5-Cog Battery for Detecting Cognitive impairment and Dementia

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5-Cog Battery to improve detection of cognitive impairment and dementia: UH3 Protocol

Principal Investigator:

Dr. Joe Verghese M.B.B.S.

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PRÉCIS

Study Title

5-Cog Battery to improve detection of cognitive impairment and dementia

Objectives

Despite the availability of numerous cognitive assessment tools, cognitive impairment related to dementia is frequently under-diagnosed in primary care settings, and is a more prevalent problem among older African-Americans and Hispanics than among older whites. To overcome the technical, cultural and logistic barriers of current cognitive screens and dementia care in primary care settings we propose to validate a 5-minute cognitive screen (5-Cog) coupled with a decision tree to identify persons at high risk of developing dementia in multi-ethnic primary care populations with socio-economic challenges. The primary objective is to test the ability of the 5-Cog battery and decision tree paradigm to improve dementia care in primary care patients with cognitive concerns.

The 5-Cog battery includes the Picture based Memory Impairment Screen (PMIS),[1] Motoric Cognitive Risk Syndrome (MCR) diagnosis,[2-4] and a brief non-memory picture based test (Symbol Match). Our cognitive assessment algorithm will sort patients with 'cognitive impairment' from those with 'no cognitive impairment'. Moreover, it is coupled with a decision tree to guide clinicians through the follow up on any 5-Cog results.

Design and Outcomes

We propose to conduct a single-blind randomized clinical trial (RCT) in 1,200 primary care patients age 65 and older presenting with cognitive complaints. Non-medical professionals will administer the 5-Cog in the intervention group and a 5-minute health literacy and grip strength assessment in the active control group.

Interventions

The interventions will be given after randomization and before the patients sees the physician. After completing the intervention or control assessments, the tester will provide results to the treating physician with follow-up recommendations based on the decision tree.

Participants randomized to the active control will receive a health literacy questionnaire, the Short Assessment of Health Literacy (SAHL) and grip strength assessment to match time (5 minutes), tester exposure and decision tree procedure in the 5-Cog arm. To parallel the study procedures and flow in the 5-Cog arm, a decision tree for the active control arm will also be created. Results of the control screen and the decision tree will be presented to the physicians at the same visit.

Sample Size and Population

Our testing will be carried out in an urban, multi-ethnic Bronx patient population. We will use a randomized block design to place 1,200 patients into either 5-Cog or control groups. Patients will be stratified by gender and age (< or >75 years).

STUDY TEAM ROSTER

Administrative Core:
Principal Investigator (Dr. Verghese): will head the Management Team and its Cores. He will assign responsibilities to team members and integrate their feedback to ensure timely progress. To this end, he will chair regularly scheduled, full-team meetings with standing agendas and predictable cycles of reports. Dr. Verghese will also hold smaller, Core meetings in order to manage specific concerns and unforeseen issues. If necessary, he will also meet individually with team members on an *ad hoc* basis. Dr. Verghese manages programs by promoting a sense of participation and ownership by all investigators and staff. He is strongly committed to an open management style, encouraging staff to identify problems and propose solutions.
Project Manager (Emmeline Ayers): will assume fiscal and administrative management, including supervising budgets, tracking adherence to timelines, and maintaining collaborative relationships among the PI, investigators and cross-consortium coordinating team (CCCT) members. She will also be responsible for coordinating with members of the CCCT to conduct pilot studies and facilitate sharing of data and paradigms. She will prepare reports for the NIH and the IRB.
Study Coordinator will supervise daily operations of this project. He/She will coordinate patient recruitment and scheduling of screening days with the research assistants. The coordinator will be responsible for protocol development, procedure implementation and personnel management of the research assistants and office coordinators. He/She will monitor and back-up databases, conduct quality control audits and clean as well as prepare datasets for the statistical core and for institutional and other advisory board reports.

Clinical Core:
Supervisors (Drs. Ehrlich and Zwerling): will oversee training of personnel administering the 5-Cog, and protocol implementation within a primary care setting. They will be responsible for administrative discussions with partners at Montefiore. *Dr. Ehrlich* is the Associate Chief of the Division of Geriatrics at Montefiore Medical Center and the Medical Director of Montefiore's Home Health Agency. *Dr. Zwerling* is the Associate Director of the Montefiore-Einstein Center for the Aging Brain and has experience developing programs to enhance health professionals' capacity to screen, diagnose and develop personalized plans of care for cognitively impaired patients within the Montefiore Health System.
Operations manager (Dr. Ansari): Dr. Ansari is Medical Director of the primary care clinic where our trial is based. He will act as a guide on the logistical side of the operation working with clinic staff and the project manager to develop and implement protocols in the clinics.
Trainer (Dr. Chalmer): is a board certified geriatrician and experienced clinician-educator who will train the research assistants involved in this study as well as liaise with the doctors to identify barriers and facilitate implementation of the paradigms.

Cognitive Core:
Neuropsychologist (Dr. Weiss): has experience conducting pilot studies on the utility of brief neurocognitive/neuropsychological evaluations in the clinical assessment of older adults.
Consultant (Dr. DeGutis): will guide us in refining our diagnostic tools for cognitive impairment in older adults.

Statistical Core:
Biostatistician (Dr. Wang): will be responsible for choosing proper analytical tools to determine

the statistical relevance of data generated in each of the research aims. Dr. Wang is a biostatistician who has participated in a range of studies including multiple clinical trials and several large epidemiological studies.
Healthcare Economist (Dr. Rasekh) is a Healthcare Analyst at Montefiore and will be responsible for overseeing the cost effectiveness analysis of this proposal.

Data Management Core:
Records Manager (Dr. Malik): Dr. Malik is a board certified geriatrician, and has a wealth of experience utilizing our electronic medical record (EMR) system (EPIC) for research purposes. She will liaise with the EPIC systems programmer to extract relevant patient information.
Database programmer: will be responsible for the development, upkeep, and maintenance of a centralized database in which all project data will be stored. They will work with the EPIC programmer and EPIC data analyst to integrate data collected from the EPIC system with study data.

Health-disparities Core:
Test Development (Dr. Walker): has been conducting NIH-funded translational research in underserved populations for over 25 years. She will advise us on health disparities issues in implementation as well as in analysis.

1 STUDY OBJECTIVES

1.1 Primary Objective

The 5-Cog battery and decision tree will improve dementia care in primary care settings for patients with cognitive concerns. Improved dementia care will be measured by new Mild Cognitive Impairment syndrome (MCI) or dementia diagnoses, laboratory investigations to rule out reversible causes of cognitive impairment, new dementia medication prescriptions, and specialist referrals for dementia care, and will be tracked using the electronic medical record (EMR) system.

1.2 Secondary Objectives

Utilization (emergency room visits and hospitalizations) for patients in both arms will be tracked and reviewed at regular intervals throughout the study period. Utilization is defined in terms of specialty visits, emergency room visits, and hospitalizations up to 12 months following the screening visit. This will be tracked via the EMR in both groups.

2 BACKGROUND AND RATIONALE

2.1 Background

Cognitive impairment related to dementia is frequently under-diagnosed in primary care settings despite the availability of numerous assessment tools.[5-7] Missed detection delays treatment of reversible conditions as well as provision of support services and critical planning.[8] This problem is more prevalent among older African-Americans and Hispanics than among older whites.[5-7]

Picture Memory Impairment Screen (PMIS): A major limiting factor in identifying dementia in health disparate populations are the lack of cognitive screens that account for cultural differences and variable literacy rates. Also, many cognitive screens are lengthy and not designed for non-specialist use, limiting their application in primary care. The Memory Impairment Screen (MIS) is a brief, 4-item delayed free- and cued-recall test that was developed and validated in an urban U.S. population,[9] and recommended for dementia screening.[10-12] However, the MIS requires minimum reading skills, which limits its use in low literacy populations.[11] To address limitations of the MIS and other language-based cognitive screeners,[10] we developed the PMIS that uses pictures. The PMIS minimizes educational bias, and expands the scope of dementia screening to low literacy populations. In our validation study in India,[1] the PMIS discriminated between cognitively normal older adults and those with dementia, regardless of age, sex, education or depression.[1]
The PMIS takes 4 minutes, which includes a minimum 2-minute delay period between picture presentation and recall. During this delay, another cognitive test can be given as an interference task, which prevents patients from using strategies such as mentally rehearsing items that may lead to false negative 'normal' performance. In the 5-Cog, we will fill the 2-minute interference period with the MCR diagnosis and paper-based Symbol Match Test. We developed highly reliable alternate forms of the PMIS, which enable repeated administration.[12] Professionals and non-professionals (health aides with 10 years schooling) successfully administered the PMIS in rural and urban populations in India and USA.[13, 14] High inter-rater reliability was seen between administration of PMIS by clinicians and nurses.[15] The PMIS picture items were administered on a computer screen

and using cards.[16] These findings support the feasibility of using the PMIS in various settings and by personnel with different levels of expertise.

Motoric Cognitive Risk Syndrome (MCR): Many pre-dementia syndromes based on cognitive tests or biomarkers have been proposed[17, 18] but their requirement for specialized equipment and medical professionals to conduct examination limits feasibility in resource-poor primary care settings. Increasingly, the simultaneous existence of motor and cognitive impairments has been recognized as an important clinical marker of brain pathologies. Hence, incorporating measures of motor function (gait speed) into dementia risk assessments may improve predictive power.[19] We described the MCR syndrome; characterized by cognitive complaints and slow gait.[4, 20] The MCR criteria are similar to those used for Mild Cognitive Impairment syndrome (MCI).[21, 22] We substitute the cognitive test criterion in MCI with gait speed in MCR, but retain the remaining MCI criteria (cognitive complaints and absence of dementia). *MCR diagnosis is easy to implement because it only requires verification of cognitive complaints and a stopwatch to measure gait speed over a fixed distance.*
In a multi-country study of over 26,000 persons aged 60 and older, MCR affected 1 in 10 participants.[20] Advancing age was associated with MCR but there were no sex differences in prevalence. Participants with MCR had a higher disease burden and performed worse on cognitive tests than non-MCR participants.[20] MCR was associated with a 70% increased risk of developing cognitive decline (on MMSE).[20] The association of MCR with cognitive impairment was robust even when the analysis was restricted to cognitively healthy adults (Mini-Mental State Examination scores ≥28), supporting MCR as a very early clinical marker of cognitive decline.[20] MCR diagnosis in older adults was associated with deficits in executive function, attention and language as well as overall cognitive status.[23] In 4 longitudinal cohort studies, participants with MCR were twice as likely to develop dementia, and were at 2.2 times the risk of developing Alzheimer's disease specifically.[20, 24, 25] MCR predicted dementia with greater accuracy than its individual components of either slow gait or subjective cognitive complaints.[20] Because MCR is diagnosed independently of cognitive tests, we avoid redundancy (diagnostic circularity) by not using the same tests to define both pre-dementia and dementia syndromes. In our multi-country study, clinical overlap between MCR and MCI cases was only 39%; indicating that the presence of either syndrome alone failed to identify a large pool of at-risk seniors.[2]
From a diagnostic perspective, MCR offers several benefits over other pre-dementia assessments. Gait speed has high reliability between different protocols,[26, 27] excellent validity in predicting health outcomes,[26, 27] and is recommended as a geriatric vital sign.[28] Non-professionals can easily be trained to measure gait speed in a minimal amount of time and without expensive equipment, making screening cheap and efficient in clinical settings. Hence, timing gait and asking brief cognitive questions to define MCR is practical and feasible in resource-poor settings, and can help streamline high-risk individuals for further investigations. The entry criteria for our study requires presence of cognitive complaints. Hence, MCR diagnosis procedure in the 5-Cog arm only requires measurement of timed gait over a fixed distance, and determination of slow gait using previously established cutscores in our population.

Paper-based Symbol Match Test: Match is a tablet-based test of executive functions and speed developed by the CCCT at University of California San Francisco (UCSF). Our team has created a paper-based version of the Symbol Match stimuli to act as a screening tool

which may identify patients with cognitive impairment who were not identified by the PMIS or MCR.

2.2 Study Rationale

Our group has two decades of experience developing tools to detect dementia in health disparate populations. Notably, we developed the PMIS, which is a brief cognitive screener that relies on culture fair pictures and does not need to be administered by a medical professional.[1] The PMIS demonstrated sensitivity of 95% and a specificity of 99% for detecting dementia in a low-literacy population in India.[1] We also validated the MCR diagnosis in multiple cohorts in many countries.[2-4] This highly accessible clinical test relies on the presence of slow gait and cognitive self-complaints to identify individuals at high risk of converting to dementia. Both the PMIS and the MCR are highly sensitive and specific first-line assays that can be followed up with more thorough and complex cognitive testing.[2-4]

Building on our work, we propose to validate a 5-minute screen (**5-Cog**) to identify persons with or at high risk of developing dementia, and to flag them for further evaluation. We propose to do this in multi-ethnic Bronx primary care populations with socio-economic challenges. The 5-Cog battery will include the PMIS, MCR syndrome diagnosis, and brief non-memory picture based test, Symbol Match.

The 5-Cog will sort out patients with or at high risk of developing 'cognitive impairment' from those with 'no cognitive impairment'. The 5-Cog battery will overcome many of the implementation barriers of previous cognitive screens;[13, 29, 30] it will be fast, low cost, easy to implement (requires only pen, paper and stopwatch), administered by non-clinicians (research assistants) after minimal training, not educationally or culturally biased, not confounded by depression and will not require informants.

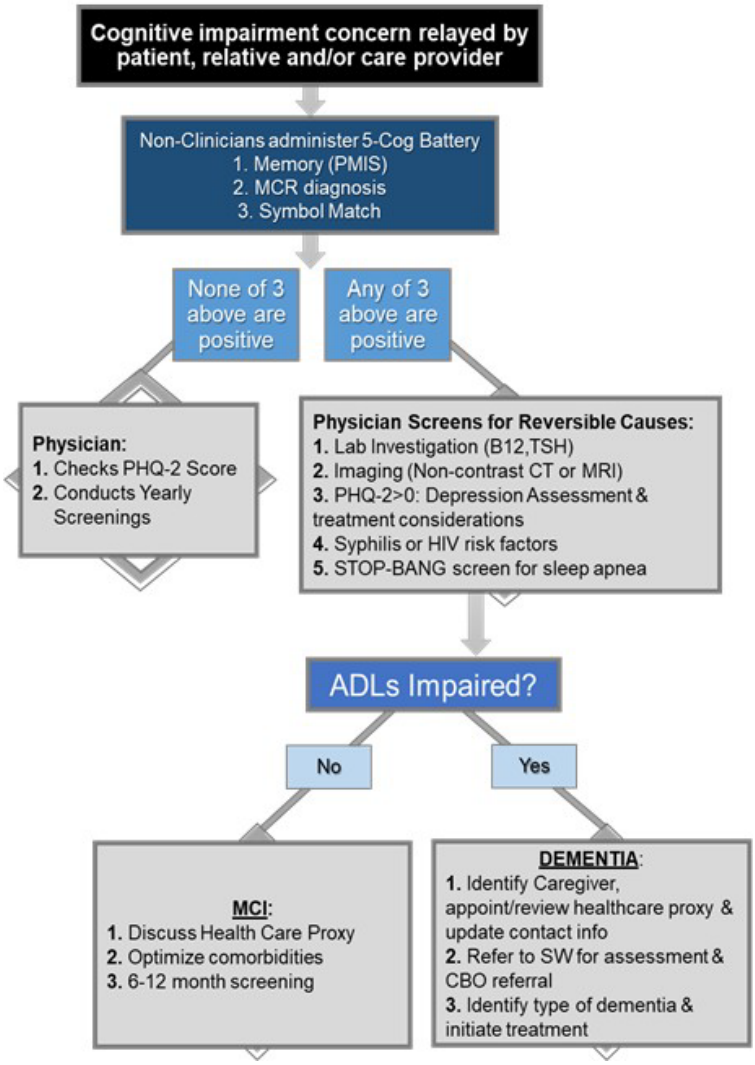
3 STUDY DESIGN

We propose to conduct a single-blind RCT to validate the 5-Cog battery and decision tree (Fig. 1). The trial will span 42 months and involve an ethnically diverse Bronx primary care population of 1,200 older patients with cognitive concerns (Fig. 2). We chose an active control (health literacy and grip) to balance time and tester exposure in the 5-Cog group. Our primary outcome is improved dementia care, which is an outcome that informs health decisions and is valued by primary care clinicians, older patients and their caregivers. We bring together an inter-disciplinary team with major aging and clinical trial experience. We have developed partnerships with clinicians in our primary care clinic site.

Design considerations: We will take a pragmatic, real world approach in our trial. We will not ask physicians to deny patients any procedures offered routinely. For instance, clinicians have access to the PMIS and other cognitive screeners (not included in the 5-Cog screen) in our EMR. We will not ask clinicians to avoid using these screeners in enrolled patients. But we will track cognitive screener use by clinicians in control and 5-Cog arms via the EMR. We hypothesize that time constraints and other barriers as well as the absence of the MCR and Symbol Match procedure in the EMR will limit use and efficacy of cognitive screeners by primary care physicians. The proportion of older women is higher than men in our clinics and aging studies.[3, 14, 31] Consistent with our pragmatic approach,

we will not strive for equal sex distribution within a study arm, but balance sex distribution by selecting gender as a stratification variable. There is no trial design without weakness and we will clearly state these in any publications.

Figure 1. 5-Cog Flow & Decision Tree



Recruitment: We will enroll 1,200 older patients with cognitive concerns (reported by patient or noted by caregivers or clinic staff) over 30 months; estimated enrollment rate is 8-10 per week. This enrollment rate conservatively assumes a >50% refusal rate from potentially eligible participants. Our enrollment rate in our pilot study at the same clinical site was about 6-8 per week when participants were asked to complete a longer battery of assessments. While we anticipate that many potential participants may be attending our primary care clinics for their Medicare Annual Wellness visit,[12] we will also recruit patients attending the clinics for other medical reasons. Montefiore Medical Center is the main healthcare system for Bronx county; one of the most ethnically diverse communities in the nation with an elderly population of 140,000 (U.S. census data). Patients age 65 and older account for >20,000 primary care visits at Montefiore annually; ensuring an adequate pool for recruitment. The non-clinician tester will approach all patients age 65 and over attending our primary care clinic sites. Those expressing interest will be screened at the same visit to determine eligibility. Information regarding demographics, socio-economic status and medical illnesses will be collected.

Primary Outcome: Our primary outcome is **improved dementia care**. This outcome is collected prospectively from EMR and related medical records by data analysts (blinded to study arm allocation and test results), and do not require patient interviews. This primary outcome is defined as meeting any one of the following endpoints within 90 days of the clinic visit at which the patient was randomized. Similar composite endpoints to define

dementia care have been used in several prior clinical trials in cognitively impaired patients.[32-36]

1. New diagnosis of dementia (relevant ICD-10 codes) or MCI (331.83) documented in the EMR. The recent DSM-V criteria[37] include categories of 'major neurocognitive disorder' and 'mild neurocognitive disorder,' which overlap with dementia and MCI. These categories will also be included but a recent internal audit indicated that they are as yet not in widespread use in our primary care clinics (cf. specialty clinics).
2. Tests ordered for reversible causes of cognitive impairment as recommended by the published guidelines of professional societies (e.g. thyroid function tests, B-12 level, CT or MRI scans).[15, 38-41]
3. New prescriptions for dementia medications in EMR.
4. Referral for cognitive/dementia evaluation by specialists (Neurology, Geriatrics or Psychiatry) in EMR.

Secondary/exploratory outcomes: Health care utilization data (*secondary outcome*) is abstracted from EMR. Additional tests (described below) take approximately 60 minutes of participants' time. To avoid interrupting clinic flow, these tests will be done at the same visit as the enrollment, but after the patient sees their clinician. These tests are *exploratory outcomes* used to generate new hypotheses or provide insights into 5-Cog efficacy.

a) **Health care utilization (secondary outcome).** Utilization (emergency room visits and hospitalizations) for patients in both arms will be tracked up to 12 months from the clinic visit at which the patient was randomized and reviewed at regular intervals by data analysts throughout the study period. The data analysts will have no participant contact and be blinded to study assignment. The EMR system is in place in our institution. All visit notes and diagnoses are to be entered within 48 hours of the encounter. A series of electronic reminders is sent to clinicians to complete delinquent entries. Patients in both arms will be covered by risk or shared savings reimbursement arrangements Montefiore has with private health insurance companies or will be fee-for-service Medicare beneficiaries attributed to the Montefiore Next Generation Accountable Care Organization.[42-44] Montefiore either processes or has access to claims data for these patients, enabling analysis of encounters and costs through the Montefiore EMR and reports received monthly from CMS. The detailed claims-level data will allow for tracking and analysis of the utilization of numerous healthcare services. A significant amount of data on care and services that patients receive from providers outside of Montefiore will also be available for inclusion in our analyses.

b) **Neuropsychological Battery (exploratory outcome):** The battery will take 60 minutes to complete and will include the measures below (Table 1). The tests are selected from those used for diagnostic testing in our dementia clinic, and with established norms for different ethnic groups and educational levels.[14] The battery will be supervised by Dr. Weiss (Cognitive Core); blinded to 5-Cog results. The battery is administered in English or Spanish to probe general mental status (MoCA) as well as specific cognitive domains, particularly memory (Hopkins Verbal Learning Test-R[45]), processing speed (Symbol Digit Modalities Test[46]), language (letter fluency,[47, 48] category fluency,[48] Boston Naming Test[48]), and visuo-spatial abilities (clock drawing[12]).[49] *For ethical reasons, if results from the neuropsychological testing are in the dementia range, Dr. Weiss will inform the treating physician after the 90-day window to determine improved dementia care outcomes.*

Table 1. Neuropsychological Assessments

Domain	**Tasks**
Mental Status	MoCA
Premorbid Estimate/ Reading ability	Wechsler Test of Adult Reading (WTAR)/ Word Accentuation Test (TAP)
Memory	Hopkins Verbal Learning Test- R(HVLT-R)
Naming	Boston Naming- Short Form
Fluency	Controlled Oral Word Association Test (FAS); Animals
Timed Transcription	Symbol Digit Modalities Test
Clock	Clock Drawing Test
Mood	Geriatric Depression Scale-30 item

c) **Advance care planning (exploratory outcome):** We will explore whether 5-Cog screening leads to higher rates of advance care planning such as referrals to social work or Alzheimer's Association or having health care proxies or living wills recorded in the EMR.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

Our target population is seniors with cognitive concerns in primary care clinics. While we anticipate that many potential participants might be attending Medicare Annual Wellness visit, we will also recruit eligible patients who will be attending the primary care clinic for other medical reasons.

4.1 Inclusion Criteria

1) Age 65 and older. **2**) Presence of cognitive concerns expressed by patient or caregiver or identified by health care providers. **3)** Registered as patient at Montefiore Medical Center and have a primary care doctor appointment that day. **4)** Able to see and hear well enough to complete intervention or control assessments. **5)** English or Spanish speaking.

4.2 Exclusion Criteria

1) Prior diagnosis of dementia or MCI as ascertained by ICD-10 codes or the presence of prescription for anti-dementia medications (cholinesterase inhibitors or Memantine) in EMR. Patients with a diagnosis containing any of the following terms will be excluded:

a. "Dementia"
b. "Mild Cognitive Impairment"
c. "Alzheimer's Disease"
d. "Creutzfeldt-Jakob Disease"
e. "Major Neurocognitive Disorder"
f. "Minor Neurocognitive Disorder"

Patients with any of the following medications documented in their EMR will be excluded (generic = brand):

a. Donepezil = Aricept
b. Memantine = Namenda
c. Rivastigmine = Exelon
d. Galantamine = Razadyne
e. Donepezil and Memantine = Namzaric

2) Adults who are permanent residents of a nursing facility.
3) Patients who do not speak English or Spanish.
4) Patients who are not seeing a primary care physician at the clinic that day.
5) Patients who are blind, deaf or cannot hear loud voice even with hearing aids.

Recruitment, enrollment, and participation of participants in this project are not limited by gender, skin color, racial/ethnic group, or economic status. We will monitor recruitment and retention patterns to ensure adequate representation of women and minorities. Since this study focuses exclusively on geriatric syndromes, it will not include children.

4.3 Study Enrollment Procedures

Potential participants may be referred by the clinic staff to the non-clinician research assistant (RA) by a message sent in the EMR, a phone call to the RA or by approaching the RA in person. Once a referral is received the RA will review the patient's electronic medical records or medical chart to determine their eligibility for participation based on the criteria above. Next, they will locate the patient within the clinic by asking the clinic staff to identify the patient.

Potential participants may also be identified by reviewing the daily clinic schedule on the electronic clinic schedule calendar. The RA will review all patients' charts that are ≥65 years and older with an appointment at the clinic that day to determine their eligibility based on the criteria described above. Next, they will locate the patient within the clinic by asking the clinic staff to identify the patient.

After identifying the patient referred by a clinic staff member the RA will confirm the cognitive complaint. Before offering a patient enrollment in the study, the RA will ensure that they (or their family member or friend, or a clinic staff member) have a cognitive complaint or concern about them. This information will be recorded in the database.

If the potential participant was identified by the RA from the daily schedule and determined to be eligible based on criteria from the EMR, the RA will greet the patient and say "I am X, and I am a RA. We are conducting a research study here at the clinic." The RA will give a study flyer to the potential participant and say, "Would you mind please reviewing this flyer and answering the questions on it? I will give you a few minutes, and will come back to review it with you. Do you have any questions, or problems reviewing

Flyer Questions:
"Are you concerned about your memory?"
Yes ☐ No ☐
"Are your loved ones concerned about your memory?"
Yes ☐ No ☐

this flyer?" If the patient is there with family or friends, the RA can encourage the patient to let their family or friend review it with them if they are comfortable.

If the patient says or marks "Yes" to either of the questions on the flyer OR was referred to you by another source because of concerns about their memory or cognition, say, "It looks like you may be eligible for our study. We are conducting a research study to validate a new cognitive screening tool. If you are interested in participating in the study, I will ask you to complete some tasks that involve memory, health and mobility. You will receive a total of $10 for completing the 5-minute assessment before seeing your doctor. In addition, to the 5-minute assessment before seeing your doctor, if you are interested in completing a 60-minute cognitive assessment after you see you doctor we will pay you an additional $10. Are you interested in participating?"

Those expressing interest should be invited to come to the research office to complete the informed consent, randomization and the assessments.

COVID-19 amendment to enrollment and recruitment procedures: In response to the COVID-19 pandemic the recruitment process described above will be conducted over the telephone rather than in person. Below are descriptions of the study enrollment and recruitment procedures for the various recruitment and enrollment pathways.

Instead of the RA recruiting the participant through the flyer at the clinic waiting room, the RA will reach out to the participant over the phone on the day before their appointment to tell them about the study, screen them and conduct informed consent (see section 6.2 for details). The RA will ask the same questions as are on the flyer to potential participants over the telephone on the day before their appointment.

In a case where the patient was identified to the RA by a clinic staff member or physician, the RA will screen them for eligibility through their medical chart and if they have an appointment scheduled, they will reach out to the patient on the day before their appointment to tell them about the study, screen and conduct the verbal informed consent.

5 STUDY INTERVENTIONS

5.1 Interventions & Administration

Intervention arm (5-Cog): The 5-Cog battery coupled with a decision tree is a simple, 5-minute procedure that will identify older persons with cognitive impairment in primary care settings, and flag them for further evaluation. The 5-Cog battery includes the PMIS,[1] MCR diagnosis,[2-4] and the paper-based Symbol Match Test. The 5-Cog battery will be given after randomization and before the patients sees the physician. After completing the 5-Cog screening, the tester will send a message through the EMR system to provide 5-Cog results and a decision tree to the treating physician. The cognitive assessment algorithm will sort patients with 'cognitive impairment' from those with 'no cognitive impairment'.

Active control: Participants randomized to the active control will receive a health literacy questionnaire and grip strength assessment to match time (5 minutes), tester exposure, and gait assessment procedure in the 5-Cog arm. The Short Assessment of Health Literacy (SAHL) has comparable tests in English and Spanish, with good reliability and validity.

Participants are presented with 18 test items. For each term, a key word with related meaning and a distractor word unrelated in meaning to the test term are presented. This tests the participant's comprehension as well as pronunciation of health-related terms. The test takes 3 minutes and requires minimal training. Grip strength is measured in dominant hand with a Jamar handgrip dynamometer.[50-52] Grip strength is a validated health indicator in aging.[50-52] Low grip strength is a component of frailty definitions and predicts disability.[50-52] To parallel the study procedures and flow in the 5-Cog arm, a decision tree will be created. Results and the decision tree will be sent to the physicians through the EMR system at the same visit.

5.2 Handling of Study Interventions

The tester will obtain informed consent, prior to randomizing patients to either the 5-Cog or control interventions. We will follow the example of other pragmatic clinical trials of dementia screening in primary care clinics[53] by randomizing at the patient level rather than at the level of providers or clinics. This will minimize effects of unmeasured case mix differences and clinic-level clustering. As noted by Fowler et al,[53] the risk for **"**spillover**"** from having participating primary care clinics treat both intervention and usual-care patients is likely to be small given low levels of dementia detection.[54] The patient-based randomization should conservatively bias results in favor of usual care. Dr. Wang (Statistics Core) will computer-generate a randomized block design which will be used to assign study identification numbers and place patients into either 5-Cog or control groups.

The IRB requires us to disclose the tests to participants in both study arms; therefore, it is not feasible to blind patients. Participants and the RA who carries out the 5-Cog or health literacy and grip strength assessments are not blinded to group assignment. However, investigators, data analysts collecting outcome data of improved dementia care, and the statistician remain blinded to individual assignments.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

We will not ask physicians to deny patients any procedures offered routinely. Clinicians have access to the PMIS and other cognitive screeners in the EMR. We will not ask clinicians to avoid using these screeners in enrolled patients. But we will track cognitive screener use by clinicians in control and 5-Cog arms via the EMR.

5.3.2 Required Interventions

Not applicable

5.3.3 Prohibited Interventions

Patients with any of the following medications documented in their EMR prior to enrollment will be excluded (generic = brand):

a. Donepezil = Aricept
b. Memantine = Namenda
c. Rivastigmine = Exelon
d. Galantamine = Razadyne
e. Donepezil and Memantine = Namzaric

5.4 Adherence Assessment

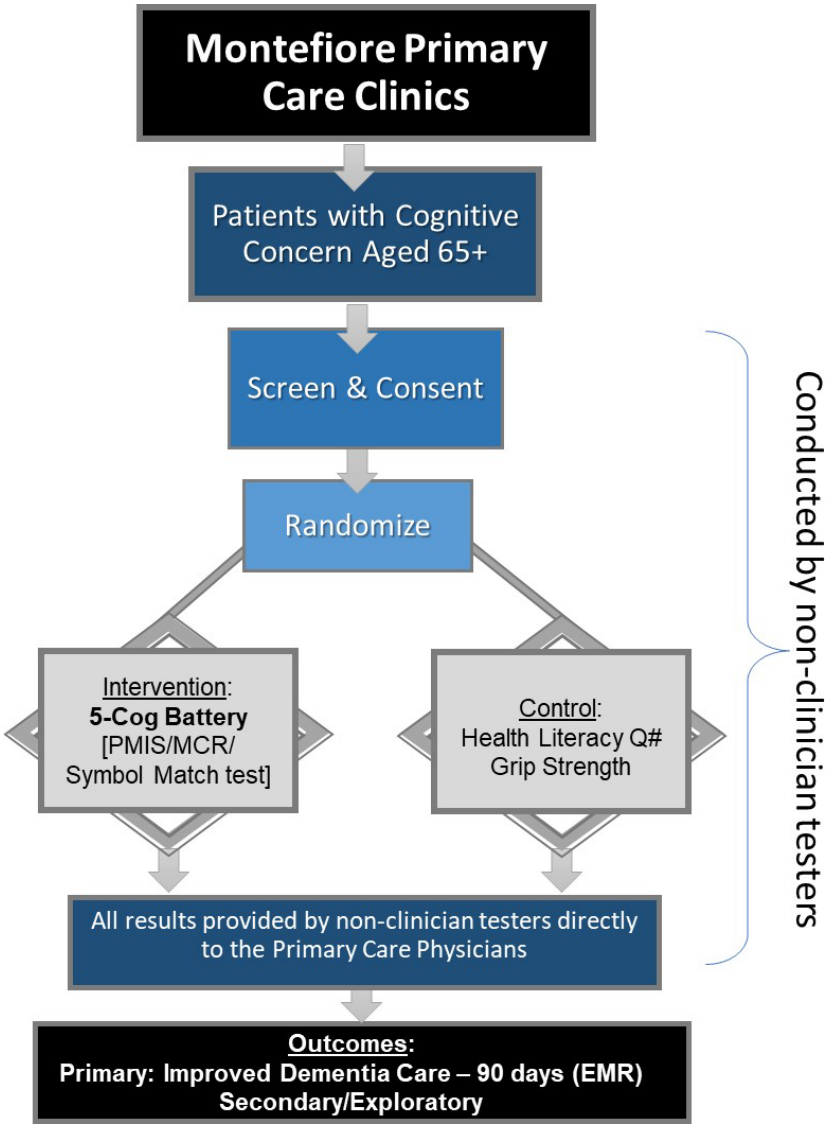
Our primary outcome is based on information from EMR on Bronx-based patients receiving primary care in our institution. This will minimize missing data issues. We will aggressively implement data management processes (supervised by the Data Core). The goals of data management are to ensure (a) data collected during the study are properly and accurately entered and documented, (b) data are stored in an electronic format that allows easy retrieval and exportation, and c) participant confidentiality. The study programmer in collaboration with the statistician manages the data. They will work with other Data and Statistical Core team members to correct identified issues and conduct quality audits of database.

We realize that not all patients will complete all of the additional tests for exploratory outcomes. However, our sample of 1,200 participants is a sufficient pool to conduct sensitivity analyses for exploratory outcomes even assuming a refusal rate of 50% for some or all of these additional tests used for secondary and exploratory outcomes.

6 STUDY PROCEDURES

6.1 Schedule of Evaluations

Figure 2. Study Flow


Montefiore Primary Care Clinics
Patients with Cognitive Concern Aged 65+
Screen & Consent
Randomize
Intervention:
5-Cog Battery
[PMIS/MCR/
Symbol Match test]
Control:
Health Literacy Q#
Grip Strength
All results provided by non-clinician testers directly to the Primary Care Physicians
Outcomes:
Primary: Improved Dementia Care – 90 days (EMR)
Secondary/Exploratory
Conducted by non-clinician testers

6.2 Description of Evaluations

6.2.1 Screening Evaluation

The RA will review all patients' charts that are ≥65 years and older with an appointment at the clinic on the following day to determine their eligibility based on the criteria described above. Next they will reach out to the patient over the telephone.

After identifying the eligible patients the RA will confirm that they have an appointment on the following day and describe the study to them and ask them if they would be interested in participating. If interested, the RA will confirm the cognitive complaint. Before offering a patient enrollment in the study, the RA will ensure that they (or their family member or friend, or a clinic staff member) have endorsed a cognitive complaint or expressed concern about them.

Consenting Procedure

Those with cognitive complaints, expressing interest in the study will be invited to participate at their appointment on the following day. Consent will be obtained from participants through a verbal consent process prior to enrollment. The non-clinician tester will obtain verbal consent over the telephone prior to the patient coming to the clinic for their appointment when they will also be randomized and receive the study assessments.

The consent script describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the script can be given to each participant and this fact will be documented in the participant's record. Language in the consent form will describe data sharing. For example, *"We will store information about you in a "bank", which is a library of information from many studies. This information cannot be linked to you. In the future, researchers can apply for permission to use the information for new studies to prevent, diagnose, or treat disease. Your information may be kept for a long time, perhaps longer than 50 years. If you agree to the future use, some of your de-identified health information (not linked to you) may be placed into one or more scientific databases. These may include databases maintained by the federal government."*

6.2.2 Randomization & Assessments

Randomization

The tester will obtain informed consent, prior to randomizing patients to either the 5-Cog or control interventions. We will follow the example of other pragmatic clinical trials of dementia screening in primary care clinics[53] by randomizing at the patient level rather than at the level of providers or clinics. This will minimize effects of unmeasured case mix differences and clinic-level clustering. As noted by Fowler et al,[53] the risk for **"**spillover**"** from having participating primary care clinics treat both intervention and usual-care patients is likely to be small given low levels of dementia detection.[54] The patient-based randomization should conservatively bias results in favor of usual care.

Dr. Wang (Statistics Core) will computer-generate a randomized block design which will be used to assign study identification numbers and place patients into either 5-Cog or control groups. Patients will be stratified by gender and age (< or >75 years). Briefly, an encrypted file containing the group assignment is prepared for each study identification number. The file is stored in RedCap the database program used for this trial. The assignments are presented to the RA in sequential order at the time the participant is enrolled, following the eligibility assessment, and administer the indicated screen. Participants and the RA who administers the tests are not blinded to group assignment. However, investigators, data analysts collecting outcome data, and the statistician remain blinded to individual assignments.

Assessments

Intervention arm (5-Cog): This simple, 5-minute procedure will identify older persons with cognitive impairment in primary care settings, and flag them for further evaluation. The 5-Cog battery includes the PMIS, MCR diagnosis,[6-8] and the paper-based Symbol Match test. Our cognitive assessment algorithm will sort patients with or at high risk of developing 'cognitive impairment' from those with 'no cognitive impairment'. Moreover, it is coupled with a decision tree to guide clinicians through the necessary steps to follow up on 5-Cog results. Because primary care clinicians and staff may not have the time to complete even a 5-minute screen,[12, 15, 16] non-clinicians (RAs) will administer the 5-Cog and communicate the results to primary care physicians for further action.

Active control: Participants randomized to the active control will receive a health literacy questionnaire and grip strength assessment to match the time (~5 minutes), tester exposure, and gait assessment procedure in the 5-Cog arm. The SAHL has comparable tests in English (SAHL-E) and Spanish (SAHL-S), with good reliability and validity in both languages. Participants are presented with 18 test items. For each term, a key word with related meaning and a distractor word unrelated in meaning to the test term is presented. This tests the participant's comprehension as well as pronunciation of health-related terms. The test takes 3 minutes to complete and requires minimal training. Grip strength is measured in dominant hand with a Jamar handgrip dynamometer.[50-52] Grip strength is a validated health indicator in aging.[50-52] Low grip strength is a component of frailty definitions and predicts disability.[50-52] To parallel the study procedures and flow in the 5-Cog arm, a decision tree will be created. Results and the decision tree will be presented to the physicians at the same visit.

Additional Assessments: In order to avoid interrupting the normal clinic flow, these additional assessments, which will be used as covariates or exploratory outcomes in our analyses, will be done following the clinician's assessment of the patient. These exploratory measures will help us generate and test new hypothesis and provide insights into the effects of the 5-Cog battery. We realize that not all patients will be able to complete part or all of the tests due to other commitments. Nonetheless, our overall sample size of 1,200 participants provides a sufficient pool assuming a non-completion rate of 50%.

a. Patient characteristics: Demographic, socio-economic status and medical illness

burden.
b. Neuropsychological battery – due to safety concerns with in person visits, as of July 27th, 2020 participants will be offered the opportunity to complete the neuropsychological evaluation over the phone or via video conference.

6.2.3 Outcome assessment

Our primary outcome is **improved dementia care**. This outcome is collected prospectively from EMR and related medical records by data analysts and do not require patient interviews. This primary outcome is defined as meeting any one of the following endpoints within 90 days of the clinic visit at which the patient was randomized.

1. New diagnosis of dementia (relevant ICD-10 codes) or MCI (331.83) documented in the EMR. The recent DSM-V criteria[37] include categories of 'major neurocognitive disorder' and 'mild neurocognitive disorder,' which overlap with dementia and MCI. These categories will also be included but a recent internal audit indicated that they are as yet not in widespread use in our primary care clinics (cf. specialty clinics).
2. Tests ordered for reversible causes of cognitive impairment as recommended by the published guidelines of professional societies (e.g. thyroid function tests, B-12 level, CT or MRI scans).[15, 38-41]
3. New prescriptions for dementia medications in EMR.
4. Referral for cognitive/dementia evaluation by specialists (Neurology, Geriatrics or Psychiatry) in EMR.

7 SAFETY ASSESSMENTS

Participant safety will be monitored once an individual is enrolled in the study. We do not expect any serious adverse events during the non-invasive assessments that will take place in both study arms. Answering health questionnaires and cognitive assessments involve minimal psychological, social, or other risks.

7.1 Specification of Safety Parameters

Trained RAs, who will monitor the subject for any adverse events, will perform all assessments. The RA will stop the testing procedures if subjects feel stressed or get embarrassed by their performance, and relay the information immediately to Dr. Verghese or one of the supervising clinicians (Drs. Chalmer, Ansari, Ehrlich, or Zwerling). In addition, Dr. Chalmer and Dr. Ansari will be available at the clinic site during the conduct of the trial, and Dr. Verghese will be available by cellular telephone at all times to address any safety concerns or clinical issues.

All abnormal findings from the clinical, motor, and neuropsychological assessments will be documented and the participant and their primary care physician will be informed of all clinical results that are relevant to patient care following the 90 day window for primary outcome ascertainment.

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

7.3 Adverse Events and Serious Adverse Events

Adverse Events (AEs): Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. AEs encompass both physical and/or psychological harms.

Serious Adverse Events (SAEs): An adverse event that meets any of the following criteria:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires prolonged hospitalization
- Causes persistent or significant disability or incapacity
- Is another condition which investigators judge to represent significant hazards

7.4 Reporting Procedures

AE Reporting: All AEs will be collected on an Adverse Event Form in electronic format and recorded in the RedCap database. All AEs experienced by the participant will be reported in Safety Reports sent twice a year to the NINDS Program Official.

SAEs Reporting: When SAEs occur that are unanticipated (i.e., events other than those described in the protocol, consent form and DSMP), and that are related to the intervention, they will be reported to NINDS Program Officer within 48 hours of study's knowledge of the SAE. The expedited report will be followed by a detailed, written SAE report as soon as possible. Follow up information may be required.

Relatedness: The potential event relationship to the study intervention and/or participation is assessed by the site investigator. The comprehensive scale to categorize an event is listed below:

- Definitely Related: The AE is clearly related to the investigational procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
- Possibly Related: An AE that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
- Not Related: The AE is clearly not related to the investigational procedure - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

Expectedness: AEs must be assessed as to whether they were expected to occur or unexpected, meaning not anticipated based on current knowledge found in the protocol and the consent form. Categories are:

- Unexpected: The nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol or consent form.
- Expected: The event is known to be associated with the intervention or population under study.

Classification of AE Severity:

- Mild: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient – i.e. no doctor visit or medical treatments were required.
- Moderate: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning – i.e. minimal medical treatment was needed, possible doctor visit or physical therapy.
- Severe: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating – i.e. medical attention was required, possible hospitalization.

Note: Severity is not synonymous with seriousness. SAEs are a subset of the reported AEs.

7.5 Follow-up for Adverse Events

AEs will be followed until the participant discontinues the study.

7.6 Safety Monitoring

Prior to beginning data collection, we will convene an internal safety monitoring committee who will be responsible for monitoring participant safety and study progress. The committee will be comprised of investigators on the project team. Before beginning recruitment, Dr. Verghese and the safety committee will reconfirm that our sites have appropriate safety measures in place. The internal safety monitoring committee will meet with the entire research team to review the study protocols. Particular attention will be paid to outcome definition, study design, procedures for recording and reporting adverse events, informed consent procedures and documentation.

At the initial meeting, the internal safety monitoring committee may recommend modifications or clarification of the protocol, and it will formulate its operating procedures (e.g., meeting schedule, reports due dates for the study statistician, unblinding policy, and what interim data may be released to the investigators). At the initial meeting the plans for interim monitoring for efficacy and futility will be presented to the internal safety monitoring committee as an aid for monitoring the trial.

We will train competent staff to conduct the assessments, ensure they understand the data collection procedures and process, and understand adverse event reporting requirements.

Trained clinical assistants, who will monitor the subject for any adverse events, will perform all assessments. We do not expect any serious adverse events during these non-invasive interventions. The clinical assistant will stop the testing procedures if subjects feel stressed or get embarrassed by their performance, and relay the information immediately to Dr. Verghese or one of the supervising clinicians (Drs. Chalmer, Ansari, Ehrlich, or Zwerling). In addition, Dr. Ansari and/or Dr. Chalmer will be available at the clinic site during the conduct of the trial, and Dr. Verghese will be available by cellular telephone at all times to address any safety concerns or clinical issues.

8 INTERVENTION DISCONTINUATION

Subjects may withdraw voluntarily from participation in the study at any time and for any reason. However, participants will continue to be followed, with their permission, as long as they completed the 5-Cog or health literacy and grip strength assessments.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

We propose to conduct a single-blind RCT to validate the 5-Cog battery coupled with decision tree in an ethnically diverse Bronx primary care population of 1,200 older patients with cognitive concerns. We chose an active control (health literacy and grip) to balance time and tester exposure in the 5-Cog arm. Our primary outcome is improved dementia care.

Primary Outcome: The primary outcome is improved dementia care, defined as meeting any one of the following endpoints within one month of the clinic visit at which the patient was randomized.

1. New diagnosis of dementia (relevant ICD-10 codes) or MCI (331.83) documented in the EMR. The recent DSM-V criteria include categories of 'major neurocognitive disorder' and 'mild neurocognitive disorder,' which overlap with dementia and MCI. We will track these diagnoses but not use these solely to define the outcome as they are as yet not being widely used as diagnostic or billing codes in our primary care sites.
2. Tests ordered for reversible causes of cognitive impairment as recommended by published guidelines of professional societies (e.g. thyroid function tests, B-12 level, CT or MRI scans).
3. New prescriptions for medications for dementia or MCI indications in EMR.
4. Referral for specialist evaluation for cognitive impairment (Neurology, Geriatrics or Psychiatry) in EMR.

9.2 Sample Size and Randomization

This randomized study has 600 subjects for each of the 2 groups. Assuming a non-completion rate of EMR entries of 10% over 90 days and that 25%, 30% or 35% of control subjects will experience 'improved dementia care,' we can detect odds ratios of 1.46, 1.43 or 1.42, respectively, on the effect of 5-Cog on improving dementia care with 80% power using a two-sided test with significance level of 0.05. There is a paucity of studies examining efficacy of brief cognitive screens in primary care. One non-randomized trial of

screening by medical assistants coupled with a decision tree in primary care clinics showed new physician action in 17% of patients with a positive screen in intervention sites compared to 1% in control sites. [36] Action included new dementia diagnosis, referral to specialist or initiating dementia treatment (similar to our primary outcome). While our projected effect size used for sample size estimation is conservatively lower than that reported in this previous study,[36] the effect size from this previous study was not used to calculate power given its preliminary, non-randomized nature but is presented in support of our assumptions. A review of 8 studies of detection of mild dementia in primary care showed that sensitivity ranged from 9% to 41%.[55] Detection rates in clinics are even lower for earlier dementia stages such as MCI.[56] These observations support our assumptions of lower rates of improved dementia care in our control group.

Cohort retention: This is not a major issue for this RCT as primary outcomes are based on clinical encounters information collected from EMR and other administrative data sources in patients residing in Bronx County and receiving primary care in our institution. Also, primary outcomes do not require repeat in-person testing after baseline assessments.

- *Non-completion:* We realize that not all patients will complete the additional tests described above as covariates or exploratory outcomes. We will complete as many of the tests as possible depending on patients' availability. Nonetheless, our overall sample size of 1,200 participants provides a sufficient pool to conduct sensitivity analyses assuming non-completion rate of 50%.
- *Over- or under-detecting cognitive impairment:* Given the high sensitivity and validity of 5-Cog procedures for dementia detection, we do not expect under-detection to be a major issue. We will set PMIS cutscores to maximize sensitivity and will improve cognitive concern ascertainment. A major consequence of over-detection is the strain on limited primary care resources resulting from more dementia assessments. Our decision tree provides guidance to primary care physicians regarding next steps in cognitively impaired patients. Red flags are built within our decision tree to channel patients for specialist evaluations. These steps were developed in consultation with our primary care partners. We will carefully monitor clinical, logistical and economic impact of introducing 5-Cog in our primary care sites, and make any necessary system changes to optimize clinical encounters. It is encouraging that introducing PMIS into our local EMR has not resulted in significant bottlenecks or overburdening specialists. We have also not observed any significant bottlenecks or negative feedback from primary care staff regarding implementing the first phase of the 5-Cog battery at our site.

9.2.1 Treatment Assignment Procedures

Patients will be assigned to screening using stratified block randomization. Dr. Wang, who is not involved in subject testing or interventions will generate a computerized block randomization scheme to assign study identification numbers to either 5-Cog or control arms. Patients will be stratified by gender and age (< or >75 years). Briefly, an encrypted file containing the group assignment is prepared for each study identification number. The file is stored in RedCap the database program used for this trial. The assignments are presented to the research assistants (RA) in sequential order at the time the participant is enrolled, following the eligibility assessment, and

administer the indicated screen. Participants and the RA who administers the tests are not blinded to group assignment. However, investigators, data analysts collecting outcome data, and the statistician remain blinded to individual assignments.

9.3 Interim analyses and Stopping Rules

Due to the non-invasive nature of the protocol, it is not expected that early termination will be required due to adverse events. However, constant monitoring of the participants by Dr. Verghese, other investigators, and research staff will be maintained to ensure that AEs are not occurring. Early study termination will occur in the event of any unanticipated serious adverse event determined to be possibly, probably or definitely related to study procedures.

9.4 Outcomes

9.4.1 Primary outcome

Our primary outcome is **improved dementia care**. This outcome is collected prospectively from EMR and related medical records by data analysts (Administrative & Statistics Cores) and do not require patient interviews. This primary outcome is defined as meeting any one of the following endpoints within 90 days of the clinic visit at which the patient was randomized. Similar composite endpoints to define dementia care have been used in several prior clinical trials in cognitively impaired patients.[32-36]

1. New diagnosis of dementia (relevant ICD-10 codes) or MCI (331.83) documented in the EMR. The recent DSM-V criteria[37] include categories of 'major neurocognitive disorder' and 'mild neurocognitive disorder,' which overlap with dementia and MCI. These categories will also be included but a recent internal audit indicated that they are as yet not in widespread use in our primary care clinics (cf. specialty clinics).
2. Tests ordered for reversible causes of cognitive impairment as recommended by the published guidelines of professional societies (e.g. thyroid function tests, B-12 level, CT or MRI scans).[15, 38-41]
3. New prescriptions for dementia medications in EMR.
4. Referral for cognitive/dementia evaluation by specialists (Neurology, Geriatrics or Psychiatry) in EMR.

9.4.2 Secondary outcomes

Health care utilization (emergency room visits and hospitalizations) for patients in both arms will be tracked up to 12 months from the clinic visit at which the patient was randomized and reviewed at regular intervals by data analysts throughout the study period. The data analysts will have no participant contact and be blinded to study assignment. The EMR system is in place in our institution. All visit notes and diagnoses are to be entered within 48 hours of the encounter.

9.5 Data Analyses

We will examine data for potential outliers and analyze the robustness of our findings

against them. We will perform per-protocol analysis to assess the sensitivity of our findings to protocol deviations. Furthermore, the impact of baseline imbalance will be determined by comparing the analysis outcomes with and without controlling for baseline attributes. Chi-square test will be used to compare 'improved dementia care' outcome within 90 days post-intervention between the intervention and control groups. Logistic regression model adjusted for covariates will also be used. We will use **intention to treat analysis**.[57] Pre-specified baseline covariates to account for **confounders** in the planned analysis include age, gender, education, and chronic illnesses. Baseline distribution of covariates will be compared to assess adequacy of randomization. We do not discount residual/unmeasured confounding – though this is more of an issue in observational studies without randomization. We will report adjusted and crude estimates of associations to assess confounding, and discuss limitations of the study.

Primary outcome: Chi-square test will be used to compare 'improved dementia care' outcome within 90 days post-intervention between the intervention and control groups. Logistic model adjusted for covariates will also be used.

Heterogeneity of treatment effect (HTE) is the nonrandom, explainable variability in the direction and magnitude of treatment effects for individuals within a population. The main goals of HTE analysis are to estimate treatment effects in clinically relevant subgroups and to predict whether an individual might benefit from a treatment. In this RCT, we will specifically address HTE due to gender (male/female), ethnicity (African-American/Hispanic/Caucasian) and education (less than high school/ high school graduate). Treatment effects in these subgroups will be evaluated using stratified analysis. Alternative, an interaction term between the subgroup characteristic and treatment group will also be tested.

Secondary outcome: Utilization is defined in terms of specialty visits, emergency room visits, and hospitalizations up to 12 months following the screening visit. This will be tracked via the EMR in both groups. The rates of utilization will be compared between the two groups using analytical approaches described for the primary outcome. We will also compare 'days free of utilization' (number of days from screening to first episode of health care utilization over follow-up) in both groups using linear mixed effect and survival models.[58, 59]

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

During the initial phase, the database programmer will work closely with the project manager to establish a centralized database and archiving system. Data collection of baseline assessments by the research assistants is in-person and entered in real time into the centralized database which will be programmed using RedCap. This system has automated checks for ranges of values and logical validity of data entered and imports subject data directly from the computerized test data files. This system provides immediate access to individual subject data and can generate a summary report of the entire database. The database programmer will also work with the EMR programmer and data analyst to integrate data collected from the EMR system with study data.

ATLAS, a modern data platform to use clinical and health data from Montefiore patients, will also be used to export clinical data for outcomes and integrated with RedCap data. The EMR systems programmer will develop reports to easily export relevant data from the EMR system to provide to the EPIC systems data analyst. The analyst will check exported data files for data integrity and flag in the event of inconsistent or missing data.

Forms or screens will be designed to meet the data collection needs, applying standards for the structuring of variables to permit the pooling of shared/common variables across the consortium. The database manager will develop a data entry/management system so that the interviewers can not only enter the data directly into the computer during the interview, but they can also run reports and compute scores during the interview if need be. Data collected from both methods will be integrated by the database programmer and stored in the centralized database.

10.2 Data Management

The project manager will have day to day responsibility for data management, cleaning and quality checks, with consultation from Dr. Wang. The project manager will serve as primary point of contact for data entry and management needs.

The Statistical Core will work with the Data Management Core on the structure of spreadsheets and data tables containing endpoint data to facilitate the merging of such data with clinical assessment data.

Hard copies of documents will also be maintained by the Data Management Core and subjected to quality control procedures. A codebook will be maintained that contains variable names, labels and values for all variables collected. As clean data are accumulated, the project manager will re-run data editing programs periodically as a final quality control check. Any inconsistencies identified will be validated with the original source and stored in report form for evaluative purposes. From the cleaned data, data sets will be compiled for analysis purposes. Data sets will be frozen on a semi-annual basis by the statistical team. As projects are completed (closed), cleaned data sets, their data dictionaries, and their command files and output files will be archived.

The exchange of data across the consortium will be reviewed by the Data Sharing and Harmonization Committee of the Cross-Consortium Coordinating Team (CCCT) and handled by the Analysis Committee so that files from different studies are merged properly and contain only data that have been double entered and verified (see Section 13 for details of committees).

Data sharing: A data sharing agreement with collaborators at Northwestern University will account for sharing data across sites which include the following data elements:

Demographic information, including all elements (except years) of dates related to an individual (including birthdate, admission date, discharge date, date of death, and exact age if over 89)

Data extracted from EHR

Financial data about care linkable to clinical data using pseudo IDs

Healthcare utilization data

10.3 Quality Assurance

10.3.1 Training

We will train competent staff to conduct the interventions and assessments, ensure they understand the nature of the interventions, and understand adverse event reporting requirements. All study staff will take the Safety Training Class, an online training venue that provides an overview of human subjects safety surveillance and reporting requirements in clinical research studies. The intent of the course is to help clinical study investigators and staff understand and implement NIA and regulatory requirements for safe, high quality clinical research. The topics covered include Good Clinical Practice, Human Subject Protections, Adverse Events and Unanticipated Problems, Safety Monitoring and Reporting Requirements, Safety Monitoring and Oversight: DSMPs and Safety Officers, Regulatory Requirements and Responsibilities of PIs, and Data and Safety Monitoring Plans (DSMP).

They will also all successfully complete the required CITI training courses.

10.3.2 Metrics

The outcomes are collected prospectively from the EMR and related sources by study data analysts and do not require patient interviews. Data analysts who ascertain outcomes will have no participant contact and will be blinded to study assignment. The EMR system is in place in our clinic and hospital settings, and all aspects of clinic visits, emergency room visits or hospitalization in Montefiore Healthcare system are captured. All visit notes and diagnoses are to be entered within 48 hours of the encounter. A series of reminders are send to clinicians via EMR to complete delinquent entries.

10.3.3 Protocol Deviations

Protocol deviations will be documented and reviewed in bi-annual reports sent to the internal safety monitoring committee.

10.3.4 Monitoring

A study protocol, Manual of Operations and DSMP for all study activities will be developed during study setup and approved by the IRB and internal safety monitoring committee prior to initiating recruitment. Data will be maintained in a Database Manager System (RedCap).

The database system will have automated checks for ranges of values and logical validity of data entered and will be programmed to import subject data directly from the computerized test data files. Imported data files will be checked for data integrity and flagged in the event of inconsistent or missing data. Hand entered data will be verified using double entry routines to guard against key punch errors. This system will provide

immediate access to individual subject data and can generate a summary report of the entire database. The database will contain provisions for password protection and distribution of analytic data files containing only necessary information on an as-needed basis; there will be an interface to export all or selected data from RedCap and transfer these to any of the statistical packages (SAS, S-PLUS, Stata, SPSS) used by the project investigators.

Full backups of the entire database will be performed daily. For added security, copies of the databases are kept in two separate physical locations in locked, fire-resistant containers. Database files will be maintained by the Database Management Core and subjected to quality control procedures. Summary reports will be generated and reviewed by the project manager and PI as requested.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB responsible for oversight of the study.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. The tester will obtain informed consent, prior to screening and randomizing patients to either the 5-Cog or control intervention. The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and this fact will be documented in the participant's record. Language in the consent form will describe data sharing. For example, *"We will store information about you in a "bank", which is a library of information from many studies. This information cannot be linked to you. In the future, researchers can apply for permission to use the information for new studies to prevent, diagnose, or treat disease. Your information may be kept for a long time, perhaps longer than 50 years. If you agree to the future use, some of your de-identified health information (not linked to you) may be placed into one or more scientific databases. These may include databases maintained by the federal government."*

11.3 Participant Confidentiality

This protocol, the informed consent, all recruitment materials, assessments and scripts as well as any subsequent modifications to these documents will be reviewed by the IRB prior to study start date. Any data, forms, reports, and other records that leave the site will be identified only by a participant identification number (Participant ID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by the IRB or the NINDS.

As of July 27th 2020, participants will be offered the opportunity to complete neuropsychological evaluations over the telephone or via video conference. Interviews collected on video conference or over the phone will NOT be recorded.

11.4 Study Discontinuation

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

12 ETHICAL CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki and the Institutional Review Boards.

To maintain confidentiality all study records will be identified by a coded number. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring.

13 CROSS CONSORTIUM COMMITTEES

The Consortium for Detecting Cognitive Impairment, Including Dementia (DetectCID), is a collaborative network of research programs that are performing cross-site validation of paradigms, tools, and protocols that will increase the frequency, and improve the quality of patient evaluations for detecting cognitive impairment in primary care and other everyday clinical settings. The members of the consortium include Albert Einstein College of Medicine, Northwestern University and The Regents of the University of California San Francisco (UCSF). The DetectCID Consortium was created pursuant to joint funding from the National Institute of Neurological Disorders and Stroke and the National Institute on Aging under grant number UG3NS105557, and the exchange of Data is for the research activities of DetectCID.

The committees described below guide cross consortium projects and are not responsible for local governance.

Steering Committee

The Steering Committee is the governing leadership and decision-making body for the project. It includes the PI of each project as a voting member, and up to 4 NINDS non-voting members. Co-PIs and Project Managers are encouraged to attend all meetings, although only one vote will be allocated to each project. This Committee's primary purview will be to maintain the cross-project scientific synergy of the Consortium. They will oversee cross-validation projects, establish milestones and timelines, and monitor progress. They will coordinate the activities of and gather input from critical stakeholders whose investment and support are important for project success, including the Food and Drug Administration, Centers for Medicare & Medicaid Services, Alzheimer's Association, etc. This Committee will review proposals for cross-site projects and ensure equitable shared-data publication practices across sites. They will also receive reports from and provide scientific, logistical, and administrative governance for the other Committees. The Steering Committee will meet via videoconference monthly throughout the project for a minimum of 1 hour. These meetings may be extended to 1.5 hours, with one hour dedicated to private discussion, and 30 minutes joined in a regular rotation by representatives from one of the other Committees or stakeholder groups, who will provide a report of their key activities, issues, and recommendations, and receive feedback from the Steering Committee to guide their progress.

Analysis Committee

The Analysis Committee is responsible for study design and statistical analysis. This Committee will be dedicated to providing a sophisticated approach to research design and statistical analysis plans for the data being collected throughout the Consortium and with an emphasis on cross-validation projects. While the exact membership of these Committees will be determined by the Steering Committee, this Committee should have at least one expert in statistics, research design and/or data science from each site. This Committee will maintain an updated and clear understanding of the key scientific goals of the project, as articulated by the Steering Committee, and will work with the project leadership to derive specific statistical analysis plans to most effectively answer the Consortium's scientific questions. Regular discussion of analytic plans and methods across projects will ensure that the best statistical approaches are shared when common problems arise. This Committee will also facilitate sharing of analytic code to reduce redundancy and maximize efficiency of data analysis across the Consortium. This Committee may choose to meet less frequently (i.e., only quarterly) during the middle years of the project but will likely require monthly meetings during early and later project periods.

Data Sharing and Harmonization Committee

The Data Sharing and Harmonization Committee is responsible for identifying opportunities for, and implementing, practices that promote data sharing and harmonization. While the exact membership of these Committees will be determined by the Steering Committee, this Committee should include a scientist from each site who is familiar with that site's patient data collection practices, and individuals with research technology expertise. Project managers are encouraged to attend these meetings, and individuals with administrative/regulatory expertise will be included as needed. The team will develop an overview of the protocols, paradigms, and available data generated by different Consortium sites, and will provide recommendations, subject to final approval by the Consortium Steering Committee, for how those resources would most effectively be shared and included in cross-validation studies. This may include potentially harmonizing the collection of certain common data elements across sites (e.g., the exact protocol for collection of demographic and clinical severity information, etc.) to promote unified datasets for later analysis. They will evaluate and may adopt elements of already well-established harmonization schemas, such as some of the NACC standards for ADCs. It will be the purview of this Committee to ensure maximal data sharing of Consortium data, both within and beyond the Consortium, and to investigate and make recommendations about data sharing tools and repositories that would be facilitate this sharing. This Committee will likely be responsible for establishing reliance agreements across site IRBs to facilitate sharing of de-identified clinical data. This Committee may choose to meet less frequently (i.e., only quarterly) during the middle years of the project but will likely require monthly meetings during early and later project periods.

Clinical Practice Committee

The Clinical Practice Committee is responsible for paradigm implementation and maintaining relationships with primary care providers, health systems, and health disparities populations. This Committee will be responsible for guiding successful strategies for the implementation of protocols in everyday clinical settings across health disparities populations, and to guide implementation research protocols and benchmarks for success. While the exact membership of these Committees will be determined by the Steering Committee, this Committee should include

representatives with expertise in implementation science, primary care, and health disparities research. Meetings will be monthly to initiate the work, and during the planning phases for the implementation projects; frequency may be less often (quarterly at minimum) during other phases.

14 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee. Any presentation, abstract, or manuscript will be made available for review by the NINDS prior to submission.

AMENDMENTS

7/15/2020 – Section 10.1. Data Collection Forms was updated to include that Atlas will be used to collect outcome data.

7/15/2020 – Section 6.2.2 Randomization & Assessments – Additional Assessments was amended to include that due to safety concerns about in person visits because of the COVID-19 pandemic, participants will be offered the opportunity to complete neuropsych assessments over the telephone or via video conference.

7/15/2020 - 11.3 Participant Confidentiality was amended to add that although participants may agree to complete the neuropsychological evaluation over the telephone or via video conference the interview will not be recorded.

8/25/2020 – 6.2 Description of Evaluations: Consenting procedure – In light of the COVID-19 pandemic, we have amended to the protocol to include an oral consent process in order to reduce exposure for both the research staff and the participants.

12/2/2020 - 6.2 Description of Evaluations: Screening Evaluation and Consenting procedure – In light of the COVID-19 pandemic, we have amended the protocol to include that ***only*** an oral consent process will be used to consent participants (rather than offering a written consent as well). In addition, recruitment and screening was amended to describe that these procedures will now take place over the phone.

12/2/2020 - 4.3 Study Enrollment Procedures: A new section (COVID-19 amendment to enrollment and recruitment procedures) is added to the end of this section to describe the changes to the recruitment and enrollment procedures that will be made in response to the pandemic.

12/9/2022 - 10.2 Data Management: A data sharing section under data management is added to describe the data sharing agreement and what specific data will be shared under the collaboration

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