Safety and Tolerance of the Slit Stent II Lacrimal Stent for the Treatment of Nasolacrimal Duct Obstruction

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CLINICAL MONITOR:	University of Michigan Institute of Clinical and Health Research (MICHR) Clinical Research Monitoring Program

Investigator Signature Page

My signature below certifies that I have read and understand this protocol and agree to conduct the study in accordance with the specified protocol procedures and FDA's Good Clinical Practice requirements.

PRINCIPAL INVESTIGATOR NAME (Printed):	Date:
PRINCIPAL INVESTIGATOR SIGNATURE:	Date:

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1.0 BACKGROUND

A stable tear film is essential for good visual function. On the other hand, excessive tearing (i.e., **epiphora** – a very common condition [1]) can be a major cause for loss of quality of life [2], interfering with activities such as driving, reading, watching TV, being outdoors, and social interactions, in addition to being a major risk for tear duct infection (dacryocystitis), especially in children [3]. The constant dabbing of the cheeks can also lead to skin irritation and puts the eyes at risk of infection. While the prevalence of epiphora is not known, the incidence of symptomatic nasolacrimal duct obstruction in 1996-2000 in the US was 30.47 per 100,000, or approximately 120,000 new cases per year [1]. Globally, the incidence is even higher, with case series publications from India, Singapore and South Korea suggesting a significant global disease burden. In the treatment of epiphora, and in order to facilitate proper healing, surgeons frequently place a temporary silicone tube within the healing lacrimal drainage system to stent the passages during the healing process [4-7]. Many thousands of these procedures are performed each year, and the longer the stents stay in place, the higher the likelihood of long-term surgical success [8-11]. However, the stents occupy space within the very narrow lacrimal drainage apparatus, delaying maximal improvement in tear drainage until the stent is removed weeks to months after the procedure. This issue is further exacerbated in cancer patients on chemotherapy such as docetaxel (Taxotere) chemotherapy for breast cancer [12], which requires prolonged stenting. Despite the fact that stents have a hollow lumen, there are no stents on the market in which the lumen is open to tear drainage – possibly because of the engineering challenge of creating an opening into the lumen that is large enough to allow tears to flow in but not so large that the stent becomes too weak and fragile that it breaks prematurely. Through an active collaboration between an ophthalmologist and a mechanical engineer, we have developed a lacrimal stent that has a slit opening strategically constructed to drain tears into the lumen, while optimizing the basic characteristics of the silicone tubing for the purpose of intraluminal drainage. Such a stent could revolutionize the use of stents in the treatment of symptomatic, debilitating epiphora.

1.1 Preliminary Clinical Data / Prior Clinical Experience

This study is of the Slit Stent II medical device, a novel variation on a well-established surgical tool, namely a silicone tube used to temporarily stent the lacrimal drainage system following a recanalization procedure to treat epiphora. Hence, its use in human patients is based on a solid clinical foundation [see literature summary below.] Silicone stents have been used successfully for decades to maintain the patency of the lacrimal drainage apparatus as the tissues heal following dacryocystorhinostomy (DCR) surgery. The Slit Stent II is a modification of the "BIKA for DCR" silicone stent manufactured by FCI (FCI SAS; Besancon, France) and approved for use throughout the world, including in the United States [13-16].

Literature has reported the use of lacrimal stents since 1998 [6, 9, 14, 17-19]. In the following 20 years, multiple articles involving over 1,000 patient subjects have examined DCR with and without stents, with techniques involving polyurethane or silicone stents, using bicanalicular or monocanalicular stents [3-7, 9-11, 16, 20-40]. In 2016, Fayers *et al* reported a prospective, randomized, controlled, interventional trial involving 300 adult subjects, half of whom received

bicanalicular stents, concluded that there is a statistically significantly higher success rate in EN-DCR surgery with stents compared with no stent [31].

The specific stent used in this study (without our modifications, however) is the subject of four prior publications involving 485 adult subjects [13-16]. As previously mentioned, this is the BIKA for DCR bicanalicular stent manufactured by FCI SAS, Besancon, France. These publications looked at the relative success and complications of monocanalicular stents versus bicanalicular stents; external DCR versus endonasal DCR; and the unciformian endonasal technique versus the maxillary endonasal technique. Of note is that in all cases the silicone stent, BIKA for DCR, was used as the standard and its use was routine.

1.2 Rationale for Study and Use of the Slit Stent II Device

The Slit Stent II has an internal lumen that is open to the ocular surface at the interpalpebral fissure, such that tears can drain through the lumen of the stent. After it is placed into the lacrimal system and into the nose, the slit openings into the lumen will allow tears to drain into the nose, which is where tears normally drain, rather than flow over the lid margin and onto the cheek (epiphora).

2.0 PRODUCT DESCRIPTION

2.1 Intended Use

Temporary post DCR lacrimal stenting

2.2 Indications for Use

Nasal bicanalicular intubation is indicated in treatment of epiphora in adults in cases of Dacryocystorhinostomy (conventional or laser).

2.3 Device Description

A lacrimal stent is hollow silicone tubing with a non-traumatic tip. The tubing is securely attached into malleable stainless steel probes that are used to guide the silicone tubing through the lacrimal drainage apparatus. The device is used to maintain an open lacrimal path between the surface of the eye and the nasal passages, particularly during a healing process following injury or surgery.

The BIKA for DCR lacrimal stent is a bicanalicular intubation device used for intubation of the lacrimal drainage apparatus, especially in cases of dacryocystorhinostomy (conventional or laser). The silicone tube acts as a conformer during the healing process while facilitating drainage of tears

through capillary action around the stent. In cases of canalicular lacerations, the silicone tube guides wound healing and prevents the onset of synechia.

The BIKA lacrimal stent consists of a single unit including a silicone tube (length: 280 mm, external diameter: 0.94 mm), and one steel probe at each end of the silicone tube (length: 53 mm, external diameter: 0.8 mm) with round tips (see Figure 1, below).

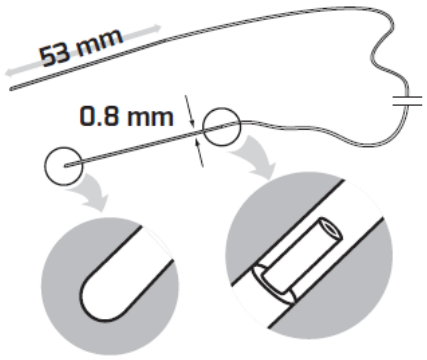

Fig. 1: BIKA for DCR

The BIKA for DCR is a sterile, single-use device, and is an FDA cleared device.

The Slit Stent II (investigational) device is created by modifying an existing FDA cleared lacrimal stent (Bika, manufactured by FCI Opthalmics- see figure 1 above) by adding additional 3 mm (+/- 0.5 mm) and 35 mm (+/- 3.5 mm) long slits of equal depth. See figure 2 below.

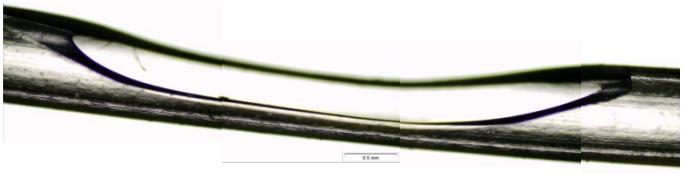

Figure 2. A 3 mm long slit into the silicone tubing.

The axial cutouts located on the stent allow drainage of tears from the ocular surface to the nasal/oropharynx cavities through the internal lumen of the stent. See figure 3.

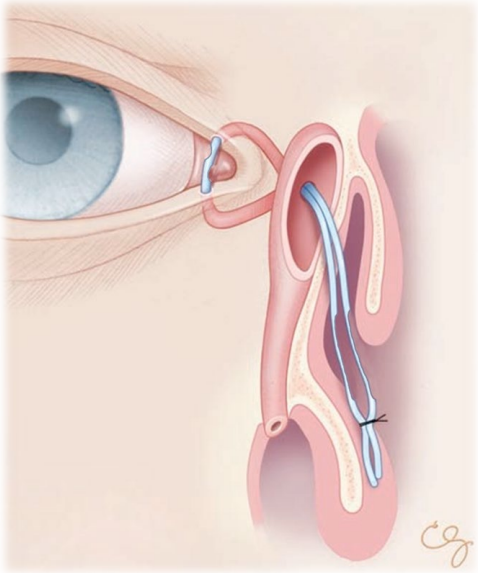

Figure 3. Stent with multiple cut-outs placed as part of a standard DCR procedure allow for improved draining of tears and resolution of symptomatic tearing.

All modifications to the stent are inspected under an optical microscope at a magnification of at least 5x to ensure they are free from cutting defects, which could impact the structural integrity of the Slit Stent II. To ensure that the Slit Stent II can withstand the forces experienced during implantation and removal, additional mechanical integrity tests were performed. Comparing the implantation forces to the maximum insertion and removal force, we determined that the modified Slit Stent II will have excellent tensile strength – essentially identical to unmodified stent – to prevent mechanical failure in patient use. Each section was tested to determine the maximum elongation and force it can withstand before failure.

After modification at the University of Michigan, the Slit Stent II is then packaged and sent to FCI Opthalmics for sterilization, packaging and return to Michigan for use in the clinical trial.

3.0 RISK/BENEFIT ANALYSIS

3.1 Comparison with Other Alternative Devices

Devices for post-DCR temporary stenting are ubiquitous and widely used. There are no foreseeable risks for the modified slit stents beyond the standard risks associated with DCR with stenting.

As in any type of surgery, there are risks linked to the material or to developments of the initial pathology. Potential complications associated with the placement of the BIKA for DCR stents include, but are not limited to the following:

Post-operative complications:
- bleeding from nose
- infection
- conjunctival or nasal pruritus
- nasal mucosa or caruncular irritation
- reversible shrinkage of the palpebral fissure
- exteriorization or loss of the stent tubing
- punctal/canalicular injury
- canaliculitis

Device related complications could include, but are not limited to:
- Device dislocation into the oropharynx
- Corneal abrasion
- Conjunctival abrasion
- Secondary surgical interventions related to the Slit Stent II device (surgical repositioning, removal, or replacement)

This is the only device that will allow tears to drain through the lumen.

3.2 Minimization of Potential Risks

Standard surgical technique will be used. Post-operative ocular surface antibiotic drops will be used in the usual manner. Subjects will be observed closely to detect any adverse events or complications that may have occurred.

3.3 Potential Benefits

Benefits include more rapid resolution of epiphora symptoms and longer retention of the stent for a better long-term surgical outcome.

3.4 Justification for the Investigation

- Investigate whether a stent with slits at the interpalpebral fissure is well tolerated
- Determine whether epiphora improves following DCR and Slit Stent II placement

4.0 OBJECTIVES

1) Assess tolerance of patients to placement of Slit Stent II (Glasgow Benefits Index and Patient Stent Tolerance and Irritation Assessment)
2) Assess ocular surface irritation (objective and subjective) following stent placement (Glasgow Benefits Index and Patient Stent Tolerance and Irritation Assessment; Conjunctival and corneal epithelial surface exam and staining under the slit lamp)
3) Assess change in quality of life following surgery (Glasgow Benefits Index and Lac-Q Questionnaire)
4) Assess change in tearing/epiphora symptoms before and after surgery (Glasgow Benefits Index and Lac-Q Questionnaire)

5) Assess change in conjunctival tear lake measurement before and after surgery
6) Assess bacterial growth on stents after removal

All criteria will be summarized within the Slit Stent II treatment group. Formal comparisons will be made to no treatment effect and to the standard treatment (control group).

5.0 OUTCOMES ASSESSMENT TIMETABLE

Patients will be assessed at 1-day post op by phone, and exams at 5-14 days post-DCR surgery (1st post-op visit), 2-4 months post-DCR surgery (usually 2nd post-op visit), and 4-7 months post-DCR surgery.

6.0 STUDY DESIGN

Double arm, single blind, prospective randomized study

7.0 SUBJECT POPULATION

This is a single center study that will be conducted at the University of Michigan (Ann Arbor, Michigan). Fifty (50) subjects will be enrolled and treated with either the experimental Slit Stent II (25 patients) or the control stent BIKA for DCR (25 patients). Patients who are currently scheduled to undergo a DCR (dacryocystorhinostomy) as per standard of care will be offered participation in the study. Patients who elect to participate in the study will be consented and then randomized to the treatment or control arm.

7.1 Inclusion Criteria

Subjects in whom the subject and study eye meet all of the following criteria are candidates for this study:

1. 22 years of age or older.
2. Eligible for unilateral DCR surgery with stenting for treatment of epiphora secondary to nasolacrimal duct obstruction. Ability to instill post-operative eye drop
3. Signed written, informed consent.
4. Willingness and ability to comply with schedule for follow-up visits and postoperative evaluations.

7.2 Exclusion Criteria

All subjects in whom the subject or study eye meets any of the following criteria will be excluded from the study:

- Subjects less than 22 years of age
- Subjects scheduled for bilateral DCR surgery
- Subjects with known sensitivity to silicone
- Subjects with a current condition that, in the investigator's opinion, would interfere with the treatment.

- Inability to use eye drops
- Subjects with a known sensitivity to required study medications (e.g. antibiotic drops) if an alternative medication is not available.
- Subjects under legal guardianship or who, in the investigator's opinion, lack the mental capacity to provide written informed consent for study participation.

8.0 STUDY DURATION AND EXAMINATION SCHEDULE

8.1 Study Duration

The study duration will be 6 months (+/- 1 month) for all study patients.

8.2 Examination Schedule

The following examination schedule will be followed from screening through the postoperative visits:

- Screening (Day -60 to Day 0 Preoperatively)
- Device implantation operation
- Phone call Assessment at 1 day post op
- Phone call Assessment at 45 days post op (+/- 15 days)
- Day 5-14 postoperatively
- Day 30-120 postoperatively (with stent removal)
- 5-7 month final post-operative exam

The screening visit should be completed anytime within the 60 days prior to the scheduled surgery. Unscheduled visits may be completed at the investigator's discretion or as medically necessary before or after the implant surgery.

All final exam procedures will be completed at the second post-operative study visit.

9.0 STUDY PROCEDURES

Subjects who elect to participate in this study will complete the study as outlined below. Subjects will be randomly assigned to the experimental vs. control stents using a randomized block design with 1:1 allocation to treatment and control. Stents will be provided to the surgical team on the day of surgery by the Study Coordinator. Surgical team, recruitment staff, and scheduling staff will be masked to treatment assignment until day of surgery. All tests and measurements should be obtained in accordance with the procedures specified in this protocol. If it is not possible to perform a measurement or examination due to the individual eye's specific ocular pathology, the reason for not performing the test or measurement should be documented on the source documents.

The investigator may designate one or more surgeon sub-investigators at his/her investigative site. A surgeon sub-investigator may evaluate subjects for the study and perform the Slit Stent II lacrimal stent intubation. Surgeon sub-investigators will be listed on all applicable investigator regulatory documents (including the delegation of responsibilities log) and will complete all sponsor-required training for the study.

For the pre-op and all post op study visits, the Lac-Q Questionnaire will be administered by an interviewer, and the interviewer will record the subject's responses directly onto the corresponding questionnaire CRFs or source documents and calculate the Lac-Q score. For post op visits, the Lac-Q Questionnaire will be given prior to other questionnaires.

For the two post-op study visits, the Quality of Life (QOL) questionnaire (Glasgow Benefit Inventory (GBI)- see Appendix A) and the Patient Stent Tolerance and Irritation Assessment (see Appendix C) will be administered by an interviewer, in this order, and the interviewer will record the subject's responses directly onto the corresponding questionnaire CRFs or source documents and calculate the GBI score.

When multiple questionnaires are given at the same visit, the order shall always be: 1) Lac-Q, 2) GBI QOL, and 3) Patient Stent Tolerance and Irritation Assessment.

9.1 Slit Stent II Intubation Evaluation

Candidates for the Slit Stent II may be identified from the investigator's clinical practice or may be referred by outside ophthalmologists. All screening examination procedures will be performed by the investigator or trained personnel working under the investigator's supervision.

9.1.1 Referring Physicians

Subjects may be referred to the investigator for enrollment in the study. Evaluation of the lacrimal complaint and eligibility for DCR surgery and for the study will be assessed independently by the investigator.

9.1.2 Bilateral and Fellow Eye Treatment

Same day bilateral implantation of the Slit Stent II will not be allowed in the study.

9.1.3 Screening Eye Examination (Day -60 to Operative Day 0)

Informed consent must be signed and dated before any study procedures are performed that are specific for the study and not part of the routine evaluation or examination. A copy of the informed consent must be given to the subject and documented in the source documents. After informed consent is obtained, each potential Slit Stent II candidates will be evaluated in order to determine his/her eligibility for study participation. The complete ophthalmic clinical evaluation will take place before informed consent. Any assessment that is required on the screening CRF which was not completed as part of standard clinical exam will be completed after the consent is

obtained. Demographics and an ocular history, medical history, allergies and current medication list will be obtained. Please refer to the flow chart in **Appendix D** for the schedule of events for each listed study activity. The complete screening eye examination of the operative eye and subject histories will include, where medically possible:

- **Demographics** (Date of birth, gender, ethnicity. Age is calculated from the subject's date of birth and the informed consent date; subjects must be at least 22 years of age at the informed consent date.)
- **Medical history**
- **Medication list** (Baseline medication history should include all current prescribed medications and all routinely taken non-prescription medications)
- **Ocular history-** Baseline ocular history at the screening examination should include known ophthalmic conditions and prior eye surgeries.
- **Lac-Q questionnaire (Appendix B)**
- **Lacrimal system probing/irrigation**
- **Corrected visual acuity and manifest refraction-** Corrected visual acuity is measured in each eye after manifest refraction using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts. The distance from the subject's eyes to the ETDRS chart should be 3 meters. The standard ETDRS chart light box will be used. ETDRS Chart 1 will be used for the Right eye and Chart 2 for the Left Eye. Chart R will be used for manifest refraction. Room illumination will be at highest illumination (Appendix E).
- **Intraocular pressure-** Intraocular pressure measurement is measured by the iCare tonometry method. IOP measurement should be performed after visual acuity measurements.
- **Slit lamp biomicroscopy** of lid margins, puncta, conjunctiva and cornea- Slit lamp biomicroscopy with use of fluorescein should include a complete survey of the lid margins, puncta, conjunctiva and cornea. The Oxford scheme will be used to grade corneal and conjunctival staining. Any abnormalities such as corneal infiltrates and punctate erosions should be documented. The tear lake is measured using a slit lamp by narrowing the slit and shortening it to 1 mm or 0.2 mm, placing the slit light beam on the inferior lid margin tear lake, and using the beam to measure the vertical height of the fluid between the lid margin and the location of the top of the tear lake on the conjunctiva or cornea.

Other optional diagnostic tests may be performed at the investigator's discretion (e.g., dacryoscintigraphy, Jones test, etc.) to further evaluate the subject for nasolacrimal duct obstruction surgery or as dictated by the clinical situation. The results of optional diagnostic tests will be maintained in the source documents but will not be recorded on the CRFs.

9.2 Concomitant Medication

Subjects are permitted to take prescribed or non-prescription medications and supplements before and after the DCR procedure, at the discretion of the investigator. Medications used

during the operative procedure will be documented in the source documents for the operative procedure but will not be captured on the case report forms, unless the medication was used to treat an intraoperative adverse event or complication.

9.3 Stent Intubation Procedure (Operative Day 0)

The staff should confirm that the informed consent form (ICF) for the study has been signed, dated and a copy was given to the subject. The surgical staff is responsible for assuring that any additional surgical consent forms or HIPAA forms required by the clinic or institution are signed before surgery. Subject history and other tests or measurements from the screening examination or that are otherwise dictated by the subject's condition may be performed at the discretion of the investigator, to provide accurate baseline measurements or to determine continuing eligibility for the nasolacrimal duct intubation surgery.

The study statistician will create (via randomized block design) a treatment assignment list and provide it to the study coordinator only. The study coordinator will provide the correct stent at the time of the operation. Type of stent will not be recorded in patient record. Patient will not be told which stent was installed.

9.3.1 Subject Preparation

The subject will be prepared for surgery, and the operated side will be prepped and draped in the surgeon's usual sterile fashion for ophthalmic surgery. The DCR surgical procedure will be performed under standard Anesthesia conditions as per standard clinical care at the University of Michigan. Medications administered perioperatively may include sedation or anesthesia, antibiotics, and other surgical antimicrobials (e.g., povidone iodine) or medications used during any concomitant surgical procedure (e.g., steroids, antimetabolites). Local anesthesia will be performed at the surgeon's discretion based on the subject's clinical condition and surgical plan using the surgeon's standard drug regimen fashion.

9.3.2 Stent Intubation General Surgical Procedure

DCR surgery with stenting will be performed in a standard fashion opening the lacrimal sac, creation of an osteotomy connecting the nose to the lacrimal sac, and placing the stent under direct visualization. There are two techniques: External DCR and Endonasal DCR.

The external DCR involves (1) skin incision over the lacrimal sac, (2) exposure of lacrimal bone, (3) creation of an osteotomy into the nasal cavity using a bone-removal instrument, (4) opening of the lacrimal sac, (5) opening of the nasal mucosa, (6) placement of the lacrimal stent, (7) closure of the mucosa and surgical wound.

The endonasal DCR involves (1) visualizing the middle meatus in the nose, (2) identifying the position of the lacrimal sac (using a canalicular probe or light source), (3) creation of an osteotomy with a bone removal device to expose the lacrimal sac to the nasal cavity, (4) opening of the lacrimal sac, (5) placement of the lacrimal stent.

The selection of the DCR surgical technique will be determined by the surgeon and dictated by the clinical condition and lacrimal duct anatomy and pathology. This study does not aim to assess the efficacy of DCR surgery, and considers DCR surgery to be a well-established and efficacious surgical procedure for the treatment of epiphora secondary to nasolacrimal duct obstruction.

Operative records should be kept during the procedure or dictated postoperatively that describe medications used, the surgical technique for stent placement, concomitant surgical procedures, any operative complications or adverse events, and any planned or anticipated secondary surgical procedures. The position of the stent with respect to the location of central slit position relative to medial canthal interpalpebral function will be recorded on the CRFs. Medications used in conjunction with the surgical procedure will be described in the operative records and will not be recorded on the CRFs. The operative records will be retained in the source documents.

9.3.3 Postoperative Care

Written postoperative instructions will be given to each subject and reviewed prior to discharge. The following postoperative eye drops will be prescribed for the following minimum times:[1]

- An antibiotic-steroid combination eye drop (e.g. Tobramycin-Dexamethasone or Neomycin-Polymyxin-Dexamethasone) placed 4 times daily for 2 weeks, then twice daily for 2 weeks, then once daily for at least 2 weeks or until stent removal, as determined by the surgeon.

Additional medications including, but not limited to, erythromycin ointment and bacitracin ointment will be used at the discretion of the operating surgeon. All postoperative eye drop usage will be recorded on the source documents and on the CRFs. Other prescription or nonprescription medications, including pain medications, may be taken as needed throughout the study.

9.4 Follow-Up Visits (Day 1 phone call, Day 5-14 Postoperatively, Day 30-60 phone call, Day 30-120 Postoperatively, Month 5-7 Postoperatively)

A study flow chart summarizing the follow-up examination schedule and required procedures to be performed at each study visit is provided in **Appendix D**. All subjects will be seen for a 1st post-operative visit 5-14 days after the DCR with intubation, for a 2nd post-operative visit at 30-120 days after intubation, and for a final visit at month 5-7 postoperatively, with the exact timing dependent on patient findings and surgeon discretion. Unscheduled visits may be completed at the investigator's discretion or as medically necessary.

During the Day 1 and Day 30-60 phone assessments, the patient will be asked about any

[1] An alternative antibiotic or anti-inflammatory drug and dosage regimen may be used to conform with clinic or hospital formulary or prescribing requirements, with sponsor approval. An example would be neomycin-polymyxin-dexametasone eye drop (i.e. "Maxitrol").

postoperative swelling or pain or other adverse effects. If the patient reports any symptoms that would require a follow-up visit, we will ask the patient to return to the University of Michigan if possible. If this is not possible due to transportation issues, we will have them return to their referring ophthalmologist.

The following procedures will be performed **at the day 5-14 and day 30-120 post-operative visits** unless noted otherwise.

- **Documentation of interim medical, ocular, and medication histories** since previous visit. The ocular history should capture any changes in the study eye since the previous visit; and, any relevant changes to the fellow eye that are necessary to evaluate an adverse event or anomaly in the study eye. The medication history should capture any changes in prescribed medications or routinely taken non-prescription medication since the previous visit.
- **Subjective reports of tearing-** we will capture the subject's report of their tearing symptoms since the surgery procedure
- **Corrected distance visual acuity** - Corrected visual acuity is measured in each eye by the ETDRS chart at 3 meters using the manifest refraction obtained at the previous visit. If there is a 2-line or more reduction in visual acuity from the last corrected visual acuity, a repeat manifest refraction in each eye will be performed.
- **Intraocular pressure**- Intraocular pressure measurement is measured by the ICare tonometry method, performed after visual acuity measurement had been completed.
- **Slit lamp biomicroscopy** (including conjunctiva and cornea), with use of fluorescein- Slit lamp biomicroscopy should include a complete survey of the conjunctiva and cornea, and of the tear lake. The Oxford scheme will be used to grade corneal and conjunctival staining. The tear lake is measured using a slit lamp by narrowing the slit and shortening it to 1 mm or 0.2 mm, placing the slit light beam on the inferior lid margin tear lake, and using the beam to measure the vertical height of the fluid between the lid margin and the location of the top of the tear lake on the conjunctiva or cornea.
- **Visual inspection of stent integrity and slit positioning**- External and slit lamp exam of the medial canthal area and the medial commissure. The presence of the lacrimal stent within the medial commissure, between the puncta, will be documented as (1) present, slit in fissure, (2) present, slit not in fissure, or (3) not present.
- **Lac-Q questionnaire (Appendix B)**
- **Glasgow Benefit Inventory Questionnaire (Appendix A).**
- **Patient Stent Tolerance and Irritation Assessment (Appendix C)**
  - **The 3 questionnaires will always be given in the same order: 1) Lac-Q, 2) GBI, and 3) Stent Tolerance Assessment.**
- **Other diagnostic tests**– Jones I, Jones II or lacrimal irrigation at investigator's discretion
- **Adverse events, complications, visual disturbances**- Visual disturbances are any unexpected, expected, or pre-existing sight related occurrences that are not captured in any of the examinations or measurements, such as nystagmus or diplopia.

Unexpected or new reports of visual disturbances related to the device or surgical procedure should be recorded on the complications/adverse event case report form.

In addition to the above procedures, **at the day 30-120 visit**, we will collect, examine (photo) and culture all stents after retrieval from the nose. Culturing will consist of placing the retrieved stent in a standard container and submitting it to microbiology for culture and sensitivities.

Removal of the stent entails cutting the holding suture in the nose with scissors under direct visualization, with the help of a nasal speculum if needed, cutting the stent itself with scissors once to linearize it, and then pulling the stent out either from the nose or from the puncta using forceps.

Upon stent removal, the surgeon will comment on whether stent removal was technically simple, moderate or difficult (binary). This will be recorded on the CRF.

At the Final Visit, month 5-7, the following procedures will be performed:

- **Documentation of interim medical, ocular, and medication histories** since previous visit. The ocular history should capture any changes in the study eye since the previous visit; and, any relevant changes to the fellow eye that are necessary to evaluate an adverse event or anomaly in the study eye. The medication history should capture any changes in prescribed medications or routinely taken non-prescription medication since the previous visit.
- **Lac-Q questionnaire (Appendix B)**
- **Glasgow Benefit Inventory Questionnaire (Appendix A).**
  - **The 2 questionnaires will always be given in the same order: 1) Lac-Q, 2) GBI.**
- **Corrected distance visual acuity** - Corrected visual acuity is measured in each eye by the ETDRS chart at 3 meters. If there is a 2-line or more reduction in visual acuity from the last corrected visual acuity, a repeat manifest refraction in - each eye will be performed.
- **External exam of the medial canthal area and the medial commissure**
- **Slit lamp biomicroscopy of the puncta, lid margins and ocular surface.** The Oxford scheme will be used to grade corneal and conjunctival staining. The tear lake is measured using a slit lamp by narrowing the slit and shortening it to 1 mm or 0.2 mm, placing the slit light beam on the inferior lid margin tear lake, and using the beam to measure the vertical height of the fluid between the lid margin and the location of the top of the tear lake on the conjunctiva or cornea.
- **Adverse events, complications, visual disturbances**- Visual disturbances are any unexpected, expected, or pre-existing sight related occurrences that are not captured in any of the examinations or measurements, such as nystagmus or diplopia.

Unexpected or new reports of visual disturbances related to the device or surgical procedure should be recorded on the complications/adverse event case report form.

Because of the distances involved, we can anticipate that some patients will not be able to make the trip to Ann Arbor due to distance or transportation issues, especially in the case of successful surgery with symptomatic resolution. In those cases, we will document this matter in the report form and make a phone-call assessment of patient status, which will be reported.

Other optional diagnostic tests such as lacrimal irrigation/ or Jones 1 or Jones 2 tests may be performed at the investigator's discretion to further evaluate the subject's postoperative outcome or as dictated by the clinical situation. These tests and their results will be recorded accordingly on the CRFs.

Extensive effort will be made by telephone and mail to contact subjects who miss a scheduled follow-up visit to arrange a new appointment.

Postoperative observations and adverse events will be documented in the subject's medical records. Complications or adverse events that are observed by the investigator or reported by the subject should be recorded on the CRFs. For all adverse events and complications, a description of the event, date first observed, any action taken, and ultimate outcome will be recorded.

For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a serious adverse effect) and; 2) an assessment of the causal relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s). Adverse events present at the end of study will be followed until resolved or the Sponsor Investigator determines no further follow-up for the study is required. Any findings related to the adverse event that are obtained after the final study visit is completed will be documented in the subject's medical records and the relevant findings will be recorded on the adverse event and adverse event summary CRFs.

9.5 Secondary Surgical Interventions

All secondary surgical interventions will be recorded in the subject's medical records and CRFs and recorded as an adverse event and reported to the IRB according to local policies and to the FDA according the regulations found in 21 CFR 812.

9.6 Safety Monitoring

Subjects will be observed closely to detect any adverse events or complications that may have occurred. On the day of treatment and at each follow-up visit, subjects should be asked a non-leading question, such as "How are your eyes?" to determine whether any complications or adverse events might have occurred since the last visit. The presence or absence of adverse

events or complications will be documented. All exam findings, work-up, management, and sequelae relevant to an AE will be recorded on the AE CRF.

Ophthalmic safety will be evaluated by slit lamp biomicroscopy of the operated eye. In the case of an adverse event or complication, these tests, and any others deemed necessary, may be repeated before the next scheduled visit at the investigator's discretion. Appropriate supportive and/or definitive therapy may be administered as required. Any complications or adverse events will be recorded in the medical record/CRF.

9.7 Post-Study Procedures

Subjects will be discharged from the study after the second scheduled examination is complete.

9.8 Device Accountability

All use of the Slit Stent II will be under the direct supervision of the principal investigator or his/her designee. The investigational stents will be clearly labeled as investigational use only, and will have a clearly marked serial number. The receipt date and serial number will be recorded. The stents will be stored at the Kellogg Eye Center in a secure fashion, with access limited to the study team and their designee.

All records of receipt, use, and disposition of the devices will be maintained by the study team. At the completion of the study, there will be a final reconciliation by study personnel of devices shipped, implanted, and devices remaining. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused devices. Stents destroyed on site will be documented in the study files.

9.9 Early Withdrawal from Study

Subjects will be advised that they are free to withdraw from the study at any time. The investigator may discontinue a subject if a serious adverse event occurs and it is in the subject's best interest not to continue in the study, or if the subject moves and the subject cannot complete the remainder of the follow-up visits. When a subject withdraws early from the study, a final examination will be performed at the time of withdrawal, if possible.

10.0 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

A detailed statistical analysis plan (SAP) will be developed for analysis of all data for this study. Required analyses and target endpoints that will be included in this SAP are summarized below. The methods by which each of these analyses is performed will be included in the SAP. The required analyses and target endpoints for the Slit Stent II include, but are not limited to, those listed below. If there are any discrepancies between the statistical analyses described in the SAP versus this protocol, the SAP will prevail. Tabulation of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® and/or R software. All subjects who are enrolled in this study will be included in the safety analysis. All testing and confidence intervals will use a two-sided significance level of 5%.

Specific analyses for the six listed objectives are very similar to one another. Data will be summarized by treatment group (Slit Stent II or BIKA for DCR): counts and percentages for categorical variables, means and standard deviations for continuous variables. Additionally, 95% confidence intervals will be provided for each treatment group and for the difference between treatment groups. The confidence intervals for differences are keys to exhibiting the similarity between the Slit Stent II and the existing BIKA stent.

As this is a randomized experiment, control for pre-treatment variables is not necessary. However, a sensitivity analysis controlling for the baseline measurement of the outcome variable will be conducted. For example, post-surgery Lac-Q will be regressed on treatment and pre-surgery Lac-Q. If pre- and post-surgery measures are highly correlated, the confidence interval for the treatment effect will be narrower (more precise). If measurements are made at multiple post-surgery time-points, (generalized) linear mixed models will be used to estimate an overall (fixed) treatment effect while accounting for any correlation between measurements on the same person (random intercept).

10.1 Sample Size

The recommended study size is 50 subjects: 25 in the treatment arm (Slit Stent II) and 25 in the control arm (BIKA for DCR). The sample size recommendation is based on two factors.

- It provides reasonable accuracy for estimates of proportions, means, and differences of proportions and of means. For categorical variables, the maximum half width of a 95% Wilson confidence interval for a single proportion is 0.18 (for n=25) and for a difference of two proportions is 0.27 (n_1=n_2=25). For continuous variables, the margin of error for a Welch t-interval for a mean is 0.41 standard deviations, and for a difference of two means it is 0.57 standard deviations. For example, if the standard deviation of the GBI score is 25 points, the margin of error for the confidence interval for the difference of treatment group GBI means is 14 points.
- It provides excellent power to show the new variation is non-inferior to the common lacrimal stent as measured by the GBI: Based on previous studies of lacrimal stents [11, 41-47] that assessed GBI, we estimate the standard deviation is about 25 points on the GBI scale and we set a non-inferiority boundary of $\delta = 20$ points (20/25 = 0.80, a 'large' effect in Cohen's taxonomy). If in fact the devices are equivalent (i.e., they have equal mean GBI scores, $\mu_{SSII} = \mu_{BIKA}$), then we have 87% power to demonstrate non-inferiority based on a single GBI measurement. Using all repeated observations would increase power even against a tighter non-inferiority boundary.

10.2 Accountability

Accountability by postoperative visit will be calculated as illustrated in Table 10.2-1 below.

Table 10.2-1: Accountability by Postoperative Visit

		Day 0	Day 5-14	Day 30-120
Available for Analysis[2]	n/N[1](%)			
Missed Visit[3]	n/N[1] (%)			
Discontinued[4]	n/N[1] (%)			
Active[5]	n/N[1] (%)			
Lost to follow-up[6]	n/N[1] (%)			
% Accountability = Available for Analysis (Enrolled - Discontinued - Active)				

Where,

1 Enrolled (N) = total number of subject eyes enrolled in the study.

2 Available for analysis = total number of eyes for whom data are available at each postoperative interval.

3 Missed visit = total number of eyes that missed the visit, but were otherwise accounted for. Includes those eyes that missed the visit but were seen at a later visit.

4 Discontinued = total number of eyes that discontinued follow-up prior to completion of the study for any reason (e.g., device explant, moved away).

5 Active (not yet eligible for the interval) = total number of eyes that have not yet reached the visit interval.

6 Lost to follow-up = total number of eyes for whom a visit at the prescribed visit or later was not completed and who are not considered to be active or discontinued.

10.3 Screening

The screening data for all subjects who are screened, but do not meet eligibility criteria, will not be analyzed or tabulated nor collected on the CRFs. The reason for screen failure will be captured on the CRFs.

10.4 Subject Characteristics

The number of subjects included in the safety and/or effectiveness evaluations, subjects completing the study, and the reasons for any withdrawals will be tabulated by counts and percentages. Continuous data will be summarized by mean, standard deviation, and Tukey's five-number summary. Categorical demographic data will be summarized using counts and percentages. Abnormal medical histories, ocular histories, and prior/concurrent medications obtained on the screening visit will be presented in data line listings.

10.5 Outcome Criteria

Complications and adverse events are the primary safety outcomes to be evaluated. All complications and adverse events and their rates of occurrence will be reported. Changes in the subject's symptoms (tearing, irritation) and quality of life as measured by the GBI are the primary effectiveness outcomes.

10.5.1 Adverse Events and Complications

All subject questionnaire data, complications, and adverse events will be tabulated and summarized.

10.5.2 Glasgow Benefit Inventory (GBI) Questionnaire

The effectiveness parameter evaluated will be the mean composite score for the GBI administered post-treatment at the 1-4 month post-operative follow-up visit. The GBI will be administered at each post-operative visit. It is believed that the positive effect of the surgery will have manifested itself in GBI score by the 2nd follow-up visit. A 95% t confidence interval will be used to estimate the mean score.

Scoring the GBI will follow the standard protocol (**Appendix A**). Positive scores indicate improvement from pre-treatment; negative scores indicate deterioration.

As part of the GBI protocol, it is expected that researchers may need to change the format or appearance of items to suit their purposes.

10.5.3. **Lac-Q Questionnaire (Appendix B)**

This study does not aim to assess the effectiveness of the DCR procedure, which is a well-established surgical procedure for the treatment of epiphora secondary to nasolacrimal duct obstruction. Furthermore, the study does not aim to assess the effectiveness of using a silicone lacrimal stent as part of a lacrimal procedure. Rather, the primary goal of this study is to assess patient tolerance of the Slit Stent II, which introduces novel cuts into the traditional stent that allow for intraluminal tear drainage. The secondary goal of the study is to confirm that the Slit Stent II functions like any other silicone lacrimal stent as an adjunct to a lacrimal procedure. The effectiveness of the procedure in relieving the tearing symptoms and associated social isolation will be assessed at the pre-op visit and at each post-op visit. Scoring will follow the standard protocol (Appendix B). The Lac-Q questionnaire will always be given first among the questionnaires.

10.5.4 Other Outcome Measures

Other outcome measures, such as slit lamp biomicroscopy, will be reported in data line listings.

10.6 Dropouts/Lost-to-Follow-up

Subjects may drop out at any time during the study. All treated subjects/eyes will be included in the safety analysis.

10.7 Missing data

The amount of missing data will be minimized by careful recordkeeping and diligent follow-up. Modern imputation methods will be used to complete specified analyses. To assess the impact of missing data, sensitivity analyses will be conducted. The primary endpoints will be assessed in worst case and best case scenarios. The number of missing data points in this type of study is anticipated to be small. The sensitivity analyses will likely yield results similar to the main analysis.

The study results will be submitted for publication or presentation regardless of the study outcome following the conclusion or termination of the trial.

11.0 ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with FDA's Good Clinical Practice regulations.

11.1 Informed Consent

In accordance with the provision of 21 CFR Part 50, each subject will provide written informed consent for participation in this study prior to enrollment into the study.

The study will be explained to the prospective subject by the investigator or his designee. The nature of the experimental product will be explained together with potential hazards of the surgical procedure, including any possible adverse reactions. The subject will be informed that he/she is free to terminate participation in the study for any reason. One copy of the signed consent form will be retained in the medical record, and one copy will be given to the subject.

11.2 Institutional Review Board

This protocol and the ICF will be approved initially and reviewed annually by the University of Michigan Institutional Review Board (IRB). Progress reports will be submitted at the completion of the study or at least once yearly, whichever comes first, to the IRB. Serious adverse events will be reported to the IRB and the FDA in accordance with IRB Reporting Criteria Guidelines and applicable FDA regulations for serious adverse events.

11.3 Complications and Adverse Events

Adverse events will be recorded from the time of surgical implantation of the device until the final visit. Ophthalmic complications or adverse events that are observed by the investigator or

reported by the subject should be recorded on the CRFs. For all adverse events and complications, a description of the event, date first observed, any action taken, and ultimate outcome will be recorded.

For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a *serious adverse effect*) and; 2) an assessment of the causal relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse effects felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor Investigator.

All adverse events will be reported to the IRB according to local policies and to the FDA according the regulations found in 21 CFR 812.150.

Complications and adverse events that occur in the study can be caused by the Slit Stent II, by the standard stent, or by the surgical DCR procedure, and are identical to the risks already associated with DCR surgery and BIKA for DCR stent placement (see Section 3.1). Potential complications include, but are not limited to the following:

- bleeding from nose
- infection
- irritation or discomfort
- conjunctival or nasal pruritus
- nasal mucosa or caruncular irritation
- reversible shrinkage of the palpebral fissure
- exteriorization or loss of the stent tubing
- punctal/canalicular injury
- canaliculitis
- Synechia of the nasal mucosa
- Induced mucocele
- Device dislocation into the oropharynx
- Corneal abrasion
- loss of the device (falling out or inadvertently swallowing)
- Conjunctival abrasion
- Secondary surgical interventions related to the Slit Stent II device (surgical repositioning, removal, or replacement)
- False passages
- Separation of the silicone from the steel guide

- Breakage of the stent during insertion or postoperatively
- Stricturotomy

All ophthalmic adverse events should be recorded on the adverse event forms in the CRFs. Adverse device effects /events that are determined by the sponsor investigator to be vision-threatening should be considered to be reportable as described below.

Adverse events that occur in association with a device that is used in conjunction with the Slit Stent II will be reported separately.

Postoperative observations that, after sponsor investigator review, are determined to be part of the normal healing process that occurs after the nasolacrimal intubation procedure are not considered to be reportable events.

11.3.1 Serious and Unanticipated Adverse Device Effects (UADE)

An unanticipated adverse device effect is defined as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects."

11.3.1.1 Sponsor Investigator Responsibilities

The Sponsor-Investigator will promptly review documented adverse effects and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse effect; 2) if there is a reasonable possibility that the adverse effect was caused by the investigational device or, if applicable, other study treatment or diagnostic product(s); and 3) if the adverse effect meets the criteria for a *serious adverse effect*.

In accordance with 21 CFR Part 812.150(a)(1) and (b)(1), the sponsor shall promptly report the results of an evaluation of any serious and unanticipated adverse device effect to FDA as soon as possible, but not later than 10 working days after the sponsor investigator first receives notice of the effect. The UADE should also be reported to the University of Michigan IRB according to the IRB reporting guidelines. Complications and non-serious or anticipated adverse events should be documented and tabulated but need not be submitted by the sponsor investigator to the FDA as individual reports. All vision threatening adverse events should also be reported to FDA, and the reviewing IRB, and all participating investigators in the same manner as reporting a serious and unanticipated adverse device effect.

11.3.2 Non-serious or Anticipated Adverse Events

Non-serious or anticipated adverse events and complications should be documented on the CRFs and tabulated for reporting as required according to the FDA and IRB reporting guidelines.

11.4 Monitoring

11.4.1 Medical Monitor

An independent Medical Monitor will be appointed to review each Serious Advent Event. Any Serious Adverse Events will be reported to Dr. Joseph, the sponsor of the study, who will in turn notify the Medical Monitor. The Medical Monitor will review the event, request any additional data if necessary, and make a determination regarding expectedness and relatedness. Also, the Medical Monitor will determine if this safety data increases the risks to subjects on the trial. All non-serious adverse events will also be reviewed by the Medical Monitor on a quarterly basis.

Dr. Joseph will be responsible for reporting the events to the IRB and the FDA as appropriate.. The Medical Monitor review will be maintained in the study records.

The Medical Monitor may meet in person or through a teleconference with other individuals with clinical expertise as needed.

11.4.2 Clinical Trial Monitor

To assure adequate protection of the rights of human subjects, per 21 CFR §812.40, 812.43 and 812.46, this study will be monitored by the University of Michigan Institute of Clinical and health research (MICHR). Routine monitoring will be scheduled at appropriate intervals, with more frequent visits occurring at the beginning of the study. A site activation visit will take place, followed by routine monitoring visits. Additional visits can be scheduled at the request of the Sponsor-Investigator.

The established monitoring plan will ensure the quality and integrity of the data throughout the study conduct to verify adherence to the protocol, completeness and accuracy of study data and samples collected, dispensing and inventory of the device, and compliance with regulations.

11.5 Source Documents / Case Report Forms

Adequate records will be maintained for the study including subject medical and surgical records, signed ICFs, and device use records. All original source documentation will remain at the investigative site. Study data that are stored at the investigator site in any electronic medical records system, including measurements that are obtained electronically, will be printed and retained in the study files.

All study data will be recorded onto CRFs designed for the study. Copies of the CRFs will be retained with the Sponsor-investigator’s study files.

11.6 Deviation from the Protocol

The sponsor investigator will not intentionally deviate from the protocol without prior IRB approval, unless such deviation is necessary to manage a medical or ocular urgency or emergency. The sponsor investigator will notify the IRB of any protocol deviation to protect the

life, vision, or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event any later than 5 working days after the emergency occurred. All other revisions and/or amendments to the protocol that affect subject treatment, study outcome, or subject safety should be submitted in writing to the IRB for approval prior to implementation. The sponsor investigator should maintain a record of all protocol deviations showing the dates of, and the reason for, each protocol deviation.

Changes that affect the scientific soundness of the study or the rights, safety, or welfare of human subjects may also require FDA approval, in addition to sponsor and IRB approval, prior to implementation. The sponsor investigator will obtain such approvals, if required, according to the regulations found in 21 CFR 812.35.

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Appendix A: Glasgow Benefit Inventory (Adapted)

THE GLASGOW HEALTH STATUS QUESTIONNAIRES MANUAL, 1998

Introduction

The overall success of any medical or surgical intervention cannot be obtained from measures of technical success alone and changes in patient quality of life resulting from the intervention must also be considered. Another area of interest is the state quality of life patients have due to their health problem.

While there are existing measures of health status and patient satisfaction which can be used to assess state quality of life and changes brought about by ORL interventions; none of these measures were generated specifically for the ORL department. Therefore, limitations such as length, administration style and insensitivity to nonacute disorders, like those generally seen in an ORL clinic, mean that the evaluations generated from these measures for ORL interventions are not as sensitive as when these measures are used to assess other interventions. It was, therefore, decided to generate two health status questionnaires, a state questionnaire and a change questionnaire, which would be specifically sensitive to ORL health problems and interventions but also generalizable across different ORL health problems and interventions. The questions are independent of any specific intervention/health condition and the subject of the questions remains constant. Each of the questions addresses an aspect of health-related quality of life which is not dependent on the disease of interest or the context of the intervention. However, the text is altered for each question to allow focusing on to the intervention or health condition of interest to improve sensitivity. The questions are then generic in nature but referenced to a temporal event (intervention) in the GBI or condition in the GHSI.

The change questionnaire, called the Glasgow Benefit Inventory (GBI), measures the change in health status produced by surgical interventions. For this measure, the definition of health status is the general perception of well-being, including total psychological, social and physical well-being. Given that maximal sensitivity to change was critical, it was decided to ask directly about the change in health status resulting from surgery, rather than take pre- and post- operative measures and subtracting one from the other. The paper, (pages 18 to 31), shows the findings of a study investigating the sensitivity of the GBI to the change in health status resulting from 5 different ORL interventions.

The state measure we developed is called the Glasgow Health Status Inventory, (GHSI) which measures the effect of a health problem on the quality of life of a person and allows cross-

comparison among many health conditions, among different health interventions, and among demographic and cultural subgroups.

The GBI is a post-intervention questionnaire which assesses the interventions effects on the health status of the patients. The GHSI can be used at any point in time and measures the general quality of life the person experiences and how health problems affect this. While the GBI is maximally sensitive to a change in health status brought about by a specific event (e.g. an operation), the GHSI gives a general measure of the health status of the person at any specific time.

GBI - Glasgow Benefit Inventory

The GBI contains 18 change in health status questions which assess how the intervention has altered the quality of life of the person. The GBI is easily adapted to be used for different interventions. Before use, the GBI must be adapted so that the intervention of interest is specified. This is done by replacing the words in italics (*operation/intervention)* in each question into the intervention of interest. See the examples below. GBI was developed and validated as a measure of patient health for otorhinolaryngological procedures. It has been validated for use following oculoplastic procedures, including DCR [19,20,21,22,23], ptosis [24,25], ectropion and entropion surgery [26], and botulinum toxin for blepharospasm [27.]

Example of all-purpose GBI question:
Since your *operation/intervention, have you found it easier or harder to deal with company?**

Examples of focused GBI questions:

Since your operation, have you found it easier or harder to deal with company?
Since your received your hearing aid, have you found it easier or harder to deal with company?
Since your speech therapy, have you found it easier or harder to deal with company?
Does the condition of your nose affect how you deal with company?

Scoring

The response to each question is based on a five-point Likert scale ranging from a large deterioration in health status through to a large improvement in health status, (see example below).

1. Has the result of the *operation/intervention affected the things you do?**				
Much worse	A little or somewhat worse	No change	A little or somewhat better	Much better
1	2	3	4	5

To help control for response bias, half of the questions have the answers ranging from a large improvement to a large deterioration while the other half range the other way. The GBI questionnaire is scored into a total score and also 3 subscales:- a general subscale, (12 questions), a social support subscale, (3 questions), and a physical health subscale, (3 questions). All these scores range from –100 to +100.

Score all questions so that a score of 1 is given to the answer with the worst change in health status and 5 to the answer with the best change in health status.

Total Score
- Sum all the responses (Qu. 1-18)
- Divide by 18 (to obtain an average response score)
- Subtract 3 from the average response score
- Multiply by 50.

General Subscale Score
- Sum 12 of the responses (Qu. 1,2,3,4,5,6,9,10,14,16,17 and 18)
- Divide by 12 (to obtain an average response score)
- Subtract 3 from the average response score
- Multiply by 50.

Social Support Score
- Sum 3 of the responses (Qu. 7,11,15)
- Divide by 3(to obtain an average response score)
- Subtract 3 from the average response score
- Multiply by 50.

Physical Health Score
- Sum 3 of the responses (Qu. 8,12,13)
- Divide by 3(to obtain an average response score)
- Subtract 3 from the average response score
- Multiply by 50.

The GBI questionnaire (Modified for this study):

1. Has the result of the tear duct surgery affected the things you do?				
Much worse	A little or somewhat worse	No change	A little or somewhat better	Much better
1	2	3	4	5

2. Have the results of the tear duct surgery made your overall life better or worse?				
Much better	A little or somewhat better	No change	A little or somewhat worse	Much worse
5	4	3	2	1

3. Since your tear duct surgery, have you felt more or less optimistic about the future?				
Much more optimistic	More optimistic	No change	Less optimistic	Much less optimistic
5	4	3	2	1

4. Since your tear duct surgery, do you feel more or less embarrassed when with a group of people?				
Much more embarrassed	More embarrassed	No change	Less embarrassed	Much less embarrassed
1	2	3	4	5

5. Since your tear duct surgery, do you have more or less self-confidence?				
Much more self-confidence	More self-confidence	No change	Less self-confidence	Much less self-confidence
5	4	3	2	1

6. Since your tear duct surgery, have you found it easier or harder to deal with company?

Much easier	Easier	No change	Harder	Much harder
5	4	3	2	1

7. Since your tear duct surgery, do you feel that you have more or less support from your friends?

Much more support	More support	No change	Less support	Much less support
5	4	3	2	1

8. Have you been to your family doctor, for any reason, more or less often, since your tear duct surgery?

Much more often	More often	No change	Less often	Much less often
1	2	3	4	5

9. Since your tear duct surgery, do you feel more or less confident about job opportunities?

Much more confident	More confident	No change	Less confident	Much less confident
5	4	3	2	1

10. Since your tear duct surgery, do you feel more or less self-conscious?

Much more self-conscious	More self-conscious	No change	Less self-conscious	Much less self-conscious
1	2	3	4	5

11. Since your tear duct surgery, are there more or fewer people who really care about you?

Many more people	More people	No change	Fewer people	Many fewer people
5	4	3	2	1

12. Since you had the tear duct surgery, do you catch colds or infections more or less often?

Much more often	More often	No change	Less often	Much less often
1	2	3	4	5

13. Have you had to take more or less medicine for any reason, since your tear duct surgery?

Much more medicine	More medicine	No change	Less medicine	Much less medicine
1	2	3	4	5

14. Since your tear duct surgery, do you feel better or worse about yourself?

Much better	Better	No change	Worse	Much worse
5	4	3	2	1

15. Since your tear duct surgery, do you feel that you have had more or less support from your family?

Much more support	More support	No change	Less support	Much less support
5	4	3	2	1

16. Since your tear duct surgery, are you more or less inconvenienced by your *tearing* problem?

Much more inconvenienced	More inconvenienced	No change	Less inconvenienced	Much less inconvenienced
1	2	3	4	5

17. Since your tear duct surgery, have you been able to participate in more or fewer social activities?

Many more activities	More activities	No change	Fewer activities	Many fewer activities
5	4	3	2	1

18. Since your tear duct surgery, have you been more or less inclined to withdraw from social situations?

Much more inclined	More inclined	No change	Less inclined	Much less inclined
1	2	3	4	5

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Appendix B: Lac-Q Questionnaire

The Lac-Q Questionnaire:
The Lac-Q questionnaire, published in 2011, is a patient symptom questionnaire developed for lacrimal drainage surgery.[1-2] The questionnaire contains two scores, one is specific for eye-symptoms, and the other assesses the social impact of symptoms. (see below)

Lac-Q - The Lacrimal Symptom Questionnaire **Name:** **Number:** **Date:**

Social and lifestyle impact of tear duct problem

Which of these five statements is true about the tear duct problem overall in the last eight weeks?
Please tick the box next to any true statement.

- Friends or family have commented about the watery eye problem. ☐
- The watery eye problem has caused embarrassment in company. ☐
- The watery / sticky eye problem has interfered with everyday activity, for example (underline each that applies):
  Reading .. Driving .. Wearing make-up
  Wearing glasses .. Hobbies
  Other activity (specify): ☐
- The vision is sometimes blurred because of the watery / sticky eye problem. ☐
- Medical attendance: visit to the family doctor's surgery, or the hospital eye clinic, because of tear duct problem. ☐

(Scoring: score one point for each box ticked, maximum score =5)

Total score for social impact: ☐

Problems with each eye separately

For each of the four problems (watery eye, pain, sticky eye or swelling), put a tick in the box next to the statement which best describes the situation over the last eight weeks.
Use the left hand column for the left eye, and the right hand column for the right eye.

	Left		Right
• Watery eye			
No watery eye problem	☐	0	☐
The eye waters occasionally, mainly outdoors	☐	1	☐
Troublesome watering of the eye, indoors and outdoors, some days	☐	2	☐
Troublesome watering of the eye most days	☐	3	☐
Troublesome watering of the eye every day	☐	4	☐
• Pain in or around the eye; soreness of eyelids			
No pain	☐	0	☐
Some pain or soreness, but has not sought medical advice or treatment	☐	1	☐
Pain or soreness, has used prescription eyedrops	☐	2	☐
Painful and swollen (lacrimal abscess), requiring antibiotics or surgical drainage	☐	4	☐
• Sticky eye			
No problem with sticky eye	☐	0	☐
The eye is sometimes sticky in the mornings	☐	1	☐
The eye is sticky every day in the mornings	☐	2	☐
The eye has sticky or mucous discharge throughout the day	☐	3	☐
There is infected discharge leaking through the skin of the lower eyelid (fistula)	☐	4	☐
• Swelling or lump at the medial canthus (mucocoele)			
No swelling or lump	☐	0	☐
Swelling present, but only intermittently	☐	1	☐
Swelling present all the time	☐	2	☐

(Scoring: use numbers in central column) **Total scores for each eye:** ☐ ☐

Lac-Q score (sum of three total scores): ☐

Scores for the filled in questionnaire:

Social and lifestyle impact score (sum of social impact questions)

Left eye symptom score (sum of “left” column of symptom questions)

Right eye symptom score (sum of “right” column of symptom questions)

Lac-Q score (sum of all three total scores above)

LAC-Q QUESTIONNAIRE REFERENCES

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Appendix C: Patient Stent Tolerance and Irritation Assessment

The following questions were designed specifically for this study to assess the following concepts of interest 1) patient tolerance of the slit-stent II, and 2) ocular surface irritation secondary to the stent. These questions will be administered by an interviewer to patients at both the 5-14 and 30-120 day post-op visits.

Patient Stent Tolerance and Irritation Assessment

1. Which of the following five statements best describe your tolerance of the Stent?				
Not tolerated	Tolerated with major discomfort	Tolerated with moderate discomfort	Tolerated with minor discomfort	Well Tolerated
4	3	2	1	0

2. Since your tear duct surgery, which of the following four statements best describe your eye irritation symptoms caused by the Stent?			
No eye irritation	Minor eye irritation	Moderate eye irritation	Severe eye irritation
1	2	3	4

Scores for the filled in questionnaire:

Tolerance Score (question 1)

Irritation Score (question 2)

Total score (sum of question 1 & 2)

Appendix D: Study flow chart-

Procedure	Screen (within 60 days of Surgery)	Surgery	**Postoperative Visits**				
			Day 1 Phone call	5-14 days	**Day 45 (30-60) Phone call**	30-120 days	Month 5-7
Informed Consent	X						
Medical History	X			X		X	X
Ocular History	X			X		X	X
Medication List	X	X		X		X	X
Demographics	X						
Corrected Visual Acuity [1]	X			X		X	X
Manifest Refraction	X			X[2]		X[2]	X[2]
Lac-Q Questionnaire	X			X		X	X
GBI Questionnaire				X		X	X
Patient Stent Tolerance and Irritation Assessment				X		X	
Lacrimal system probing/ irrigation	X						
Intraocular Pressure (IOP)[3]	X			X		X	X
Slit Lamp biomicroscopy (cornea, conjunctiva)	X			X		X	X
Stent Culture						X	
Visual inspection of stent integrity				X		X	
External exam				X		X	X
Complications and Adverse Events		X	X	X	X	X	X
DCR Surgery		X					

[1] ETDRS chart at 3 meters should be used

[2] Manifest Refraction will be performed if there is 2-line or more reduction in visual acuity from Screening

[3] IOP will be measured by ICare

Appendix E: Manifest Refraction and Visual Acuity

Manifest Refraction

Beginning approximate refraction: The patient's current spectacles (if worn for distance viewing) are measured with a lensometer; if no spectacles, retinoscopy or auto refraction is performed. One of these measurements is used as the beginning approximate refraction.
Refraction must be performed at 3 meters from ETDRS chart R. Room illumination must be kept consistent throughout the study (highest illumination). The beginning approximate refraction at the first visit can be from lensometry of the patient's distance spectacles, retinoscopy, or autorefractor findings. At subsequent follow-up visits, the manifest refraction recorded at the previous visit will be used as the beginning approximate refraction. The phoropter or trial frame may be used for refraction.

Begin by testing the RIGHT eye. With the beginning approximate refraction in place,

Determine Sphere Power: In general, instructions are to 'push plus' and to add minus correction only if the visual acuity is thereby improved demonstrably; i.e. the patient is able to read 1 or more additional letters on a line or to read letters on a smaller line. With the patient looking at the smallest line legible on the visual acuity chart, add + 0.25 spherical lens in front of the eye. Ask the patient, "Is it better, worse, or no change?"
If the patient responds that vision is made better or is the same, replace the spherical lens with one that is +0.25 more plus. Continue checking to see if the patient will accept more plus by repeating the method above. Stop when presenting the additional +0.25 lens makes the patient's vision worse.

If the patient's response to adding + 0.25 is that vision is made worse, remove the +0.25, then add a lens which is -0.25 more minus or less plus over the eye. If this lens improves the patient's vision, even by one letter, continue checking to see if the vision improves by adding minus. Stop when there is no improvement in vision.

Re-challenge with +0.25 sphere as before until the patient responds that the +0.25 sphere makes the vision worse. The sphere endpoint is the best vision with the most plus or least minus lens power.

Determine and Refine Cylinder Axis: Ask the patient to look at a line on the visual acuity chart, which is one or two line larger than the smallest line they can read. Ask the patient to focus on a round letter such as “C”, “G”, or “O”.

If no cylinder is present in the beginning approximate refraction, place the Jackson cross-cylinder with the positive axis (white) first at 90º, then at 180º, then 45º and 135º. If the patient states that the vision is improved at any one of these four axis positions, place cylindrical lens power in the refractor at the preferred axis and proceed to refine the axis. If the patient prefers no power at any of the four positions, skip the refining cylinder power step.

If cylinder is present in the beginning approximate refraction, position the cross-cylinder first with the positive axis 45º to the right of the cylinder axis (position one), the positive axis at 45º to the left of the cylinder axis (position two). Flip the cross cylinder and ask which position improves the vision. If the patient responds that neither position is better and if this was the first test of axis position, move the axis of the cylinder 15º to the right or left and repeat.

If the patient prefers one position to the other, rotate the cylinder axis toward the preferred axis of the crossed-cylinder. For positive cylinder, in the direction of the white dot. (When the patient states there is no difference upon flipping the cross cylinder, i.e. that one position of the cross cylinder is no better than the other position, proceed to refining cylinder power).

Refine cylinder power: Ask the patient to look at a line on the visual acuity chart, which is one or two line larger than the smallest line they can read and ask them to focus on a round letter.
Align the cross cylinder first with the positive axis and then with the negative axis coincident with the cylinder axis. Ask the patient which is better.

If the patient prefers the positive (white) axis coincident with the cylinder axis, increase the power of the cylinder by 0.25 diopter.
If the patient prefers the negative (red) axis coincident with the cylinder axis, reduce the cylinder power by 0.25 diopters and retest.

For each 0.50 diopter change in cylinder power, adjust the sphere by 0.25 diopters of the opposite power.

End the refraction: End the refraction by challenging with +0.25 spherical power and adjust the sphere until the patient responds that the additional positive sphere makes the vision worse.
Record the lens correction obtained in this refraction for the eye on the CRF.

Visual Acuity
Begin by testing the RIGHT eye. Best-corrected visual acuity will be measured at 3 meter using ETDRS charts. Chart 1 will be used for the right eye and Chart 2 for the left eye. Room lighting should be at maximum brightness.

Record each letter identified correctly by circling the corresponding letters on the Visual Acuity Form. Letters read incorrectly and letters for which no guesses are made are not marked on the form. Each letter read correctly is scored as one point. Record the total number of letters read correctly. The score for each line (which is zero if no letters are read correctly) and the total score for each eye is recorded on the Visual Acuity Form (CRF) after testing is completed.

Record the visual acuity in Snellen Equivalents as the lowest line read with one or no misses.

Repeat the entire process for the left eye.

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