NASOLACRIMAL DUCT OBSTRUCTION STUDY 3 NLD3

A Randomized Trial Comparing Immediate Probing in an Office Setting with Deferred Probing in a Facility Setting for Treatment of Nasolacrimal Duct Obstruction in Children 6 to <10 Months Old

PROTOCOL

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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. Many cases will resolve spontaneously or with massage.[1-3] Many studies of primary treatment of NLDO have been reported. These case series have largely been retrospective, uncontrolled, and conducted in single centers.

In children with NLDO symptoms, Peterson and Robb found that 58 of 65 (89%) blocked ducts spontaneously resolved by 13 months of age.[2] Peterson and Robb did not report the age distribution for the cohort, but they do note that 67% percent of the spontaneous resolutions occurred before 6 months of age.[2] Nelson and colleagues reported that among 113 infants enrolled into a study between 1 month and 10 months of age (median age = 5 months), 107 (95%) had NLDO spontaneously resolved by 13 months of age.[4] Ghuman and colleagues found spontaneous resolution in 128 (32%) of 402 eyes treated with massage and antibiotics by 13 months, however the ages at which the children had initiated medical management were not specified.[5] Paul reported that among 55 children with infantile NLDO who were first examined at 3 months of age or younger, 51 of 55 (91%) had ducts that were open at 12 months.[6] With regard to spontaneous resolution in children who still have NLDO symptoms by a certain age, the Paul report showed that among 37 eyes with NLDO symptoms at 6 months, 26 (70%) were clear without surgical intervention by 12 months of age and that among 23 eyes with NLDO symptoms at 9 months, 12 (52%) had cleared by 12 months.[6] The substantial uncertainty regarding an estimate of spontaneous resolution is a primary reason for conducting the current study.

Probing is the most widely-used initial treatment for NLDO in infancy. Our group recently completed a prospective observational study which found a 78% (95% CI = 74% to 82%) success proportion of probing among children aged 6 to <12 months.[7] This overall success proportion was similar to that reported by others,[5, 8-10] better than the 69% reported by Katowitz and Welsh,[8] though worse than the 92% reported by Robb.[11]

Two differing approaches to nasolacrimal probing have been most often been used: (1) immediate office probing (early probing – generally soon after 6 months of age) and (2) medical management (episodic antibiotic eye drops with massage of the lacrimal sac) until 9-13 months of age followed by probing under general anesthesia or conscious sedation (deferred probing). The advantages of early probing are the avoidance of general anesthesia or conscious sedation, immediate resolution of symptoms, fewer physician visits, fewer antibiotic prescriptions, lesser cost per procedure, and possible prevention of fibrosis from inflammation in the nasolacrimal duct. The advantages of deferred probing include more subject comfort with the procedure and possible avoidance of a surgical procedure completely.

Both early and deferred probing approaches are usually successful for treatment of NLDO. Early probing done in the office setting with restraint and only topical anesthesia was successful in 92% of children in a retrospective review of a series of 2369 infants.[12] 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. In our previous prospective observational study of probing, 84% of the probings performed in an office setting were done under one year of age and 64% of the probings performed in a surgical facility were done at one year of age or older.[7] The study found that the 239 eyes that underwent office probing procedures had a slightly lower proportion with success (72% [95% CI = 66% to 78%]) compared with the 661 eyes that underwent surgical facility probings (80% [95% CI = 77% to 84%]).[7] Limiting the office probing cohort to the 132 eyes from 105 subjects aged 6 to <10 months old, the proportion with success was 75% (95% CI = 66% to 82%) and limiting the facility probing cohort to the 223 eyes from 183 subjects aged 12 to <16 months old, the proportion with success was 80% (95% CI = 74% to 85%) (PEDIG, unpublished data). We speculated that the lower success with office probings might be due to a less robust procedure (e.g., probe passed only once) being performed in the office setting. However, because our study was not randomized and because the investigators who performed office probings did so nearly exclusively, we could not eliminate the possibility that subject selection bias and/or an investigator effect may be important factors underlying the observed difference in success between the office and facility settings.

The optimal approach to the management of NLDO in the first year of life remains uncertain. Our prospective observational data suggest a slightly reduced chance of success with immediate office probing; however, immediate office probing may be more cost-effective even if the proportion with success is lower. For a subject undergoing a single operation, immediate office probing is less expensive than deferred probing in a facility because there is no fee for anesthesia, the facility, or for medications prescribed during the pre-operative observation period. Some portion of this lower cost would be offset however by the additional cost of a second procedure if the initial office probing is not successful. Deferred facility probing is more expensive per procedure; however, the overall costs are reduced by the number of children whose NLDO spontaneously resolves while waiting to perform the procedure in a facility. This has been widely discussed by clinicians and has been studied using clinical decision analysis.[13] Using a hypothetical spontaneous resolution rate of 70%, Kassoff found that deferred facility probing had a higher cost than immediate office probing.[13] In a preliminary model developed with the assistance of Kevin Frick, PhD, we found that a hypothetical spontaneous resolution rate of about 75% equalizes the costs between immediate office probing and deferred facility probing and that a higher spontaneous resolution rate could cause the overall cost to shift in favor of deferred facility probing being less costly (personal communication, 1/17/2008).

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.

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

Office probing is a probing performed without sedation, general anesthesia, or anesthesiologist attendance. Topical anesthesia is used along with restraint of the infant.

Facility probing is a probing performed under general anesthesia or conscious sedation in a hospital outpatient surgery department or an ambulatory surgical center.

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 determine the cost-effectiveness of treating NLDO using immediate office probing compared with deferred probing in a facility setting. As part of the primary objective, the study will determine the proportion of eyes experiencing spontaneous resolution among subjects randomized to the deferred probing group.

Secondary objectives are:

- To determine the success proportion for eyes undergoing immediate office probing as an initial procedure
- To determine the success proportion for eyes undergoing deferred facility probing as an initial procedure

Additional objectives will be detailed in a separate analysis plan.

1.4. Synopsis

This study is designed to prospectively evaluate in subjects between 6 to <10 months of age the cost-effectiveness of probing performed as soon as possible in the office compared with a period of observation followed by a probing procedure in a surgical facility, if needed.

The primary treatment outcomes will be evaluated using the clinical signs assessment that our research group has used in our previous studies of NLDO[7]: treatment success or failure, determined with an assessment of the three clinical signs of nasolacrimal duct obstruction—epiphora, increased tear lake, and mucous discharge. Treatment success for the primary outcome at 18 months of age will be defined as the absence of these three clinical signs, regardless of whether the subject underwent surgery or the NLDO spontaneously resolved without surgery.

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.

Enrollment

Children 6 to <10 months of age with epiphora, increased tear film, and/or mucous discharge considered by the investigator to be due to NLDO will be enrolled into the study. It is estimated that the study will enroll 220 children. The enrollment exam will include an assessment for clinical signs of NLDO and an ocular exam.

Randomization

Each child will be randomized to one of the following two groups:

- Immediate office probing: probing to be performed in the office either the same day or within two weeks (referred to as 'immediate probing group').
- Deferred facility probing: probing to be performed 26 to 30 weeks after enrollment if any of the clinical signs persist at the 26-week visit (referred to as 'deferred probing group').

Randomization will be by subject so children undergoing surgery in both eyes will have both eyes assigned to the same treatment group.

Pre-surgery Treatment

For the deferred probing group between randomization and the day of surgery:

- Lacrimal massage will be prescribed for use twice daily when discharge is present. Lacrimal massage may also be prescribed for use at other times at investigator discretion.
- Antibiotic eye drops will be prescribed for use when discharge is purulent, with instructions that they should be used until the purulent discharge is gone.

For the immediate probing group, whether to use lacrimal massage and/or antibiotic eye drops during this time is at investigator discretion.

Follow-up Phone Contact and Examination

Subjects will have a phone call 12 weeks ($\pm$2 weeks) after randomization and a visit 26 weeks ($\pm$2 weeks) after randomization. These contacts will be after surgery has occurred for the immediate probing group and before surgery has occurred for the deferred probing group.

For the deferred probing group:

- Subjects whose NLDO has resolved at the 26-week visit will not undergo surgery, but will return for the primary outcome exam at 18 months of age.
- Subjects whose NLDO has not resolved at the 26-week visit will undergo surgery within 4 weeks and will then return for the primary outcome exam at 18 months of age.

All subjects will have a primary outcome exam at 18 months of age ($\pm$4 weeks). At the primary outcome exam, a masked examiner will perform an assessment for the presence of epiphora, increased tear film, or mucous discharge.

Additional visits are at investigator discretion.

Surgery and Surgical Setting

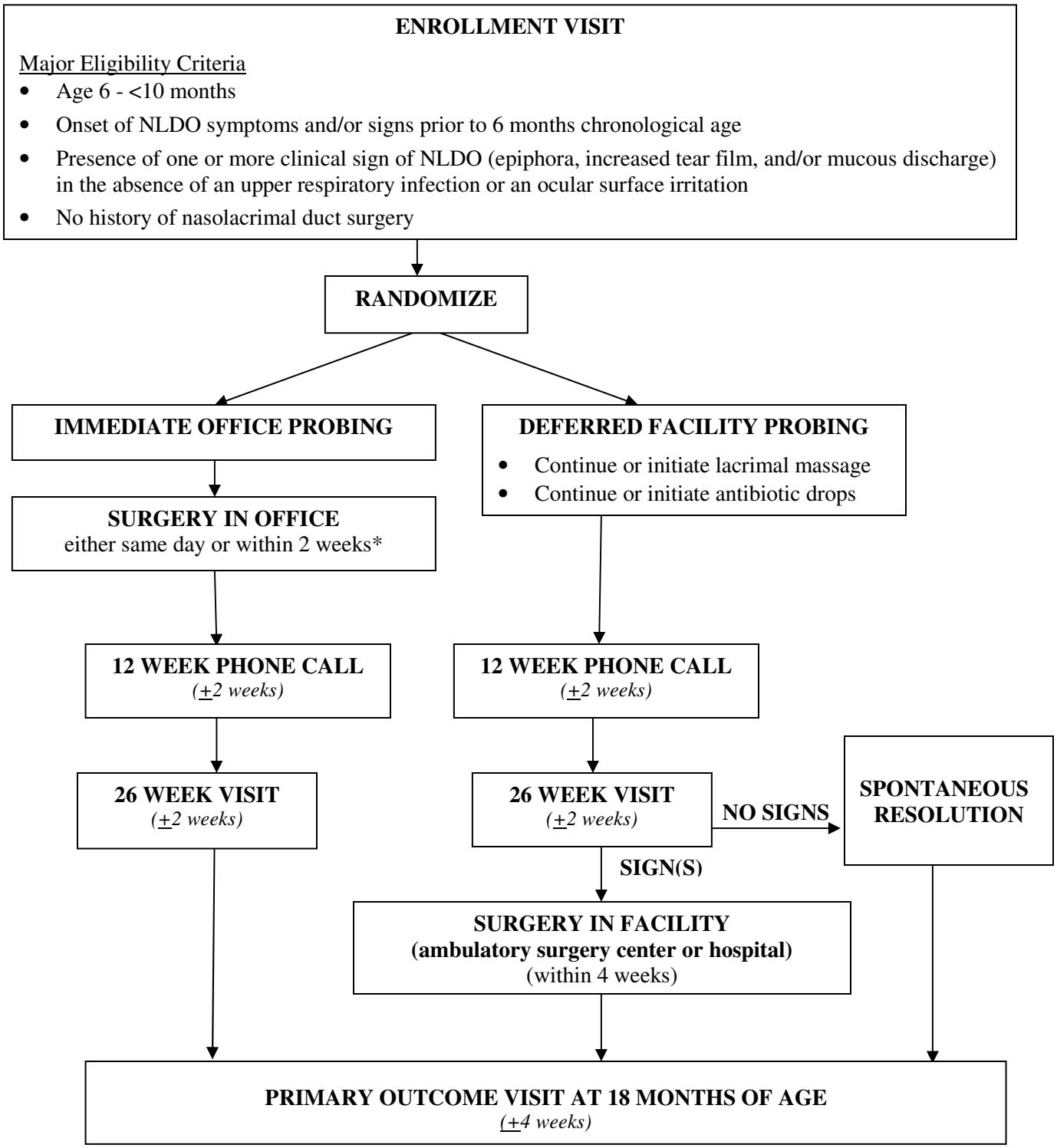
- Subjects in the immediate probing group will undergo probing performed in the office setting within two weeks of randomization (could be same day).
- Subjects in the deferred probing group will undergo probing performed in an ambulatory surgery center or hospital within four weeks after the 26-week visit if any clinical signs of NLDO are present at the 26-week visit.

Post-Surgical Treatment

Antibiotic/steroid eye drops will be used 2-4 times daily for one week after surgery. For recurrent NLDO occurring more than a week after surgery, an antibiotic will be prescribed. Lacrimal massage may be prescribed at investigator discretion.

Reoperation prior to the primary outcome visit at 18 month of age visit is at investigator discretion and can be probing in office, probing in a facility, nasolacrimal intubation, or balloon catheter dilation. Reoperations should be timed such that the primary outcome visit at 18-month of age is at least one month after surgery, or at least one month after tube removal for nasolacrimal intubation procedures. Presence of one or more clinical signs of NLDO will be verified prior to reoperation, either on the day of surgery or at a preoperative visit.

1.5. Flow Chart



*If surgery will not be completed the same day as randomization, it is at investigator discretion whether to prescribe lacrimal massage and/or antibiotics pre-operatively.

Note: in both treatment groups, decision for reoperation prior to 18 months of age and choice of procedure are at investigator discretion, however reoperations should not be performed prior to 6 weeks after the initial surgery and should be timed such that the 18-month of age primary outcome visit is at least one month after surgery, or at least one month after tube removal for nasolacrimal intubation procedures.

CHAPTER 2: ENROLLMENT VISIT

2.1. Eligibility Assessment and Informed Consent

Subjects with unilateral or bilateral signs of NLDO will be enrolled and consented prior to randomization.

2.2. Eligibility and Exclusion Criteria

The following criteria must be met for enrollment into the study:

- Age 6 to <10 months
- Onset of NLDO symptoms and/or signs prior to 6 months chronological age in study eye(s)
- Presence in study eye(s) of epiphora, increased tear film, and/or mucous discharge in the absence of an upper respiratory infection or an ocular surface irritation that investigator believes is due to NLDO
- At least one open punctum present in study eye(s)

A history of NLDO treatment with lacrimal massage, topical antibiotics or steroids, or systemic antibiotics is permitted.

The following are exclusion criteria:

- History of nasolacrimal duct surgery including probing, nasolacrimal intubation, balloon catheter dilation, or dacryocystorhinostomy in study eye(s)
- History of trauma to the lacrimal drainage system of the study eye(s)
- Glaucoma in study eye(s)
- Corneal surface disease in study eye(s)
- Microphthalmia in study eye(s)
- Down Syndrome
- Craniosynostosis
- Goldenhar sequence
- Clefting syndromes
- Hemifacial microsomia
- Midline facial anomalies

2.3. Historical Information

The following data will be placed in the research record: demographic data (including gender, race, ethnicity, date of birth,) use of topical antibiotics, and use of lacrimal massage.

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 with recording of presence or absence of the following:
    - 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.

If diagnostic or therapeutic eye drops 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 20 minutes afterwards.

2. Ocular exam

An eye examination should be performed to document normal lids, ocular adnexa, at least one open punctum in the affected eye(s) and anterior segment structures.

- Refraction, fundus examination, and intraocular pressure are performed at investigator discretion.

CHAPTER 3: RANDOMIZATION AND PRE-SURGERY TREATMENT

3.1. Randomization Groups

Randomization is performed on the PEDIG website.

Subjects will be randomized to one of the following groups:

- Immediate office probing: probing to be performed in the office either the same day as randomization or within two weeks
- Deferred facility probing: probing to be performed in a facility within four weeks after completion of the 26-week visit if any of the clinical signs persist.

The initial surgical procedure for both treatment groups is probing only (see section 5.3.). Neither nasolacrimal intubation nor balloon catheter dilation should be performed as an initial procedure.

Subjects with both eyes enrolled in the study will have both eyes assigned to the same treatment group.

The Jaeb Center will construct a Master Randomization List using a permuted block design stratified by site, which will specify the order of treatment group assignments.

3.2. Pre-Surgery Treatment

3.2.1. Lacrimal Massage

Between randomization and the day of surgery, lacrimal massage will be prescribed for the deferred probing group and may be prescribed at investigator discretion for the immediate probing group. When prescribed, lacrimal massage is to be performed twice daily when discharge is present. Lacrimal massage may also be done at other times at investigator discretion.

3.2.2. Antibiotic Eye Drops

The deferred probing group will be prescribed commercially-available antibiotic eye drops to be used when purulent discharge is present between randomization and the day of surgery. Immediate probing group subjects may be prescribed antibiotic eye drops in a similar fashion at investigator discretion. Antibiotic eye drops will be dispensed to the deferred probing group at randomization and may be dispensed to immediate probing group subjects at investigator discretion.

Parents of subjects prescribed antibiotic eye drops will be instructed to use 1 drop up to 4 times a day as needed when the discharge is purulent. Parents should report to the investigator purulent discharge which persists after 5-7 days of treatment, as other antibiotics may be used at investigator discretion in these cases. Eye drops may be discontinued when the discharge is clear.

CHAPTER 4: FOLLOW UP EXAMINATIONS

4.1. Visit Schedule

Follow up consists of the following visits and scheduled contacts:

- A phone call 12 (±2 weeks) weeks from randomization
- A visit 26 weeks (±2 weeks) from randomization
- A masked primary outcome exam at 18 months of age (±4 weeks)

Subjects should complete all follow-up exams regardless of whether their symptoms have improved and/or resolved, and regardless of whether they receive surgery.

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

4.2. 12-week Phone Call

Parents will receive a phone call from the clinical site 12 weeks (±2 weeks) after randomization. The office probing group will have had surgery by the time of this call, whereas the deferred probing group will not have had surgery yet.

The main purpose of the call will be to keep in contact with the family; however, data will be collected on whether symptoms of NLDO are present.

4.3. 26-week Visit

Subjects will have a visit 26 weeks (±2 weeks) from randomization. The office probing group will have had surgery by the time of this visit, whereas the deferred probing group will not have had surgery yet.

At the visit, an assessment for the clinical signs of NLDO (see section 2.4) will be performed. The assessment may be performed by any study-certified examiner at the site, including the investigator.

For subjects in the deferred probing group:

- If one or more clinical signs of NLDO are present, the subject will undergo probing in a facility (ambulatory surgery center or hospital) within 4 weeks and will return for the primary outcome visit at 18 months of age.
- If no clinical signs of NLDO are present, the subject's NLDO will be considered to have spontaneously resolved and the subject will not undergo surgery. The subject will return for the primary outcome visit at 18 months of age.
    - If a subject with both eyes enrolled in the study has clinical signs of NLDO in one eye but none in the other eye, the remaining affected eye will undergo surgery and the other eye will be treated as a having spontaneously resolved.
    - If signs return and are sufficiently persistent to warrant surgery, the subject may undergo probing (see section 5.1).

4.4. Primary Outcome Exam

All subjects in both treatment groups will have a primary outcome exam at 18 months of age (±4 weeks) regardless of whether they had surgery.

An assessment for the clinical signs of NLDO (see sections 2.4 and 4.4.2) will be performed by a certified examiner who is masked to the subject's treatment group.

Additional data to be collected at this visit will include presence of upper respiratory symptoms or ocular surface irritation, e.g. conjunctivitis.

4.4.1. Timing of Visit

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. However, the exam will be completed and the data used for analysis even if the subject comes to the office with either of these conditions (i.e. the visit will not be rescheduled).

4.4.2. Masked Assessment of Clinical Signs of NLDO

A study-certified examiner will perform a masked assessment of clinical signs of NLDO in the enrolled eye(s). The examiner cannot be the surgeon who performed the initial probing or any subsequent surgeries but may be another investigator at the site, or any other study personnel provided the individual is certified in the performance of the assessment and masked to treatment group.

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 is considered a failure for analysis.

CHAPTER 5: SURGERY AND POSTSURGERY TREATMENT

The initial surgical procedure for both treatment groups is probing only (see section 5.3.). Neither nasolacrimal intubation nor balloon catheter dilation should be performed as an initial procedure.

Choice of procedure for reoperations is at investigator discretion and can be probing (either in office or facility), nasolacrimal intubation or balloon catheter dilation (see section 5.5).

5.1. Timing of Surgery

The timing of the surgery will be determined by the randomization.

- For the immediate probing group, surgery should be performed either the same day as randomization or within 2 weeks after randomization.
- For the deferred probing group, if at the visit timed 26 weeks from randomization one or more clinical signs of NLDO are present, surgery should be performed within four weeks following the 26-week visit.
    - Surgery may be performed later for deferred group subjects who at the 26-week visit appear to have spontaneously resolved, but later have signs of NLDO. The only stipulation is that surgery be performed at least one month before the primary outcome visit at 18 months of age is completed, otherwise it should be deferred until after the visit.

5.2. Surgical Considerations

1. Preoperative medications
    - For the immediate pre-operative period (2-3 days before surgery): for both groups, topical and systemic antibiotics are at investigator discretion. Topical antibiotics will be dispensed from study-provided stock of commercially-available topical antibiotics (see section 3.2.2). Systemic steroids may be given as clinically indicated (e.g., for treatment of reactive airway disease).

2. NPO orders
    - For office probings, it is at investigator discretion whether to prohibit food and drink for a certain period of time prior to surgery. For facility probings, the NPO duration will be as required by the particular facility.

3. Anesthesia
    - For office procedures, topical anesthesia will be used.
    - For procedures performed in an ambulatory surgery center or hospital, general anesthesia or conscious sedation will be used. Medications and airway management are chosen collaboratively by the surgeon and the anesthesiologist.

4. Restraint
    - For office procedures, there will typically be some form of infant restraint used.

5. 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.

6. Post-operative medications

- A commercially-available topical antibiotic/steroid combination will be administered upon completion of the procedure and will be prescribed to be used 2-4 times daily for one week following surgery (see section 5.4).

7. Surgical cancellations

- If the procedure is cancelled due to a medical reason, it will be rescheduled based on the medical condition and NLDO symptoms.

Note that the above considerations apply not only to the initial surgery but also to any re-operations (see section 5.5) that occur while the subject is in the study.

5.3. Probing Procedure

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

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

Inferior turbinate infracture is at investigator discretion; however, we expect this procedure will not be performed during office probings.

If a procedure other than probing is performed, the occurrence and rationale will be indicated on the surgery form.

5.4. Medical Management

A commercially-available topical antibiotic/steroid combination should be used 1 drop 2 to 4 times per day for one week after surgery. The antibiotic/steroid combination will be dispensed from study-provided stock.

For recurrent purulent discharge occurring more than one week after surgery, a commercially-available topical antibiotic drop may be prescribed (see section 3.2.2). Whether to prescribe is at investigator discretion.

Lacrimal massage may be prescribed at investigator discretion (see section 3.2.1).

5.5. Reoperation

During the postoperative observation phase, the decision to reoperate and the procedure type is at investigator discretion. The procedure performed can be a probing in office, a probing in a facility, a nasolacrimal intubation, or a balloon catheter dilation.

The timing of reoperation is subject to the following:

- Reoperations should not be performed prior to 6 weeks after the initial surgery.
- Repeat probing (in office and in facility) and balloon catheter dilation should occur at least one month before the primary outcome visit at 18 months of age is completed, otherwise reoperation should be deferred until after the visit.
    - For reoperations that are nasolacrimal intubations, procedures should occur so that silicone tubes can be retained for 2-5 months but removed at least one month before the primary outcome visit at 18 months of age is completed, otherwise reoperation should be deferred until after the visit.

The same surgical considerations (see section 5.2) apply for reoperations as apply for initial surgeries.

CHAPTER 6: MISCELLANEOUS CONSIDERATIONS IN FOLLOW UP

6.1. Subject Withdrawals

The parents or guardian may withdraw their child from the study at any time. Such withdrawal is expected to be a very infrequent occurrence in this study in view of the surgery's and testing procedure's 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.

6.2. Subjects Not Undergoing Surgery

Some subjects will not have surgery as part of the study because their NLDO spontaneously resolved. In addition, there may be some subjects who have not met the criteria for spontaneous resolution, but whose symptoms have improved to the point where the parents and/or the investigator elect not to proceed with surgery. In both cases, the subjects should continue in the study and complete all follow up exams. For analysis, these subjects' outcome will be based on whether clinical signs are present at the primary outcome visit at 18 months of age, and their cost of treatment will not include the cost of surgery.

6.3. Risks

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

6.4. Risks of Examination Procedures

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

6.5. Risks of Surgery

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

For surgical procedures in general, there is a rare risk of vomiting and aspiration (<1%). The risk of aspiration 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.

For surgical procedures that are done under general anesthesia, there is a rare risk (<0.1%) of morbidity from general anesthesia in children in this age group.

Probing 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, with general inhalational anesthesia, or with conscious sedation. In the PEDIG study of 955 eyes undergoing probing, surgical and post-surgical complications were reported infrequently; there was one reported episode of laryngospasm which was managed without sequelae and one report of mild bleeding from a lacrimal punctum.[7]

6.6. Reporting of Adverse Events

Each site is responsible for informing its IRB of serious treatment-related adverse events and for abiding by any other reporting requirements specific to his or her IRB. Serious treatment-related complications will be reported expeditiously to the Data and Safety Monitoring Committee, which will receive a compiled adverse event report semi-annually. Following each DSMC data review, a summary will be provided to IRBs.

6.7. Drug Allergies

For subjects who are allergic to the study-specified medications, alternate medications may be prescribed. In such an instance the product used would be recorded on the appropriate data form.

6.8. Travel Reimbursement

The parent/guardian of each subject will be compensated $30 for completion of the 26-week visit and $30 for completion of the primary outcome visit at 18 months of age. If there are extenuating circumstances, and the patient is unable to complete study visits without additional funds due to travel costs, additional funds may be provided.

6.9. Study Costs

The subject or his/her insurance will be responsible for the costs that are considered standard care. This includes the initial examination for diagnosis of NLDO, all surgical procedures, and all costs involved in managing surgical complications.

The study will pay for the 26-week visit and the primary outcome visit at 18 months of age.

The study will provide the topical antibiotics and the topical antibiotic/steroid combination drug.

6.10. 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 subjects.

6.11. 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 contact the parent/guardian to maintain rapport or to facilitate visit scheduling. A subject newsletter, study updates, and a study logo item and/or another type of small gift may be sent periodically. Subjects (specifically their parents and guardians) will be provided with a summary of the study results in a newsletter format after completion of the study by all subjects.

6.12. Risk Assessment

This protocol falls under DHHS 46.404 which is research not involving greater than minimal risk.

CHAPTER 7: SAMPLE SIZE ESTIMATION AND STATISTICAL ANALYSIS

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

7.1. Sample Size Estimation

Given that the proportion of subjects with treatment success at 18 months of age is expected to be similar for both treatment groups, particularly after reoperations are taken into account, sample size is not being determined in the context of a treatment group comparison. Rather, because the cost factor in the economic model to be used in the primary analysis is driven largely by the proportion of deferred probing group subjects which have NLDO spontaneously resolve without surgery, sample size is being determined within the context of the width of the confidence interval on this proportion. Table 1 shows the 95% confidence interval on the spontaneous resolution proportion given the specified spontaneous resolution proportions and the specified numbers of subjects randomized.

Table 1: Confidence Intervals for Proportion of Spontaneous Resolution in the Deferred Probing Group

Deferred Probing Group									
	Number of Subjects Randomized to Deferred Probing Group[a]								
	100			150			200		
SR%	N Probed	N SR[b]	95% CI on SR%[c]	N Probed	N SR[b]	95% CI on SR%[c]	N Probed	N SR[b]	95% CI on SR%[c]
25%	75	25	16 to 34%	112	38	18 to 32%	150	50	19 to 31%
50%	50	50	40 to 60%	75	75	42 to 58%	100	100	43 to 57%
75%	25	75	66 to 84%	37	113	68 to 82%	50	150	69 to 81%
90%	10	90	84 to 96%	15	135	85 to 95%	20	180	86 to 94%

SR = spontaneous resolution

[a]The total number randomized would be twice these numbers.

[b]N with SR = the expected number of subjects in the deferred probing group whose NLDO will spontaneously resolve given the specified spontaneous resolution proportion and the specified number of subjects randomized.

[c]95% CI on SR% = 95% confidence interval on the spontaneous resolution proportion given the specified spontaneous resolution proportion and the specified number of subjects randomized.

With the proportion of subjects with spontaneous resolution determined with data from 100 subjects randomized to the deferred probing group, a point estimate of 50% would have a confidence interval of 40% to 60%, while a point estimate of 75% would have a confidence

interval of 66% to 84% and a point estimate of 90% would have a confidence interval of 84% to 96%.

In order to have outcome data on 100 subjects randomized to the deferred probing group, and accounting for 10% loss to follow up, the study plans to enroll 220 children total, half of which will be randomized to each treatment group.

7.2. Statistical Analysis

7.2.1. Primary Analysis

The primary analysis will be a comparison of the cost effectiveness between treatment groups. The analysis will be performed using an economic rollback model that takes into account for each subject the cost of treatment and the treatment outcome at 18 months of age.

The primary estimate of cost will be based on the type, number, and setting of all procedures performed between randomization and 18 months of age**,** and the drugs prescribed. These utilization figures will be multiplied by the representative cost associated with each to determine aggregate cost per subject. Representative costs will be determined by averaging the total allowable cost for each procedure obtained from actual explanations of benefits to facilities and providers as well as by obtaining data on such allowable costs for large insurers.

Effectiveness will be based on the primary outcome at 18 months of age. Treatment success will be defined as the absence of any clinical signs (presence of epiphora, increased tear film, or mucous discharge) on masked assessment at 18 months of age. A subject whose NLDO spontaneously resolves without surgery and who still does not have any of the three clinical signs present at 18 months of age will be considered a treatment success for the primary analysis.

The primary analysis will determine whether the observed spontaneous resolution proportion differs from the 'break point' spontaneous resolution proportion which is found in the economic model to equalize costs between the treatment strategies. Preliminary economic modeling has estimated this break point at about 75%. If the upper limit of the confidence interval on the observed spontaneous resolution proportion is lower than the 'break point' proportion, the conclusion would be that the immediate office strategy is less costly. If the lower limit of the confidence interval on observed spontaneous resolution proportion is higher than the 'break point' proportion, the conclusion would be that the deferred facility probing strategy is less costly. If the confidence interval for the observed spontaneous resolution proportion includes the break point proportion, the conclusion would be that we cannot say that either strategy is less costly than the other.

The primary analysis will follow the intention to treat principle in which a subject's treatment outcome and cost of treatment will be assigned to the randomized treatment group, regardless of what treatment the subject received.

7.2.2. Secondary Analyses

Secondary analyses include determining the success proportion for eyes undergoing office probing as an initial procedure, and the success proportion for eyes undergoing deferred facility probing as an initial procedure. The outcome will be treatment success/failure at 18 months of

age; however for these analyses, any subject who undergoes a second procedure prior to 18 months of age will be considered an automatic treatment failure.

An additional secondary analysis will compare parental satisfaction between treatment groups.

Additional objectives will be detailed in a separate analysis plan.

7.3. Interim Analyses

No formal interim analyses of the outcome data are planned because data on the entire cohort is needed to obtain the desired precision on the point estimate for the proportion of deferred group subjects whose NLDO spontaneously resolves.

CHAPTER 8: REFERENCES

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The Jaeb IRB has classified the protocol under DHHS 46.405, which is research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

*****For sites covered by the Jaeb IRB, this supercedes what is written in section 6.12 of the protocol.*****