Optimal Medication Management in Alzheimer's Disease and Dementia

DATA AND SAFETY MONITORING PLAN

PREFACE

Investigators should consider using this template when developing the Data and Safety Monitoring Plan (DSMP) for clinical studies sponsored by the National Institute on Aging (NIA).

Note that all instructions and explanatory text are shown in italics and should be replaced with the study specific text. There is no need to include sections that are not relevant to the particular study.

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1.0 PARTICPANTS SAFETY

1.1 Potential Risks and Benefits for Participants

Potential Risks:

Potential risks associated with deprescribing include an adverse drug withdrawal event, return of symptoms, and anxiety about the deprescribing process. However, potential risks can be minimized or prevented by using a patient-centered, physician-led, structured deprescribing process. Additionally, potential risks of deprescribing need to be weighed against potential risks of continuing an inappropriate medication. Deprescribing studies, where the intervention involves withdrawal of medications which have been determined to be inappropriate in the individual (which is what our intervention will involve) have been generally shown to be safe. Our intervention involves providing tools (including patient/care partner and clinician education) and opportunities (through patient/ care partner and clinician engagement) for patients, care partners, and physicians to identify medications which may be suitable for withdrawal in an individual and to discuss deprescribing as one component of optimal medication management. The decision to deprescribe a medication will be made by the primary care physician and the patient/care partner through shared decision making. It is possible that discussing deprescribing of medications may lead to anxiety and stress to the patient. However, previous qualitative studies indicate that where there is a discussion of the reasons why the medication is being recommended for withdrawal and shared decision making about deprescribing, this anxiety is minimal.

Potential benefits of the proposed Research to the subject and others

For older individuals with ADRD, taking more medications is associated with greater risk of adverse drug events, drug interactions, treatment burden, and cognitive changes from medication side effects. Clinician guided deprescribing has been shown to be safe, effective, and improve outcomes for older patients. Participants may benefit from learning about potential deprescribing as part of medication management and may benefit from shared decision making with their PCPs regarding medication management. Individuals with Alzheimer's Disease and Related Dementias (ADRD) or Mild Cognitive Impairment (MCI), which often precedes dementia, may also benefit from discontinuing or de-intensifying unnecessary or potentially inappropriate medications – especially those which may have cognitive side effects.

Information gathered from this research has the potential to improve outcomes for patients with ADRD-MCC. Educating patients and clinicians on optimal medication management can improve health outcomes. If effective, this simple, scalable,

pragmatic study design across multiple clinics may ultimately be replicated in other healthcare systems and settings.

1.2 Adverse Event and Serious Adverse Event Collection and Reporting

There are two primary elements to the safety monitoring plan: periodically comparing rates of potential serious adverse events between intervention and control clinics; and chart abstractions of a sample of patients who experience a potential serious adverse event in each group. For this intervention, we define a potentially serious adverse event as an Emergency Department (ED) encounter, an inpatient hospitalization, or mortality. In the target population of older adults with ADRD and MCI plus 2 or more chronic medical conditions, we anticipate baseline annual hospitalization rates of approximately xxx as well as estimated mortality rates of xxx% independent of the intervention.

Comparing rates of potential serious adverse events: Every 3 months we will compare rates of ED encounters, hospitalizations, and mortality between groups who have received the intervention (have been sent a mailing) from intervention clinics, and those who would have been eligible to receive the initial mailing from control clinics. These rates will be reported to the DSMB.

Chart abstractions: All deaths among individuals who have received the intervention (have been sent a mailing) from intervention clinics, and those who would have been eligible to receive the initial mailing from control clinics will be reviewed by a trained chart abstractor to determine whether the death occurred within 3 months of a medication adjustment by the patient's primary care physician. Similarly, every third hospitalization and ED visit for these two groups will be reviewed to determine the primary diagnosis for that hospitalization or ED visit and whether the potential serious adverse event occurred within 3 months of a medication adjustment by the patient's primary care physician. (The abstraction sample of admissions and ED visits will be generated weekly.) All chart abstractions will be conducted by a trained clinical chart abstractor who will not need to be blinded to clinic intervention vs. control groups. The co-PIs and study staff (other than the biostatistician) will remain blinded to the intervention or control clinic of individuals whose records are abstracted. This section describes the procedures and timelines for adverse events (AE) and serious adverse events (SAE) collection and reporting. It should also include the definition, grading scale and "study relatedness" criteria for adverse events and specify the recipients of adverse event and serious adverse event reports (e.g., the IRB, the NIA, the Safety Officer or Data and Safety Monitoring Board).

All educational material provided to clinicians will include contact information for the Principal Investigator (PI) and Project Manager (PM). For any reports of potentially

serious adverse events or other concerns from intervention site clinicians, the PI will contact the PCP to discuss the potential concern and will also conduct a medical record review and abstraction. Since only clinicians in intervention clinics will have the ability to report concerns, these chart abstractions will be unblinded. All potential concerns will be noted and discussed with the DSMB at regular meetings (or immediately for any serious adverse event potentially due to the intervention) and will be reported to the IRB. Follow-up will extend until discharge from the hospital for hospitalizations or completion of any acute care services associated with an adverse event.

1.3 Protection Against Study Risks

This section provides information on how adverse events and other risks to participants in the study will be mediated and should specify any events that would preclude a participant from continuing with the intervention. This section should also include the informed consent procedures and measures to protect participants against risk during the study. In general, the format and content of this section are similar to the Human Subjects section of the application.

Informed Consent Process.

Due to the educational nature of the intervention, we have requested a waiver of informed consent for eligible patients and clinicians in the intervention clinics.

The pragmatic trial will be conducted at the level of the clinic … Options for pragmatic trial consent range from 1) full individual level recruitment and written informed consent, to 2) recruitment information sent to all eligible candidates with an 'opt out' clause, to 3) general information on the intervention provided to all eligible patients with an option for further inquiry. We have discussed these three options with the IRB and have requested option 3 as an acceptable approach to consent for the intervention. This is based on the following factors:

- The intervention is educational and designed to prepare participants (patient/care partners and clinicians) for a discussion between patients/care partners and PCPs about optimal medication use. The intervention does not in itself alter patient medication prescribing.

- Medication reconciliation at every visit is already part of the standard of care.

- Any changes in medication regimens will be made by the PCP and patient/care partner through shared decision making. This is consistent with usual care.

- There is no requirement for patients/ care partners or clinicians to engage in discussions about medication optimization upon receipt of intervention materials.

- The intervention is pragmatic and designed to test a scalable process that can be implemented across multiple clinics to foster a sustainable culture of medication optimization for individuals with ADRD.

We have developed an informational cover letter to be included with materials sent to patients which provides general information on the intervention. The informational letter will indicate that patients may wish to discuss medication discontinuation with their physician but are under no obligation to do so.

We have also included a slide in the clinician presentation that provides general information on the intervention. All educational material provided to clinicians will include contact information for the study PI and PM.

2.0 INTERIM ANALYSIS

There will be periodic assessment of potentially serious adverse events as described above in Section 1.2.

There are no stopping rules for the study. Interim assessment of potential adverse events will be shared with the DSMB, which may make recommendations to NIA regarding study continuation.

3.0 DATA AND SAFETY MONITORING

Any medication discontinuation decisions will be made by patients' primary care physicians (PCP) in conjunction with patients and care partners as part of usual care.

The *Data and Safety Monitoring Board (DSMB)* will act in an advisory capacity to the NIA Director to monitor participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses.

The study biostatistician will prepare periodic reports for the DSMB and the chart abstractor will compile information to be summarized by the biostatistician. Neither of these study staff will be blinded to study arm.

3.1 Frequency of Data and Safety Monitoring

Reports on comparative rates of potentially serious adverse events (described in Section 1.2) will be prepared by the study biostatistician for the DSMB every 3 months.

Any potentially serious concern from a clinician in an intervention clinic will be evaluated by the study PI within 48 hours. If the PI is unavailable, the co-PI will work with the tudy staff to evaluate the concern. Serious adverse events thought likely to be due to the intervention will be reported to the DSMB within 24 hours of medical record review.

3.2 Content of Data and Safety Monitoring Report

Please see the Optimize Study Data Safety Reporting Template.

3.3 DSMB Membership and Affiliation

3.4 Conflict of Interest for DSMB's

DSMB members have been reviewed by NIA and found to be free of conflicts for the purpose of the study.

3.5 Protection of Confidentiality

All data and summary information presented to the DSMB will be deidentified.

3.6 DSMB Responsibilities

Please refer to the DSMB charter for the Optimize study.