NASOLACRIMAL DUCT OBSTRUCTION STUDY NLD1

A Prospective Study of Primary Surgical Treatment of Nasolacrimal Duct Obstruction in Children Less Than Four Years Old

PROTOCOL

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PROTOCOL AMENDMENT 6-10-05

This amendment provides for an additional follow up visit for patients who at the outcome visit have symptoms of an upper respiratory infection and meet criteria for treatment failure.

Previous Protocol

The protocol previously stated that the parent will be given written instructions that indicate if a patient has an upper respiratory infection (URI), the parent should reschedule the outcome exam for when the patient is no longer symptomatic. However, if the patient *comes in to the outcome exam* with a URI the exam should proceed and not be rescheduled.

Current Protocol

The protocol has been changed to add an additional follow up visit 1-3 weeks later for patients who have symptoms of a URI at the outcome visit and meet criteria for treatment failure. All assessments for the outcome visit will be repeated at the additional visit (clinical signs, Dye Disappearance Test, Questionnaire). Outcome data from the additional visit will be analyzed in the primary analysis.

Parents will be instructed to reschedule this additional visit in 1-3 weeks if the patient has a URI, however, if the patient presents for the additional visit with URI symptoms all assessments will be completed and the patient will have no further study follow up.

Rationale for Protocol Change

About 13% (5 of the first 39) of patients completing the outcome visit have been reported to have URI symptoms at the time of the visit. When assessing for clinical signs of NLDO in the presence of URI symptoms, we can be confident in the classification of treatment success, but we can be far less confident in the classification of treatment failure as the clinical sign(s) and symptoms present could be a product of the URI as opposed to being a sign of persistent NLDO.

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CHAPTER 1: BACKGROUND AND SUMMARY

1.1. Rationale for the Study

Nasolacrimal duct obstruction (NLDO) is a common ocular condition in the first year of life. Most cases will resolve spontaneously or with massage.[1-3] Many studies of primary treatment of nasolacrimal duct obstruction have been reported. These case series have largely been retrospective, uncontrolled, and conducted in single centers.

Peterson and Robb found that 58 of 65 (89%) blocked ducts spontaneously resolved by 8-13 months of age, in children with NLDO symptoms.[2] Paul reported 51 of 55 (91%) with infantile NLDO were open at twelve months.[4] Paul did note in an extrapolation of his data that 70% of children with NLDO symptoms at 6 months were clear by 12 months of age. Nelson and colleagues noted that 107 of 113 (95%) infants with a history or findings of NLDO (onset 2 to 7 months of age) spontaneously resolved by 13 months of age.[5] Thus about 70-90% of cases will experience spontaneous resolution by 13 months of age.[2, 5]

Simple probing is the most widely-used initial treatment for NLDO in infancy. Two differing approaches to simple probing have been most often been used, immediate office probing (early probing – generally after 6 months of age), and medical management (episodic antibiotic drops with massage of the lacrimal sac) until 9-13 months of age followed by probing under general anesthesia (late probing). The possible advantages of early probing are the avoidance of general anesthesia, immediate resolution of symptoms, lesser cost, and prevention of fibrosis from inflammation in the nasolacrimal duct. The advantages of late probing include more comfort with the procedure and possible avoidance of the procedure completely.

Both early and late probing approaches are usually successful for treatment of NLDO. Early office probing was successful in 92% of children in a series of 2369 infants.[6] These authors found a decline in success proportions with this office-based approach after 9 months of age. Success proportions of 77% to 97% have been reported in children younger than 18 months with conventional probing with anesthesia. A number of studies have found that probing was highly successful and without an age-related decline until at least 4 years of age and beyond.[7-10] Robb noted success proportions of 93% after 18 months of age.[7] However, there is a suspicion among other clinicians of a clinically-important decline in the success proportions among progressively older age groups of preschool children.[10-12] Katowitz and Welsh found an overall success proportion of only 55% after 13 months of age and 41% after 18 months of age.[11] Kashkouli et al recently noted a smaller age effect with success proportions of 89% in children 13-24 months of age and 72% in children 25-60 months of age.[13] The authors speculated that this reduction in overall success was due to more patients with complicated NLDO undergoing late treatment. Clinicians have argued that the decline would be expected due to increasing fibrosis of the nasolacrimal duct. Because of this experience, many clinicians will do a more complicated initial procedure for children after 18 months of age, including infracture of the inferior turbinate, nasolacrimal duct intubation, multipass probing,[14] and balloon catheter dilation.[15] A large prospective interventional case series might help to clarify whether there is an age-related decline in success.

Balloon catheter dilation has become popular for the initial surgical treatment of NLDO especially in children older than one year. This procedure involves probing of the nasolacrimal duct with a semiflexible wire probe with an inflatable balloon on the tip. The most commonly used product is the LacriCATH (Quest Medical, Inc, An Atrion Company, Allen, Texas, formerly Atrion Medical Products). This procedure has been reported to be highly successful. Becker and colleagues found a 96% success proportion (26 of 27 patients).[15] One retrospective case series comparing probing to balloon dilation as a primary treatment has been reported.[16] Success proportions of 86% and 90% respectively were reported (29 patients in each group). The authors further noted no decline in success with balloon dilation beyond 36 months of age.

Nasolacrimal intubation has been used for primary treatment by clinicians in older children or when the duct feels tight. While generally successful, there is less certainty of the success proportions for this procedure when performed as a primary treatment. It is also unknown how often this procedure is used for initial treatment.

Probing of the nasolacrimal duct for the repair of NLDO is a very successful procedure in infancy and childhood. Simple probing has long been the standard approach, though the age at which the procedure declines in effectiveness is controversial. Clinicians have been urged by manufacturers of medical equipment to consider intubation and balloon dilation even in the age range in which probing is highly successful, to further increase the chance of success.

The high success proportions of primary surgical procedures and the varied approaches to the timing and use of general anesthesia make a randomized clinical trial at this time impossible to develop within the PEDIG structure, even with the addition of investigators from the American Society of Oculoplastic and Reconstructive Surgery (ASOPRS). A prospective non-randomized study of the outcomes from many centers of all strategies might allow better estimates of success for the techniques most often used over an extended age range. Such a study might help to define factors associated with failure of each of the techniques.

PEDIG is conducting a separate randomized clinical trial (RCT) comparing treatments for persistent NLDO. The study procedures and infrastructure developed for that trial are to be used for this study, reducing the overall costs of this project.

Outcomes of nasolacrimal duct obstruction surgery have generally been assessed with a report of symptoms by parents and an assessment of signs by the surgeon. Published case series have generally used the same approach, often categorizing the results in terms of both symptoms and signs with four- or three-level scores.[3, 17] A mail-in questionnaire was utilized in one retrospective study as the sole measure of the outcome.[18] The authors' questionnaire evaluated the presence of watery or sticky eyes, as well as the aggravation of these symptoms by colds, allergy, or windy conditions.

Some clinicians have relied on the fluorescein Dye Disappearance Test, in which the clearance of fluorescein added to the tear film after 5 minutes is considered evidence of nasolacrimal patency to aid in the diagnosis.[19] MacEwen and colleagues, rather than relying on time or on recovery of the dye in the nose, proposed a 4-level grading scheme for the amount of dye remaining in the tear film at 5 minutes.[20] They classified stages 0 and 1 as normal, while stages 2

and 3 were abnormal. In this study we propose a modification of this classification with a 3-level scheme consisting of normal, abnormal, and indeterminate, the details of which are covered in a separate procedures manual.

The study is being coordinated by the Jaeb Center for Health Research in Tampa, Florida and is being funded through a cooperative agreement from the National Eye Institute. The organizational structure of the study group and study policies are detailed in the Pediatric Eye Disease Investigator Group (PEDIG) Bylaws.

1.2. Definitions

Nasolacrimal duct obstruction (NLDO) is a blockage of the tear drainage system leading to epiphora, increased tear film, and/or mucous discharge from the eyes in the absence of an upper respiratory infection, ocular surface irritation or glaucoma.

- **Simple NLDO**– a single obstruction in the nasolacrimal duct which is easily passed during the probing procedure
- **Complex NLDO**– a blockage or multiple blockages anywhere along the tear drainage pathway that causes more difficulty than usual with probe passage, such as a blockage at the valve of Hasner, a tight inferior turbinate blocking flow, canalicular problems, or multiple obstructions in the NLD

Congenital NLDO is the onset of NLDO symptoms prior to 6 months of age.

Epiphora is tear overflow onto the periocular skin.

Simple probing is the passage of a metal nasolacrimal probe through one or both canaliculi and through the nasolacrimal duct.

Balloon catheter dilation is the probing and dilation of the nasolacrimal duct with a hydrostatic balloon catheter. LacriCATH from Quest Medical Inc., An Atrion Company, Allen, Texas.

Nasolacrimal intubation is the probing and placement of a temporary stent. The stent may be mono- or bi-canalicular.

Inferior turbinate infracture is the nasal displacement of the inferior turbinate performed surgically.

1.3. Study Objectives

The primary objective of the study is to report the success proportions of simple probing within different age groups of patients under 2 years of age. Secondary objectives are to obtain descriptive data regarding symptoms and quality of life in patients receiving simple probing. Additional objectives are detailed in a separate analysis plan.

1.4. Synopsis

Enrollment

Children 6-<48 months of age with presence of epiphora, increased tear film, and/or mucopurulent discharge, who are undergoing a primary surgical procedure for NLDO are consented and enrolled into the study prior to surgery. It is estimated that the study will enroll 800 children.

At enrollment, the exam will include an assessment for clinical signs of NLDO, a Dye Disappearance Test (DDT), and an ocular exam. The parent will complete a questionnaire on the child's symptoms and quality of life.

Surgery

Selection of the surgical procedure to perform is at investigator discretion. If both of a patient's eyes are undergoing procedures, the surgeon must be planning prior to the surgery to perform the same procedure on both eyes.

Follow Up

Follow up normally consists of a single outcome exam, with the timing of the visit dependent on the surgical procedure as follows:

- Patients treated with simple probing or with balloon dilation will have an outcome exam 1-month (± 1 week) after surgery
- Patients treated with intubation will have an outcome visit 1 month (± 1 week) after tube removal (note: tube removal should occur between 8 weeks and 5 months after surgery)

The outcome visit will be completed earlier if the investigator determines that a second surgical procedure is warranted before the start of the visit window for the outcome exam. The outcome exam will take place prior to performing the second procedure.

At the outcome exam, a study-certified examiner other than the surgeon will perform an assessment for the presence of epiphora, increased tear film, or mucous discharge.

A Dye Disappearance Test will also be completed and the parent will complete a questionnaire on the child's symptoms and quality of life.

Additional visits are at investigator discretion.

CHAPTER 2: ENROLLMENT VISIT

2.1. Eligibility Assessment and Informed Consent

Patients undergoing a primary procedure for NLDO will be enrolled. For patients enrolling with bilateral NLDO who are undergoing a first procedure on both eyes, both eyes will be enrolled in the study.

The study consent may be obtained and patient enrollment completed when the consent for the surgical procedure is obtained or up to and including the day of the surgical procedure.

2.2. Eligibility Criteria

The following criteria must be met for the patient to be enrolled in the study:

- Age 6 - < 48 months
- Parent/guardian has the ability to complete a written questionnaire
- *For patients with two eyes requiring surgery at enrollment*: investigator is planning to perform the same type of surgical procedure on both eyes
- None of the following are present:
  - Craniosynostosis
  - Goldenhar sequence
  - Clefting syndromes
  - Hemifacial microsomia
  - Midline facial anomalies

<u>For the study eye(s):</u>

- Onset of NLDO symptoms and/or signs prior to 6 months chronological age
- Presence of epiphora, increased tear film, and/or mucopurulent discharge in the absence of an upper respiratory infection or an ocular surface irritation
- No history of nasolacrimal duct surgery including simple probing, nasolacrimal intubation, balloon catheter dilation, or dacryocystorhinostomy
- Undergoing primary NLDO surgery
- At least one punctum present
- No glaucoma present
- No corneal surface disease
- No history of ipsilateral trauma to the lacrimal drainage system
- Microphthalmia not present

2.3. Historical Information

The following data will be placed in the research record: demographic data (including gender, race, ethnicity, date of birth,) onset of symptoms, use of topical antibiotics, use of NLD massage, and presence or absence of clinically-evident dacryocele. Presence or absence of Down Syndrome will also be recorded.

2.4. Screening/Examination Procedures

The following screening/examination procedures will be performed on the study eye(s):

1. Assessment for the clinical signs of NLDO

Inspection of ocular surface and tear film should be completed and the following should be recorded as present or absent:

- Epiphora
- Increased tear film
- Mucous discharge

For study eligibility, at least one of the above clinical signs must be present in the absence of an upper respiratory infection or an ocular surface irritation.

This assessment should be completed prior to the Dye Disappearance Test. Also, if eyedrops (cycloplegic or otherwise) are to be administered at the visit, the assessment of clinical signs of NLDO should be performed either before administration of the drops or at least 30 minutes afterwards.

2. Dye Disappearance Test

The Dye Disappearance Test is performed after the assessment of clinical signs of NLDO. Also, if eyedrops (cycloplegic or otherwise) are to be administered at the visit, the Dye Disappearance Test should be performed either before administration of the drops or at least 30 minutes afterwards.

The procedures for performing and evaluating the Dye Disappearance Test are detailed in a separate procedures manual.

3. Parent Questionnaire

Once the patient has been consented to the study, the patient's parent or guardian will complete a Likert-style questionnaire. The questionnaire will contain symptom-related questions and quality of life questions.

- Each symptom-related question which will be answered separately for each study eye, and a symptom score will be calculated for each.
- The quality-of-life questions will be answered at the person level and are designed to assess both the patient's and parent's quality of life.

4. Ocular exam

An eye examination should be performed documenting normal lids, ocular adnexa, and anterior segment structures.

5. Additional procedures

A refraction, fundus examination, and intraocular pressure may be performed at investigator discretion.

2.5. Scheduling Surgery

The timing of the surgery will be chosen by the investigator but should occur within one month of the enrollment visit. Study informed consent should be obtained within the time frame guidelines of the site's governing IRB. Surgical consent should be obtained according to the investigator's routine practice.

CHAPTER 3: SURGERY

The timing of the surgery will be chosen by the investigator, but should occur within one month of enrollment.

Selection of the surgical procedure to be performed is at investigator discretion, with the stipulation that if both of a patient's eyes are undergoing procedures at this time, the surgeon must be planning to perform the same type of procedure on both eyes.

3.1. General Considerations

1. Preoperative medications
   - Topical and systemic antibiotics are at investigator discretion. Systemic steroids may be given as clinically indicated (e.g., for treatment of reactive airway disease).

2. Anesthesia
   - For office procedures, topical anesthesia and restraint are chosen by the investigator. For procedures performed with conscious sedation or general anesthesia, the medications and airway management are chosen by the surgeon and anesthesiologist.

3. Nasal packing
   - The nose may be packed with gauze soaked in phenylephrine, oxymetazoline, or similar agent for vasoconstriction of the nasal mucosa per the investigator's surgical routine.

4. Post-operative medications
   - Topical antibiotics, systemic antibiotics, and topical steroids may be used at the discretion of the investigator. Oral steroids may be used at investigator discretion.

5. Surgical cancellations
   - If the procedure is cancelled due to a medical reason, reschedule at investigator discretion based on the medical condition and NLDO symptoms.

3.2. Surgical Procedures

Selection of the surgical procedure to perform is at investigator discretion; however, the selected procedure should be performed according to the methods summarized below.

A form to be completed after surgery will document the following data: preoperative medications, postoperative medications, through which punctum(a) the nasolacrimal duct was probed, classification of the blockage as either simple or complex, description of the nature of a complex blockage, whether patency was confirmed, whether the procedure was done in the office or under anesthesia (or sedation), and whether inferior turbinate infracture was performed. Additional data specific to the procedure are listed with the appropriate procedure.

3.2.1. Simple Nasolacrimal Duct Probing

Simple nasolacrimal duct probing consists of punctal dilation of at least one punctum and the passage of a probe into the nose. The type and style of the probe is at investigator discretion.

Patency should be confirmed with metal on metal, visualization of probe beneath the inferior turbinate, or recovery of fluorescein-colored saline from the nose after irrigation through the nasolacrimal duct.

Inferior turbinate infracture is at investigator discretion.

3.2.2. Balloon Catheter Nasolacrimal Duct Dilation

Balloon catheter nasolacrimal duct dilation consists of punctal dilation of at least one punctum and the passage into the nose of a semiflexible wire probe with an inflatable balloon on the tip. Probing prior to passage of the balloon is at investigator discretion. Passage of the balloon catheter to the nasal floor should be confirmed with metal on metal or by visualization. The manufacturer's inflation protocol is followed. Inflate balloon to 8 atmospheres (atm) for 90 seconds (using LacriCATH inflater filled with saline), deflate for one minute, reinflate for 60 seconds and then deflate. Withdraw to the point at which the 10 mm mark is located 5 mm from the punctum, inflate for 90 seconds, deflate for one minute, reinflate for 60 seconds, then deflate and remove.

Inferior turbinate infracture is at investigator discretion.

Balloon catheters are available in both 2mm and 3mm diameter sizes. It is suggested (not required) that the 2mm balloon be used in children 30 months and younger, while the 3mm balloon be used in children 31 to <48 months old. The catheter is not reusable.

Data to be collected include size of balloon used, whether the manufacturer's inflation protocol was followed, and whether balloon tip was identified in the nose.

3.2.3. Nasolacrimal Intubation

Nasolacrimal duct intubation consists of punctal dilation of at least one punctum with the passage of a flexible lacrimal probe into the nose and the placement of a temporary stent in the nasolacrimal duct. The probe style and size as well as the brand of stent are chosen by the investigator. Placement of monocanalicular or bicanalicular stent is at the discretion of the investigator. The method of securing the stent (when secured) is at investigator discretion.

Inferior turbinate infracture is at investigator discretion.

Data to be collected include: whether a monocanalicular or bicanalicular stent was used, type of stent used (e.g. Crawford, Crawford with internal suture, Monoka, Ritleng), and whether stent was secured in the nose.

3.2.4. Inferior Turbinate Infracture

The nose may be packed with gauze soaked in neosynephrine, oxymetazoline, or similar agent for vasoconstriction. Using a nasal speculum the inferior turbinate is identified. A pediatric periosteal elevator or similar instrument is used to displace the turbinate nasally.

CHAPTER 4: POSTOPERATIVE OBSERVATION PHASE AND OUTCOME EXAM

4.1. Visit Schedule

Post-operative follow up normally consists of a single outcome exam to be timed as follows:

- For patients treated with simple probing or with balloon dilation: 1 month (± 1) week after surgery
- For patients treated with intubation: 1 month (± 1 week) after removal of the tubes

Additional visits prior to the outcome exam are at investigator discretion.

4.2. Removal of Tubes

The silicone tubes may be removed after 8 weeks, but should be removed before 5 months.[21, 22] No study assessments will be performed at the visit at which the tubes are removed.

The following information will be recorded:

- The date the tubes are removed, or are displaced inadvertently by the patient leading to removal
- Whether the tube was removed with the patient awake or with conscious sedation
- Whether the tube was completely removed
- If a Monoka tube was used, whether the footplate was in the correct location and not pulled into the canaliculus.

4.3. Medical Management

Medical management (including the use of antibiotics) during the post-operative phase is at investigator discretion.

4.4. Re-operation

The decision and timing to reoperate during the postoperative observation phase is at investigator discretion. If another nasolacrimal procedure is planned prior to the start of the window for the outcome exam, the outcome exam should be scheduled early and completed before the re-operation.

Patients who undergo re-operation before the start of the window for the outcome exam will be considered an automatic treatment failure.

4.5. Outcome Exam

The outcome exam consists of completion of the parent questionnaire, assessment of clinical signs by a certified examiner other than the surgeon, and performance of the Dye Disappearance Test.

Additional data to be collected at this visit will include:

- Presence of upper respiratory symptoms or ocular surface irritation
- Complications attributable to surgery including the following: punctal damage with a slit >=2 mm, nose bleeds requiring packing, dacryocystitis, pyogenic granuloma formation, and corneal abrasion.

4.5.1. Timing of Visit

The outcome exam will be completed early if the patient is felt by the surgeon to require another procedure prior to the protocol-specified time for the outcome exam (see section 4.4). In such cases, the outcome exam must be performed prior to the second procedure, and the decision to perform a second procedure will be recorded as the reason the exam is being performed out of window.

Written instructions to the parent for this visit will include the advisory to reschedule the outcome visit if the child has an upper respiratory infection or ocular surface irritation. If the patient comes to the office with either of these conditions, the exam will be completed, although an additional visit may be required (see section 4.6).

4.5.2. Testing Procedures

The following testing procedures will be completed at the outcome visit:

- Symptom and quality of life questionnaire completed by the parent prior to the exam (see section 2.4)
- Assessment for the clinical signs of NLDO by a certified examiner other than the surgeon (see section 2.4 and section 4.5.2.1)
- Dye Disappearance Test performed by any certified examiner (see section 2.4)

4.5.2.1. Assessment of Clinical Signs of NLDO

A study-certified examiner other than the surgeon will perform a masked assessment of clinical signs of NLDO in the enrolled eye(s). The examiner may be another investigator at the site, or any other study personnel provided the individual is certified in the performance of the assessment.

The assessment of clinical signs must be done before any other testing or the administration of any eye drops. The evaluation will include inspection with a hand light for the presence of epiphora, increased tear film, or mucous discharge. The presence of any of these signs would be considered a failure.

4.6. Additional Outcome Exam

Patients who at the outcome exam have an upper respiratory infection and appear to be treatment failures (i.e. one or more clinical signs of NLDO are present) will have an additional outcome exam 1-3 weeks later to allow for re-assessment of treatment outcome once the upper respiratory infection has resolved.

The assessments to be performed at this additional exam are the same as those performed at the previous outcome exam, procedures which are outlined in section 4.5.2.

Parents of patients who need this additional visit will be instructed to reschedule it in another 1-3 weeks if the patient's upper respiratory infection still hasn't resolved, however, if the patient presents for the additional visit with an upper respiratory infection all assessments will be completed and the patient will have no further study follow up.

CHAPTER 5: MISCELLANEOUS CONSIDERATIONS IN FOLLOW UP

5.1. Patient Withdrawals

A patient (and in this case the parents or guardian) may withdraw from the study at any time. Such withdrawal is expected to be a very infrequent occurrence in this study in view of the testing procedures' similarity to routine clinical practice. If the parents or guardian indicate that they want to withdraw the child from the study, the investigator personally should attempt to speak with them to determine the reason.

5.2. Risks

There are no risks involved in this study that would not be part of usual care.

5.3. Risks of Examination Procedures

The procedures in this study are part of daily pediatric eye care practice in the United States and pose no known risks.

5.4. Risks of Surgery

All surgical procedures are standard care. The risks involved in the study are identical to those that would be present for a patient undergoing the same procedure, but who is not participating in the study.

Some probing procedures may be performed in the office at investigator discretion following their standard indications. For surgical procedures which are done under general anesthesia, there is a very low risk of morbidity from general anesthesia in children in this age group. The risk related to all NLDO surgery is aspiration. This risk is well recognized and would be the same regardless of whether the procedure was performed as part of the study or in normal clinical practice.

The simple probing procedure has a risk of self-limited nasal bleeding at the time of surgery and for a few days postoperatively (< 10%). There is an unlikely chance of prolonged nasal bleeding requiring nasal packing or cauterization (<1%). There is a risk of damage to the punctum through which the probe is passed. These risks are likely the same when performed awake with restraint or with general inhalational anesthesia.

For both balloon catheter dilation and nasolacrimal intubation there is a risk of damage to the punctum(a) ("punctal slitting"), nasal bleeding at the time of surgery and for a few days post-operatively, as well as dacryocystitis. There is a very low risk of a need for nasal packing or nasal cautery for nose bleeding that does not stop (<1%). For the intubation, there is also a risk of premature loss of the tubes, pyogenic granuloma and corneal abrasion. There is little information on the frequency of these problems with the surgical approaches being studied. Al-Hussain and colleagues found after intubation punctal slitting in 10%, dacryocystitis in 2%, and extrusion in 25%.[23] In 63 intubations in childhood, Dortzbach and colleagues reported 11 extrusions, 6 infections, 1 corneal abrasion, and 1 pyogenic granuloma.[24]

5.5. Reporting of Adverse Events

Each investigator is responsible for informing his/her IRB of serious treatment-related adverse events and for abiding by any other reporting requirements specific to his or her IRB.

Data on the complications of the study treatments will be tabulated regularly by the Coordinating Center for review by the Steering Committee. Serious complications will be reported expeditiously to the Data and Safety Monitoring Committee, which will receive a full adverse event report semi-annually. Following each DSMC data review, a summary will be provided to IRBs.

5.6. Patient Payments

The parent/guardian of each patient will be compensated $25 for the single study follow-up visit. If the patient requires and completes the additional follow-up visit specified in section 4.6, the parent/guardian will be compensated an additional $25.

If there are extenuating circumstances, additional funds may be provided for travel if expenses exceed $25 and the patient will be unable to complete the visit without the reimbursement of the travel expenses.

5.7. Discontinuation of Study

The study may be discontinued by the Steering Committee (with approval of the Data and Safety Monitoring Committee) prior to the preplanned completion of enrollment and follow-up for all patients.

5.8. Contacts by the Jaeb Center for Health Research

The Jaeb Center serves as the PEDIG Coordinating Center. The Jaeb Center will be provided with the parent/guardian's contact information. The Jaeb Center staff may make phone contacts to facilitate visit scheduling. A patient newsletter, study updates, and a study logo item may be sent. Patients will be provided with a summary of the study results in a newsletter format after completion of the study by all patients.

CHAPTER 6: SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

The estimation of sample size and statistical analysis plan are summarized below and detailed in separate documents.

6.1. Sample Size Estimation

The study plans to enroll 625 children in the 6-24 month age range who are being treated for NLD by simple probing and who do not have Down Syndrome. The sample size estimation was based on the expected width of the 95% confidence interval on the proportion of successes for different age groups of patients undergoing simple probing. Assuming that success proportions vary with age, the expected width of the 95% confidence interval on the proportion of successes by age will be approximately $\pm$.03 for the 6 to 12 month age group (300 children with expected success proportion of 90%), and $\pm$.05 for the 13 to 24 month age group (300 children with expected success proportion of 80%).

Recruitment of children receiving other procedures (balloon or intubation), older children (>24 months) receiving simple probing, and children with Down Syndrome will proceed until the goal of 625 children eligible for the primary analysis is met.

It is estimated that the study will enroll about 800 children total.

6.2. Statistical Analysis

The primary analysis will include patients 6-24 months old who are undergoing simple probing procedure and who do not have Down Syndrome.

For the primary analysis, treatment success will be defined as the absence of any clinical signs (presence of epiphora, increased tear film, or mucous discharge) on assessment by a study-certified examiner other than the surgeon. Re-operation prior to the start of the visit window for the outcome exam will be considered an automatic treatment failure. For patients who require and complete the additional visit as specified in section 4.6, the results of the clinical signs assessment performed at this visit will be analyzed in the primary analysis.

Point estimates and 95% confidence intervals on the proportion of patients with treatment success will be calculated for each age group.

Secondary analyses will describe symptoms and quality of life in patients undergoing simple probing based on data obtained from the questionnaire.

Data from patients undergoing balloon catheter dilation or nasolacrimal intubation will be evaluated separately, as will data from patients with Down Syndrome.

CHAPTER 7: REFERENCES

1. Price H. Dacryostenosis. J Pediatr 1947; 30:300-305.
2. Petersen RA, Robb RM. The natural course of congenital obstruction of the nasolacrimal duct. J Pediatr Ophthalmol Strabismus 1978; 15:246-50.
3. Kushner BJ. Congenital nasolacrimal system obstruction. Arch Ophthalmol 1982; 100:597-600.
4. Paul TO. Medical management of congenital nasolacrimal duct obstruction. J Pediatr Ophthalmol Strabismus 1985; 22:68-70.
5. Nelson LR, Calhoun JH, Menduke H. Medical management of congenital nasolacrimal duct obstruction. Ophthalmology 1985; 92:1187-90.
6. Stager D, Baker JD, Frey T, Weakley DR, Jr., Birch EE. Office probing of congenital nasolacrimal duct obstruction. Ophthalmic Surg 1992; 23:482-4.
7. Robb RM. Success rates of nasolacrimal duct probing at time intervals after 1 year of age. Ophthalmology 1998; 105:1307-9; discussion 1309-10.
8. Kushner BJ. The management of nasolacrimal duct obstruction in children between 18 months and 4 years old. J Aapos 1998; 2:57-60.
9. el-Mansoury J, Calhoun JH, Nelson LB, Harley RD. Results of late probing for congenital nasolacrimal duct obstruction. Ophthalmology 1986; 93:1052-4.
10. Kashkouli MB, Kassaee A, Tabatabaee Z. Initial nasolacrimal duct probing in children under age 5: cure rate and factors affecting success. J Aapos 2002; 6:360-3.
11. Katowitz JA, Welsh MG. Timing of initial probing and irrigation in congenital nasolacrimal duct obstruction. Ophthalmology 1987; 94:698-705.
12. Mannor GE, Rose GE, Frimpong-Ansah K, Ezra E. Factors affecting the success of nasolacrimal duct probing for congenital nasolacrimal duct obstruction. Am J Ophthalmol 1999; 127:616-7.
13. Kashkouli MB, Beigi B, Parvaresh MM, Kassaee A, Tabatabaee Z. Late and very late initial probing for congenital nasolacrimal duct obstruction: what is the cause of failure? Br J Ophthalmol 2003; 87:1151-3.
14. Clark RA. Dilation probing as primary treatment for congenital nasolacrimal duct obstruction. J Aapos 2002; 6:364-7.
15. Becker BB, Berry FD. Balloon catheter dilatation in pediatric patients. Ophthalmic Surg 1991; 22:750-2.
16. Gunton KB, Chung CW, Schnall BM, Prieto D, Wexler A, Koller HP. Comparison of balloon dacryocystoplasty to probing as the primary treatment of congenital nasolacrimal duct obstruction. J Aapos 2001; 5:139-42.
17. Lueder GT. Neonatal dacryocystitis associated with nasolacrimal duct cysts. J Pediatr Ophthalmol Strabismus 1995; 32:102-6.
18. Sturrock SM, MacEwen CJ, Young JD. Long-term results after probing for congenital nasolacrimal duct obstruction. Br J Ophthalmol 1994; 78:892-4.
19. Zappia RJ, Milder B. Lacrimal drainage function; 2. The fluorescein dye disappearance test. Am J Ophthalmol 1972; 74:160-162.
20. MacEwen CJ, Young JD. The fluorescein disappearance test (FDT): an evaluation of its use in infants. J Pediatr Ophthalmol Strabismus 1991; 28:302-5.
21. Migliori ME, Putterman AM. Silicone intubation for the treatment of congenital lacrimal duct obstruction: successful results removing the tubes after six weeks. Ophthalmology 1988; 95:792-5.

22. O'Donnell BA, Adenis JP, Linberg JV, Rose GE, Sullivan TJ, Wobig JL. The failed probing. Clin Experiment Ophthalmol 2001; 29:276-80.
23. Al-Hussain H, Nasr AM. Silastic intubation in congenital nasolacrimal duct obstruction: a study of 129 eyes. Ophthal Plast Reconstr Surg 1993; 9:32-7.
24. Dortzbach RK, France TD, Kushner BJ, Gonnering RS. Silicone intubation for obstruction of the nasolacrimal duct in children. Am J Ophthalmol 1982; 94:585-90.