Glaucoma Drop Aid Study

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# TABLE OF CONTENTS

1 List of Abbreviations ........................................................................................................4
2 Protocol Summary .............................................................................................................4
3 Background/Rationale & Purpose .....................................................................................5
   3.1 Background Information ............................................................................................5
   3.2 Rationale and Purpose ...............................................................................................5
4 Objectives ..........................................................................................................................6
   4.1 Study Objectives .........................................................................................................6
   4.2 Study Outcome Measures ..........................................................................................6
      4.2.1 Primary Outcome Measures ................................................................................6
      4.2.2 Secondary Outcome Measures ............................................................................7
5 Study Design ......................................................................................................................7
6 Potential Risks and Benefits ..............................................................................................7
   6.1 Risks ...........................................................................................................................7
   6.2 Unknown Risks ...........................................................................................................7
   6.3 Potential Benefits ......................................................................................................8
   6.4 Analysis of Risks in Relation to Benefits ...................................................................8
7 Study Subject Selection ....................................................................................................8
   7.1 Subject Inclusion Criteria .........................................................................................8
   7.2 Subject Exclusion Criteria .........................................................................................8
8 Study Intervention .............................................................................................................8
9 Study Procedures ..............................................................................................................9
   9.1 Screening and Consent ..............................................................................................9
   9.2 Day of Enrollment and Randomization .....................................................................10
9.3 Follow-Up Study Visits ...............................................................................................10
      9.3.1 3 Week Phone Call: ..........................................................................................10
      9.3.2 Final Study Visit: At least 6 Weeks after Enrollment (SOC Clinic Visit) ..........10
   9.4 Early Termination Visit ..............................................................................................10
   9.5 Non-Study Visits (Unscheduled Visits) ....................................................................11
10 Assessment of Safety and Data Safety Monitoring Plan (DSMP) ..................................11
   10.1 Definitions ...............................................................................................................11
   10.2 Safety Review ..........................................................................................................12
   10.3 Reporting Plans .......................................................................................................12
   10.4 Stopping Rules ........................................................................................................12
11 Data Handling and Record Keeping ...............................................................................13
   11.1 Confidentiality .........................................................................................................13
   11.2 Source Documents ..................................................................................................13
   11.3 Case Report Forms ................................................................................................13
   11.4 Study Records Retention .........................................................................................14
12 Statistical Plan ................................................................................................................14
   12.1 Study Hypotheses ....................................................................................................14
   12.2 Sample Size Determination .....................................................................................15
   12.3 Statistical Methods ..................................................................................................16
13 Ethics/Protection of Human Subjects ............................................................................16
14 Literature References ......................................................................................................17
15 Appendix ..........................................................................................................................18
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.

15.2 Case Report Forms (CRF)

15.2.1 Eligibility Assessment Form

15.2.2 Documentation of Informed Consent

15.2.3 Home Study Diary

15.2.4 Satisfaction Survey

15.3 Drop Aid Label and Instructions

15.3.1 Drop Aid Label

15.3.2 Simply Touch Eye Drop Applicator Instructions

15.3.3 Fabrication Autodrop Eye Drop Guide

15.3.4 Owen Mumford OP 6100 Autosqueeze

15.4 AE, SAE, and UP Tracking and Reports

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

15.4.2 SAE and UP Report Form (Sample)
1 List of Abbreviations

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

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: No Glaucoma Drop Aid Device
- Drop Aid Devices:
  - 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. 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.

Glaucoma is commonly treated with prescription eye drops. It is critical that patients receive the correct dose and frequency of eye drop medication as prescribed. This will prevent disease advancement and decrease the chances of vision loss. However, patient compliance with medication limits symptom improvement due to deliberate misuse, financial concerns, or unintentional issues in drug delivery. Some patients have difficulty putting in the correct amount of eye drops themselves. 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. In order to ensure patients are receiving the correct amount of drops with each use, drop aids are available at local pharmacies for purchase. These are not commonly recommended because they can be costly and their usefulness has not yet been proven. 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.

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. 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. 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. Self-reported studies also showed that approximately 25% of patients reported problems with early exhaustion of eye drop bottles. 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. 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.
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. 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 serves, 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 significantly 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.

\[ H_0: \mu_0 < \mu_d - \delta \]
\[ HA: \mu_0 \geq \mu_d - \delta \]

Where \( \mu_0 \) is the true mean IOP change from baseline to the six week visit without the drop aid device, \( \mu_d \) 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.

\[ H_0: \mu_s < \mu_{sd} - \delta \]
\[ HA: \mu_s \geq \mu_{sd} - \delta \]

Where \( \mu_s \) is the mean patient satisfaction without the drop aid device, \( \mu_{sd} \) 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.

\[ H_0: \mu_y < \mu_n - \delta \]
\[ HA: \mu_y \geq \mu_n - \delta \]

Where \( \mu_y \) is the mean patients who claimed interest in long term use of the device, \( \mu_n \) 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

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.

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

15.2.1 Eligibility Assessment Form

<table>
<thead>
<tr>
<th>Study Name:</th>
<th>Glaucoma Drop Aids</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRB Protocol #:</td>
<td>H-34905</td>
</tr>
<tr>
<td>Protocol Version # and/or Date:</td>
<td></td>
</tr>
<tr>
<td>Principal Investigator:</td>
<td>Manishi Desai, MD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SUBJECT # _____________________</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>INCLUSION CRITERIA</th>
<th>Yes</th>
<th>No</th>
<th>Location of supporting source documentation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Must be &quot;yes&quot;</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1. Age 18 years or greater</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Patient of Boston University Eye Associates</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Currently on the same topical ophthalmic medications for treatment of glaucoma for minimum of two months</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This subject is:

☐ Eligible for participation   ☐ Ineligible for participation

<table>
<thead>
<tr>
<th>Signature:</th>
<th>Date:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Printed Name:</th>
<th></th>
</tr>
</thead>
</table>
15.2.2 Documentation of Informed Consent

<table>
<thead>
<tr>
<th>Participant:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Version of consent used:</td>
<td></td>
</tr>
<tr>
<td>Consent obtained by:</td>
<td></td>
</tr>
<tr>
<td>Date of consent:</td>
<td></td>
</tr>
</tbody>
</table>

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:** ___________________

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Medication Name: ________</th>
<th>Start Date: ______________</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>End Date: ______________</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medication Name: ________</td>
<td>Start Date: ______________</td>
</tr>
<tr>
<td></td>
<td>End Date: ______________</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medication Name: ________</td>
<td>Start Date: ______________</td>
</tr>
<tr>
<td></td>
<td>End Date: ______________</td>
<td></td>
</tr>
</tbody>
</table>

*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

Step 1: Wash your hands.

Step 2: Remove applicator from case, wash with soap and water. Rinse and dry.

Step 3: Hold the eye drop bottle at about a 45 degree angle as shown. Apply one drop onto round flat tip of applicator. Do not touch bottle to applicator.

Step 4: Staring intently at your eye in the mirror, carefully bring the eye drop up to the eye. With the other hand, pull down check to expose lower eyelid. Let eye drop touch and transfer onto the inside lower eyelid.
15.3.3 Fabrication Autodrop Eye Drop Guide

AutoSqueeze™ and AutoDrop® are trademarks of Owen Mumford Ltd

Made in England by

Owen Mumford

www.owenmumford.com
15.3.4 Owen Mumford OP 6100 Autosqueeze

AutoSqueeze

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
colluye assurant une
pression maximum.
Facilita el uso de los
contenedores. Se
ajust al contenedor
para proporcionar
más presión.
Vereinfacht das
Verabreichen von
Augentropfen. Eintropfhilfe
zum Aufstecken auf
Augentropfentaschen
zur Unterstützung der
Dosierung.

1. Remove cap
from eye
drop bottle.
Enlever le
capuchon
du flacon.
Retirar el
tapón del
frasco de
gotas.
Drehen Sie den
Verschluss der
Augentropfen-
tasche 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
unten 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
delicatement.
Coloque la
boquilla del
frasco sobre el
ojo y presione
el frasco
ligeramente.
Halten Sie die
Öffnung der
Augentropfentasche
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 Augentropfentasche
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**

<table>
<thead>
<tr>
<th>Pip ID #</th>
<th>Date</th>
<th>AE</th>
<th>AE description</th>
<th>SAE**</th>
<th>Relationship with study intervention, per MD: <strong>Definite, Probable, Possible, Unlikely, Unrelated</strong></th>
<th>Expected?</th>
<th>Severity Grade*</th>
<th>UP??</th>
<th>Date reported to sponsor (if applicable)</th>
<th>IRB reporting (expedient for UFs, vs progress report)</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

**SAE Classification.** AE is an SAE if it meets one of the criteria below.

- Death
- Life-threatening
- Hospitalization
- Permanent disability or incapacity
- Congenital anomaly/birth defect
- Medically important event

**Severity Grade**

1. Mild AE (not requiring treatment)
2. Moderate AE (noted with treatment)
3. Severe disability to carry on normal activities (required professional medical attention)
4. Severe, life threatening or disabling AE
5. Death

**Unanticipated problem.** If AE meets all three criteria below report to IRB within 2 days.

- Suspected
- Unrelated
- Possibly related to the research
- Expected

---

Page 27 of 31
15.4.2 SAE and UP Report Form (Sample)

<table>
<thead>
<tr>
<th></th>
<th>Printed Name of Designated Individual(s) Completing this Report</th>
<th>Signature of Designated Individual(s) Completing this Report</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
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<tr>
<td>2.</td>
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<td>3.</td>
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<tr>
<td>4.</td>
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<td></td>
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<tr>
<td>5.</td>
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</table>

<table>
<thead>
<tr>
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<th>Printed Name of PI</th>
<th>Signature of PI</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td></td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Printed Name of Safety Monitor</th>
<th>Signature of Safety Monitor</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
### Subject Information

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Date of Birth</th>
<th>Age (at time of event)</th>
<th>Sex</th>
<th>Height</th>
<th>Weight</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Adverse Event</td>
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<tr>
<td>Unanticipated Problem</td>
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</tbody>
</table>

### SAE/UP Information

<table>
<thead>
<tr>
<th>AE Diagnosis</th>
<th>Date and Time of Onset</th>
<th>Date and Time at End of Event</th>
<th>Was the event related to the study intervention</th>
<th>Severity Grade</th>
<th>SAE Criteria</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>definate</td>
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<tr>
<td>probable</td>
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<td>new or prolonged hospitalization</td>
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<td>discharge date: ______</td>
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<tr>
<td>congenital anomaly/birth defect</td>
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<tr>
<td>significant disability/incapacity</td>
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<td>relavant medical event</td>
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</table>

### Relevant Medical History

<table>
<thead>
<tr>
<th>Medical Condition or Event</th>
<th>Ongoing or Resolved</th>
<th>Onset Date</th>
<th>End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Ongoing</td>
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<tr>
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<tr>
<td>4.</td>
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<tr>
<td>5.</td>
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<td></td>
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</tr>
</tbody>
</table>
### Relevant Laboratory/Imaging Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Date of Test</th>
<th>Result of Test</th>
<th>Normal or Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
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<tr>
<td>2.</td>
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</tbody>
</table>

### Concomitant Medications

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Dose</th>
<th>Frequency</th>
<th>Route/Location</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
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<td>5.</td>
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<tr>
<td>Event description:</td>
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<tr>
<td>Include course of the event, signs/symptoms, diagnostic test results, therapeutic measures for the event, etc.</td>
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<table>
<thead>
<tr>
<th>Relatedness Assessment:</th>
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<tbody>
<tr>
<td>Record a brief reason for the PI's assigned causality</td>
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</tbody>
</table>