

Glaucoma Drop Aid Study

ClinicalTrials.gov number: NCT02867995

Protocol Version Number: 1.5

Protocol Version Date: 16 November 2017

Funding Mechanism: Boston Medical Center

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1 List of Abbreviations

Abbreviation	Abbreviation definition
AE's	Adverse events
BMC	Boston Medical Center
BUMC	Boston University Medical Campus
cc	Cubic centimeters
FDA	Food and Drug Administration
ID	Identification
IOP	Intraocular Pressure
IRB	Institutional Review Board
mL	Milliliters
SAEs	Serious adverse events
SOC	Standard of care
UP	Unanticipated problem
VA	Visual acuity

2 Protocol Summary

Title:	Glaucoma Drop Aid Study
Population:	Male and Female patients of Boston University Eye Associates, 18 or older, having been receiving the same topical medication for treatment of glaucoma for a minimum of two months
Intervention:	Control: <ul style="list-style-type: none"> No Glaucoma Drop Aid Device Drop Aid Devices: <ul style="list-style-type: none"> Simply Touch Eye Drop Applicator Fabrication Autodrop Eye Drop Guide Owen Mumford OP 6100 Autosqueeze
Objectives:	To determine the efficacy of drop aid devices for improving medication compliance, visual function, and decreasing medication waste for patients at BMC
Design/Methodology:	Arm A: No intervention- Control Arm B: Active Comparator- Eye Drop Aids Participants will be randomly assigned into one of the study arms. If placed into Arm A, no drop aid device will be assigned. If placed into Arm B, participants will be assigned one of the three drop aid devices (Simply Touch Eye Drop Applicator, Fabrication Autodrop Eye Drop Guide, or the Owen Mumford OP 6100 Autosqueeze).
Total Study Duration:	Approximately 1 year
Subject Participation Duration:	Subject participation length is variable based on appointment wait times and availability. The minimum duration of this study is 6 weeks.

3 Background/Rationale & Purpose

3.1 Background Information

Glaucoma is a disease characterized by an increased intraocular pressure, resulting in damage to optic nerve.⁵ This disease can be diagnosed by measuring visual field loss, identifying other changes in the physical structures of the eye and by measuring IOP. If untreated, glaucoma can result in preventable vision loss.⁵

Glaucoma is commonly treated with prescription eye drops.^{2,4} It is critical that patients receive the correct dose and frequency of eye drop medication as prescribed.^{2,4,5} This will prevent disease advancement and decrease the chances of vision loss.⁵ However, patient compliance with medication limits symptom improvement due to deliberate misuse, financial concerns, or unintentional issues in drug delivery.³ Some patients have difficulty putting in the correct amount of eye drops themselves.⁴ Common problems are from a patient missing their eye, delivering too much medication, or they are unable to squeeze the bottle properly. This can create further problems with pharmacy refills, as well as financially from buying an increased number of prescriptions.³ In order to ensure patients are receiving the correct amount of drops with each use, drop aids are available at local pharmacies for purchase.⁴ These are not commonly recommended because they can be costly and their usefulness has not yet been proven.^{2,4} Although if a drop aid proves to be effective, they may result in a decrease of cost for the patient in the long term by allowing a decrease in premature completion of the bottle.^{3,4}

This study aims to determine the efficacy of glaucoma drop aids delivery of ophthalmic medications by improving medication compliance, visual function, and decreasing medication waste in the patient population at BMC.

This study will be conducted in compliance with the protocol, applicable regulatory requirements, and BMC/BU Medical Campus Human Research Protection policies and procedures.

3.2 Rationale and Purpose

The ophthalmology department at Boston Medical Center sees on average 275 glaucoma patients weekly, 80 percent of which are placed on glaucoma medications. It is critical for these patients to receive the correct dose and frequency of their eye drops, in order to prevent disease advancement and decrease the chances of vision loss.⁴ However, a majority of patients are unable to properly deliver the eye drops into their eyes due to poor vision or difficulty squeezing drop bottles.^{3,4} Furthermore, when patients are able to instill drops into their eyes, they often deliver more than a necessary amount, leading to premature completion of the bottle. This is an issue in the United States, as most glaucoma patients are on 2 to 3 different medication drops and Medicare Part D sponsors permit refills at only 70% of predicated days of use, accounting for about half of glaucoma patient population.¹ Self-reported studies also showed that approximately 25% of patients reported problems with early exhaustion of eye drop bottles.¹ The average size of a glaucoma medication bottle is around 10 cc and these medications, when used 2 to 3 times daily, are expected to last patients an entire month. When used in excess or reduction, problems may occur with pharmacy refills, an addition to financial burdens from buying an increased number of prescription refills.¹ In the absence of good medication compliance and response, patients often have to undergo costly surgical procedures that can place them at an increased risk of infection and loss of vision, while still requiring postoperative management with ophthalmic drops, in addition to being closely monitored by eye care providers.¹

In order to ensure patients are receiving the correct amount of drops with each use, there are many drop aid assistive devices available for purchase on the market; however, these drop aids are not routinely offered to our patients because of their unproven cost benefit ratio, and the poorly studied efficacy of the devices.⁴ Although, if a drop aid proves to be effective, the cost of the drop aid devices would more than pay themselves through the improvement in medication compliance and visual function of our patients. The “Glaucoma Drop Aid Study” aims to determine if using drop aids during the administration of eye drop medication leads to better results for patients with glaucoma at Boston Medical Center. The implications of this study may show an improved delivery system of ophthalmic medications thus improving medication compliance, visual function, and even decreasing medication waste.

4 Objectives

4.1 Study Objectives

The primary objective of this study is to compare efficiency of various drop aids for glaucoma medications objectively via changes in intraocular pressure. The different drop aids that are utilized are the Simply Touch Eye Drop Applicator, the Fabrication Autodrop Eye Drop Guide, and the Owen Mumford OP 6100 Autosqueeze. The central hypothesis is that the use of a drop aid device increases efficiency of glaucoma medication when comparing changes in intraocular pressure.

A secondary objective of this study is to evaluate how often a patient missed their eye when instilling drops with various drop aids in order to assess whether drop aids can decrease medication waste, increase medication compliance, and improve visual function. Additionally, the study will analyze how satisfied the patient is with their drop aid and the likelihood they would continue to use one outside of the study. These satisfaction means will be evaluated with a patient satisfaction survey approximately 3 weeks and 6 weeks after enrollment.

4.2 Study Outcome Measures

The efficiency of various drop aids will be measured through the subject’s glaucoma progression at the end of the study. On the day of enrollment, the subject’s IOP and visual acuity will be measured as part of their standard of care exam. This information is recorded as the baseline exam, and will be compared to measure the patient’s glaucoma progression at the end of the study. Subjects will be required to record the date on which they began each of their glaucoma eye drop bottles, and the date each bottle was finished in a study diary provided by the research team. Subject’s satisfaction will be measured through a brief satisfaction survey approximately 3 weeks after their enrollment. After at least 6 weeks of study participation, subject will be followed up with their regularly scheduled glaucoma provider where they will fill out a second brief satisfaction survey. The study diary will be collected and a routine eye exam will be conducted, with their IOP checked as part of a standard of care clinic visit.

All surveys were created by a member of the research team. The satisfaction survey includes five questions to assess the precision of the drop aid device, overall patient satisfaction, and willingness to use the device long term. The questions are multiple choice questions in which the patient circles the answer that best reflects their response.

Reference Section 12.0 for further statistical analysis explanations.

4.2.1 Primary Outcome Measures

The objective of this study is to compare efficiency of various drop aids for glaucoma medications objectively via changes in intraocular pressure.

4.2.2 Secondary Outcome Measures

The following secondary outcomes will also be measured:

1. Number of times a patient missed their eye when instilling eye drops
2. Patient satisfaction responses with treatment arms
3. Intention to use a drop aid long term

5 Study Design

This interventional clinical trial is a prospective, single center, randomized controlled study. Patients being treated for their glaucoma at BMC's Yawkey Eye Clinic will be selected. Patients will be randomly placed, without manipulations by the principle investigator or any member of the research team, on one of the drop aid devices (including Fabrication Autodrop Eye Drop Guide, Simply Touch Eye Drop Applicator, Owen Mumford OP 6100 Autosqueeze), in addition to a no drop aid control, for a total of 4 groups.

Subjects have an equal chance of being randomized to one of the following study arms:

- Arm A: No intervention – Control
- Arm B: Active Comparator- Eye Drop Aids Including:
 - Simply Touch Eye Drop Applicator
 - Fabrication Autodrop Eye Drop Guide
 - Owen Mumford OP 6100 Autosqueeze

The primary endpoint is the comparison of baseline IOP measurement and follow-up IOP measurement. This comparison will determine the efficacy of using a drop aid. The secondary endpoints include the precision of the drop aid, patient satisfaction, and their likelihood to use a drop aid outside of the study. Data collection for assessment of study objectives will be obtained via standard of care clinic visits and completion of study diary and satisfaction survey by the patient with assistance of research team, if needed.

See the Appendix section 15.1 for a schematic of the study design and section 15.3 for drop aid labels and instructions.

6 Potential Risks and Benefits

6.1 Risks

Risks and possible discomforts involved with study participation are associated with eye dropper use and the possibility of a breach of confidentiality. The use of the assigned drop aid does not pose any additional risk to subjects from only using an eye drop bottle for administration. Both methods of eye drop administration pose the same risk of corneal abrasion or infection from poking the eye with the device/bottle, or using a dirty device/bottle. Subjects will be advised by the investigator on how to decrease these risks when administering drops with the assigned device.

There is the unlikely possibility of breach of confidentiality. Confidentiality will be protected as stated in Section 11.1 of this protocol.

6.2 Unknown Risks

There may be unknown risks or discomforts involved. Study staff will update all subjects in a timely manner with any new information that may affect their health, welfare, or decision to participate in this study.

6.3 Potential Benefits

Study participants may benefit from participation by improved eye drop compliance, decrease in medication refill requirements, receiving a drop aid at no cost, and an overall increased satisfaction with eye drop medications. It is also possible that subjects may not receive any direct benefit from participation, but they will be helping investigators learn about the benefits of drop aids as well as better understand the efficacy of its usage for patients at BMC.

6.4 Analysis of Risks in Relation to Benefits

The project allows for potential improvement in patients' medication compliance. These drop aids are designed to help deliver only the necessary amount of medication and target the eye to allow for easier delivery of medications. The drop aids involved in this study are targeted toward improving patient experience when using glaucoma medications. This may reduce patient frustration and increase adherence to medication allowing for better glaucoma treatment outcomes. The risks of this study include a minimal risk of loss of confidentiality. The risk is minimal in comparison to the potential benefits of: improved medication compliance, monetary benefits of decreased number of refills, increased patient satisfaction with eye drop medications, and community benefit of understanding the effectiveness of drop aids.

7 Study Subject Selection

7.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Age 18 years or older
- Currently on the same topical medication for treatment of glaucoma for a minimum of two months
- Patient of Boston University Eye Associates
- Agrees to use the drop aid with each delivery, return to the clinic after approximately 6 weeks of using the drop aid, document completion of medication drops, and fill out survey at the end of the 6 weeks

7.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Changes glaucoma medication within the past two months or recent glaucoma surgery
- Not a patient of the Boston University Eye Associates

8 Study Intervention

Arm A: No intervention – Control

Arm B: *Active Comparator* – Eye Drop Aids Including:

- Simply Touch Eye Drop Applicator
- Fabrication Autodrop Eye Drop Guide

- Owen Mumford OP 6100 Autosqueeze

Drop Aid devices were funded by a Boston Medical Center grant award. Devices were purchased by the grant award at no cost to the patients. Drop aid devices will be ordered online using the funds provided by the grant award. Upon arrival to Boston Medical Center, drop aid devices will be stored in locked cabinets that only the research team can access. Each drop aid will have a study-specific label indicating it is an investigational device provided by BMC. Administration of the drop aid devices will occur after consenting procedures and randomization to a treatment or control arm. Patients will be instructed by a member of the research team how to use the device. Patients will be expected to use the device each time they administer their eye drops as directed by their provider.

Compliance to drop aid device will be assessed via patient satisfaction surveys. Patient satisfaction surveys ask the participant to confirm the usage of drop aid device after administration of device at the 3 week phone call and 6 week follow-up.

Reference Appendix sections 15.3 for drop aid labels and instructions.

9 Study Procedures

See the Appendix section 15.1 for the schedule of events.

The following study procedures will be performed for study-specific purposes:

- Review of inclusion/exclusion criteria for eligibility
- Informed consent
- Study specific medical, ophthalmic, and family history
- Randomization: eligible subjects will be randomized into either Arm A or Arm B, and assigned no device or one of the three drop aid devices
- Completion of phone call satisfaction survey approximately three weeks after enrollment
- Completion of satisfaction survey at follow-up visit approximately six weeks after enrollment
- Collection of information regarding length of medication usage
- Collection of information regarding any AEs, SAEs, or UPs.

The following procedures will be performed as SOC:

- Ophthalmic exam prior to enrollment
- Ophthalmic exam six weeks after enrollment

9.1 Screening and Consent

Glaucoma ophthalmology patients who are thought to be eligible for the study based on the eligibility criteria and review of their medical record by the investigator and/or designated study team member will be approached about study participation. The patient's provider (who could be an investigator) will introduce the study to the patient. The provider will alert the investigator (if they are not already an investigator) and/or the designated study team member to assist with enrollment. The following will then be completed by the investigator and/or the designated study team member:

- Review of study inclusion/exclusion criteria
- The consent form will be reviewed with the patient and all study related questions will be answered in a private exam room or consult room.
 - Both the patient and the investigator or the designated study team member conducting the consent form will sign

- The patient will be sent home with a copy of the fully executed consent form
- The patient will also be given the contact information of the principal investigator, clinical research coordinator, and 24-hour emergency number as listed below:

Manishi Desai, MD
Principal Investigator
Manishi.Desai@bmc.org
(617) 414-4071

Marissa Fiorello
Clinical Research Coordinator
Marissa.Fiorello@bmc.org
(617) 414-8848

BMC Department of Ophthalmology
Emergency after Hours
(617) 638-8000, dial 0 for operator, and ask for on-call ophthalmologist

- Study-specific review of medical record and demographics

9.2 Day of Enrollment and Randomization

- Subject's IOP and VA will be measured as part of SOC exam
- Dispense study diary
 - Patients will be requested to record the number of days taken to complete the glaucoma medication bottle
- Randomization: After enrollment, subjects will be randomly assigned to Arm A or Arm B, and assigned no device or one of the three drop aid devices
- Subject will be instructed on how to use the drop aid by a member of the research team
- Subject will be requested to administer their drops with the drop aid, or no drop aid if randomized into the control group, with every use
- A member of the research team will confirm the subject's phone number and schedule a time for the 3 week phone call

9.3 Follow-Up Study Visits

9.3.1 3 Week Phone Call:

- Subject will complete satisfaction survey for all drop aid treatment or control groups over the phone
- Confirm next SOC clinical visit

9.3.2 Final Study Visit: At least 6 Weeks after Enrollment (SOC Clinic Visit)

- Subject will complete a satisfaction survey in person
- Subject's study diary will be collected
- Routine eye exam will be conducted
 - IOP and VA will be checked as part of SOC clinic visit
- Study participation is complete

9.4 Early Termination Visit

The subject can be terminated early from the study if there is a change in eye medication as determined by their SOC provider. Subjects can also be withdrawn from the study if they demonstrate non-compliance for study procedures.

9.5 Non-Study Visits (Unscheduled Visits)

At non-study visits a standard office ophthalmology exam will be completed.

Reference Appendix section 15.1 for schedule of events.

Reference Appendix section 15.2 for complete CRF used for all study visits which include patient satisfaction survey and study diary.

10 Assessment of Safety and Data Safety Monitoring Plan (DSMP)

10.1 Definitions

The following definitions will be used in the assessment of safety:

Adverse Event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Serious Adverse Event (SAE) is any adverse event that

- (1) results in death;
- (2) is life-threatening;
- (3) results in inpatient hospitalization or prolongation of existing hospitalization;
- (4) results in a persistent or significant disability/incapacity;
- (5) results in a congenital anomaly/birth defect; or
- (6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Life-threatening means that the event places the subject at immediate risk of death from the event as it occurred.

Unanticipated Problem is defined as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected; AND
- is related or possibly related to participation in the research; AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject’s predisposing risk factor profile for the adverse event.

10.2 Safety Review

Both the risks listed in Section 6.1 and unknown risks will be monitored throughout this minimal risk study. The PI will have overall responsibility for the study. The PI will review all AEs, SAEs, and UPs. During the review, the PI will complete the form designated in Appendix 15.4.1 in which the AE will be graded and the relatedness will be determined. All SAEs and UPs will be promptly reported to the BUMC IRB as designated in Section 10.3. The SAE Report demonstrated in Appendix Section 15.4.2 will be completed for all SAEs and UPs.

Dr. Manishi Desai is the PI and will be responsible for the study. Dr. Desai will be notified within 1 week of any events determined an AE or SAE and 2 days of any event determined a UP. Dr. Desai will review all AEs/SAEs within 2 weeks and all UPs within 5 days. After this review, any recommended changes will be made to the PI and the co-investigators in addition to the BUMC IRB as deemed necessary by the PI.

Reference Appendix section 15.4 for all AE, SAE, and UP tracking and report examples.

10.3 Reporting Plans

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems, safety monitors’ reports, and Adverse Events to the BMC/BU Medical Center IRB in accordance with IRB policies:

- Unanticipated Problems occurring at BMC/BU Medical Campus involving a fatal or life-threatening event will be reported to the IRB within 2 days of the investigator learning of the event.
- Unanticipated Problems occurring at BMC/BU Medical Campus not involving a fatal or life-threatening event will be reported to the IRB within 7 days of the investigator learning of the event.
- Reports from safety monitors with recommended changes will be reported to the IRB within 7 days of the investigator receiving the report.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.
- Reports from safety monitors with no recommended changes will be reported to the IRB at the time of continuing review.

10.4 Stopping Rules

A subject will be withdrawn from the study for any of the following reasons but are not limited to:

- Change to eye drop regimen as determined by their SOC provider

- Failure to comply with drop aid instructions
- SAE or UP resulting from the administered study device

The study will be stopped if the PI, Dr. Manishi Desai, determines that the number of AEs, SAE, and/or UPs exceed that of SOC ocular procedures.

11 Data Handling and Record Keeping

11.1 Confidentiality

The clinical research staff in the Department of Ophthalmology at BMC has sole accessibility to view patient identifiers for eligibility review. After the patient is consented into the study, each patient will receive a unique study ID number to protect subject identity. Subject identifiers and study ID numbers will be linked in a secure, password-protected master database located in a departmental networked server, housed behind BMC's firewall. The master database will allow for subject re-identification, as necessary, for strict research-specific purposes. Only study personnel will have access to the master database.

Any paper records related to this study will be stored in locked cabinets or in a locked office. Any data that is analyzed by an outside source will not contain any identifiers. In the event that any information is stored on external storage, the data will be encrypted. Patient information will not be used in any other way than described in this protocol.

A description of this clinical trial will be available on <http://clinicaltrials.gov>, as required by U.S. Law. The website will not include information which can identify any of the subjects. At most, the website will include a summary of the results. The subject is able to search for the study at any time on the website by utilizing the ClinicalTrials.gov number shown on the first page of this protocol.

11.2 Source Documents

All source documents for this study will include the electronic medical record and the study-specific documents which includes the following:

- CRFs in Appendix section 15.2
- Patient Satisfaction Survey Appendix section 15.2.4
- AE, SAE, and UP tracking reports in Appendix section 15.4

Data generated by the methods described in the protocol may be recorded in the subjects' medical records and/or study progress notes. Data may be transcribed legibly on CRFs supplied for each subject or directly inputted into an electronic system or any combination thereof.

11.3 Case Report Forms

The study case report form (CRF) will be the primary data collection instrument for the study. All data requested on the CRF will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, "N/D" will be written. If the item is not applicable to the individual case, "N/A" will be written. All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data will be entered above it. All such changes will be initialed

and dated. There will be no erasures or white-out on CRFs. For clarification of illegible or uncertain entries, the clarification will be printed above the item, then initialed and dated.

See the Appendix section 15.2 for the following CRFs: Eligibility Assessment Form, Documentation of Informed Consent, Home Study Diary, and the Satisfaction Survey.

11.4 Study Records Retention

In accordance with BMC policy, the study records will be retained for at least seven years after completion of the study. Additionally, as required by the BMC/ BUMC IRB, documentation of informed consent of subjects will be retained for at least three years after the study is closed. All of the required records may be preserved in hard copy, electronic, or other media form and must be accessible for inspection and copying by authorized individuals.

12 Statistical Plan

12.1 Study Hypotheses

12.1.1. Primary Objective: Intraocular Pressure

Formal hypothesis: Drop aids will be cost-effective in delivery of ophthalmic medications by improving baseline IOP measures to six week visit.

Testable hypothesis: Patient baseline IOP measures will be a statistically significant improvement in accordance to the usage of a drop aid device.

Null hypothesis: The patients, who are assigned to a drop aid device baseline IOP measures will not have a statistically significant change with the usage of a drop aid device when compared to patients not assigned to a drop aid device.

Alternate hypothesis: Patients not assigned to a drop aid device will result in larger significant change when compared to patients who are assigned to a drop aid device.

$$H_0: \mu_0 < \mu_d - \delta$$

$$H_A: \mu_0 \geq \mu_d - \delta$$

Where μ_0 , is the true mean IOP change from baseline to the six week visit without the drop aid device, μ_d is the true mean IOP change from baseline to the six week visit with the drop aid device.

12.1.2. Secondary Objective: Drops Missed

Formal hypothesis: Drop aids will be effective in delivering the proper amount of drops, thereby reducing the number of missed drops for patients.

Testable hypothesis: Differences in drops missed with drop aid device compared to without drop aid device will show efficacy in drop aid device.

Null hypothesis: Patients assigned to a drop aid device will not result in less drops missed when compared to patients who are not assigned to a drop aid device.

Alternate hypothesis: Patients assigned to a drop aid device will result in minimal missed drops when compared to patients who are not assigned to a drop aid device.

12.1.3. Secondary Objective: Patient Satisfaction

Formal hypothesis: Drop aid devices will prove greater patient satisfaction than administrations without a drop aid device.

Testable hypothesis: Mean patient satisfaction to those assigned to a drop aid device compared to mean patient satisfaction scores to those not assigned to a drop aid device.

Null hypothesis: Patients assigned to a drop aid device will not show greater patient satisfaction than patients not assigned to a drop aid device.

Alternate hypothesis: Patients assigned to a drop aid device will show greater patient satisfaction than patients not assigned to a drop aid device.

$$H_0: \mu_s < \mu_{sd} - \delta$$

$$H_A: \mu_s \geq \mu_{sd} - \delta$$

Where μ_s , is the mean patient satisfaction without the drop aid device, μ_{sd} is the mean patient satisfaction with the drop aid device.

12.1.4. Secondary Objective: Intention of Long term use

Formal hypothesis: Patients assigned to a drop aid device will claim greater interest in long term use of the drop aid device, than declining long term use of the drop aid device.

Testable hypothesis: Mean patients claiming interest in long term use of the drop aid device compared to mean patient declining interest in long term use of the drop aid device.

Null hypothesis: Patients assigned to a drop aid device will not show greater mean interest in long term use of the drop aid device.

Alternate hypothesis: Patients assigned to a drop aid device will show greater mean interest in long term use of the drop aid device.

$$H_0: \mu_y < \mu_n - \delta$$

$$H_A: \mu_y \geq \mu_n - \delta$$

Where μ_y , is the mean patients who claimed interest in long term use of the device, μ_n is the mean patient who denied interest in long term use of the device.

12.2 Sample Size Determination

The sample size was determined by the maximum number of subjects which could be randomized given the budgetary constraints of the grant funding. It was determined that a total of ten patients per group was financially feasible, thus a total of 40 patients will be enrolled in this study in approximately 1 year.

Enrolling the projected 40 subjects in 1 year is feasible, as the ophthalmology department sees approximately 275 glaucoma patients weekly. Due to the high volume of the glaucoma clinic, the study team should be able to easily recruit their target. Additionally, the study team is comprised of multiple

investigators and research assistants who have been delegated tasks on this protocol which can provide full-time recruitment coverage.

12.3 Statistical Methods

A variety of statistical analysis will be used to analyze the results. A paired t-test will be the primary method of analysis. Any significant differences measured will be between the pre and post intervention, with the patient serving as their own control. However, the analysis will not be limited to a paired t-test and will also likely include ANOVA, chi-squared, p-value, linear regression, among others. Other outcomes such as length of time until completion of drops will also be measured and compared to no drop aid controls. Significant differences will be measured with similar statistical analysis as stated previously. Satisfaction of use will be measured with a survey and results will be averaged among those in the same cohort. Any significant differences will also be measured with similar statistical analysis stated previously.

13 Ethics/Protection of Human Subjects

This study is to be conducted according to applicable US federal regulations and institutional policies (which are based in federal regulations, guidance, and ICH Good Clinical Practice guidelines).

This protocol and any amendments will be submitted to the Boston Medical Center and Boston University Medical Campus IRB, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. Consent will be documented as required by the IRB.

14 Literature References

1. American Glaucoma Society. American Glaucoma Society. https://www.americanglaucomasociety.net/patients/position_statements/glaucoma_eye_drop_availability. Published July 2009. Accessed October 25, 2017.
2. Ghate, D., & Edelhauser, H. Barriers to glaucoma drug delivery. *Journal of Glaucoma*. 2008; 17(2), 147-56. doi:10.1097/IJG.0b013e31814b990d
3. Rivers, P. Compliance aids--do they work? *Drugs & Aging*. 1992; 2(2), 103-11. doi:10.2165/00002512199202020-00004
4. Salyani, & Birt. Evaluation of an eye drop guide to aid self-administration by patients experienced with topical use of glaucoma medication. *Canadian Journal of Ophthalmology/Journal Canadien D'ophtalmologie*. 2005;40(2), 170-174. doi:10.1016/S0008-4182(05)80028-6.
5. Sommer, Alfred. Intraocular Pressure and Glaucoma. *American Journal of Ophthalmology*, 1989; 107 (2), 186-188.

15 Appendix

15.1 Schedule of Events: Source documents include medical records, satisfaction surveys, and all other information necessary to reconstruct and evaluate the clinical trial. See table 1 below for schedule of events.

Table 1: Schedule of Events. This table demonstrates the procedures to completed at each study visit.

Procedures	Screening and Consent	Randomization	3 Week Phone Call	6 Week Follow-up Visit
Informed consent	X			
Study specific review of medical/ophthalmic history	X			
Study specific review of demographics	X			
Review of inclusion/exclusion criteria	X	X	X	X
IOP and VA check	X			X
Randomization		X		
Dispense drop aid (if applicable)		X		
Teach/emphasize drop aid usage and compliance (if applicable)		X	X	
Dispense study diary		X		
Confirm contact information	X	X	X	
Schedule/Confirm Follow-up Visits	X	X	X	
Completion of satisfaction survey			X	X
Collect study diary				X
Assessment of possible AEs and/or SAEs			X	X

15.2 Case Report Forms (CRF)

15.2.1 Eligibility Assessment Form

Study Name:	Glaucoma Drop Aids
IRB Protocol #:	H-34905
Protocol Version # and/or Date:	
Principal Investigator:	Manishi Desai, MD

SUBJECT # _____				
INCLUSION CRITERIA <i>Must be "yes"</i>	Yes	No	Location of supporting source documentation	Notes
1. Age 18 years or greater	<input type="checkbox"/>	<input type="checkbox"/>		
2. Patient of Boston University Eye Associates	<input type="checkbox"/>	<input type="checkbox"/>		
3. Currently on the same topical ophthalmic medications for treatment of glaucoma for minimum of two months	<input type="checkbox"/>	<input type="checkbox"/>		

This subject is:

Eligible for participation **Ineligible for participation**

Signature:	Date:
Printed Name:	

15.2.2 Documentation of Informed Consent

Participant:	
Version of consent used:	
Consent obtained by:	
Date of consent:	

Check all that apply (provide necessary details in the notes space below):

- The study was explained and the consent form was reviewed with the participant.
- All of the participant’s questions were answered and all the consent elements, such as purpose, procedures, and risks were reviewed.
- The participant was given sufficient time to consider participation.
- The participant agreed to participate in the study and personally signed and dated the consent form.
 - Verbal consent/assent was obtained (as approved by the IRB).
 - Obtained consent from Legally Authorized Representative (as approved by the IRB).
- The consent form was signed and dated by the researcher.
- The consent process was witnessed by an impartial witness (if applicable).
- The participant was given a copy of the signed informed consent form.
- The consent process was completed *prior to the start of research procedures*.

Notes about the consent process (i.e. who was involved in consent process, what questions did the participant have, translator number, whether a teach-back process was used, etc.):

Signature or initials of person completing this form: _____

Date form completed: _____

15.2.3 Home Study Diary

Individual(s) completing this form: Study Subject Research team member: _____ (initials)

Date of completion: _____

Study ID	
Medication Name: _____	Start Date: _____ End Date: _____
Medication Name: _____	Start Date: _____ End Date: _____
Medication Name: _____	Start Date: _____ End Date: _____

Please complete this paper and bring it to your next eye appointment along with your drop aid and eye drops

15.2.4 Satisfaction Survey

Study ID: _____

Name of study team member completing this form: _____

Date: _____

Study Visit: 3-week phone call Follow-up clinic visit

1. Do you like the drop aid?
 - a. Yes
 - b. No
 - c. I am not on a drop aid
 - d. I did not use the drop aid
2. Is it easier to instill drops with the help of the drop aid compared without the drop aid?
 - a. Yes
 - b. No
 - c. I am not on a drop aid
 - d. I did not use the drop aid
3. How many times did you miss instilling drops with the help of drop aid?
 - a. None
 - b. 1
 - c. 2
 - d. 3 or more
 - e. I am not on a drop aid
 - f. I did not use the drop aid
4. How many times do you miss instilling drops just using your glaucoma drops?
 - a. None
 - b. 1
 - c. 2
 - d. 3 or more
5. Would you use the drop aid long term?
 - a. Yes
 - b. No
 - c. I am not on a drop aid
 - d. I did not use the drop aid

15.3 Drop Aid Label and Instructions

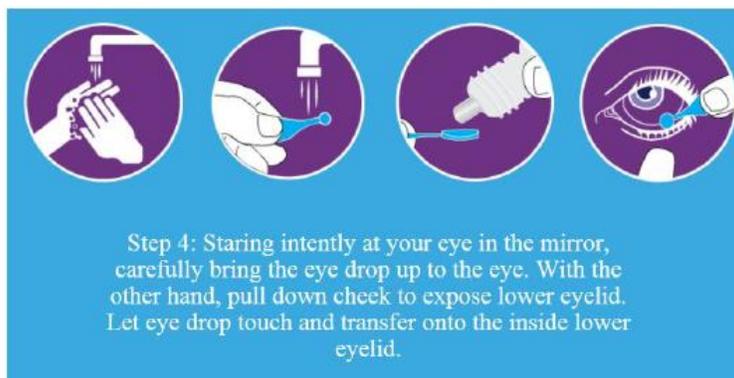
15.3.1 Drop Aid Label

The label below was placed on each individual drop aid box in order to identify it as an investigational device provided by BMC.

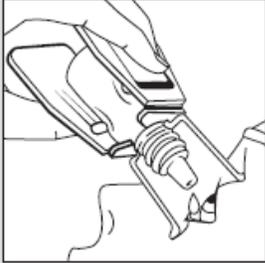
**CAUTION- Investigational device.
Limited by Federal (or United States)
law to investigational use.**

*Provided by Dr. Manishi Desai at Boston Medical Center
Department of Ophthalmology*

15.3.2 Simply Touch Eye Drop Applicator Instructions



15.3.3 Fabrication Autodrop Eye Drop Guide

	<p>AutoSqueeze can also be used in conjunction with AutoDrop.</p>	<p>AutoSqueeze peut également être utilisé avec AutoDrop.</p>	<p>AutoSqueeze puede utilizarse conjuntamente con AutoDrop.</p>	<p>AutoSqueeze kann auch zusammen mit dem AutoDrop verwendet werden.</p>
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AutoSqueeze™ and AutoDrop® are trademarks of Owen Mumford Ltd

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OP/8100/11/0000/03

15.3.4 Owen Mumford OP 6100 Autosqueeze



OP6100

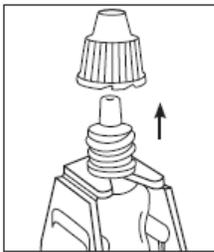
Instructions
Mode d'emploi
Instrucciones de uso
Gebrauchsanleitung

Making bottle squeezing easier. Clips onto eyedrop bottles to provide extra leverage.

Facilite l'utilisation des flacons. Clips pour flacons de collyre assurant une pression maximum.

Facilita el uso de los contenedores. Se ajusta al contenedor para proporcionar más presión.

Vereinfacht das Verabreichen von Augentropfen. Eintropfhilfe zum Aufstecken auf Augentropfenflaschen zur Unterstützung der Dosierung.

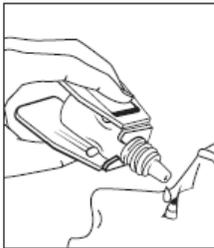


1. Remove cap from eye drop bottle.

Enlever le capuchon du flacon de collyre.

Retirar el tapón del frasco de las gotas.

Drehen Sie den Verschluss der Augentropfenflasche ab.



2. Locate the keyhole slot around the base of the bottle neck.

Positioner l'ouverture autour de la base du col du flacon.

Situar la ranura alrededor de la base del cuello del frasco.

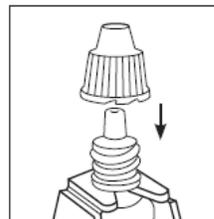
Stecken Sie den Flaschenhalter unterhalb des Gewindes, über den Hals der Flasche.

3. Position the bottle nozzle over the eye and gently squeeze.

Positionner l'embout du flacon au-dessus de l'œil et presser délicatement.

Coloque la boquilla del frasco sobre el ojo y presione el frasco ligeramente.

Halten Sie die Öffnung der Augentropfenflasche über das Auge und drücken Sie die Flügel vom AutoSqueeze ganz leicht zusammen.



4. Replace cap on eye drop bottle.

Remettre le capuchon sur le flacon.

Tapar de nuevo el frasco.

Die Augentropfenflasche mit dem Verschluss verschließen.

15.4 AE, SAE, and UP Tracking and Reports

15.4.1 Internal AE, SAE and UP Report Tracking Log (Sample)

Internal AE/UP Report Tracking Log

This log tracks assessment and reporting of internal AEs. AEs should be assessed for seriousness, severity, whether or not they are expected, and whether they are related. From this information, a determination of expedited reporting can be made. Events that are serious (OR pose a greater risk of harm than was previously known or recognized), at least possibly related to the research, and unexpected are Unanticipated Problems (UPs) and must be reported within two days to the BUMC IRB. The sponsor may have different reporting requirements. Other events (non-UPs) should be reported to the IRB at the time of the progress report. If the study is monitored by an outside independent monitoring committee then their report(s) will suffice instead of an AE summary at the time of the progress report. Investigators monitoring their own studies may use this log to submit to the IRB at the time of progress report. Please refer to the BU AE Reporting policy at: <http://www.bumc.bu.edu/Dept/Content.aspx?DepartmentID=293&PageID=9923>.

Ptp ID #	Date AE	AE description	SAE? ¹	Relationship with study intervention, per MD: <i>Definite, Probable, Possible, Unlikely, Unrelated</i>	Expected?	Severity Grade ²	UP? ³	Date reported to sponsor (if applicable)	IRB reporting (expedited for UPs, vs. progress report)
			<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> expected <input type="checkbox"/> unexpected		<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> UP reporting date: <input type="checkbox"/> Progress report
			<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> expected <input type="checkbox"/> unexpected		<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> UP reporting date: <input type="checkbox"/> Progress report
			<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> expected <input type="checkbox"/> unexpected		<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> UP reporting date: <input type="checkbox"/> Progress report
			<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> expected <input type="checkbox"/> unexpected		<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> UP reporting date: <input type="checkbox"/> Progress report
			<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> expected <input type="checkbox"/> unexpected		<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> UP reporting date: <input type="checkbox"/> Progress report
			<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> expected <input type="checkbox"/> unexpected		<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> UP reporting date: <input type="checkbox"/> Progress report
			<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> expected <input type="checkbox"/> unexpected		<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> UP reporting date: <input type="checkbox"/> Progress report
			<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> expected <input type="checkbox"/> unexpected		<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> UP reporting date: <input type="checkbox"/> Progress report
			<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> expected <input type="checkbox"/> unexpected		<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> UP reporting date: <input type="checkbox"/> Progress report
			<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> expected <input type="checkbox"/> unexpected		<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> UP reporting date: <input type="checkbox"/> Progress report
			<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> expected <input type="checkbox"/> unexpected		<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> UP reporting date: <input type="checkbox"/> Progress report
			<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> expected <input type="checkbox"/> unexpected		<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> UP reporting date: <input type="checkbox"/> Progress report
			<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> expected <input type="checkbox"/> unexpected		<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> UP reporting date: <input type="checkbox"/> Progress report
			<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> expected <input type="checkbox"/> unexpected		<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> UP reporting date: <input type="checkbox"/> Progress report
			<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> expected <input type="checkbox"/> unexpected		<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> UP reporting date: <input type="checkbox"/> Progress report
			<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> expected <input type="checkbox"/> unexpected		<input type="checkbox"/> yes <input type="checkbox"/> no		<input type="checkbox"/> UP reporting date: <input type="checkbox"/> Progress report

¹ SAE Classification: AE is an SAE if it meets any of the criteria below.	² Severity Grade	³ Unanticipated problem: If AE meets all three criteria below report to IRB within 2 days.
<ul style="list-style-type: none"> - Results in death - Life threatening - Requires prolonged hospitalization - Results in disability or incapacity - Congenital Anomaly/birth defect - Medically important event 	<ul style="list-style-type: none"> 1 - Mild AE (not requiring treatment) 2 - Moderate AE (resolved with treatment) 3 - Severe (inability to carry on normal activities/required professional medical attention) 4 - Severe: life threatening or disabling AE 5 - Death 	<ul style="list-style-type: none"> - Unexpected - Related possibly related to the research - Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

15.4.2 SAE and UP Report Form (Sample)

Designated Study Personnel Completing and Reviewing this Report		
Printed Name of Designated Individual(s) Completing this Report	Signature of Designated Individual(s) Completing this Report	Date
1.		
2.		
3.		
4.		
5.		
Printed Name of PI	Signature of PI	Date
Printed Name of Safety Monitor	Signature of Safety Monitor	Date

Subject Information						
Type of Event	Date of Birth	Age (at time of event)	Sex	Height	Weight	BMI
<input type="checkbox"/> Serious Adverse Event			<input type="checkbox"/> Male <input type="checkbox"/> Female	<input type="checkbox"/> Inches <input type="checkbox"/> cm	<input type="checkbox"/> lbs <input type="checkbox"/> kg	
<input type="checkbox"/> Unanticipated Problem						

SAE/UP Information						
AE Diagnosis	Date and Time of Onset	Date and Time at End of Event	Was the event related to the study intervention	Severity Grade	SAE Criteria	Outcome
			<input type="checkbox"/> definite <input type="checkbox"/> probable <input type="checkbox"/> possible <input type="checkbox"/> unlikely <input type="checkbox"/> unrelated	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> death <input type="checkbox"/> life threatening <input type="checkbox"/> new or prolonged hospitalization Admission date: _____ Discharge Date: _____ <input type="checkbox"/> congenital anomaly/birth defect <input type="checkbox"/> significant disability/incapacity <input type="checkbox"/> important medical event	<input type="checkbox"/> recovered/resolved <input type="checkbox"/> recovered/resolved with sequelae <input type="checkbox"/> recovering/resolving <input type="checkbox"/> not recovered/not resolved <input type="checkbox"/> fatal Date: _____ <input type="checkbox"/> unknown

Relevant Medical History			
Medical Condition or Event	Ongoing or Resolved	Onset Date	End Date
1.	<input type="checkbox"/> Ongoing <input type="checkbox"/> Resolved		
2.	<input type="checkbox"/> Ongoing <input type="checkbox"/> Resolved		
3.	<input type="checkbox"/> Ongoing <input type="checkbox"/> Resolved		
4.	<input type="checkbox"/> Ongoing <input type="checkbox"/> Resolved		
5.	<input type="checkbox"/> Ongoing <input type="checkbox"/> Resolved		

6.	<input type="checkbox"/> Ongoing <input type="checkbox"/> Resolved		
7.	<input type="checkbox"/> Ongoing <input type="checkbox"/> Resolved		
8.	<input type="checkbox"/> Ongoing <input type="checkbox"/> Resolved		

Relevant Laboratory/Imaging Tests			
Test	Date of Test	Result of Test	Normal or Abnormal
1.			<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal
2.			<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal
3.			<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal
4.			<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal
5.			<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal

Concomitant Medications						
Drug Name	Start Date	Stop Date	Dose	Frequency	Route/Location	Indication
1.						
2.						
3.						
4.						
5.						

Adverse Event Information	
<p>Event description: Include course of the event, signs/symptoms, diagnostic test results, therapeutic measures for the event, etc.</p>	
<p>Relatedness Assessment: Record a brief reason for the PI's assigned causality</p>	