Published in final edited form as:
Clin Trials. 2021 June ; 18(3): 343–350. doi:10.1177/1740774520988291.

Randomized controlled trial of an education-based intervention to improve medication adherence: Design considerations in the medication adherence in glaucoma to improve care study

Jullia A Rosdahl[1], **Aaron M Hein**[2], **Hayden B Bosworth**[2,3,4], **Sandra Woolson**[4], **Maren Olsen**[4], **Miriam Kirshner**[4], **Anna Hung**[4], **Kelly W Muir**[1,4]

[1]Department of Ophthalmology, Duke University School of Medicine, Durham, NC, USA

[2]Department of Medicine, Duke University School of Medicine, Durham, NC, USA

[3]Department of Population Health Sciences, Duke University School of Medicine, Durham, NC, USA

[4]Durham Center of Innovation to Accelerate Discovery and Practice Transformation, Durham Veterans Affairs Health Care System, Durham, NC, USA

Abstract

Background: Glaucoma treatment requires patients to follow daily, often times complex, eye drop regimens, but adherence is poor for many patients, putting them at risk for irreversible vision loss. A comprehensive approach is needed to address the challenges in the self-management of glaucoma. The purpose of this study is to improve glaucoma medication adherence in Veterans with medically treated glaucoma using an education-based intervention.

Methods/design: This study is a single-site randomized controlled trial enrolling 200 Veterans and their companions, if companions are involved in their care. It has two arms: an intervention group and a control group. Participants in the intervention group receive an educational session with a non-physician interventionist and are provided with an AdhereTech smart bottle with the reminder functions activated. The control group is designed as an attention control such that they have a session on general eye health and are provided with a smart bottle but without the reminder functions activated. The primary outcome is the proportion of prescribed doses taken on schedule over 6 months following randomization according to the smart bottle. Secondary outcomes include intensification of glaucoma treatment, cost of intervention delivery, and cost-effectiveness of the intervention over 12 months.

Discussion: The education-based intervention that we are testing is comprehensive in scope, to encompass a variety of barriers to adherence that glaucoma patients encounter, but personalized

Corresponding author: Kelly W Muir, Department of Ophthalmology, Duke University School of Medicine, 2351 Erwin Rd., Box 3802 DUMC, Durham, NC 27710, USA. kelly.muir@duke.edu.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Trial registration
The study was registered with the ClinicalTrials.gov registry (No. NCT03052257).

to address issues facing individual patients. Particular attention was given to feasibility in the real-world setting, as the high throughput of patients and lack of reimbursement for educational encounters in ophthalmology would limit implementation of a resource-intensive intervention.

Keywords

Glaucoma; adherence; compliance; ocular hypertensive therapy

Background

Glaucoma is the leading cause of irreversible blindness worldwide and the second leading cause in the United States.[1,2] While there is no cure for glaucoma, treatments that lower intraocular pressure (IOP) have been shown to reduce the risk of vision loss from glaucoma.[3–6] While laser and surgical treatment options are available, topical eye drop medications are the most common treatments for glaucoma,[3,7] given their relatively favorable safety and efficacy profile.[8]

Glaucoma medication regimens can be complex, particularly in patients with advanced or progressive disease. Patients with advanced disease may also be at risk of vision loss due to IOP fluctuations. In order to avoid IOP fluctuations, glaucoma medications must be taken at a regular time each day, possibly multiple times per day, depending on the specific medication.

Glaucoma is a chronic, asymptomatic disease and even when effective at reducing long-term disease progression, medical therapy does not provide noticeable benefit to patients. Most patients who are prescribed glaucoma medications are expected to continue taking these medications throughout their lifetime. Given these challenges, it is not surprising that adherence to glaucoma medications is poor, ranging from 10% to 83%,[9–12] putting patients at risk of permanent vision loss. Adherence requires multiple steps, including filling the prescription, using the medication at the right time, instilling the drop onto the eye, and completing these steps every day.

There are many situations that contribute to poor adherence to glaucoma medications, including the complexity of the medication regimen, situational/environmental factors, factors related to healthcare delivery, and factors related to the patient, including physical limitations.[13] Patients who have a poor understanding of glaucomatous vision loss are less likely to be adherent to the prescribed treatment regimen.[14] Education about glaucoma may improve adherence, particularly for patients with low health literacy[15] but may not be sufficient for many patients facing other barriers to adherence. Mnemonic aids have been shown to help patients remember to take medications as directed;[16] however, most patients, even experienced eye drop users, have difficulty correctly administering their eye drops when observed.[17] A comprehensive approach to improving adherence is needed to address the challenges in the self-management of glaucoma.

The approach that we have used is based on the Health Decision Model. This model contains elements of the Health Belief Model and Social Cognitive Theory which purports that adherence is dependent on experiences and preferences of the patient, social interactions,

knowledge, attitudes, and beliefs.[18] Our approach includes an educational component, a personalized component (based on self-reported adherence and self-efficacy surveys), as well as mnemonic aids and targeted drop-instillation education.

The design of a trial to test an intervention to improve glaucoma medication adherence presented several challenges. Adherence to the prescribed eye drop regimen cannot be measured in the same way as adherence to pills. Glaucoma can lead to blindness but the course is long and asymptomatic until the late stages, making detection of progression within a reasonable study window challenging. These are among the study design challenges that we discuss in detail in this article.

Trial methods overview

This study is a single-site randomized controlled trial and its purpose is to improve glaucoma medication adherence in Veterans with medically treated glaucoma. This trial is funded by the US Department of Veterans Affairs (VA) Health Services Research and Development Service (IIR 15–113; clinicaltrials.gov registration # NCT03052257). It is being conducted under the approval of the Institutional Review Board of the Durham VA Medical Center. Participant accrual is complete and study activities are on-going.

This study took place at the Eye Clinic of the Durham VA Medical Center which serves as a referral center for North Carolina, southern Virginia, West Virginia, northern South Carolina, and eastern Tennessee. This study has enrolled 200 Veterans and their companions (family or friend), if available.

Study design considerations

Prior studies of educational interventions to improve glaucoma medication adherence have either excluded potential participants who do not administer their own drops or not incorporated companions who are involved in the participant's glaucoma care.[19] Interviews of patients with glaucoma, however, indicate that approximately 20% of glaucoma patients have a companion helping in their glaucoma care.[20,21] Accordingly, we decided to encourage companions to participate in the study if the companion helped administer drops or helped the participant remember to take his or her drops. As this was a novel aspect in this study design, we stratified randomization based on companion status.

Summary of intervention

This is a two-armed study with an intervention group and an attention control group. The intervention was developed in an iterative process with feedback from Veterans with glaucoma as part of a preliminary study. Subsequently, the intervention was pilot-tested and further refined to improve feasibility. The intervention (Table 1) is provided by an interventionist who is a non-physician health care worker. Participants in the intervention group receive an educational session and are provided with a smart bottle with the reminder function activated. The reminder function alerts the participant via audible alert, visible flash, text message, or a call to a landline (depending on the participant's preference), if the bottle has not been opened to access the medication within 2 h of the prescribed dosing time.

The control group was designed as an attention control such that the participants in the control group have a session with the interventionist that includes a slide presentation on general eye health that is similar in length to the intervention visit; they are also provided with a smart bottle but without the reminder function activated. The smart bottle records the date and time of opening of the bottle for participants in both groups.

Study design considerations

The development and pilot-testing of the intervention were performed by a physician in the role of the interventionist. In regular clinical care, however, patient education is usually performed to a greater extent by an ophthalmic technician. We decided that using an ophthalmic technician in the role of interventionist would facilitate implementation of the intervention should the trial be successful.

We considered the potential benefits of a staged intervention, or booster interventions, following the initial educational session with the ophthalmic technician. Unlike diabetes teaching, nutrition, and other behavioral counseling for chronic disease, glaucoma education is not a billable service and we expected that the intervention would not be easily adopted in practice if it required repeated time commitments from the ophthalmic technician. Accordingly, our educational intervention is delivered at a single time point. In pilot work, the intervention took approximately 45 min. During the clinical trial, the length of the intervention was recorded to aid in cost-counting.

The study design includes an active control to minimize the potential confounding variable of time with the study staff as a factor influencing medication adherence. The participants in the control group may have improved adherence due to general eye health education. If that is the case, then such improvement would bias the findings toward a null hypothesis. As such, if participants in the intervention group demonstrate better adherence than participants in the control arm, we would have enhanced confidence in the effect of the intervention.

Study population, recruitment, and randomization

Potential study participants were identified by a data pull of Veterans with upcoming appointments at the Durham VA Eye Clinic who met the inclusion/exclusion criteria (based on ICD10 codes, pharmacy records, lack of recent intraocular surgery, Table 2). Potential participants with confirmed eligibility were mailed a letter with information about the study and a phone number with the option to call to opt out of further contact regarding the study. Veterans who were mailed a letter and did not opt out were called by the study coordinator to discuss potential study participation. If the Veteran was interested, screening questions were asked to identify potential participants who were likely to be poorly adherent to their glaucoma medications. In a preliminary study, responses to the screening questions were associated with glaucoma medication adherence.[22] The screening questions were (1) “How confident are you that you always remember to use your glaucoma medications?” with answer choices: not at all confident, somewhat confident, and very confident; (2) “In the past 4 weeks, did you ever forget to take your medicine?” If the Veteran answered “not at all confident” or “somewhat confident” to question 1 and “yes” to question 2, and was interested in participating in the study, then the Veteran was asked to arrive 1.5 h before their

scheduled appointment for the enrollment visit. If the Veteran had assistance in managing his or her glaucoma treatment from a companion, the companion was also encouraged to attend the enrollment visit.

At the enrollment visit, written informed consent was obtained and baseline surveys were administered (Table 3). All participants were provided with a smart bottle to house their glaucoma medication; if the participant was taking more than one glaucoma medication, the most frequently dosed medication was chosen for assessment. The smart bottle records the date and time that it is opened. For participants in the intervention arm only, the reminder function was activated.

Following baseline data collection, the participants were randomized in a 1:1 allocation to either the intervention or control group. Neither the participant nor study team was masked to randomization status.

Study design considerations

We sought to maximize recruitment and retention by limiting travel to the VA for participants. Mailing a letter offering the potential participant the opportunity to opt out and performing the screening questions over the phone helped to achieve this goal. In working with a study population with a high prevalence of visual impairment, it was important to consider screening tools that did not depend on vision-based tasks such as a visual analog scale for reporting medication adherence. In addition, study visits are scheduled to coordinate with the participants' scheduled clinical visits at the Durham VA.

Many studies of glaucoma medication adherence limit participants to those who are prescribed only one medication. We chose to include a wider spectrum of patients but stratified randomization based on once daily or more-than-once daily dosing, as evidence suggests that adherence is worse for complex regimens.[23]

Outcomes measured

The primary outcome is the proportion of prescribed doses taken on time from the date of randomization through 6 months according to the smart bottle; the primary outcome is derived as a ratio of the number of times the bottle was opened within the appropriate dosing window to the required number of doses prescribed. The acceptable dosing window for a once daily dosed medication is defined as ±5 h, for a twice-a-day dosed drug is ±3 h, and for a 3-times-a-day dosed drug is ±1 h. These periods of time were chosen based on the half-lives of the most commonly prescribed glaucoma medications. The active window for potential dosing is 24 h after the first dose is taken regardless of the time of day; that is, the clock resets 24 h after the first dose, not at midnight or another arbitrary hour, in order to accurately describe medication events for participants who may take their medications late in the evening. A dose taken more than 24 h after the first dose, however, will not be counted as taken within the acceptable window. To further evaluate patterns of adherence over time, we will investigate the proportion of prescribed doses taken during each 30-day interval following randomization.

The first secondary outcome is the proportion of Veterans in the intervention group compared to the control group that are prescribed more intensive glaucoma therapy, defined as addition of adjuvant glaucoma medication or recommendation for laser or glaucoma surgery in the 12 months following randomization. Intensification of therapy was chosen as an outcome as it represents the treating physician's assessment that the glaucoma is not adequately controlled. The other secondary outcome relates to the labor and non-labor cost of intervention delivery, health care costs, and cost-effectiveness. Costs of intervention delivery captured in each arm include labor costs for one-time training of the interventionist, labor costs to deliver the adherence intervention, and non-labor costs of the smart bottles and eye drop aids provided to patients. Patient (and caregiver) costs to attend one-on-one sessions are also captured. Healthcare costs for inpatient and outpatient glaucoma-related VA services and medications will be obtained from VA administrative data sets. In the base-case cost-effectiveness analysis, the main incremental cost-effectiveness ratio will be calculated in terms of cost per percentage improvement in medication adherence.

Study design considerations

Adherence outcomes can be measured in several ways, including proportion of prescribed doses taken or proportion of doses taken on time. If the latter is chosen, the window of accessibility for dosing can vary. Because the patients in our study are cared for by multiple doctors, what they were told regarding the exact timing of the dosing will vary (twice daily versus every 12 h, for example). On one hand, taking a dose well outside the window of activity for the drug is unlikely to be clinically useful, but on the other hand, a patient might be following instructions properly but not taking the medication at the exact same time every day. To include these considerations, we chose to use the proportion of prescribed doses taken on time as the primary outcome, but allow the acceptable dosing windows to be generous enough to account for practice variation. The windows that we have chosen are ±5 h for a once daily dosed drug, ±3 h for a twice daily dosed drug, and ±1 h for a three times daily dosed drug.

Many patients are also on multiple glaucoma medications; to simplify the data collection while still capturing potential lapses in adherence, we elected to measure the adherence to the most frequently dosed medication. We chose this strategy over only enrolling patients receiving monotherapy, as such a limitation might skew the study population to those with mild disease. Using multiple smart bottles to measure adherence for every glaucoma medication for every participant was cost-prohibitive.

We considered several potential secondary outcomes in the design of the study, in particular, visual field progression and intraocular pressure. As confirmed visual field progression often takes years to manifest in a population with mixed disease severity, it was not a feasible primary outcome for this study. We sought a surrogate measure of disease worsening that would be clinically relevant but measureable within a 12-month timeframe. If a physician deems that the patient's glaucoma is progressing, he or she is likely to escalate therapy by adding a medication, performing a laser procedure or glaucoma surgery. Accordingly, we developed a composite measure including any of these three escalations and labeled it as intensification of therapy.

Analyses

Primary outcome

The primary hypothesis is to test if there is a significant difference between the intervention and control groups in the mean proportion of prescribed doses taken, defined as described above. We assumed that the mean is normally distributed and set the type-I error rate at $\alpha = 0.05$ and the type-II error rate at $\beta = 0.20$, representing power at 80% to detect significant differences. The estimated standard deviation from the preliminary work[22] of mean percent adherence is 23.5. To detect a mean difference of 10% between groups, we need 90 patients per arm. Inflating the sample size to account for 10% attrition, we planned to enroll and randomize n = 200 patients. We anticipate approximately 20% of these patients will have a companion enrolled as well. Descriptive statistics will be used to summarize the study variables; a sensitivity analysis will be considered if any baseline imbalance is found, to ensure any observed effect is due to the intervention and not to a baseline imbalance. Primary and secondary outcomes in the intervention group will be compared to the control group on an intent-to-treat basis; that is, patients will be analyzed as part of the group to which they were assigned, regardless of intervention adherence.

We will use a general linear regression model to test for a between-group difference in mean proportion of prescribed doses over 6 months. The coefficients in this model will include an indicator variable for intervention group and centered stratification variables as recommended in the Committee for Proprietary Medicinal Products (CPMP) guidelines.[24] We will use additional linear regression models to test for a between-group difference adjusting for the stratification variables, once versus multiple times per day dosing and companion status, as well for race, as some evidence in the literature suggests that African American race is a risk factor for poor adherence.[25] We will formally evaluate the intervention effect by testing that the intervention group indicator differs from zero and reports the mean difference and corresponding 95% confidence interval (CI). A mean difference significantly greater than 0 provides evidence that intervention group patients have a greater mean proportion of prescribed doses taken.

In addition to the preceding model, as a secondary analysis, 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.

Secondary outcomes

We will use logistic regression to test for between-group difference in our secondary outcome of rates of intensification of glaucoma therapy at the 12-month follow-up. We will formally evaluate the intervention effect by testing that the intervention group coefficient differs from zero and reports the difference in proportions and 95% CI of the difference.

Finally, costs of delivering the intervention to each patient in each arm will be calculated. Total costs for VA health care utilization will be estimated using a generalized linear regression model using a similar specification as noted above. Estimation of the incremental cost-effectiveness ratio of cost per medication adherence will be based on cost and improvement in medication adherence during the study period. We will use second-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. In addition, we will conduct subgroup analyses to see if there are differences in cost-effectiveness based on companion status and how many times per day the medications are dosed.

Discussion

The Medication Adherence In Glaucoma To Improve Care (MAGIC) study is a randomized controlled trial to test the efficacy of a comprehensive education-based intervention to improve medication adherence in glaucoma patients. The intervention was developed with input from Veterans and is based on a validated health behavior model. It is comprehensive in scope, to encompass the variety of barriers to adherence that glaucoma patients encounter, but personalized to address issues facing individual patients. The intervention has also been designed to be feasible for implementation in non-research clinical eye clinics, with the use of an ophthalmic technician leading the intervention, easily accessible assessments, brochures, and video, and a commercially available medication monitor. We hope that the design considerations that we discussed will help other investigators developing studies in this important area.

The medication monitor used in this study is novel in that it alerts users to missed doses only rather than issuing an automated reminder at a set time each day. The understanding of the importance of fluctuation in intraocular pressure in progression of glaucoma is still evolving, but there is evidence that wide fluctuations in pressure may be deleterious, at least in advanced disease.[6,26] If improved timing of the dosing regimen leads to better visual outcomes, mnemonic aids such as this device may be useful to many glaucoma patients. Glaucoma is not the only ophthalmic condition for which patients must take regular medication. Patients with uveitis often need daily eye drops and patients with macular degeneration may be prescribed a particular vitamin regimen. We hope that the intervention utilized in this clinical trial, if successful, may be beneficial to patients with a spectrum of ophthalmic disease.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by VA Health Services Research & Development IIR 15-113 (K.W.M.).

References

1. Kingman S Glaucoma is second leading cause of blindness globally. Bull World Health Organ 2004; 82(11): 887–888. [PubMed: 15640929]
2. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. Bull World Health Organ 2004; 82(11): 844–851. [PubMed: 15640920]
3. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the collaborative initial glaucoma treatment study comparing initial treatment randomized to medications or surgery. Ophthalmology 2001; 108: 1943–1953. [PubMed: 11713061]
4. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial. Arch Ophthalmol 2002; 120(10): 1268–1279. [PubMed: 12365904]
5. Kass MA, Heuer DK, Higginbotham EJ, et al. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 2002; 120(6): 701–713; discussion 829–830. [PubMed: 12049574]
6. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 2000; 130(4): 429–440. [PubMed: 11024415]
7. Weinreb RN, Aung T and Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA 2014; 311: 1901–1911. [PubMed: 24825645]
8. Gedde SJ, Schiffman JC, Feuer WJ, et al. Treatment outcomes in the tube versus trabeculectomy (TVT) study after five years of follow-up. Am J Ophthalmol 2012; 153(5): 789–803. [PubMed: 22245458]
9. Tielsch JM, Katz J, Singh K, et al. A population-based evaluation of glaucoma screening: the Baltimore Eye Survey. Am J Epidemiol 1991; 134: 1102–1110. [PubMed: 1746520]
10. Gurwitz JH, Glynn RJ, Monane M, et al. Treatment for glaucoma: adherence by the elderly. Am J Public Health 1993; 83(5): 711–716. [PubMed: 8484454]
11. Patel SC and Spaeth GL. Compliance in patients prescribed eyedrops for glaucoma. Ophthalmic Surg 1995; 26(3): 233–236. [PubMed: 7651690]
12. Friedman DS, Okeke CO, Jampel HD, et al. Risk factors for poor adherence to eyedrops in electronically monitored patients with glaucoma. Ophthalmology 2009; 116(6): 1097–1105. [PubMed: 19376591]
13. Tsai JC. A comprehensive perspective on patient adherence to topical glaucoma therapy. Ophthalmology 2009; 116(11Suppl): S30–36. [PubMed: 19837258]
14. Friedman DS, Hahn SR, Gelb L, et al. Doctor-patient communication, health-related beliefs, and adherence in glaucoma results from the Glaucoma Adherence and Persistency Study. Ophthalmology 2008; 115(8): 1320–1327, 1327.e1–3. [PubMed: 18321582]
15. Muir KW, Ventura A, Stinnett SS, et al. The influence of health literacy level on an educational intervention to improve glaucoma medication adherence. Patient Educ Couns 2012; 87(2): 160–164. [PubMed: 22000272]
16. Boland MV, Chang DS, Frazier T, et al. Electronic monitoring to assess adherence with once-daily glaucoma medications and risk factors for nonadherence: the automated dosing reminder study. JAMA Ophthalmol 2014; 132(7): 838–844. [PubMed: 24830878]
17. Stone JL, Robin AL, Novack GD, et al. An objective evaluation of eyedrop instillation in patients with glaucoma. Arch Ophthalmol 2009; 127(6): 732–736. [PubMed: 19506189]
18. Eraker SA, Kirscht JP and Becker MH. Understanding and improving patient compliance. Ann Intern Med 1984; 100: 258–268. [PubMed: 6362512]

19. Newman-Casey PA, Weizer JS, Heisler M, et al. Systematic review of educational interventions to improve glaucoma medication adherence. Semin Ophthalmol 2013; 28: 191–201. [PubMed: 23697623]
20. Wolff JL, Boyd CM, Gitlin LN, et al. Going it together: persistence of older adults' accompaniment to physician visits by a family companion. J Am Geriatr Soc 2012; 60(1): 106–112. [PubMed: 22211465]
21. Wolff JL and Roter DL. Hidden in plain sight: medical visit companions as a resource for vulnerable older adults. Arch Intern Med 2008; 168: 1409–1415. [PubMed: 18625921]
22. Kumar JB, Bosworth HB, Sleath B, et al. Quantifying glaucoma medication adherence: the relationship between self-report, electronic monitoring, and pharmacy refill. J Ocul Pharmacol Ther 2016; 32(6): 346–354. [PubMed: 27058842]
23. Robin AL and Covert D. Does adjunctive glaucoma therapy affect adherence to the initial primary therapy. Ophthalmology 2005; 112(5): 863–868. [PubMed: 15878067]
24. Committee for Proprietary Medicinal Products. Committee for Proprietary Medicinal Products (CPMP): points to consider on adjustment for baseline covariates. Stat Med 2004; 23: 701–709. [PubMed: 14981670]
25. Sleath B, Blalock SJ, Carpenter DM, et al. Ophthalmolo-gist-patient communication, self-efficacy, and glaucoma medication adherence. Ophthalmology 2015; 122: 748–754. [PubMed: 25542521]
26. Asrani S, Zeimer R, Wilensky J, et al. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. J Glaucoma 2000; 9: 134–142. [PubMed: 10782622]

Table 1.

Intervention design.

Theoretical construct	Intervention element	Rationale
Social interaction	Involvement of companions	In the preliminary study, Veterans reported help from companions to administer eye drops or provide reminders for their use
Improving patients' disease understanding	One-on-one discussion, covering possibility of blindness, benefit of treatment, including use of three-dimensional eye model	Models improve health communication, especially for those with lower health literacy
Self-efficacy with the use of eye drop technique	Assessment of eye drop technique, with recommendations including eye drop aids	Patients who do not believe that they can administer drops may not even try
Patient characteristics such as poor health literacy	Glaucoma brochure	The brochure was developed with attention to health literacy and refined according to patient feedback
Improving patients' disease understanding		
Disease knowledge Self-efficacy	Eye drop administration brochure	The brochure was developed with attention to clear health communication guidelines, with drawings of eye drop administration techniques
Self-efficacy with remembering to take drops	Individualized printed dosing reminder	Patients given a chart more accurately report their prescribed eye drops
Patient preferences regarding dosing schedules and mnemonic aids	Individualized suggestions based on survey responses	The survey used in the study is associated with electronically monitored adherence
Patient experience	Smart bottle provides personalized alerts for missed doses	Daily text or voice messages can improve glaucoma medication adherence

Table 2.

Eligibility criteria.

Inclusion criteria
Upcoming scheduled appointment in the Durham VA Eye Clinic
Diagnosis of open angle glaucoma (primary open angle glaucoma, pigment dispersion glaucoma, pseudoexfoliation glaucoma, combined mechanism glaucoma, low tension glaucoma) or open angle suspect recorded in the medical record
Prescribed glaucoma eye drops
Visual field performed within the last 18 months
Exclusion criteria
Intraocular surgery in the past 3 months or anticipated in the next 3 months, as prescribed drops may change frequently during the postoperative period
Active uveitis or eye infection, as the medication regimen may vary daily in this setting
Visual acuity less than 20/70 in the better-seeing eye, as Veterans with low vision may not be able to complete the vision-dependent tasks required for the study
Lacks proficiency in English
Lacks both a cell phone and landline phone

VA: Veterans Affairs.

Table 3.

Timeline with variables.

Variable	Baseline	6 months	12 months
Patient participant measures			
Demographics: age, sex, race, ethnicity, education, marital status, living environment, and self-rated health	X		
General medical: comorbidities, glaucoma medication list, dexterity scale, and EQ-5D for quality-adjusted life years	X		X
Ophthalmologic: visual acuity, ophthalmic diagnoses, history of eye surgery or laser, and severity of most recent visual field (mild/moderate/severe)	X		X
Glaucoma knowledge assessment (Eye Q test)	X	X	
General: Rapid Estimate of Health Literacy in Adults (REALM) and survey of preferred means of communication (cell phone call, text, and landline)	X		
Self-reported glaucoma medication adherence: Self-reported Adherence and Self-efficacy Survey	X	X	X
Intermittent events, protocol deviations, and changes in vision		X	X
Observation of eye drop administration: scored for success of ≥1 drop into eye and for administration without use of excessive drops	X		
Outcome variables			
Smart bottle data: proportion of prescribed doses taken within a prescribed dosing window		X	
Intensification of glaucoma therapy: addition of adjuvant medical therapy, glaucoma laser, glaucoma surgery (via chart abstraction)			X
Cost: cost of intervention and cost of intensification of therapy		X	X

EQ-5D: EuroQol-5 dimensions.