3. Clinician-report barriers to managing care for patients with dementia, N=14 primary care clinicians.

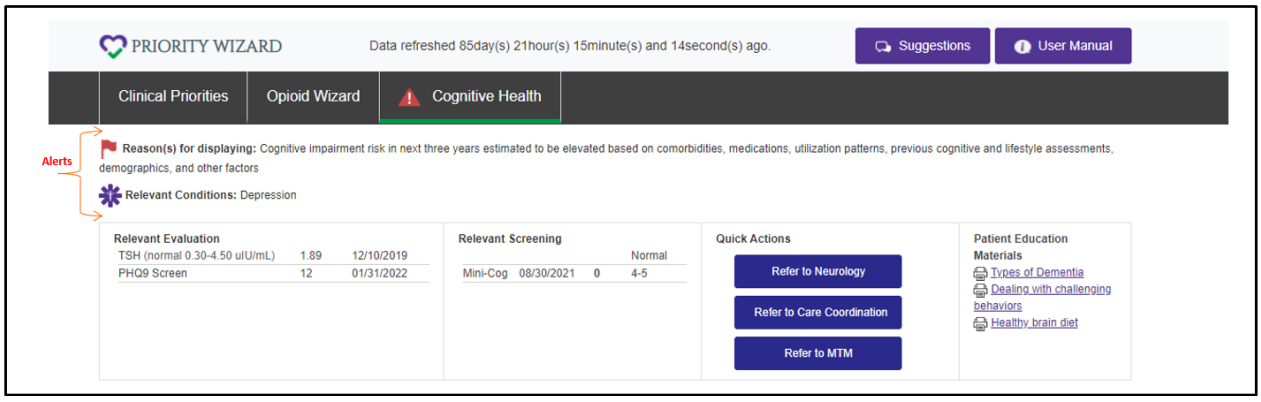
	%
Motivation to Manage Care for Dementia	
Beliefs about Capability to Manage Care/Confidence in…	
Managing care overall, without referral to specialist	71% a little or not at all confident
Starting pharmacological treatment for dementia	71% a little or not at all confident
Addressing medication safety issues	43% a little or not at all confident
Starting treatment for related depression, insomnia or agitation	29% a little or not at all confident
Accessing patient education resources	71% a little or not at all confident
Accessing care partner education resources	71% a little or not at all confident
Addressing driving safety	64% a little or not at all confident
Addressing home safety	57% a little or not at all confident
Completing advanced directive, POLST or release of information	50% a little or not at all confident
Supporting estate planning, power of attorney, legal documentation	64% a little or not at all confident
Opportunity to Manage Care for Dementia	
Environmental Influences on Managing Care	
Lack of care partner availability at visits	64% moderate or large barrier
Lack of reimbursement for managing care	14% moderate or large barrier
Lack of time in visits for managing care	100% moderate or large barrier
Usability of EHR for Managing Care	
EHR Tools make it easier to provide care and support	86% somewhat or strongly disagree

Open-ended responses from clinicians reiterated the findings above: “The biggest barrier is not having time. The patient oftentimes does not want to do the assessment or sees it as an insult. The time to discuss and reach shared understanding is not available and on top of that is the time to perform the screening.” Some offered suggestions in addition to clinical decision support tools to address barriers such as lack of confidence and time. One example was developing a “comprehensive care team approach with the ‘right person doing the right job’”.

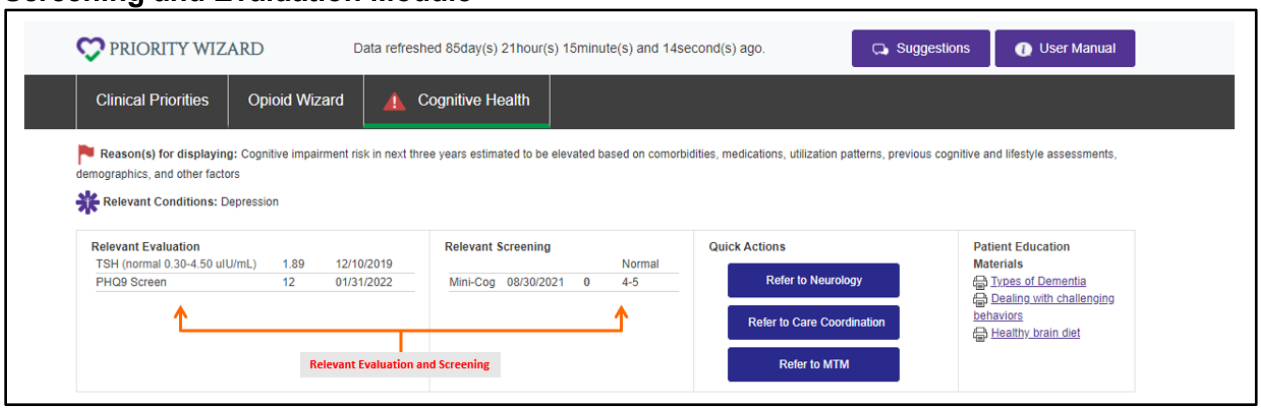
Clinicians were also asked to answer a brief set of questions about the quality of the pilot survey. All clinicians thought the items and response options were understandable, the survey was about the right length, and was comprehensive with few additional topics identified.

15.4 Clinical Decision Support Content for Diagnosis and Management of CI

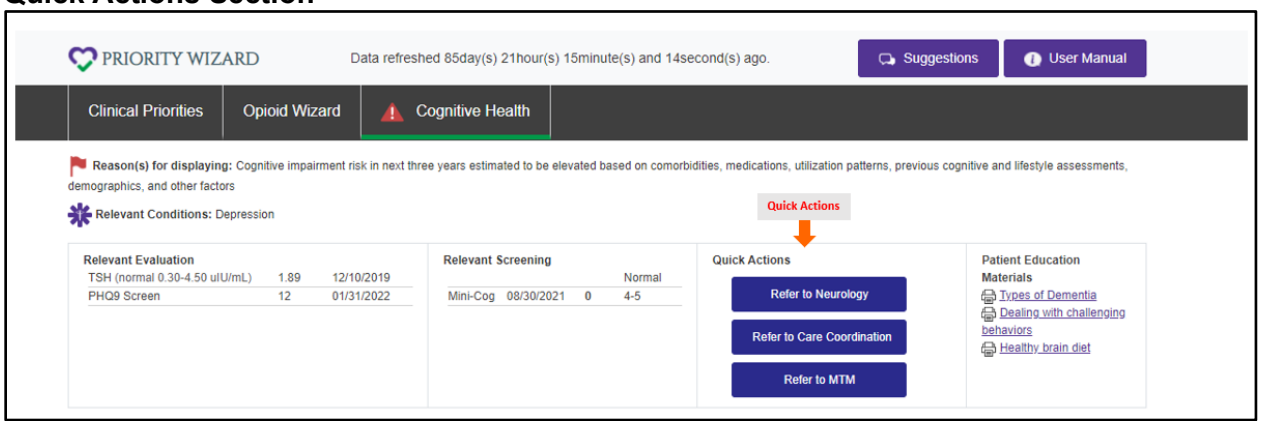
Example Alert Section



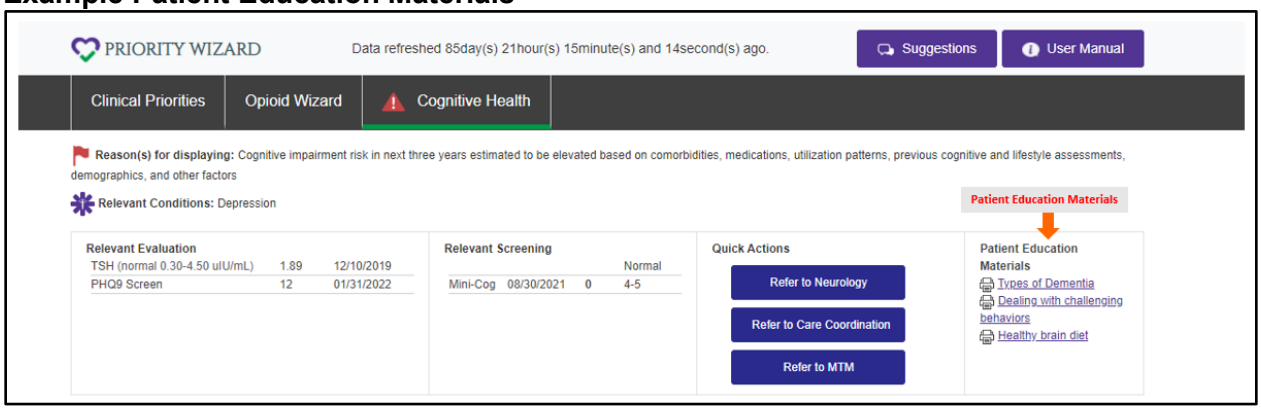
Screening and Evaluation Module



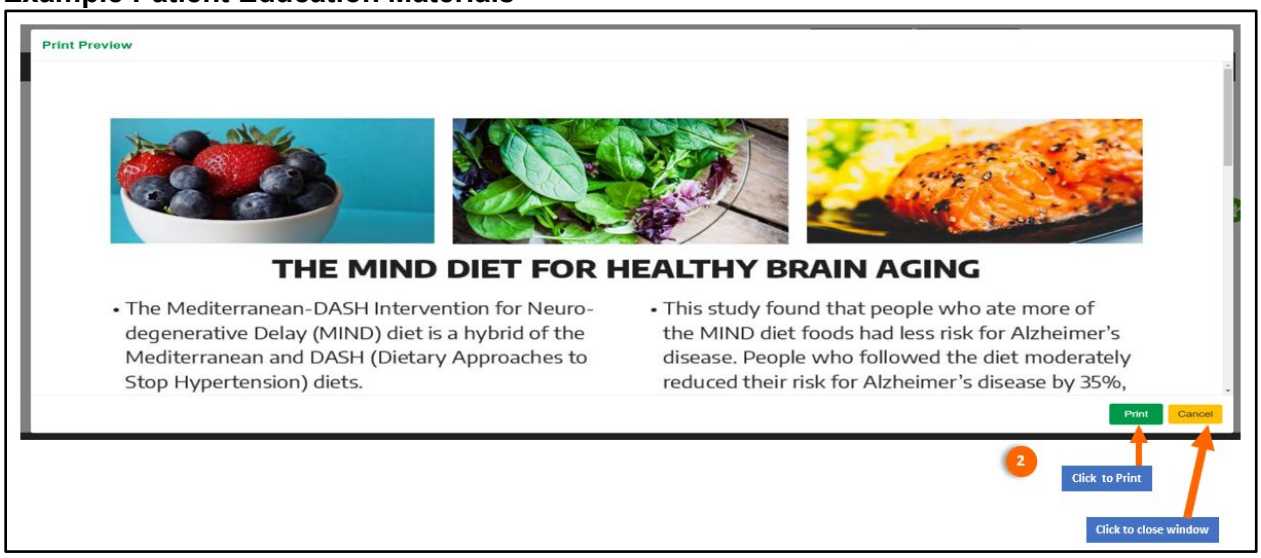
Quick Actions Section



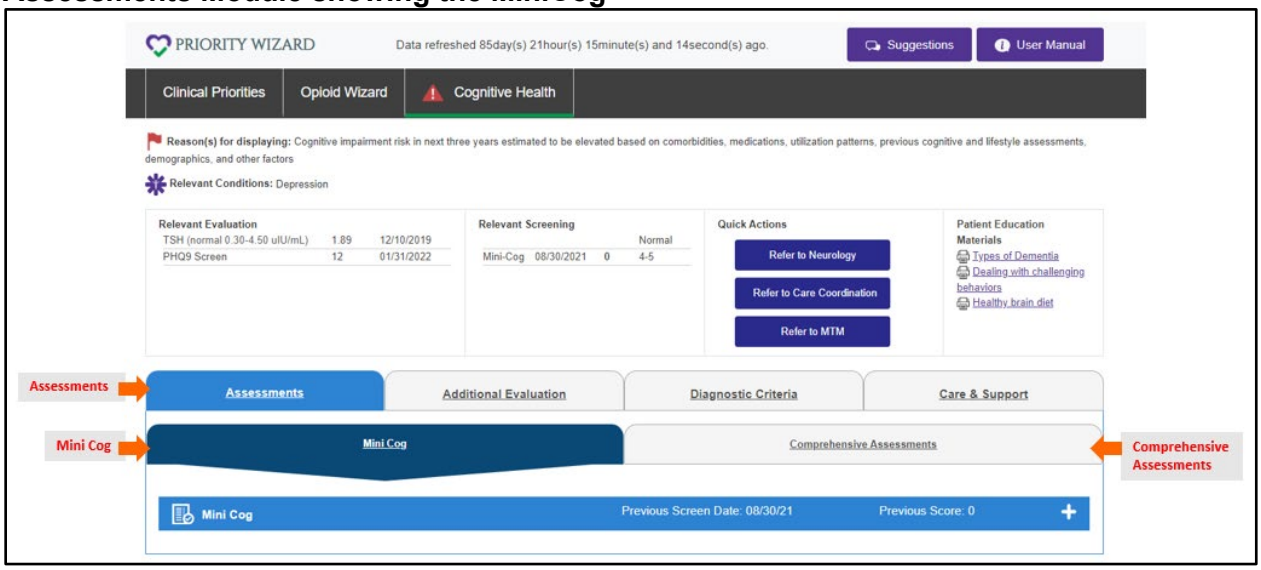
Example Patient Education Materials



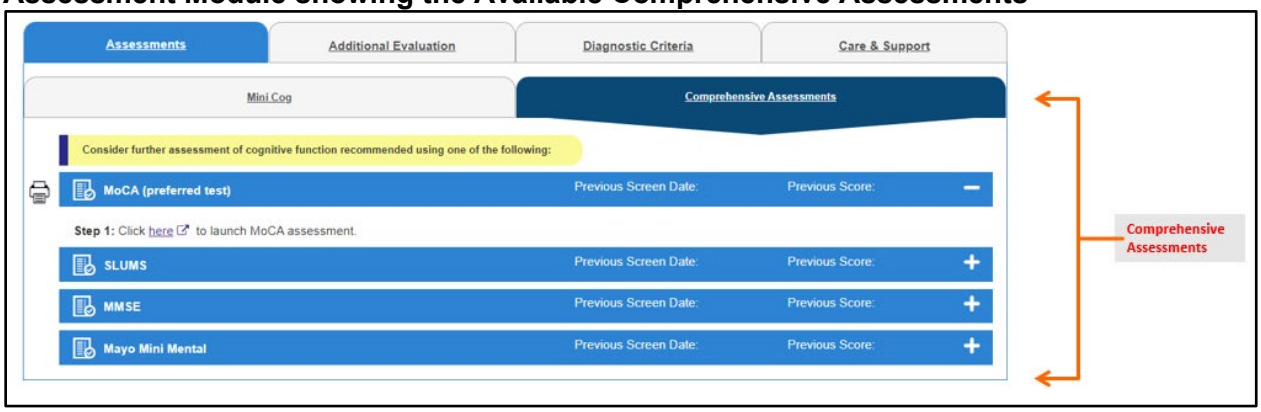
Example Patient Education Materials



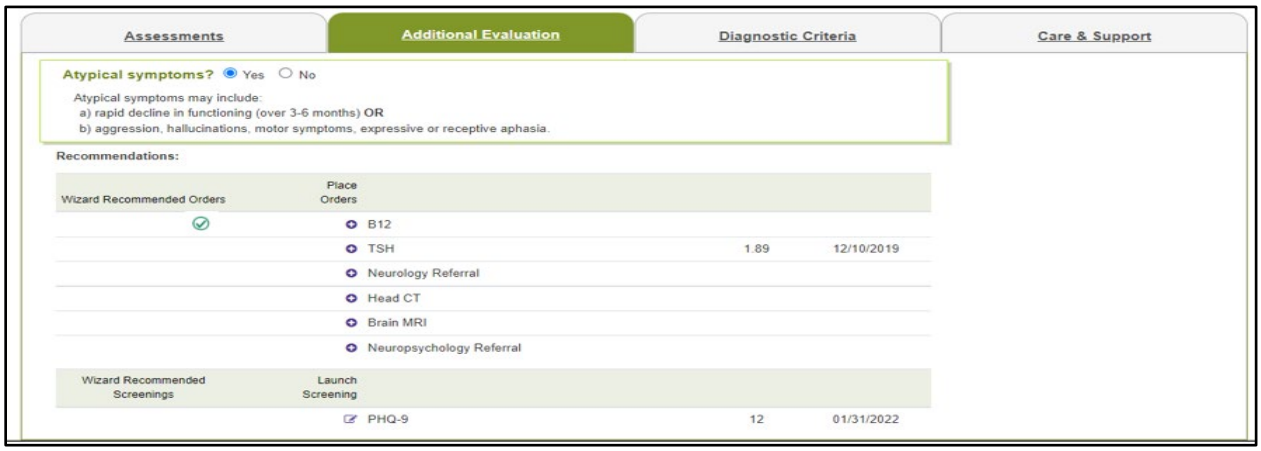
Assessments Module showing the MiniCog



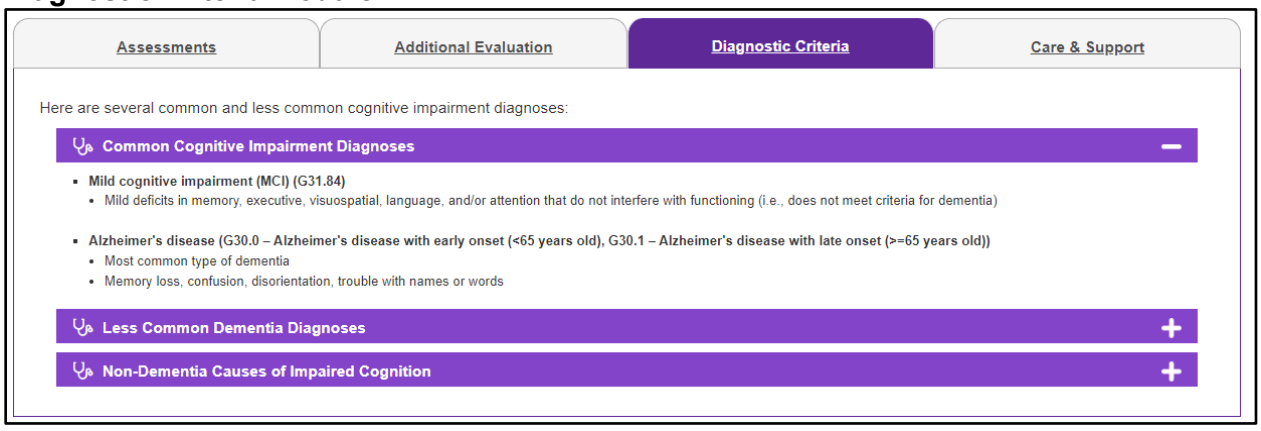
Assessment Module showing the Available Comprehensive Assessments



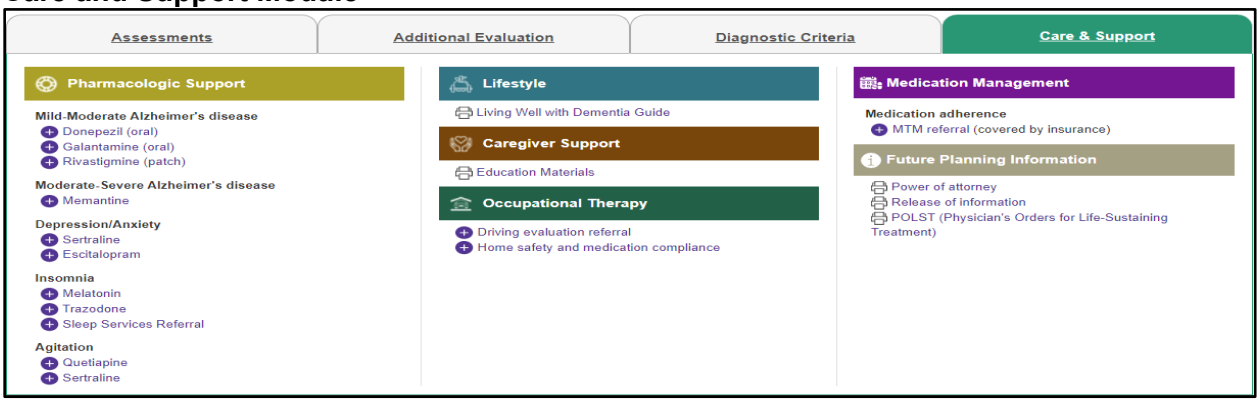
Additional Evaluation Module



Diagnostic Criteria Module



Care and Support Module



15.5 REPLICATION SITE PROCEDURES

The replication site, OCHIN, will follow all the procedures outlined in this protocol except where indicated in this appendix.

OCHIN STUDY TEAM ROSTER

Investigator	Role	Contact Information	Main responsibility/Key Roles	Dates on Project
Constance Owens-Jasey, PhD	Lead Co-Investigator	OCHIN, Inc. owensc@ochin.org	• Assure adherence to protocol at replication site • Oversee replication site activities	9/1/2022-Current
Rachel Gold, PhD, MPH	Co-I	OCHIN, Inc. rachel.gold@kpchr.org	• Assist in CDS implementation at replication stie	9/1/2022-Current
Maura Pisciotta, MS	Project Manager	OCHIN, Inc. pisciottam@ochin.org	• Support project activities at replication site • Recruit service areas for study participation	9/1/2022-2/28/2024
Joanna Georgescu, PhD	Primary Analyst	OCHIN, Inc. georgescuj@ochin.org	• Data collection planning at replication site	9/1/2022-10/31/2024
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4. SELECTION AND ENROLLMENT OF PARTICIPANTS

Primary care clinics

The OCHIN Lead Co-Investigator will collaborate with the HealthPartners Co-PIs to identify eligible service areas (groups of related clinics) that will be randomized 1:1 to the CI-CDS or UC treatment group. OCHIN will enroll at least three service areas with at least 10 total constituent primary care clinics as CI-CDS replication sites; a similar number of service areas and primary care clinics will serve as usual care (UC) replication sites. Stratified randomization by SA size may be used to balance the number of constituent clinics in each treatment group. Replication site clinics must currently have access to cardiovascular (CV) Wizard to be eligible for randomization. Service areas were chosen as a unit of randomization to avoid intervention contamination within groups of these highly related clinics.

CI-CDS and UC service areas will be approached for participation in the study. Service areas, and their constituent clinics, that agree to participate by allowing full or silent implementation of the CI-CDS system will be considered enrolled.

Recruitment will be conducted by the OCHIN study team, with support as needed from the HealthPartners staff. Eligible service areas and their clinics will be sent an introductory recruitment email with relevant study-related information, such as outlining the goals of the study, the CI Wizard tool, and an invitation to participate. Study team staff will follow-up via email, telephone, or video conference platform to answer any questions, provide demos of CI Wizard CDS, and/or share additional information regarding participation with service areas that are interested, as appropriate.

Once a service area agrees to participate, OCHIN will follow up with a Memorandum of Understanding (MOU) that outlines participation expectations, a timeline for study activities, and details regarding compensation. These MOUs will be signed by OCHIN and leadership at the participating service areas prior to starting study activities. Service areas will receive an impact payment of up to $3000 as compensation for the time spent engaging in study activities. This impact payment will be distributed by OCHIN and is provided to the service area and not to any individual within the service area or clinic.

4.3 Study Enrollment Procedures

The clinician survey will not be conducted at the replication site and thus any survey-related procedures are not applicable.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

At the replication site, the CI-CDS user interface will only be operative in intervention service areas that are approached and agree to fully implement the CI-CDS. The CI-CDS will run invisibly

in the background in all enrolled service areas. Having the CI-CDS run invisibly at all study sites ensures that study and intervention eligibility are assessed identically for all patients with visits at all study clinics in all enrolled service areas. See **Section 9.2** of this appendix for more information about randomization procedures.

CI-CDS user interface functionality may vary slightly between service areas within the replication site, such as differences in quick order availability and region-specific patient resource materials. For example, if quick orders are not feasible in some service areas, a static recommendation to place an order may be implemented instead.

The CI-CDS tool will function similarly at the replication site and the primary site, with OCHIN's EHR securely exchanging data with the HealthPartners web service at every encounter of adult patients aged 65 or older. The OCHIN EHR data securely exchanged via the HealthPartners web service will initially be saved in an operational repository at HealthPartners. Limited EHR and Wizard use data will then be securely transferred and stored in a research repository at HealthPartners used for study purposes using a random study ID to reduce the risk of breach of confidentiality. See **Section 10** of this appendix for more information on data that will be stored in this research repository.

5.4 Adherence Assessment

Print rates by rooming staff at replication site clinics will be measured and grouped by clinic and clinician but will not be reported monthly to clinic leadership.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Health care claims databases (e.g., paid amounts for emergency room visits or inpatient stays) are not available to be utilized at the replication site.

6.2. Description of Evaluations

6.2.5 Clinician surveys

The clinician survey will not be conducted at the replication site and thus these procedures are not applicable.

6.2.6 Chart audits

Chart audits will not be conducted at the replication site and thus these procedures are not applicable.

6.2.7 Patient / caregiver dyad interviews

Interviews will not be conducted at the replication site and thus these procedures are not applicable.

7. SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

Clinicians at replication site clinics can use the Feedback Tab to let the OCHIN team know of any questions or potential errors in the CDS. The OCHIN team will triage any feedback received through the Feedback Tab and communicate to the HealthPartners team if appropriate.

7.2. Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Surveillance of information stored in the Wizard repository will be used to monitor safety events at the replication site.

7.3 Clinician Feedback and Safety Events

7.3.1 Clinician Feedback

Use of the Feedback Tab at replication site clinics will generate an email that is sent to the OCHIN study team members. The OCHIN team will communicate any feedback received through the Feedback Tab to the HealthPartners Team, when appropriate. The study teams will then discuss this feedback and any necessary actions, and reply to the clinician to answer the question, discuss steps taken to address the issue, or gather additional information if needed to further trouble-shoot.

7.3.2 Safety events

Due to limitations in availability of data for emergency department visits, hospitalizations, and deaths at the replication site, we are unable to monitor these safety events at this site. We will measure suicide attempts as a safety event at the replication site.

9. STATISTICAL CONSIDERATIONS

9.2 Sample Size and Randomization

Operational considerations at the replication site make clinic-randomization impractical. To accommodate these considerations, randomization will be conducted by service area rather than clinic. Service areas eligible for randomization are those that currently have access to CV Wizard.

9.2.1 Treatment Assignment Procedures

All eligible service areas will be randomized 1:1 to CI-CDS intervention or Control to maximize the likelihood that CI-CDS and UC service areas are similar on observed and unobserved characteristics. Service areas may be stratified based on number of clinics to ensure a balanced number of clinics between intervention and control groups. Service areas in the intervention group will be approached to participate in the study, which includes turning on the CI-CDS user interface. If they do not agree, they will be invited to turn on the CI-CDS invisibly to collect data in the background. CI-CDS service areas that agree to either of these options will be considered enrolled. Service areas randomized to UC that agree to run the CI-CDS invisibly in the background will be considered enrolled.

9.4 Outcomes

9.4.2 Secondary Outcomes

Secondary Outcomes will not be assessed at the replication site and thus these procedures are not applicable.

10. DATA COLLECTION AND QUALITY ASSURANCE

The sole data source for the replication site is OCHIN EHR data. No claims-based data are available, nor will survey data be collected, at the replication site. The following EHR data will be collected from the CI-CDS tool and will be saved in an operational repository at HealthPartners. Individual and clinic identifying information, including patient name, date of birth, clinician name/ID, clinic name/ID, and department ID will then be removed from the data set and replaced by a random identifier prior to saving it into the research data repository.

Clinic-level data	Clinic name and/or ID, department ID, clinician name and/or ID
Patient-level data	Patient name (purged nightly), date of birth (purged nightly), age, gender, race, diagnosis (with dates), lab values (with dates), vitals (with dates), allergies (with dates), Rx (with dates), assessment results (with dates)
CI Wizard use data	Wizard print rates and click rates

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