Principal Investigator: Kelly Muir, MD
Protocol Title: Improve Glaucoma Medication Adherence
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Purpose

The purpose if this study is to improve glaucoma medication adherence in Veterans with medically-treated glaucoma. The study design is a single-site randomized controlled trial.

Background and Significance

Glaucoma is the leading cause of irreversible blindness worldwide[1,,,,,2] and the leading cause of blindness in African Americans.[3] The number of Americans with glaucoma is projected to increase by 50% over the next 15 years.[4] Despite advancements in the diagnosis and treatment of glaucoma, no cure exists. The only intervention that has been proven to reduce the risk of progressive loss of vision from glaucoma is lowering the intraocular pressure. Although surgery and laser treatment may be used to reduce intraocular pressure, the most common treatment for glaucoma is the prescription of topical eye drops.[5]

Glaucoma eye drops are prescribed to be taken daily, often multiple times per day, indefinitely. As with many other daily therapies for chronic, asymptomatic disease, patient adherence to the prescribed glaucoma regimen is often poor.[6,,,,,7] Patients with glaucoma who are poorly adherent to the prescribed medication regimen are more likely to experience progressive visual field loss than patients who are more adherent.[8] Factors associated with poor glaucoma medication adherence include advanced age,[9] limited health literacy skills,[10] and disabilities from comorbid conditions that make self-administration of eye drop difficult, such as arthritis.[11]

The approach to assess and address glaucoma medication adherence is guided by the Health Decision Model (HDM). The HDM suggests that adherence with the prescribed glaucoma eye drop regimen is dependent on patient experiences, patient preferences, social interactions, knowledge, attitudes and beliefs (Figure 1). The educational components of the intervention address the potential for irreversible blindness from glaucoma and increase understanding that eye drops reduce the risk of blindness. The self-reported adherence and self-efficacy surveys create the personalized response component of the intervention, which incorporates patient experience and preferences regarding most convenient dosing regimen. In addition, personalized responses are used to increase participants' self-efficacy with eye drop use. For example, participants who describe low self-efficacy with the physical task of administering the drop are taught simple tricks such as steadying the hand on the forehead, or prescribed eye drop aids to help with squeezing or aiming the bottle.

We have found in our prior work that glaucoma patients expressing poor self-efficacy regarding ability to take their drops as prescribed are less adherent in the following months according to an electronic monitor[1] so the screening questions we tested in our preliminary work target self-efficacy.

This study will expand upon previous work and incorporate the most current evidence-based strategies into the design. The authors of a 2009 Cochrane review concluded that although there were too few studies of glaucoma medication adherence of high quality to make firm recommendations, interventions that include glaucoma education and individualized care planning are most successful.[45] Boland and colleagues have shown that mnemonic aides in the form of automated text or voicemail messaging can improve adherence, at least in the short-term.[4] We know, however, that even experienced drop-users often cannot successfully administer a drop into the eye,[2] and daily reminders will not alleviate this barrier to adherence.

Accordingly, a more comprehensive approach is needed to improve glaucoma self-management.

The long-term goal of this research program is to reduce glaucoma-related blindness in Veterans. The objective of this project is to test an intervention to improve medication adherence. The proposed intervention is novel in that it was developed through a prior pilot study with input from Veterans with glaucoma and with a multidisciplinary team that includes local and national operations partners. This collaborative approach and careful attention to cost will facilitate implementation of the program should the intervention prove effective. The screening and outcomes measures have also been studied in the Durham VA Eye Clinic as part of the preliminary studies leading to this proposal.

Design

The proposed study is a randomized controlled trial of an educational intervention to improve glaucoma medication adherence. Participants will be Veterans who are patients of the Durham VA Eye Clinic with medically-treated glaucoma and their companions (family or friend) if a companion is available (we have been approved for a Waiver of Informed Consent Documentation for companions). Participants will be randomized to receive either a general eye health educational session (control arm) or an educational intervention developed to improve glaucoma medication adherence (intervention arm). All participants will be provided with a "smart bottle" (AdhereTech, NYC) to house one of their glaucoma medications. The smart bottle records the date and time that the bottle is opened. For participants in the intervention arm only, a reminder through AdhereTech will be activated. Participants randomized to the intervention will meet with the interventionist approximately 4 weeks following the enrollment visit. The intervention will be delivered one-on-one, in a private room at the Durham VA. Companions, if applicable, will accompany the Veteran in the intervention. Drop administration instruction will be directed toward the veteran participant or if applicable towards the companion. Veterans randomized to the control arm will be scheduled for a session with the interventionist approximately 4 weeks after the enrollment visit. The control visit will include review of a Powerpoint presentation on general eye health, including but not specific to glaucoma. The presentation will be delivered one-on-one, in a private room at the Durham VA. Companions, if applicable, will accompany the Veteran in the presentation. Both the intervention and the control session will last approximately 30-60 minutes. Participants in the control arm will receive an electronic medication monitor but the reminder function will not be activated. Participants will be brought in for a 6-month follow up visit and the 12 month follow up will be conducted over the telephone.

Outcomes:

Specific Aim 1. Evaluate the impact of an intervention to improve glaucoma medication adherence among Veterans at 6-month follow up.

Hypothesis 1: Veterans randomized to the intervention will have a greater proportion of prescribed glaucoma medication doses taken as measured by the electronic medication monitor in the 6 months following the intervention compared to Veterans randomized to the control arm.

The primary outcome for hypothesis 1A is the proportion of prescribed doses taken according to the electronic monitor. Participants in both arms will receive the electronic monitor or "smart bottle," which wirelessly transmits the date and time of opening of the smart bottle to the study team. From these medication events, the proportion of prescribed doses will be derived, defined as the ratio of the number of times the smart bottle was opened to the required number of doses prescribed according to the medical record over the period of time that the bottle is in use. For example, if a participant is advised to take his or her glaucoma drop twice a day for the 180 days that the bottle is in use and the smart bottle reveals 135 openings over the same time period, the proportion of prescribed doses taken is 37.5%.

Specific Aim 2. Evaluate the impact of the intervention on intensification of glaucoma therapy among Veterans at 12-months post randomization.

Hypothesis 2: The proportion of Veterans in the intervention arm that are prescribed more intensive glaucoma therapy, defined as addition of adjuvant glaucoma medication or recommendation for laser or glaucoma surgery will be less than the proportion of Veterans in the control arm who are prescribed more intensive glaucoma therapy in the 12 months following the intervention.

Baseline data collection will include cataloging the current glaucoma medication regimen prescribed to the participant. Chart abstractions will be performed at approximately 12 months following the randomization and intensification of glaucoma therapy will be defined as either 1) the addition of another glaucoma medication to the baseline regimen, 2) recommendation for glaucoma laser treatment, or 3) recommendation for glaucoma surgery in the 12 months following randomization. We will collect these data at approximately 12 months because the Metrics study suggested that 55% of participants in the control arm will have intensification of therapy within one year.

Specific Aim 3. Evaluate the incremental cost-effectiveness and budget and workflow impacts of the intervention compared to usual care.

Hypothesis 3: The intervention will be cost-effectiveness for the following ratios: 1) cost per percentage improvement in medication adherence; 2) cost per blindness averted; and 3) cost per quality-adjusted-life years saved.

A direct measurement approach will be used to estimate per-patient intervention and control arm costs. Glaucoma-related health care utilization costs will be derived from VA administrative datasets. The cost estimates will be combined with observed improvement in medication adherence and reduction in escalation in therapy to estimate the first two incremental cost effectiveness ratios. Simulation using Markov modeling will be used to estimate the incremental cost per blindness averted and quality-adjusted life years (QALYs) gained. Cost estimates and labor time data collected will be combined with glaucoma prevalence rates among Veterans to estimate overall budget and workload impacts to the VA healthcare system.

Risk/Benefit Assessment

The intervention is educational in nature and does not impose physical risks to participants. The primary risks to participants are loss of time and confidentiality. Participants' time was considered as an important factor in designing an intervention which is efficient yet hopefully effective. Actions taken to mitigate the risk of loss of confidentiality are addressed in the sections "Privacy and Confidentiality" and "Information Security." If, in the course of the study, any information becomes available that might influence the course of clinical care of the participant, this information will be communicated directly to the treating provider. The study offers no definitive benefit to participants but the knowledge gained may lead to improvements in the management of glaucoma for future patients.

Selection of Subjects

We will screen individuals until we meet the desired sample size of randomizing 200 Veterans and enroll up to 200 of their companions (family or friend) if a companion is available. Enrollment of a companion will not be required for otherwise eligible Veterans to be included in the study.

Inclusion criteria for patients at datapull:

1) Diagnosis of open angle glaucoma [primary open angle glaucoma, pigment dispersion glaucoma, pseudoexfoliation glaucoma, combined mechanism glaucoma, low tension glaucoma] recorded in the medical record,
2) Prescribed glaucoma eye drops,
3) Visual field performed within the last 9 months. As visual field testing is standard care glaucoma and we wish to establish baseline glaucoma severity, we will require that subjects have a visual field test documented in the chart within 18months of enrollment.

Exclusion criteria for patients:
1) Intraocular surgery in the past 3 months or anticipated in the next 3 months [as prescribed drops may change frequently in the perioperative period],
2) Active uveitis or eye infection [as medication regimen may vary from day to day],
3) Visual acuity less than 20/70 in the better-seeing eye, because Veterans with low vision may not be able to complete the vision-dependent tasks required for study completion.
4) Lacks proficiency in English,
5) Lacks either a cell phone or landline phone

Exclusion criteria for patients At Screener:
"How confident are you that you always remember to use your glaucoma medications? (not at all confident, somewhat confident, very confident)" and "In the past 4 weeks, did you ever forget to take your medicine?" Veterans who respond both "very confident" and "no", respectively, will be excluded.
Inclusion criteria for companions at screener:
1) Willing to participate in assisting the patient with glaucoma drops and
2) Willing to accompany the patient to the intervention visit for participants in the intervention arm or eye health education visit for participants in the control arm.

Exclusion criteria for companions: Unable or unwilling to attend baseline visit and intervention or control arm educational session with patient participant.

Exclusion criteria for patients or companions:
1) Lacks proficiency in English,
2) Lacks either a cell phone or landline phone.

Exclusion criteria for patients post randomization:
1. Decision by patient and provider to cease glaucoma medication use
2. Change in functional status such that the drops are no longer administered by the patient or the companion (such as nursing home care)

Subject Recruitment
Recruitment and Enrollment Process: We will use a recruitment strategy that was very efficient in our pilot studies. Potential participants will be identified by a data pull of Veterans with upcoming appointments at the DVAMC meeting inclusion/exclusion criteria. The medical records of potential participants identified by the data pull will be reviewed in detail to confirm eligibility based on the remaining inclusion/exclusion criteria. Potential participants confirmed to be eligible will be mailed a letter providing study information and a phone number to call to opt out of further contact regarding the study. Veterans who were mailed letters and did not opt out will be called by the study coordinator to discuss potential participation. If the Veteran is interested, screening questions will be asked to identify potential participants most likely to be poorly adherent to their prescribed glaucoma medication regimen. Veterans who screen positive for poor adherence and are interested in participation will be scheduled for an

appointment along with a companion if a companion is involved in his or her glaucoma management. Written informed consent and HIPAA authorization from the Veteran will be obtained at that time.

Recruitment Targets and Feasibility: We plan to randomize 200 Veterans (and enroll up to 200 companions if appropriate) over 24 months. Our pilot study identified 1533 Veterans meeting preliminary inclusion/exclusion criteria. In our pilot study, we used the proposed recruitment strategy and enrolled 31 Veterans over 3 months. In the proposed study, we will recruit 4-5 days/week, which greatly expands our ability to enroll and comfortably achieve our recruitment goal.

Consent Process

Potential participants who are eligible and express interest in the study after the screener phone call will meet in person with a member of the research team in a private room in the Durham VAMC or Hillandale clinic. The study will be described in detail and all questions answered. If the patient chooses to participate they will sign and date the informed consent and HIPPA forms. The signed informed consent and HIPPA documents safeguarded under lock and key at locations managed by the Durham VA Medical Center HSR&D: Legacy Tower, Durham, NC floor 6 room 636. While we will go through a consent process for companions, we were granted a Waiver of Informed Consent Documentation and a Waiver of HIPAA Authorization for the companion.

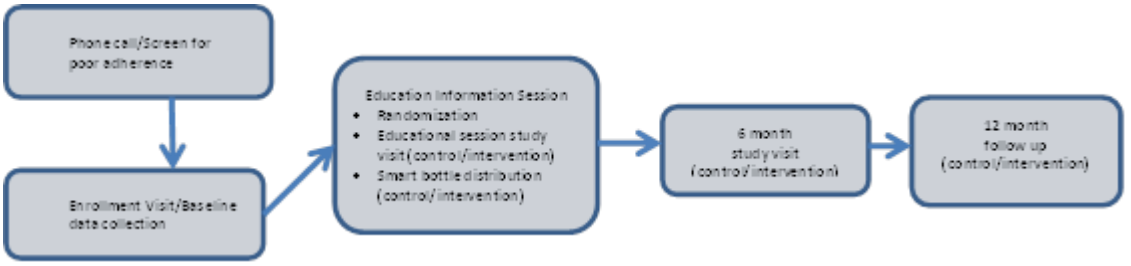
Study Interventions

The variables and data collection schedule are presented below (Table 1).
Baseline Data Collection: To reduce travel burden (and increase recruitment), we will strive to administer baseline surveys following informed consent on the day of a Veteran's scheduled appointment at the Durham VAMC or Hillandale clinic. However, we will make multiple dates and times available to the participants; and whenever possible, we will coordinate the baseline with a regularly scheduled appointment.

Randomization and Stratification: Participants will be randomized at the first informational session in a 1:1 allocation to the intervention or to the control arm. Randomization will be stratified according to if a companion is enrolled in the study with the participant. We anticipate 20% of participants will include a companion.[60] Randomization will also be stratified according to whether the glaucoma medication housed by the AdhereTech bottle is prescribed to be take once daily or more than once daily. Randomization status will be disclosed to the participant at the time of the intervention or control arm eye health education visit. Neither participants nor staff can be masked to randomization status.

Retention: To minimize participant burden and maximize their retention, screening is conducted over the phone. We will make multiple dates and times available to the participants; whenever possible, we will coordinate the baseline, education and information session and 6-month study visit with a regularly scheduled appointment. Our study staff will call participants prior to the intervention visit to confirm availability and remind them of the study appointment. In order to maximize retention during the follow-up phase of the study, study staff will contact participants by telephone as needed and ask about any problems using the smart bottle.

Study Flow:



Educational Session: Participants will meet with the interventionist approximately 4 weeks or up to several months (depending on convenience for the participant) following the enrollment visit. We will work with participants to find the most convenient time for schedule the educational session. Participants will be compensated $25 for their time. The intervention will be delivered one-on-one in a private room in the Durham VA. At the education session visit, all participants will be given a "smart bottle" (AdhereTech, NYC) to house one of their glaucoma medications. If a participant is prescribed more than one glaucoma medication, the AdhereTech bottle will house the medication that is dosed most frequently. If the participant is prescribed more than one glaucoma medication and all glaucoma medications are dosed at the same frequency, the AdhereTech bottle will house the medication that the participant has been prescribed for the longest period of time... The smart bottle records the date and time that the bottle is opened. For participants in the intervention arm only, a reminder function from AdhereTech will be activated. Patients will have the option of choosing up to three reminder methods: text message, phone call, bottle will beep. All reminder messages will comply with VA privacy standards. Companions, if applicable, will accompany the Veteran in the education session and if the companion is responsible for drop administration, drop administration instruction will be directed towards the companion.

Interventionist: The interventionist will be an ophthalmic technician trained by Dr. Muir in the content and delivery of the intervention. An ophthalmic technician is chosen as the interventionist because, in most eye clinics, the ophthalmic technician sees the patient before and sometimes after the eye care provider and is responsible for some or all of the patient education provided. Ophthalmic technicians are employed in most, if not all, VA Eye Clinics.

Intervention Arm Content:

1. Video testimonial from a glaucoma patient: (http://www.eyecareamerica.org/news/press/, (Don Saunders discusses his glaucoma diagnosis).
2. Discussion of glaucoma and the potential for blindness, facilitated by the glaucoma educator using a 3-dimensional model eye: (http://www.shopanatomical.com/ProductDetails.asp?ProductCode=ACC-JS6513&Click=26698&gdftrk=gdfV2758_a_7c884_a_7c3471_a_7cACC_d_JS6513) and photographic representation of glaucomatous vision loss
4. One-one-one demonstration of eye drop instillation techniques. The participant will also demonstrate for the study coordinator how he or she instills eye drops so that individualized feedback regarding success of instillation and possible contamination of the bottle tip can be discussed with the subject.

5. Provision of a mnemonic aid which alerts the participant to missed doses. We will develop a library of messages which can be delivered via text or voicemail to remind participants to take their eye drops. The messages will be consistent with the barriers identified by the participant on the SASES. For example, if a participant has noted difficulty taking drops while a work, the reminder may include a suggestion to keep an extra eye drop bottle at work.

6. Review of the participant manual, described below.

The educator will lead the discussion with the aid of a leadership manual, outlining the steps of the intervention, potential questions, and suggested responses. Each subject will receive a participant manual for use in the session and at home that contains:

a. An illustrated brochure on glaucoma and eye drop instillation technique that we developed to be appropriate for patients with a 4th grade reading level.

b. An individualized schedule for dosing of glaucoma medications. Subjects will be given written instructions consisting of a simple chart of the name of each eye drop, the color of the top on the bottle and the number of times per day that each medication should be used.

c. Individualized suggestions for improving adherence based on the subject's responses to the Self-reported Adherence and Self Efficacy Survey (SASES). The identification of each specific problem on the SASES will be linked to recommendations directed at resolving the problem. In such a way, the intervention will be tailored to each subject's individual needs.

Control Arm Content: The control arm is designed as an attention control that includes interaction with the interventionist. This will allow us to attribute observed differences to the content of the intervention, rather increased interaction with a provider. Veterans randomized to the control arm will be scheduled for a session with the interventionist approximately 4 weeks after the enrollment visit. The information session will be delivered one-on-one in a private room in the Durham VA. The control visit will include review of a Powerpoint presentation on general eye health, including but not specific to glaucoma. The control session will last approximately 60 minutes, similar in length to the time spent in the intervention. Participants in the control arm will receive an electronic medication monitor but the reminder function will not be activated. Companions, if applicable, will accompany patient participants to the educational session.

6 month Study Visit: At approximately 6 months after randomization, we will schedule a follow up appointment with both control and intervention arm participants. We will have participants bring back their Adhere Tech bottles and participants will be compensated $20. At the 6-month study visit we will administer the SASES survey, the NEHEP survey as well as ask about any intermittent life events; we will observe eye drop administration and if the companion is responsible for drop administration, drop administration observation will be directed towards the companion.

12 month Study Visit: At approximately 12 months following initial intervention visit we will call participants and administer the SASES survey, the National Eye Institute Visual Function Questionnaire survey, EuroQol as well as ask about any intermittent life events.
We may call participant and/or companion after the 12 month study visit to ask follow up questions on their experience in our research study.

Table 1:
Timetable of Data Collected from Patients and Companions

Patient Participant Measures	Baseline	Ed Session	6 months	12 months
Demographics: Age, sex, race, ethnicity, education, marital status, living environment, self-rated health	X			
General: Rapid Estimate of Health Literacy in Adults[63]	X			
Self-reported glaucoma medication adherence: Self-reported Adherence and Self-efficacy Survey (SASES)	X		X	X
EuroQol (EQ-5D5L) EuroQolEuroQol	X			X
Intermittent Events: Stressful life events, Changes in vision			X	X
Observation of eye drop administration	X	X	X	
Smart bottle data			X	
NEHEP	X		X	
Travel	X			
National Eye Institute Visual Function Questionnaire	X			X
Chart Abstract:				
Ophthalmologic: Visual acuity; ophthalmic diagnoses, history of ophthalmic surgery/laser, most recent visual field parameters including mean deviation and severity	X			X
General Medical: Comorbidities, Medication list	X			X

Adverse Events

All adverse events will be reported per Durham VAMC requirements.

Costs and/or Payments to Subjects

There will be no cost to research participants for any research treatment or research testing done as part of this research study. Some Veterans are required to pay co-payments for medical care and services provided by the VA. These co-payment requirements will continue to apply to medical care and services provided by the VA that are not part of this study. Participants in the study will be offered $20 to compensate for their time. Participants are welcome to discontinue study activities at any time. Companions will not be compensated.

Data and Safety Monitoring

Prospective Study: The data pull for potential participants will be obtained from the Corporate Data Warehouse. This process is typically executed with a DART application following IRB study approval. All data will be collected by members of the study team managed by the Durham VA

Medical Center HSR&D: Legacy Tower, Durham, NC floor 6 room 636. A paper chart review form will be used by the study coordinator or research assistant when reviewing patient charts from the original data pull. This information will be entered into an Illume survey once it's completed. This will allow quicker review of charts. The chart review form containing inclusion and exclusion criteria will have the patients study ID number, date of chart review, and name of study staff that completes the review. Survey responses will be collected using an Illume survey or with paper documents and then entered into an Illume survey. The paper documents of the surveys will only be used if we are unable to access the Illume surveys due to network connectivity problems. Therefore, the paper documents will only serve as a backup form of data collection. Once data can be entered into Illume the study coordinator or research assistant will do so. All study files with the exception of forms that require PHI such as consent forms are organized by study ID number and no other identifiers. The study tracking database containing study ID, full names, full SSN, addresses, phone numbers, and dates of clinic appointments will be protected using passwords and study group policies and will be accessible only to personnel on current staff listing who need to contact subjects, such as the project coordinators, research assistants, and study clinicians.The tracking database loated at R:vhadurhsrdfile1\$research\distributedapps\hsrdtrackingapp will serve as a crosswalk linking the patient PHI to their study ID. Only members of our DVAMC research team will have access to identifiers and coded data. Coded data with direct identifiers removed (i.e., name, address, telephone numbers, SSN, DOB) will be placed behind the VA firewall. DVAMC HSR&D study staff statisticians will have access to data through VINCI during the analysis phase of our study.

The in-person intervention/control session will be audio-recorded using voice recorders directly connected to VA issued laptops or desktops that meet applicable regulations for updates, encryption and information security. The "Sparky" USB audio recorder is a pass through audio recorder which does not store any data. Software is required for this device which is installed and configured by VA OI&T personnel after sanctuary exemptions have been obtained. Transcription of the qualitative interviews will be conducted utilizing VA approved software installed and configured by VA OI&T personnel after sanctuary exemptions have been obtained.

The AdhereTech data (date and time of opening the bottle) will be sent using a FIPS 140-2 secure algorithm for our authentication protocol to a secure server maintained by AdhereTech. Data will be accessed by our study staff via a secure login to AdhereTech.com. The data will be accessed from AdhereTech.com and downloaded directly into our study project folders behind the VA firewall. A crosswalk will be made to link the patient to the specific AdhereTech device they used. Adhere Tech will have coded information (i.e. device identifier only) about participants in the control arm and identified information (i.e. phone number & device identifier) for participants in the intervention arm. The patient information is entered by research study staff on the server-side of Adhere Tech through an online secure login.

Data Storage: The bottle itself contains no stored patient data whatsoever. It contains only a unique Bottle ID which is mapped to the patient's information in AdhereTech's secure backend server only. The only identifying piece of information AdhereTech stores about patients is the phone number they have requested to be contacted in the event of a dosage reminder event. Even this is optional if the participant choses to have the bottle beep as a reminder. AdhereTech follows all measures of the HIPAA security rule to ensure that patient data is properly secured and encrypted while at rest.

Data Transmission: AdhereTech does not transmit any patient information over the cellular connection. Only encoded measurements taken from the bottle and its unique bottle ID. AdhereTech utilizes a FIPS 140-2 secure algorithm for our authentication protocol and cryptographic hashing protocol to authenticate bottle connections to the AdhereTech backend

server. This ensures that all bottle data received comes only from AdhereTech bottles. AdhereTech uses the GSM network for its cellular connectivity (AT&T in the United States), in order to secure our bottle connections against main-in-the-middle eavesdropping attacks. Once connected to the cellular network, the bottle communicates using an HTTP post. AdhereTech supports an additional layer of security by utilizing HTTPS for Bottle->Server communication. AdhereTech's infrastructure machines communicate with one another on a private access-list controlled intranet using TLS/SSL. The bottle does not collect, store, or transmit any PHI. The bottle transmits measurement data to secure servers managed by AdhereTech, where they are then linked to the patient. However, the patient is only denoted by the anonymized unique ID of our choosing.

Data used for post study analysis will come from VINCI. Once data has been extracted study/OI& T personnel will extract and move relevant study data files to the secure VINCI project space allocated to this study by VINCI. OI&T and VINCI personnel not under the purview of the PI will control the servers, network, processors, firewall and software behind the VINCI firewall, including access rights granted to study personnel. VINCI personnel will be responsible for maintaining VINCI servers where study data will be kept. It will be VINCI personnel who will move, backup and remove study data from VINCI servers and who will control access to data stored on VINCI servers.

Future Data Use: Data collected during the course of the study will be maintained for use in a future data repository (the IRB documents for this planned repository have not yet been submitted). This language is included in the Informed Consent Form and HIPAA waiver to be signed by study participant.

Privacy, Confidentiality, and Information Security

1. **Lists of Data Reviewed and/or Collected for Screening/Recruitment and Conduction of Study:**

The Personal Health Information that will be obtained, used, and/or shared for this study includes:

Identifier(s)	Source(s) of Health Information
☒ Names	☒ Medical history & physical exam information: Diagnosis list: Diagnosis of glaucoma, primary open angle glaucoma, secondary glaucoma, pigment dispersion glaucoma, open angle glaucoma NOS, glaucoma suspect. Opthamology progress notes: eye exams, eye procedures, active medications, humphry visual field exam including date of exam, intraocular surgeries including type and date, active uveitis or ocular infections including type and date, visual acuity values. Primary care progress notes: active medications, comorbidities.
☒ All geographic subdivisions smaller than a State, including street address, city, county, precinct, and zip code. Describe: Home address including house number, street, city, state, zip code and PO Box number.	☒ Photographs, videotapes, audiotapes, or digital or other images – In order to ensure fidelity to the proposed intervention, approximately every 8th one-on-one session will be audio-recorded

Identifier(s)	Source(s) of Health Information
☒ All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, visit or treatment dates, etc.; and all ages over 89, Describe: Date of birth, date and time of clinic appointments (prior and future - primary care and specialty clinic visits), date of eye procedures, date of eye exams, date of eye surgeries, date of humphry visual field exam, date of eye pressure results, date of occular infections.	☐ Biologic specimens (e.g., blood, tissue, urine, saliva). Describe:
☒ Telephone numbers	☒ Progress notes
☐ Fax numbers	☒ Diagnostic / Laboratory test results
☐ Electronic mail addresses	☒ Operative reports
☒ Social Security Numbers	☐ Imaging (x-ray, CT, MRI, etc.)
☐ Medical record numbers	☐ Discharge summaries
☐ Health plan beneficiary numbers	☒ Survey / Questionnaire responses
☐ Account numbers	☐ Billing records
☐ Certificate and/or license numbers	☐ HIV testing or infection records
☐ Vehicle identifiers and serial numbers, including license plate numbers	☐ Sickle cell anemia information
☒ Device identifiers and serial numbers – of the Adhere Tech bottle	☐ Alcoholism or alcohol use information
☐ Web Universal Resource Locators (URLs)	☐ Drug abuse information
☐ Internet Protocol (IP) address numbers	☐ Mental health (not psychotherapy) notes
☒ Biometric identifiers, including finger & voice prints	☐ Psychological test results
☐ Full-face photographic images and any comparable images	☐ Genetic testing
☒ Any other unique identifying number, linked study ID, characteristic, or code, describe: Creation of a Study ID	☒ Other, describe: CAN (Care Assessment Need) Score

All non-Veterans enrolled in this study will receive the VA Notice of Privacy Practices (NOPP) and are requested to sign the acknowledgment form. The signed acknowledgment form will be maintained with the research records.

2. Data and/or Specimen Acquisition:

Data for this study will be collected through (*check all that apply*):

☒ Prospective data and/or specimen collection obtained from participants. Provide description of processes:

The data will be captured with Illume Survey; entered by research study member:

1. Chart Review - The medical records of potential participants identified by the data pull will be reviewed in detail to confirm eligibility based on the remaining inclusion/exclusion

criteria. Inclusion criteria for patients: Diagnosis of open angle glaucoma [primary open angle glaucoma, pigment dispersion glaucoma, pseudoexfoliation glaucoma, combined mechanism glaucoma, low tension glaucoma] recorded in the medical record, Prescribed glaucoma eye drops, Visual field performed within the last 9 months. As visual field testing is standard care glaucoma and we wish to establish baseline glaucoma severity, we will require that subjects have a visual field test documented in the chart within 18 months of enrollment. Exclusion criteria for patients: Intraocular surgery in the past 3 months or anticipated in the next 3 months [as prescribed drops may change frequently in the perioperative period], Active uveitis or eye infection [as medication regimen may vary from day to day], Visual acuity less than 20/70 in the better-seeing eye, because Veterans with low vision may not be able to complete the vision-dependent tasks required for study completion. (submitting a Waiver or Alteration of Informed Consent Process and Waiver or Alteration of HIPAA Authorization for screening purposes).

2. Screener call survey to asses for participant interest and poor adherence (submitting a Waiver or Alteration of Informed Consent Process and Waiver or Alteration of HIPAA Authorization for screening purposes).
3. Baseline - After patient has signed ICF and HIPAA Authorization: Demographics: Age, sex, race, ethnicity, education, marital status, living environment, self-rated health; General Medical: Comorbidities, Medication list, Ophthalmologic: Visual acuity; ophthalmic diagnoses, history of ophthalmic surgery/laser, most recent visual field parameters including mean deviation and severity; General: Rapid Estimate of Health Literacy in Adults[63] and survey of available and preferred means of communication (cell phone call or text, landline), mental cognition; Self-reported glaucoma medication adherence: Self-reported Adherence and Self-efficacy Survey (SASES); National Eye Institute Visual Function Questionnaire; EuroQol 5D-5L, National Eye Health Education Program 10 T/F questionnaire (NEHEP), Travel; Observation of eye drop administration.
4. 6 Month Study Visit - Self-reported glaucoma medication adherence: Self-reported Adherence and Self-efficacy Survey (SASES); Intermittent Events: Stressful life events, Changes in vision. Smart bottle data: Medication events collected from smart bottle device, including date and time. Wwill observe eye drop administration; NEHEP.
5. 12 Month Study Visit - Obtained over the telephone: Self-reported glaucoma medication adherence: Self-reported Adherence and Self-efficacy Survey (SASES); National Eye Institute Visual Function Questionnaire; EuroQol 5D-5L; Intermittent Events: Stressful life events, Changes in vision; From chart abstraction: General Medical: Comorbidities, Medication list; Ophthalmologic: Visual acuity; ophthalmic diagnoses, history of ophthalmic surgery/laser, most recent visual field parameters including mean deviation and severity; Intensification of glaucoma therapy: addition of adjuvant medical therapy, glaucoma laser, or glaucoma surgery.

☒ Retrospective data collection and/or specimens obtained from medical chart review/data access. Describe how data will be obtained (e.g., fileman, CDW, etc.): Potential participants will be identified by a data pull of Veterans with upcoming appointments at the DVAMC meeting inclusion/exclusion criteria. Data pull for potential participants will be obtained from the Corporate Data Warehouse. This process is typically executed with a DART application following IRB study approval. The medical records of potential participants identified by the data pull will be reviewed in detail to confirm eligibility based on the remaining inclusion/exclusion criteria. Data used for Aim 3 analysis will come from VINCI. Once data has been extracted study/OI& T personnel will extract and move relevant study data files to the secure VINCI project space allocated to this study by VINCI. OI&T and VINCI personnel not under the purview of the PI will control the servers, network, processors, firewall and software behind the VINCI firewall, including access rights granted to study personnel.

☐ Retrospective data collection and/or specimens obtained from an IRB-approved data and/or specimen repository. Indicate the repository source including name, VA location, and IRB number: .

Note: for data and/or specimens obtained from a VA approved data repository, a Data Use Agreement (DUA) must be executed prior to obtaining data and/or specimens. See VHA Handbook 1200.12 for further information.

3. Level of Data:

The following level(s) of data will be acquired/maintained for this study (*check all that apply*):

☒ Identified (e.g., names, addresses or other identifiers included)
☒ Coded (direct and/or all identifiers removed, but study code/ID included)
☐ De-Identified (all HIPAA 18 and study ID/code removed):
- ☐ Verified Statistically

OR

- ☐ Verified by Absence or Removal of HIPAA 18 and study ID

☐ Limited Data Set
☐ Other: Describe:

4. Location of Data and/or Specimens, and Data Retention Plan:

A. All data will be collected by members of the study team managed by the Durham VA Medical Center HSR&D: Legacy Tower, Durham, NC floor 6 room 636. Electronic files with PHI will be stored on a password protected secure VA server located at P:\\vhadurhsrdfile1\$projects [P:\MAGIC]. A paper chart review form will be used by the study coordinator or research assistant when reviewing patient charts from the original data pull. This information will be entered into an Illume survey once it's completed. This will allow quicker review of charts. The chart review form containing inclusion and exclusion criteria will have the patients study ID number, date of chart review, and name of study staff that completes the review. Survey responses will be collected using an Illume survey or with paper documents and then entered into an Illume survey. The paper documents of the surveys will only be used if the VA servers go down or the Illume survey is not working. Any data that is collected on paper the document will be stored at HSR&D: Legacy Tower, Durham, NC floors 6 room 636. The signed informed consent and HIPPA documents safeguarded under lock and key at locations managed by the Durham VA Medical Center HSR&D: Legacy Tower, Durham, NC floor 6 room 636. Electronic files with PHI will be stored on a password protected secure VA server located at P:\\vhadurhsrdfile1\$projects [P:\MAGIC IIRThe tracking database loated at R:vhadurhsrdfile1\$research\distributedapps\hsrdtrackingapp will serve as a crosswalk linking the patient PHI to their study ID.

B. In order to ensure fidelity to the proposed intervention, approximately every 8th one-on-one session will be audio-recorded and reviewed by Dr. Muir and the co-investigators with changes made as needed. At the start of the recording we will remind the Veteran and partner that the session is being recorded and that their assent will be captured on the recording. We will tell them that they do not have to give their names, but just say "yes" to the prompt you given them (e.g, "is it ok to record the session"). The one-on-

one session will be audio-recorded using voice recorders directly connected to VA issued laptops or desktops that meet applicable regulations for updates, encryption and information security. The "Sparky" USB audio recorder is a pass through audio recorder which does not store any data. Software is required for this device which is installed and configured by VA OI&T personnel after sanctuary exemptions have been obtained. Transcription of the qualitative interviews will be conducted utilizing VA approved software installed and configured by VA OI&T personnel after sanctuary exemptions have been obtained.

☒ Data will be also be placed at the VA Informatics and Computing Interface (VINCI; http://vaww.vinci.med.va.gov/vincicentral/VINCIWorkspace.aspx). The VA Informatics and Computing Infrastructure is a partnership between the VA Office of Information Technology and the Veterans' Health Administration Office of Research and Development. Researchers and operations staff can use VINCI to access data and statistical analysis tools in a virtual working environment through a certified VHA network computer using the VA Intranet or Virtual Private Network (VPN).

B. Data Retention Plan

☒ Research records will be maintained and destroyed according to the National Archives and Records Administration, Records Schedule Number: DAA-0015-2015-0004. Records destruction, when authorized, will be accomplished using the then current requirements for the secure disposal of paper and electronic records. Currently, destruction of research records (see DAA-0015-2015-0004, section 7.6 "Research Investigator Files" for materials included in research records) is scheduled for 6 years after the cut-off (the cut-off is the completion of the research project) and may be retained longer if required by other federal agencies. Records will not be destroyed without pre-notification to the facility records manager. .

☒ Other data retention plan, describe: Data collected during the course of the study will be maintained for use in future studies focused around investigation of glaucoma and treatment adherence.

5. Data Access and Data Recipients:

Only members of our DVAMC research team will have access to identifiers and coded data. Coded data with direct identifiers removed (i.e., name, address, telephone numbers, SSN, DOB) will be placed behind the VA firewall. DVAMC HSR&D study staff statisticians will have access to data through VINCI during the analysis phase of our study. Adhere Tech will receive the phone number and study subject ID for subjects in the intervention arm if the subject agrees to be contacted via text as a reminder to open their medication bottle.

All VA research personnel who have access to VHA records are instructed, in accordance with VA policy, on the requirements of Federal privacy and information laws and regulations, VA regulations and policies, and VHA policy. All study personnel who are VA employees working

within the VA system have fulfilled all required HIPAA and other VA security and privacy policy training requirements and have agreed to follow guidelines pertaining to the protection of patient data. All research staff sign VA Rules of Behavior, and all study staff are up-to-date with VHA Privacy Policy Training and the VA Office of Cyber and Information Security Awareness Training Course. The data security and privacy procedures summarized in that course include logging off or locking the computer when walking away from it; no sharing of access codes, verify codes or passwords; not allowing anyone else to use the computer under one's password; and disposing of sensitive information using VA-approved methods (e.g., shredder bins).

Access to study data will be removed for all study personnel when they are no longer part of the research team.

6. Data and/or Specimen Transportation and/or Transmission for all data and/or specimens involved in the study:

I. ☐ Data and/or specimens will not be transported or transmitted outside of Durham VAMC environment.

II. ☐ Data and/or specimens will be transported BETWEEN sites that are under the auspices of the Durham VA Medical Center.

a. ☐ Local DVAMC memorandum "Authorization to Use, Process, Store, or Transmit VA Sensitive Information Outside VA Owned or Managed Facilities" has been pre-filled out for each study team member who may transport the data and/or specimens off-site. This (these) forms are included with the IRB materials.

b. ☐ Containers (e.g., briefcase, bin) are labeled with the following notice (label placed on the outside of container):

NOTICE!!!

Access to these records is limited to: AUTHORIZED PERSONS ONLY. Information may not be disclosed from this file unless permitted by all applicable legal authorities, which may include the Privacy Act; 38 U.S.C. §§ 5701, 5705, 7332; the Health Insurance Portability and Accountability Act; and regulations implementing those provisions, at 38 C.F.R. §§ 1.460 – 1.599 and 45 C.F.R. Parts 160 and 164. Anyone who discloses information in violation of the above provisions may subject to civil and criminal penalties.

III. ☐ Data and/or specimens will be transmitted to other VA sites using the following method(s):

A. Data

☐ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted disk (encryption is optional).

☐ Data are coded or contain identifiers and thus will be sent

☐ Other, describe:

B. Specimens

☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional).

☐ Specimens are coded or contain identifiers and thus will be sent via VA-authorized carrier with tracking.

☐ Other, describe:

IV. ☒ Data and/or specimens will be transported non-VA/VHA sites (e.g., academic affiliates, laboratories, etc.) using the following method(s):

A. Data

☐ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted CD.

☒ Data shared with Adhere Tech (study ID and potentially phone number of subjects in the intervention arm) is entered by research study staff on the server-side of Adhere Tech through an online secure login.The AdhereTech data (date and time of opening the bottle) will be sent using a FIPS 140-2 secure algorithm for our authentication protocol to a secure server maintained by AdhereTech. Data will be accessed by our study staff via a secure login to AdhereTech.com. The data can be accessed at AdhereTech.com and downloaded directly onto a VA computer. The AdhereTech device and system does not store any PHI. A crosswalk will be made to link the patient to the specific AdhereTech device they used. Data Storage: The bottle itself contains no stored patient data whatsoever. It contains only a unique Bottle ID which is mapped to the patient's information in AdhereTech's secure backend server only. The only identifying piece of information AdhereTech stores about patients is the phone number they have requested to be contacted in the event of a dosage reminder event. Even this is optional. AdhereTech follows all measures of the HIPAA security rule to ensure that patient data is properly secured and encrypted while at rest.

Data Transmission: AdhereTech does not transmit any patient information over the cellular connection. Only encoded measurements taken from the bottle and its unique bottle ID. AdhereTech utilizes a FIPS 140-2 secure algorithm for our authentication protocol and cryptographic hashing protocol to authenticate bottle connections to the AdhereTech backend server. This ensures that all bottle data received comes only from AdhereTech bottles. AdhereTech uses the GSM network for its cellular connectivity (AT&T in the United States), in order to secure our bottle connections against main-in-the-middle eavesdropping attacks. Once connected to the cellular network, the bottle communicates using an HTTP post. AdhereTech supports an additional layer of security by utilizing HTTPS for Bottle->Server communication. AdhereTech's infrastructure machines communicate with one another on a private access-list controlled intranet using TLS/SSL. The bottle does not collect, store, or transmit any PHI. The bottle transmits measurement data to our secure servers, where they are then linked to the patient. However, the patient is only denoted by the anonymized unique ID of your choosing. Thus, no PHI is required for AdhereTech.

For intervention arm participants (in which the reminder function is activated) we will make clear in the HIPAA Authorization and Informed Consent that the Adhere tech server will have contact information on the patient if they choose to request text messaging or phone call as their reminder feature. .

☐ Data are coded or identified and will be uploaded to sponsor website using electronic case report form (eCRF) https://www.adheretech.com/users/sign_in which uses TLS 1.2, AES with 256 bit encryption (High); ECDH_P256 with 256 bit exchange. If the workstation is changed during this study we will enable any new workstation with this configuration.

☐ Other, describe:

B. Specimens N/A

☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional) or will be hand-delivered by research study personnel. Specify method of delivery:

☐ Specimens are coded and thus will be sent via VA-approved carrier with tracking or will be hand-delivered by research study personnel. Specify method of delivery:

In accordance with the HIPAA and the Privacy Act, for any coded or identifiable data or specimens released from the Durham VAMC (with the exception of Limited Data Sets), an Accounting of Disclosure (AOD) will be maintained (e.g., in a database or spreadsheet) that includes the participant's name, date of the disclosure, description of the nature of the Individually Identifiable Information (III) disclosed, purpose of each disclosure, and the name and address of the person/agency to whom the disclosure was made.

7. Risk Mitigation Strategies:

☐ Data are fully de-identified (stripped of HIPAA 18 and study ID/code) before being shared outside of Durham VAMC.

☐ Specimens are fully de-identified (stripped of HIPAA 18 and study ID/code before being shared outside of Durham VAMC.

☒ Direct identifiers will be maintained separately from data and or specimens by using a code to "identify" subjects. In a separate database (i.e., a "linking" or "cross-walk" database) this code will be linked to identifying subject information.

☐ Other, specify:

8. Suspected Loss of VA Information:

Should any incident such as theft or loss of data, unauthorized access of sensitive data or non-compliance with security controls occur it will be immediately reported according to VA policy. All incidents regarding information security/privacy incidents will be reported to the ISO and PO within 1

hour of acknowledgement of issue and done so using the VHADUR Research Events Report e-mail group (VHADURResearchEventReport@va.gov).

9. Reporting of Results:

☒ Reporting of results, such as in scientific papers and presentations, will never identify individual subjects. Data will be presented in aggregate and individual-level data will not be published.

☐ Other results reporting plan, describe:

10. Future Use of Data:

☒ Data will be retained for future use. This is described elsewhere in the protocol and is noted in the HIPAA authorization.

☐ Future Use of data is optional (i.e., not required by the research subject).

☒ Future Use of data is required for participation in the study.

☐ No future use of data is currently planned.

11. Use of Mail Merge Technology

☐ Mail merge programs will be used to generate letters and/or address labels for mailings to potential or already enrolled research subjects. The study team is aware that to reduce risk of mail merge related privacy incidents, use of mail merge programs requires a 25% accuracy check to verify that (potential) research subject name and mailing address are properly "matched". If discrepancies are found, a 100% accuracy check is required before letters may be mailed.

Data Analysis and Statistical Considerations

Specific Analyses Planned:

Specific Aim 1: Evaluate the impact of an intervention to improve glaucoma medication adherence among Veterans at 6-month follow up.

Hypothesis 1: Veterans randomized to the intervention will have a greater proportion of prescribed glaucoma medication doses taken as measured by the electronic medication monitor in the 6 months following the intervention compared to Veterans randomized to the control arm.

The primary outcome measure is each patient's proportion of prescribed doses taken in the 6 months after the intervention according to the electronic monitor. We will use general linear regression models to test for a between-group difference in mean proportion of prescribed doses over 6 months. This regression model can be written as: $Y_i = \beta_0 + INT_i*\beta_1 + FREQ_i*\beta_2 + COM_i*\beta_3$, where Y_i represents the proportion of prescribed doses that patient i has taken through the 6-month follow-up. In this model, INT_i is the intervention group indicator; therefore, β_1 represents the mean difference in proportion of prescribed doses in the INT group as compared to the control group. We will formally evaluate the intervention effect by testing that β_1 differs from zero and report the mean difference and corresponding 95% confidence interval. A mean difference significantly greater than 0 provides evidence that INT group patients have a greater mean proportion of prescribed doses taken. The model will also include stratification

variables (frequency of glaucoma medication dosing (once vs more than once daily, FREQ)), companion (COM)) as recommended in the CPMP guidelines.[66]

In addition to the preceding model, mean adherence will also be separated into six 30-day intervals and incorporated into a longitudinal model. This will allow us to understand trends of adherence over the course of the 6-month follow up period (e.g. initial improvements following the intervention followed by stability or decline). Non-linearity of these changes over time can be evaluated and contrasted between groups using SAS PROC MIXED. The richness of this adherence data will also enable us to explore particular patterns of nonadherence often associated with clinical progression of disease. For example, in exploratory analyses, we will examine whether intensification of therapy may be associated with running out of drops before the next available refill and missing the last week of dosing each month versus rationing drops such that drops are used only every 2-3 days.

Specific Aim 2: Evaluate the impact of the intervention on intensification of glaucoma therapy among Veterans at 12-month follow-up.

Hypothesis 2: The proportion of Veterans in the intervention arm that are prescribed more intensive glaucoma therapy, defined as addition of adjuvant glaucoma medication or recommendation for laser or glaucoma surgery will be less than the proportion of Veterans in the control arm who are prescribed more intensive glaucoma therapy in the 12 months following the intervention.

We will use logistic regression to test for a between-group difference in rates of therapy intensification at 12 months. This logistic regression model can be written as: $\text{Logit}(p_i) = \beta_0 + INT_i*\beta_1 + LIT_iFREQ_iLIT_i*\beta_2 + COM_i*\beta_3$, where p_i represents the probability that patient i has intensified therapy by the 12-month follow-up. Similar to above, INT_i is the intervention group indicator; therefore, β_1 represents the log-odds ratio of therapy intensification in the intervention group as compared to the control group. We will formally evaluate the intervention effect by testing that β_1 differs from zero and report the odds ratio ($\exp(\beta_1)$) and 95% CI of the odds ratio. We will formally evaluate the intervention effect by testing that β_1 differs from zero and report the odds ratio ($\exp(\beta_1)$) and 95% CI of the odds ratio. In this case, however, an odds ratio significantly less than 1.0 provides evidence that intervention group patients have lower rates of intensification of glaucoma therapy. Again, the model will also include the randomization stratification variables (healthdaily dosing frequency (FREQhealth literacy (LIT), companion (COM)).

Specific Aim 3: Evaluate the incremental cost-effectiveness and budget and workflow impacts of the intervention compared to control.

The economic analysis will be conducted in the base-case from the VA's perspective. However, we will also collect patient costs, and thus taken together, will approximate a societal perspective. The time horizon for analysis of the first two incremental cost-effectiveness ratios will be the 6-months following intervention; for blindness averted and QALYs saved, we will adopt a lifetime time horizon. Future costs will be inflated at a 2% annual rate and future costs and benefits will be discounted at 3% annually in the base-case. We will use a range of 0-5% for these parameters in sensitivity analysis.

Direct Intervention Arm Cost. The main intervention costs are labor inputs, consisting of the one-time fixed labor cost of training and the variable labor cost of conducting the adherence intervention. To calculate training cost, we will multiply Dr. Muir's and the ophthalmic technician's respective wage rates, including fringe benefits cost, by the 3 hours needed for training. Training cost will be applied in the base-case analysis, but because training cost attenuates over time as more patients are treated, it will be excluded in sensitivity analysis. For each one-on-one session and monthly booster phone calls with the patient/companion, the

interventionist will log the session and phone call times. These times will be multiplied by the technician's wage rate to estimate intervention variable labor cost. The non-labor cost inputs will consist of the smart bottles and eye drop aids provided to patients. The fixed training, variable intervention labor and non-labor inputs will be aggregated and then divided by the number of patients in the intervention arm to derive per-patient intervention cost.

Direct Control Arm Cost. Time of each one-on-one session with the patient/companion will be logged and multiplied by the technician's wage rate to estimate per-control patient cost.

Indirect cost. The VA healthcare system also incurs costs, such as administration, utilities, and custodial services that cannot be directly attributed to a given health care service but nonetheless should be included in the cost analysis. We will collect direct and indirect costs observed for ophthalmology clinic stop codes in the VA Decision Support System (DSS) extract for the Durham VA Medical Center. These will be used to calculate a direct-to-indirect cost multiplier. This multiplier will be applied to the estimated direct intervention and control arm costs to estimate their respective total costs. For both intervention and control arm costs, we will only account for costs that are likely to be incurred in "real world" clinical care; study-driven costs will be excluded. For example, the education session provided to control arm patients isn't likely to occur in usual clinical care and will not be included in the cost estimate.

Resource utilization. Expenditures are impacted not only by the cost of the intervention itself but also on other ophthalmology goods and services utilized. Therefore, we will collect glaucoma medication data from the VA Decision Support System Pharmacy extract. Using eye clinic stop codes and glaucoma diagnosis codes, we will collect outpatient costs incurred during the study period from DSS outpatient extracts.

Patient costs. Attendance of the one-on-one sessions will require the patients and/or companion to incur travel cost and may require that he/she miss work in order to attend the session. We will account for these indirect costs by asking the patients and companions to self-report how far they traveled round trip to attend the one-on-one session and whether they or their companion had to take time off from work to attend the session, and if so, how much time they took off. We will estimate travel cost by self-report and multiply the number of miles traveled by the deduction allowed by the Internal Revenue Service for medical-related travel. We will multiply time missed from work by an average hourly wage rate. The indirect costs reported in each arm will be aggregated and then divided by the respective group samples to estimate per-patient indirect cost.

Cost-Effectiveness. The 3 cost-effectiveness ratios that we will measure are: 1) cost per percentage improvement in medication adherence; 2) cost per blindness averted; and 3) cost per QALYs saved. We will consider the intervention to be cost-effective if the incremental cost-effectiveness ratio is ≤ $100,000 per QALY saved or $150,000 per QALY saved, as recently recommended.[67] The estimation of these ratios are provided in the Data Analysis section below.

Data Analysis for Cost. The analysis will begin with standard descriptive statistics of the cost and effectiveness variables. We will then conduct bivariate analyses to assess statistical significance of group mean differences. If the main outcome is significantly different between the two groups, the first incremental cost-effectiveness ratio will be based on cost and improvement in medication adherence during the study period. However, incremental cost per blindness averted and QALYs saved will require simulating costs and outcomes among a larger hypothetical population and a time horizon beyond the study period. We will estimate

these ratios by replicating the Markov model developed by the Centre for Eye Research Australia.[68] We will use 2nd order Monte Carlo simulation to incorporate probabilistic sensitivity analysis into the base-case estimates and to estimate confidence intervals of the incremental cost-effectiveness ratios. We will also conduct extensive parameter and model sensitivity analyses to assess the robustness of the base-case results. If the main outcome is not statistically significant between the two groups, then the economic analysis will focus on differences in intervention costs and health care costs between the two groups during the study period.

Budget and Workflow Impact. For planning purposes it will be helpful for VA administrators to know what impacts implementing this adherence intervention will have on budget and workflow. We will use US glaucoma prevalence information available in the literature[69] to extrapolate the number of Veterans that are likely to be affected by glaucoma annually. We will multiply this target patient population by the intervention and health care resource utilization costs observed first by the treatment arm patients and then by the control arm patients. The difference between these 2 estimates will be the incremental budget impact of the intervention. Similarly, we will multiply this target patient population by the amount of per-patient time required to conduct the intervention in the treatment and control arms and the incremental time will be the workflow impact. We will convert the incremental workflow impact to full-time equivalents (FTEs).

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