Study Title: Self-Administered Gerocognitive Examination (SAGE) for the Early Detection of Cognitive Impairment at Primary Care Provider Visits

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PROTOCOL

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Introduction

Memory deficits are common in the elderly and can be contributed to normal aging, neurodegenerative disorders, acute illnesses or other etiologies. Mild Cognitive Impairment (MCI) is a condition where individuals display cognitive impairments that are more than expected with normal aging, but not severe enough to interfere with daily function (Burke, Sengoz, & Schwatz, 2000; Portet et al., 2006). Symptoms of MCI may be reversible, some may remain stable and some may progress to neurodegenerative disorders such as Alzheimer's disease (Scharre & Trzepacz, 2013). Conditions such as depression, sleep apnea and vitamin B deficiency can affect one's memory and thinking and be reversible (Scharre & Trzepacz, 2013). Once identified, treatments can be initiated to improve the cognitive impairment that is associated with these disorders. Approximately 11% of MCI cases are reversible (Scott & Barrett, 2007). Reversal of the cognitive impairments can improve an individual's quality of life (van den Dungen et al., 2016). Approximately 10-15% of Mild Cognitive Impairment cases progress to Alzheimer's disease (Janoutova, Sery, Hosak, & Janout, 2015; Yue et al., 2012).

Cognitive impairment is becoming increasingly prevalent across the world. The increase in life expectancy is thought to contribute to this rise. An estimated 5.2 million individuals in the United States and 46.8 million individuals worldwide are currently living with dementia (Alzheimer's Disease International [ADI], 2016; Barnes et al., 2014). This number is expected to increase by 9.9 million each year, doubling after 20 years (ADI, 2016; Prince et al., 2013). By 2050 it is estimated that there will be 131.1 million individuals with dementia worldwide (ADI, 2016; Khanassov & Vedel, 2016). Alzheimer's disease is the most common type of dementia accounting for 60-80% of all dementia cases (Alzheimer's Association, 2015; Alzheimer's Association, 2017; Manenti et al., 2004). 50-75% of the current dementia cases are undiagnosed (Barnes et al., 2014; Eichler et al., 2015). Often, adults who experience subjective memory complaints do not discuss the symptoms with their physician (Adams, 2016). The average time of diagnosis is 32 months after the onset of symptoms (Jost & Grosberg, 1995; Van Vliet et al., 2013). Early diagnosis of cognitive impairment can be beneficial the following reasons: treatable causes can be reversed; pharmacological interventions can be initiated earlier; and the individuals can play an active role in the decision-making planning for their future (Adams, 2016). Alzheimer's therapeutics have also been shown to be more effective when initiated early (Yiannopoulou & Papageorgiou, 2013).

The 2010 Patient Protection and Affordable Care Act added an Annual Wellness Visit (AWV) as a Medicare benefit for Medicare recipients. As part of the Annual Wellness Visit medical providers review and update the patient's medical history, surgical history, current medications and list of current medical providers; they conduct routine measurements of height, weight, body-mass index (BMI) and blood pressure; they conduct an assessment to detect cognitive impairment; and they conduct a health risk assessment (Cordell et al., 2013; U.S. Government Publishing Office, 2016). Per the regulation, the cognitive impairment can be assessed through direct observation of the patient and through information obtained from the patient, family members, friends or others (Cordell et al., 2013; U.S. Government Publishing

Office, 2016). There are currently no established guidelines regarding the utilization of a formal assessment scale. Conducting cognitive assessments can be time consuming for the providers and can be difficult to incorporate into a time-limited visit. There are numerous validated cognitive screening assessments, however most require an administrator to conduct the assessment via a formal interview, which can be difficult to incorporate into a primary care visit. Primary care providers are in need of an easily administered cognitive screening instrument.

The Self-Administered Gerocognitive Examination (SAGE) (Scharre et al., 2010) is a reliable and valid assessment that is used to detect MCI and early dementia. It is a pen and paper assessment that has 4 interchangeable versions. Since it is self-administered it does not require an administrator to conduct the assessment and it can be conducted in almost any setting (Scharre, Chang, Nagaraja, Yager-Schweller, & Murden, 2014). The digital version of SAGE (eSAGE; commercially known as BrainTest®) is made for tablet use, consists of the identical test questions as SAGE, and is strongly associated with the validated SAGE (Scharre, Chang, Nagaraja, Vrettos & Bornstein, 2017). Both SAGE and eSAGE are tools with high specificity for cognitive impairment (Scharre et al., 2010; Scharre, Chang, Nagaraja, Vrettos & Bornstein, 2017). The SAGE and eSAGE contains questions that are more difficult than other cognitive screening instruments, such as the Mini Mental Status Exam (M. Folstein, S. Folstein, & McHugh, 1975). This allows for the detection of mild impairments. The SAGE or eSAGE could be easily incorporated into the Primary Care Provider Visit since it does not take any additional time from the provider or medical staff to administer. It could potentially allow providers to detect cognitive impairments at the initial visit or it could be used to establish a baseline score to detect changes when given yearly over time. Identification of potentially clinically relevant cognitive changes would then warrant further investigation.

Thus far no large randomized trial has demonstrated a correlation between screening and improved outcomes. This would need to be done to gain widespread acceptance of screening and case finding programs. Early detection of cognitive impairment could potentially result in the appropriate treatment of reversible cognitive impairment conditions or earlier initiation of pharmacological interventions for the management of a variety of other dementia or MCI conditions. A screening approach that reduces the number of false positive screens would improve the comfort level of physicians and patients with cognitive screening programs.

We propose to use SAGE and eSAGE to identify patients who score in the cognitive impairment range during an office visit with their primary care provider. Conversation with an individual who knows the patient well (if possible) will be performed to ascertain a significant change in the patient's cognitive skills over the previous year. We wish to determine if screening for cognitive impairment in this way leads to new diagnoses and management outcomes compared to a group of primary care providers who use their current usual method in screening for cognitive impairment during office visits.

Study Objectives and Aims

Specific Aim 1: To determine if the use of SAGE or eSAGE during a patient's office visit with their primary care provider in combination with any available input from an informant regarding cognitive change over the previous year in that individual will lead to (a) more new diagnoses and/or (b) to new management outcomes by the provider than the usual method (based on the primary care provider's normal practice) currently used for screening for cognitive impairment during such visits.

Specific Aim 2: To determine if cognitive impairment, based on using SAGE or eSAGE, by itself, during a patient's office visit with their primary care provider will lead to (a) more new diagnoses and/or (b) to new management outcomes by the provider than the usual method (based on the primary care provider's normal practice) currently used for screening for cognitive impairment during such visits.

Hypothesis

We hypothesize that the determination of cognitive impairment using the SAGE or eSAGE with and without determination of significant cognitive change over the previous year by an informant, during a patient's office visit with their primary care provider will lead to more new diagnoses and/or new management outcomes than standard of care practices used for screening for cognitive impairment.

Methods and Design

A. Subject Selection

1. Inclusion Criteria
   a. Adults 65-89 years of age who complete a non-acute care office visit.
2. Exclusion Criteria
   a. Diagnosis of mild cognitive impairment or dementia in the medical records.
   b. Diagnosis of visual loss or conditions causing visual loss in the medical records unless it is clear that the loss would not be sufficient to preclude reading standard medical forms with or without the use of visual aids.

B. Method

The Ohio State University Wexner Medical Center has over 100 primary care providers who see patients at 14 offices in central Ohio. These providers routinely see geriatric patients and routinely conduct Annual Wellness Visits.

At least two primary care offices will be involved in this trial. At least one location will serve as the control office and will continue to conduct their visits including screening for cognitive impairment as they normally do using their usual method based on the primary care provider's normal practice. At least one different location will serve as the intervention office where all the providers, as their standard of care, use a standardized method for screening for cognitive impairment consisting of using the SAGE or eSAGE test and having a conversation with an individual who knows the patient well (if possible) to ascertain if a significant change (based on primary care provider opinion) occurred in the patient's cognitive skills over the previous year.

Chart reviews will be conducted on all of the patients who meet the inclusion/exclusion criteria for the trial using a 60 day window from the initial visit. The demographics, medical history and list of current medications will be reviewed. SAGE or eSAGE test results and the primary care provider's opinion of the informant information regarding the patient's cognitive change over the previous year will be obtained. Additionally, the charts will be reviewed for the number of referrals for further evaluation/management of potential cognitive impairment (including lab work, neuroimaging, neuropsychology testing, neurology/psychiatry, occupational therapy, physical therapy, speech therapy, counseling, respite care, legal assistance (DPOA or living will), day care, home health, social work, financial planning, and cognitive research), the

initiation of pharmacological interventions for the management of cognitive impairment and the diagnosis of cognitive impairment. Charts will also be screened to assess the number of follow up visits that were scheduled after the office visit for follow up regarding cognitive issues. For the intervention office, chart reviews will be conducted on patients who complete the SAGE or eSAGE and on patients who do not complete the SAGE or eSAGE. Possible reasons for why patients would not complete the SAGE or eSAGE include: time constraints, patient noncompliance and provider oversight. There will be 2 control groups. Control group 1 consists of primary care offices that did not use SAGE or eSAGE for any of their patients and Control group 2 consists of patients handled by the intervention office who did not complete the SAGE or eSAGE. Intervention group consists of patients handled by the intervention office who did complete the SAGE or eSAGE.

SAGE and eSAGE test scoring will be compared between the intervention office and the research site.

There will be no costs to the subjects for participating in the trial and there will be no payment for participation.

Upon completion of the trial, the providers from the intervention group will be requested to complete a questionnaire to evaluate the practicality and ease of use of the SAGE and eSAGE test.

C. Outcome Measures

Primary Outcome Measures

1. Proportions of subjects in the intervention and the two control groups with diagnosis of a cognitive impairment disorder as measured by pharmacological interventions for the management of cognitive impairment.
2. Proportions of subjects in the intervention and the two control groups with any referral for further evaluation/management of potential cognitive impairment (among10 listed items).
3. Proportions of subjects in the intervention and the two control groups with at least one follow-up visit for additional investigation of a cognitive impairment disorder.

Secondary Outcome Measures

1. Number of referrals (among the 10) used for subjects in the intervention and control groups for further evaluation/management of potential cognitive impairment.
2. Proportions of subjects with pharmacological interventions for the management of the cognitive impairment in the two subgroups of the intervention arm with and without additional inputs from informants.
3. Differences of SAGE and eSAGE scoring between intervention office and research site.
4. Results of the questionnaire to evaluate the practicality and ease of use of the SAGE and eSAGE test by primary care providers and staff.

D. Sample Size Choice and Statistical Analysis Strategy

The power analysis is done using the primary outcome measure of the proportion diagnosed of cognitive impairments. With anticipated proportions of diagnosis of 0.05 (=1/20) and 0.17 (Alzheimer's Association, 2017) for the control and SAGE groups, respectively, and chosen sample sizes of 100 each, a two-sample test of proportions carried out with a two-tailed level of significance of 0.05 will have 78% power to detect the difference. (Our statistical strategy uses more powerful techniques.) We will have data from 100 subjects each from the two control and one intervention group.

For comparing the proportions between the 3 groups (all primary outcome measures and the second secondary outcome measure), we will use a logistic regression model that will control for all relevant covariates including age, gender, race, and income and education levels. The number of referrals (first secondary outcome measure) will be compared using a Poisson regression model that will also control for relevant covariates. Given enough subjects are tested using eSAGE, we will compare the proportions from the SAGE and eSAGE groups. Software JMP Version14 or later (SAS Institute, Cary NC) will be used for analysis and model diagnostics will be performed to validate the chosen statistical models. Level of significance will be set at 0.05 and adjustments will be made for multiple tests as appropriate.

E. Subjects

Three hundred subjects will be enrolled in the trial equally divided between the three arms: Control group 1, SAGE/eSAGE completers in the intervention office (Intervention group) and SAGE/eSAGE non-completers in the intervention office (Control group 2). The 100 subjects for each group will consist of the first 100 eligible subjects based on the record review.

F. Informed Consent

A waiver of written informed consent will be requested of the IRB for this trial. We will be comparing standard of care practices at two primary care offices. One location will incorporate the SAGE or eSAGE test and informant question into their standard of care practice for screening for cognitive impairment. The other location will conduct screening for cognitive impairment as they normally do. Since we are comparing standard of care practices there is no more than minimal risk to the subjects. Results are only recorded in the aggregate.

G. Data Collection and Management

This study will utilize REDCap (Research Electronic Data Capture), a software toolset and workflow methodology for electronic collection and management of clinical and research data, to collect and store data. The Ohio State Center for Clinical and Translational Science (CCTS) Research Informatics Services will be used as a central location for data processing and management. REDCap provides a secure, web-based application that provides an intuitive data manipulation interface, custom reporting capabilities, audit trail functionality, real-time data monitoring/querying of participant records, and variations of data exporting/importing. REDCap is hosted by OSUWMC IT in the Ackerman Datacenter (640 Ackerman Road; Room 345).

REDCap instance is located outside of the OSUWMC network. Non-PHI Redcap is accessible from any internet connection. No encrypted VPN tunnel is required.

REDCap supports electronic signatures by positively identifying the user through a unique username and password combination. The provisioning of accounts and user access to specific database(s) is integrated with the OSUWMC LDAP authentication service for studies

containing protected health information (PHI), the provisioning of access and specific user rights for all studies and review of content are managed by CCTS staff.

Risk-Benefit Analysis

The risks to the subjects are very low. Possible risks include anxiety associated with the completion of the SAGE or eSAGE test and having an informant give their opinion of the patient's cognition change over time. The seriousness of this risk is very low. Possible benefits to the subjects include the potential of early detection of cognitive impairments.

IRB/Patient Confidentiality

The Biomedical Sciences Institutional Review Board (IRB) at The Ohio State University will be the IRB for this trial. All of the study materials, including the study measures, will be reviewed by the IRB prior to the start of the trial. If any ethical concerns are identified they will be addressed, and the protocol will be amended, to ensure proper ethical conduct of the trial and the protection and safety of the participants. Once IRB approval is obtained the trial will begin. IRB oversight will occur throughout the entire trial.

To protect the privacy and confidentiality of the participants, all of the paper records for the trial will be kept in secured locked rooms/cabinets so that privacy of the subject's data is maintained. The only people who will have access to the records are the study investigators and their staff. Digital data stored for this study will be kept on a server inside the firewalls at the outpatient clinics and will be password protected. All data used for analysis is in aggregate and will be deidentified prior to analyses.

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