Formal Title: Support, Educate, Empower: The SEE Personalized Glaucoma Coaching Trial

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BACKGROUND AND SIGNIFICANCE

Despite evidence from randomized clinical trials that medication reduces vision loss from glaucoma, it remains the second leading cause of blindness in the United States. A critical barrier to preventing vision loss is that about one-half of glaucoma patients are essentially "untreated" because they do not adhere to their medications. Ineffective self-management behaviors and poor clinical outcomes disproportionately affect the most vulnerable members of US society. There are programs individualized to use techniques such as tailored health communication and motivational interviewing for a wide range of chronic diseases.

(HUM00112614) We developed and pilot tested the The eyeGuide program to offer personalized counseling and education to patients who are poorly adherent to their glaucoma medications as part of their ophthalmic care. In addition, my team developed and pilot tested a glaucoma-specific motivational interviewing training program for ophthalmic para-professional staff. In the eyeGuide program, a trained glaucoma coach uses a web-based application to deliver personalized high-quality, counseling and education.

Our overall objective is to test whether the Support, Educate, Empower: (SEE) Personalized Glaucoma Coaching Program, compared to enhanced standard care by the physician with additional written education materials, improves glaucoma eye drop adherence through a randomized clinical trial among approximately 230 glaucoma patients with poor adherence at enrollment. We will recruit from clinics that serve low-income and minority populations as these populations have a higher incidence of both poor adherence and outcomes from glaucoma.

Our central hypothesis is that glaucoma patients with poor adherence who receive motivational-interviewing based counseling and personalized education from a trained non-physician glaucoma coach through the SEE Program will improve their medication adherence. In the six-month SEE Program, health educators trained as glaucoma coaches use an eHealth program as a tool to deliver personalized education (e.g. based on each person's diagnosis, test results, physician's recommendations) and motivational interviewing-based counseling to guide patients to identify their barriers to optimal adherence and brainstorm solutions. Additionally, participants can choose any or all of their preferred modalities for receiving reminders when a medication dose is missed: an alarm (light or sound), an automated phone call or text message.

OBJECTIVE

Our overall objective is to test whether the SEE Program, compared to enhanced standard care, improves medication adherence through a randomized clinical trial among glaucoma patients with poor medication adherence at enrollment.

SPECIFIC AIMS

1. **Compare the efficacy of the SEE Program with enhanced standard care.** We will compare the intervention group to the enhanced standard care group to determine the intervention group will: a) have greater medication adherence over six months; b) have larger decrease in mean glaucoma-related distress; and c) have greater improvement in mean intraocular pressure.
2. **Identify moderators and mediators of SEE Program effectiveness.** a) Given the higher prevalence of blinding glaucoma among African Americans and those with low incomes, it is important to assess the program effectiveness in those groups, so we will determine if there is an interaction between treatment and race/income; we will also assess whether there is an interaction effect by sex. b) Using the theoretical frameworks of Self Determination Theory and Empowerment Theory, we hypothesize that the SEE Program will improve autonomous motivation alongside improving autonomy support, competence, and satisfaction with care. The mediating effects of these factors on improving adherence will be measured.
3. **Optimize the SEE Program for clinical dissemination using a mixed-methods evaluation of barriers and facilitators to implementation.** Using an integrated framework of the Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) model and the Consolidated Framework for Implementation Research (CFIR), we will interview participants, glaucoma coaches, and key stakeholders to optimize the program. The results will inform future large-scale intervention implementation studies.

METHODS

Specific Aim 1: Compare the efficacy of the SEE Program with enhanced standard care in improving glaucoma. medication adherence.

In Aim 1, we will test the efficacy of the SEE Program to improve medication adherence among glaucoma patients. Our study design is a randomized controlled clinical efficacy trial with an embedded mixed methods analysis. The primary outcome, medication adherence at six months, will be assessed objectively with electronic monitoring. We will test the efficacy of the intervention on improving medication adherence behavior while gathering data that will inform future program dissemination and implementation. We will conduct a parallel, two-armed RCT, recruiting participants (n=230) with self-reported poor adherence in equal numbers from two southeastern Michigan-based health systems {University of Michigan (UM) and Henry Ford (HF)}; that both serve low-income, minority populations. We will oversample African Americans to comprise at least 25% of our sample to ensure adequate power to assess improvements in this sub-population. We will enroll up to 160 participants at UM or HF. We will stop enrollment when the goal of 230 is met combining UM and HF.

We chose to work in two health systems to ensure adequate recruitment of patients who are poorly adherent to their medication and willing to participate.

The study will evaluate whether increasing glaucoma self-management support by having trained health educators provide MI-based counseling and personalized education, facilitated by an eHealth tool, improves medication adherence. We will use mixed methods (i.e., the collection, analysis, and combining of both quantitative and qualitative data) to investigate

elements important for future program implementation and dissemination. Specifically, we will use an "embedded" mixed methods design that involves collecting qualitative data during the intervention to better understand the mechanisms influencing implementation and outcomes. We will gather data on how patients, glaucoma coaches, ophthalmologists, optometrists and key eye clinic administrative personnel experience the intervention. The qualitative data combined with the trial results will drive our refinement of the intervention. This approach will ensure that the intervention has the greatest possible likelihood of future adoption should we find it has positive effects on processes and outcomes of care. The proposed study duration is five years, to allow for patient recruitment, completion of the six-month SEE Program, assessment of outcomes, and quantitative and qualitative data analysis.

Specific Aim: 2 Identify moderators and mediators of SEE Program effectiveness.

The primary moderator we will assess is income (below the federal poverty line or not). We will also assess whether race (African American or not) and sex (male or female) moderate (interact with) the effect of the SEE Program on medication adherence. The primary moderator of treatment effect (income) will be assessed with an interaction term added to a linear regression model of continuous medication adherence, adjusted for known confounders of adherence.

Specific Aim 3: Optimize the SEE Program for clinical dissemination using a mixed-methods evaluation of barriers and facilitators to implementation.

In Aim 3, we will gain an in-depth understanding of participant experience in the SEE Program and of health system key stakeholders' opinions on barriers and facilitators to implementation. Together. Aims 2 and 3 will give us a quantitative and qualitative evaluation of the SEE Program that will enable future program optimization through improved tailoring, more efficient protocols and opportunities to streamline the intervention. At the completion of these Aims, we will have developed a tool kit of all training and intervention materials to guide dissemination efforts in implementing better self-management support to improve glaucoma outcomes.

Rationale for the Intervention

Both empowerment theory and self-determination theory form the basis for our medication adherence intervention. The World Health Organization describes empowerment as a "process through which people gain greater control over decisions and actions affecting their health." Empowerment is particularly important for people who may experience a powerlessness that can come with minority status or poverty. In order for people to best manage their eye health, empowerment theory suggests that they must be supported to develop knowledge and skills to care for their health, coping skills for managing emotions that can negatively affect self-management, and motivation to improve health. Self-determination theory posits that to change a health behavior, people must feel autonomously supported and connected to their health care provider, perceive that they are competent to engage in the behavior, and be motivated to improve.

The application of MI in our study is consistent with the underpinnings of both theoretical frameworks. MI counseling engages patients by discussing priorities and obstacles to facilitate intrinsic motivation— personally compelling reasons— to change health behavior. Recent

Cochrane reviews and meta-analyses of medication adherence interventions found that MI-based counseling was the most successful approach to increasing adherence across many chronic diseases. We hypothesize that using MI-based personalized glaucoma counseling and education will increase participants' motivation, competence, and satisfaction with care, thereby increasing medication adherence and decreasing glaucoma related distress.

RESEARCH DESIGN

Recruitment:

Participant selection will occur from the UMHS and HFHS electronic health records. We will generate a list of all patients at UM and HF taking ≥ 1 ocular hypotensive medication with a diagnosis of any kind of glaucoma, suspected glaucoma or ocular hypertension who are ≥ 18 years of age. A letter will be sent to all potentially eligible participants allowing people to opt out of phone based recruitment.

Inclusion criteria:

- ≥ 18 years of age
- Taking ≥1 ocular hypotensive medication with a diagnosis of any kind of glaucoma, suspected glaucoma or ocular hypertension.
- Did not opt-out from recruitment letter.
- Able to instill eyedrops themselves.
- Have a phone- cell or landline.

Exclusion criteria:

- Do not speak English
- Have a diagnose serious mental illness (defined as schizophrenia, bipolar disorder, or a major depressive episode with psychotic features)
- Diagnosed cognitive impairment
- Do not instill their own eye drops
- Had laser or incisional glaucoma surgery within the last 3 months or scheduled during the six-month study period
- Prisoners
- Active uveitis or ocular infection
- Participated in pilot study
- Unable to attend all study visits

*We will recruit men and women equally. We will oversample African American patients to ensure at least 25% representation in the trial sample.

UM Study staff will become registered Henry Ford Health Systems volunteers. Henry Ford staff will become registered as UM volunteers. This will allow for staff to access clinic space and electronic health records at each institution.

At UM and HF, research associates will call potential participants and obtain verbal consent to give a survey assessing self-reported medication adherence to determine study eligibility. Self-reported medication adherence will be measured from a single question asking "Over the past month, what percentage of your drops do you think you took correctly?" Those who self-report <85% adherence will be invited to participate in the study. Research associates will schedule a baseline visit to complete the informed consent process, the baseline survey, measurement of intraocular pressure and measurement of visual acuity and visual fields if participants have not had a reliable test with the last year(HVF SITA 24-2, ≤20% fixation losses, ≤15% false positives[1]).

Participant Assessments: After eligibility has been confirmed and informed consent has been obtained, prior to randomization, a research associate will measure participants' intraocular pressure (IOP), record socio-demographic characteristics, administer a baseline survey including measures of glaucoma-related distress, glaucoma knowledge, perceived competence, motivation, self-efficacy, and autonomy support from their eye care team. IOP measurements will be taken at all in-person study visits. Surveys will be administered by study staff on a tablet with the ability to enlarge the font or have the survey read out loud. Eye drop instillation will be video-recorded. Additionally, we will use commercially available inertial measurement unit sensors (Xsens-dot, Movella, Netherlands) to assess the kinematics of all eye drop instillations. The sensor will be attached to the bottom of the artificial tear by a custom made silicone sleeve and will not interfere with the dispensing of the artificial tears. Snellen visual acuity will be recorded on all participants. Humphrey visual field testing (SITA Fast, 24-2) will be performed on participants who have not had a reliable visual field (SITA, 24-2) within the last year. Participants will be randomized to the SEE Program (experimental) or enhanced standard care by the physician with additional written education materials (control). Medication adherence will be monitored electronically for all participants from baseline through the end of the 6-month program period. A baseline measure of medication adherence will be obtained by an objective method (medication possession ratios assessed from pharmacy refill data for six months prior to study participation) and subjective method (survey). After six-months, a research associate will video-record eye drop instillation, administer a survey with the same behavioral and psychosocial measures and a quantitative program evaluation, and then a masked research associate will measure IOP and conduct a 15-30 minute semi-structured interview with participants in the SEE Program arm to assess their experience with the program. Additionally, we will call participants that do or did not return for the exit visit to ask if they will complete the exit surveys over the phone. All data will be entered into the REDCap

[1] Heijl A, Patella VM, Bengtsson B. *The Field Analyzer Primer: Effective Perimetry.*4th ed. Dublin, CA: Carl Zeiss Meditec, Inc; 2012.

database. Following completion of the program, pharmacy refill data will be collected for an additional 12 months to assess longer-term effects of the SEE Program.

Randomization: After baseline testing, participants will be given their randomization assignment. We will use block randomization stratified by site to allocate participants to the intervention or control groups. A randomization list using blocks of varying sizes (2, 4, and 6) will be produced in TATUM for each site. Block randomization maintains approximate group size balance during the trial. Varying the block size lowers the likelihood of knowing the group assignment of the next eligible participant. Randomized group status will be available to the research associate by email after baseline information and consent are entered into REDCap and eligibility is confirmed.

Retention strategies: Participants receive incentives: $25 for each completed study visit and $10/month for six months for using the electronic adherence monitor during the trial. The coaching program will be delivered free of charge. Participants randomized to the control arm will have the opportunity to schedule a free coaching session after completing all follow-up assessments. Participants will be given $15 to defray travel costs for each study visit. If a participant has no other means of transportation and lives within 10 miles of the clinic, transportation will be arranged instead of the travel reimbursement.

The research associates will make multiple attempts to re-schedule missed appointments within a one-month window. We will also employ a combination of retention strategies, including pre-appointment reminder calling, phone follow-up of missed appointments, updating of contact information at each visit, and distribution of materials with study phone numbers. Participants will receive a birthday card mailed to their address from the study team.

Intervention and Control Conditions

The SEE Program is a six-month personalized glaucoma coaching program. The glaucoma coach goes over tailored education from a web-based application and uses MI-based counseling to help glaucoma patients identify their barriers to optimal medication adherence and explore potential solutions. Participants attend three in-person coaching sessions. The coach also gives between-session support through four phone calls, with two phone calls between the first and second session and one phone call after each following session. Participants can elect to receive any or none of the following alarms/reminders: an audible alarm, a visual alarm, a text message one hour after a dose of medication is missed or a text message one hour after a dose of medication is missed. (**Figure 1**) The control group received enhanced standard care, receiving three mailings of glaucoma educational materials from leading eye care institutions in parallel to the three in-person coaching sessions. Glaucoma medication adherence will be monitored electronically for all participants between the baseline visit and the exit visit six months later.

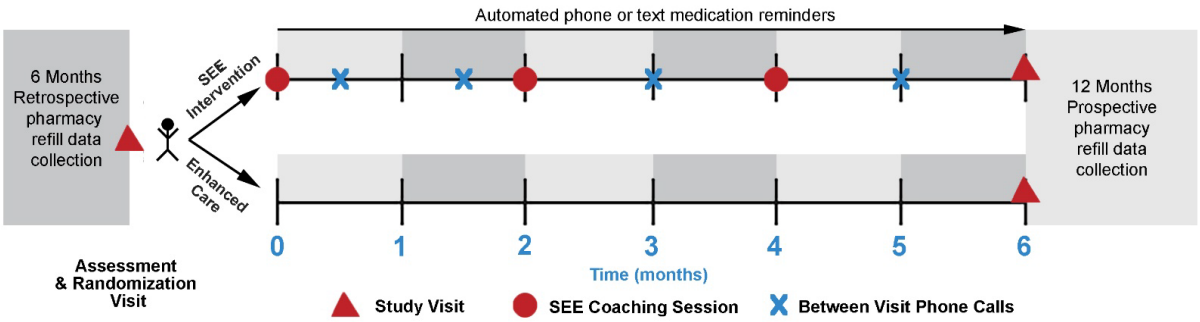

Figure 1. Schedule of SEE Trial visits for Intervention and Control arms; Primary Outcome Assessment at 6 months

Intervention: During the first in-person coaching session, the glaucoma coach uses a web-based application to generate tailored glaucoma educational materials and teach eye drop instillation. The education is tailored on the following variables: name, gender, race/ethnicity, type of glaucoma, glaucoma test results (visual field tests and optic nerve photographs), previous laser or incisional glaucoma surgeries, recommended glaucoma medications, physician's name, cell phone and internet usage, social support, and barriers to adherence. The application also generates MI-based counseling prompts to guide the conversation between the coach and patient. The coach shows the patient the tailored audio-visual educational materials on a large tablet (9"x12") that can be enlarged as needed for patients who are visually impaired. Text is read aloud. Videos can be played at higher volumes to ensure patients can hear. During the session, the coach helps the patient identify barriers to optimal adherence and uses the person's strengths and motivations to guide potential solutions. Over the course of the counseling session, the coach helps the patient put together a list of questions to ask the doctor at the next visit. At the end of each session, the coach uses the web-application to create a written action plan of the next steps to integrate medication taking into the patient's daily routine. Patients receive adherence monitors and choose any or all of their preferred modalities for receiving reminders when a medication dose is missed: an alarm (light or sound) and/or an automated phone call or text message.

Between-session phone calls are tailored to the patient's current level of adherence and focus on problem solving issues that arise. Phone calls are made using Google Voice software allowing the glaucoma coach to use his/her cell phone to call patients from a Google Voice number. This program facilitates a recorded history of call and text conversations. During the second in-person session, patients will discuss their motivation to take care of their vision and what strengths they have that they can use to enact their plan, practice instilling eye drops, and go over their daily routine for eye drop use. In the third session, patients can choose what parts of the personalized glaucoma educational content they would like to review and discuss and trouble shoot any new barriers that may have arisen. (SEE website: https://seeglaucoma.org)

Coaches have two different notes sections in the application. One is to record information for themselves to remember about the participant. The other notes section is for the counselors to record any questions the participants have that would be good to ask their physician. The

counselor then prints out a list of questions for the participant to take to their upcoming physician visit.

Patients will receive approximately 160 minutes of counseling (120 minutes in-person and four 10-minute telephone calls). This is within the range of counseling time (106±92.4 minutes) that achieved significant behavior change in a meta-analysis. The glaucoma coaches update the participants' ophthalmologist on their adherence and action plan. Participants can call their coach if questions arise.

Control condition, enhanced standard care: The purpose of the trial is to measure whether the SEE glaucoma counseling program improves glaucoma medication adherence compared to current practice. Therefore, we chose to use enhanced standard physician care as the comparator to control for the attention effect given by additional education without greatly changing the comparator group from what would currently be delivered in clinic. The enhanced standard care group will receive non-tailored educational content by mail from current gold standard providers (American Academy of Ophthalmology, National Eye Institute and Glaucoma Research Foundation) in three doses parallel to the three in-person coaching sessions.

Sub-Study: At the end of the six-month trial, we will ask all intervention participants if they would like to enroll in the twelve-month sub-study for continued medication adherence using their same adherence monitors. Participants will be reconsented for the sub-sudy and will receive incentives of $10/month by gift card or check in the mail for medication monitoring along with a retention letter. No reminders will be set on the medication monitors during this twelve-month period and participants will have no contact with the study team except for a call as a reminder to charge monitors if needed.

Participants in the sub-study will be scheduled for a final exit visit at the end of this twelve-month period. During the final exit visit, participants will complete the same surveys as in the six-month exit visit, less the Satisfaction with SEE survey and have their IOP's measured by the study team. Participants will receive a $25 incentive for the visit and $15 to offset transportation costs.

OUTCOMES

Primary Outcome: Six-Month Medication Schedule Adherence. Medication adherence will be measured objectively using electronic monitors with a bottle-in-bottle technique where all glaucoma medications are placed inside electronic pill bottles. When the bottle cap is removed, the time and date stamp is sent to our database. An adherent event is defined as using an eye drop medication within a specified time window of a dose on the previous day. For example, for an eye drop medication dosed once per day, an adherent event is defined as taking the medication within 24 ± 4 hours of the previous day's dose. We include this time window because the biological efficacy of eye drop medications decline when not taken on time. We will compare the current day's doses to the previous day's corresponding doses, ensuring that opening a bottle multiple times prior to a clinic visit does not inflate the adherence metric. Adherence will be calculated as the proportion of doses taken on time divided by total doses prescribed over the six-month study period. For participants on more than one medication,

adherence will be first measured at the medication level and then aggregated to the person level by dividing the total number of doses of all medication(s) taken on time by the total number of doses prescribed. Our primary outcome is the mean adherence in the control and intervention groups. We will also assess the proportion of patients who are ≥80% adherent.

Secondary Outcome: Glaucoma-related Distress. Glaucoma-related distress, or the emotional distress participants experience related to having glaucoma, will be measured using the Diabetes Distress Scale adapted for glaucoma (Cronbach's α= 0.93). The Diabetes Distress Scale consists of 17 items with four subscales that measure emotional burden (5 items), physician-related distress (4 items), regimen-related distress (5 items), and diabetes-related interpersonal distress (3 items). In our pilot validation study of three items from the regimen-related distress and emotional burden subscales in a glaucoma population, we found a significant association of increased glaucoma-related distress with poor electronically monitored glaucoma medication adherence (adjusted β = -2.47, standard error (SE) = 0.61, p=0.0001).

Exploratory Outcome: Intraocular Pressure (IOP). Change in IOP between the baseline and exit visit will be assessed. We will measure IOP in both arms using the iCare (Tiolat Oy, Helsinki, Finland), a method that does not require corneal anesthesia. The iCare has been shown to correlate well with gold standard IOP measurement by Goldmann applanation tonometry. We will obtain three reliable (assessed by iCare) measures of IOP at each study visit and use the median as the study visit IOP which will be recorded both in the REDCap database and in the electronic health record to communicate with the participants' ophthalmologist. IOP control greatly reduces vision loss from glaucoma and is used as a surrogate marker of glaucoma control in drug and device trials and in clinical practice. However, given the short duration of the SEE Program, we would expect this intervention to cause at most a small reduction in IOP from baseline to six months, even if diurnal measures of IOP or obtaining IOP at a set time were feasible, which is not the case. We are not powered to detect small changes in IOP. Assessing whether there is a trend toward lower IOP in intervention participants will inform future larger scale trials with a measure of IOP control as a primary outcome.

Statistical Analysis Plan

We will perform intent-to-treat analysis of all randomized participants to evaluate our primary, secondary and exploratory outcomes. We will compare the primary outcome variable, mean adherence, between the two groups using ANOVA, blocking on clinic. We will also analyze the proportion of subjects achieving ≥80% adherence between the treatment group and control group, with the Cochran-Mantel-Haenszel Test for equality of proportions. We will use Student's t-test on post-trial, 12-month medication possession ratios to assess longer-term effects of the SEE Program compared to enhanced standard care.

Additionally, we will use pre-trial medication possession ratios in ANCOVA to investigate whether treatment effectiveness is steady across different levels of pre-trial adherence. We will conduct a sensitivity analysis to test mean adherence between the two groups with ANOVA, blocking on clinic. To investigate trends in adherence over time, we will calculate adherence monthly. Spaghetti plots will visualize trends within the treatment and control groups (linear, step, decaying effect, etc.). Linear regression will test for trends of adherence over time by treatment group.

For the secondary outcome of glaucoma related distress (GRD), we will score the scale according to the measure's documentation at the baseline and exit visits and calculate change. Descriptive statistics and plots will be generated to understand the distribution of scores and change, overall and stratified by treatment group and clinic. The exit GRD score will be regressed on treatment group, adjusted for baseline GRD and clinic.

For the exploratory IOP outcome, exit IOPs will be analyzed using measures from both eyes. The distribution of IOP and IOP change will be assessed with descriptive statistics and plots. The effect of treatment on IOP will be assessed with a linear mixed regression model, adjusting for baseline IOP and clinic, and controlling for the correlation between eyes of a subject with a random subject effect.

Qualitative Data Analysis

We will select at least 13 participant interviews (to reach thematic saturation) from each of the following six categories (~78 interviews), and transcribe these verbatim.

Participants who: 1) improved adherence; 2) did not improve adherence; 3) are White; 4) are African American; 5) live under the federal poverty level; and 6) live over the poverty level. We will transcribe all interviews with glaucoma coaches and key health system stakeholders. Two researchers will categorize key ideas and phrases as codes under the five overarching domains of the CFIR framework: intervention characteristics, outer setting, inner setting, characteristics of the individuals involved, and the process of implementation. The domains will be further mapped onto the 24 constructs provided by the CFIR framework. A codebook will be developed, five transcripts will be coded, and inter-coder reliability will be calculated using Nvivo 10.0. If consensus between the two coders cannot be reached, the issue will be adjudicated by a third researcher.

Transcripts will be coded once researchers have achieved >80% agreement on >95% of the codes. Dr. Heisler, an expert in behavioral intervention trials and implementation analyses, will lead this analysis. To assess *effectiveness*, we will analyze transcripts using a mixed-methods approach. We will compare key themes between groups with high and low change in medication adherence and between people by race and income level using a joint display. Dr. Mitchell, an expert in disparities in health care experiences, will lead this analysis. To assess barriers and facilitators to future *adoption*, we will analyze SEE Program participants' attitudes with a focus on the CFIR construct "knowledge and beliefs about the intervention" where we assess participant willingness to attend additional office visits for coaching sessions. We will use the CFIR construct "implementation climate" to further explore key health system stakeholder perceptions of barriers and facilitators to both adoption and *maintenance*. Differences in barriers/facilitators across the two study sites will be assessed using joint displays to identify areas for optimization.

Sample Size Aim 1: <u>Compare the efficacy of the SEE Program with enhanced standard care in improving glaucoma medication adherence</u>**.**

We conducted brief interviews with 25 glaucoma specialists from throughout the US to gauge expert opinion regarding clinically important effect size. Their average recommendation for difference of group proportions of good adherence was 18.5 percentage points (95% CI 15.6-

21.5). Their average recommendation for difference of group mean adherence was 17.7 percentage points (95% CI 14.6-20.8). Additionally, mean medication adherence increased by 20 percentage points in our SEE Program pilot study from 65.7% (±10.3) at baseline to 85.7% (±11.8) after the program. With 97 participants in each group, a t-test has 80% power to detect a difference of 8 percentage points in mean adherence between the two groups, if the within group standard deviation (SD) is 20 (0.40 20 = 8). In our preliminary data the SD was 18, but we anticipate and plan for a possibly more diverse study group (calculated using R 'pwr' package). Our glaucoma specialists were divided on the importance of clinically important effect size, so we plan to be adequately powered for both continuous and binary adherence measures. Their average recommendation for difference of group proportions of good adherence was 18.5 percentage points (95% CI 15.6-21.5). The proposed sample size (n=97 per group) provides 80% power (at two-sided α=0.05) for Pearson's Chi Square Test of Independence to find a difference of 20 percentage points for the proportion of patients attaining good (≥80%) adherence between the intervention and control groups.

For our secondary outcome, with this sample size, we can detect a 1.1-point difference in mean change in Glaucoma Related Distress (scale 6-18) between trial arms if the SD is 2.8, as it was in our preliminary data. For this sample size in our exploratory outcome, we can detect a 1.9 mmHg difference in mean change in IOP between trial arms if the SD is 4.6 mmHg, as it was in our preliminary data. Although we will make concerted efforts to maximize retention, we will prepare for up to a 20% loss to follow-up as was experienced in our preliminary study and will enroll 115 participants in each arm for a total of 230 participants.

Sample Size Aim 2: Identify moderators and mediators of SEE Program effectiveness.

The planned sample size (97 per trial arm) provides 80% power to detect *predictor* effects of the same magnitude as the anticipated treatment effect. For the *moderator* analysis, by oversampling African Americans to comprise 25% of the study population, we are powered to detect an increase of the R2 by 4 percentage points (e.g., if the SEE program vs enhanced standard of care improves mean adherence from 60% to 70% in Whites and from 50% to 75% in African Americans, then the R2 increase is 4%). For the *mediator* analysis, using the function wp.mediation (R package WebPower), the planned sample size provides 80% power to detect mediation when the standardized difference between the mean of the mediator in the treatment group and the mean in the control group is 0.6 standard deviations with a partial correlation of the mediator and medication adherence of 0.25.

DATA AND SAFETY MONITORING PLAN

The study epidemiologist will lead the study team in quarterly review of study recruitment, adverse events, and compliance with the protocol. The study epidemiologist will work with the study statistician to prepare reports of recruitment, retention, and adverse events for the entire team.

We will follow the standard IRBMED AE/ORIO reporting plan.

Intraocular pressure will be measured at the baseline and exit study visits. If the IOP is more than 4mm Hg above the target pressure set by their ophthalmologist or, if no target pressure is set, >21 mmHg, the participant will be walked over to the eye clinic for further evaluation. The

research associate will email the participant's ophthalmologist, and Dr. Newman-Casey (for UM participants) and Dr. Darnley-Fisch (for HFHS participants) to let them know what transpired and will also send them the note from the study visit and clinic visit through the electronic health record to determine appropriate follow up. If the participant's IOP is above the target but below the threshold for immediate clinical attention, the research associate will email the participant's ophthalmologist, and cc either Dr. Newman-Casey or Dr. Darnley-Fisch in addition to sending a notification to the ophthalmologist through the electronic health record to determine the appropriate follow up interval. The research associate will keep a log of all participants whose eye pressure met criteria to be walked to clinic to be reviewed during the quarterly reports.

SECONDARY SITE

University of Michigan will have a contract in place with Henry Ford Health Systems in place prior to beginning any study activities.