PROTOCOL TITLE:

Neonatal Esophagus and Airway Interactions in Health and Disease: Mechanisms and Management of Infant Dysphagia

PRINCIPAL INVESTIGATOR:

Name: Sudarshan Jadcherla
Department/Center: Neonatal and Infant Feeding Disorders Program/Center for Perinatal Research
Telephone Number: (614) 355-6643
Email Address: Sudarshan.Jadcherla@nationwidechildrens.org

VERSION NUMBER/DATE:

Version 10(revision #9) 10/2/20

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	12/21/15	During the intervention phase while thickened formula is in use, we changed the definition of compliance from < or equal to 75% of the time to < or equal to 50% of the time	No
2	1/12/16	Allowed less percentage of PO intake at time of screening to account for provider led restrictions vs. infant led restrictions	No
3	2/26/16	1. Allowed subjects on acid suppressive therapies at the time of VFSS into our recruitment as well as allow oatmeal as a second option for thickening. 2. Added the addition of video use during manometry in our methods section. Concurrent synchronized video recordings will be performed to further validate symptoms based on objective definition of the esophageal reflexes. Documentation of symptom markers can be validated by integrating manometry with respiratory inductance plethysmography and video. 3. Updates to the PHI page and privacy section of the consent to state the infant's face will be in view of the video. 4. Updated DSMB members.	Yes
4	4/24/17	Changed reimbursement language to reflect use of ClinCard	Yes

5	6/12/17	At inception, the protocol was written as a randomized control trial comparing two different feeding approaches: flow regulation vs. thickened feeds. However, over the period, we found it difficult to recruit and retain subjects. Based on the recommendations of the DSMB and program project team, we addressed the hypotheses using alternative strategies. One of such strategies is reflected in this amendment, wherein, the proposed change instead of the interventions being randomly assigned, parents will now choose which therapeutic feeding strategy they would like to enroll their infant in. This is called the parent-preferred feeding therapeutic strategy.	Yes
6	10/18/17	Replaced redlined version of protocol with clean version	Yes
7	2/8/18	A detailed review of the protocol as written revealed multiple changes in study team members and data collection methods that had not been addressed in the body of the protocol. Although the focus and outcome measures of the study have not changed, the protocol was amended to reflect the updates suggested by the DSMB.	Yes
8	1/4/19	Updates to statistical analysis and sample size as well as updated protocol to new template	Yes for new IRB requirements
9	10/2/20	Clarification and summary of changes to the protocol thus far have been made for improved readability, reproducibility and clarity for the reader as this needs to be submitted along with the manuscript.	No

1.0 Study Summary

Study Title	Neonatal Esophagus and Airway Interactions in Health and Disease: Mechanisms and Management of Infant Dysphagia
Study Design	Single arm observational study
Primary Objective	Our overall aims are to identify novel diagnostic aerodigestive targets, define effective therapeutic interventions, and advance the mechanistic basis of therapeutic outcomes-i.e., full oral feedings.
Secondary Objective(s)	1) Examine the differences in outcomes among preterm born vs. full term born 2) Examine the differences in outcomes among those with normal versus abnormal VFSS
Research Intervention(s)/ Investigational Agent(s)	Providing esophageal manometry concurrent with video fluoroscopy swallow study (VFSS) in order to determine sensory-motor dysphagic mechanisms which will better inform treatment options
IND/IDE #	N/A

Study Population	All infants will have a diagnostic VFSS scheduled. Inclusions: Infants with feeding-related aerodigestive symptoms who are ≤ 60 weeks PMA (both pre-term and full-term) who are orally feeding ≥ 25% of at least 50% of their feeds who are on full enteral feeds with no more than 1LPM NC respiratory support. Exclusions: Genetic or metabolic syndromes, IVH grade III or greater, moderate to severe HIE, craniofacial, airway or foregut malformations or ENT or neuro surgeries. Infants who are exclusively breastfeeding are also excluded.
Sample Size	60
Study Duration for individual participants	Up to 4 weeks (initial manometry study with diagnostic VFSS, repeat manometry at 4-6 weeks as relevant), will follow feeding outcomes and growth and developmental outcomes for 1 year
Study Specific Abbreviations/ Definitions	VFSS video-fluoroscopy swallow study LP laryngeal penetration LA laryngeal aspiration

2.0 Objectives

2.1 Purpose, Specific Aims or Objectives

- Our overall aims are to identify novel diagnostic aerodigestive targets, define effective therapeutic interventions, and advance the mechanistic basis of therapeutic outcomes. Infants with aerodigestive and feeding difficulties, who had VFSS undergo Manometry study to ascertain the mechanisms of normal or abnormal swallowing. Parent-preferred therapy is implemented. Changes in therapy modes are documented. Repeat manometry study is undertaken at time-2, which is 2-4 weeks after the initial study where feasible (this may happen in those with oral feeding failures).
- Based on the VFSS results evaluations, there are 2 possible scenarios: those with abnormal or normal results. Parent preferred therapeutic feeding (flow change, thickener change, no change) strategy is implemented and we will simply monitor the progress of the feeding efficiency till discharge or four weeks, whichever is earlier. There are 2 possible outcomes: feeding success, i.e., full oral feeds without symptom requiring intervention or feeding failure, i.e., those needing any tube feeding.
- We will review the motility characteristics of the successful and failure cases to identify the diagnostic markers.

2.2 Hypothesis

- The central unifying hypothesis supported by our preliminary data is that VFSS with the addition of Manometry along with parent preferred feeding strategy is more effective in preventing long term feeding tubes in infants with aerodigestive problems and feeding difficulties.
- **Primary Hypothesis:** The addition of manometry for diagnostics and parent preferred therapy for management is more effective than VFSS with provider recommendations alone for achieving primary outcome.
- **Secondary Hypotheses: 1)** The sensory- motor characteristics of pharyngo-esophageal motility markers are distinctive between normal and abnormal VFSS results. 2) Clinical outcomes are distinct with flow modification and thickener use.

3.0 .Background

3.1 Relevant prior experience and gaps in current knowledge.

- Dysphagia or abnormalities of swallowing, is a heterogeneous condition of multiple etiologies. Pharyngeal phase is the most critical phase since imprecise regulation is associated with airway consequences such as laryngeal penetration and airway aspiration. Exact prevalence is not known, but is estimated to be about 30% to 60% among neonatal ICU graduates. Although these numbers highlight the economic burden, they ignore the quality of life for both patients and parents. The lack of a pathophysiology guided diagnostic and safe feeding management strategies continue to be critical barriers to progress in this field. The current proposal focuses on the dynamic changes in the integrative physiology of the neonatal pharynx, upper esophageal sphincter (UES), lower esophageal sphincter (LES) and esophagus during swallowing and GERD; all of which are potential therapeutic targets for neonates with dysphagia. Current treatment approaches in dysphagic infants are likely to fail due to unclear therapeutic targets. Such high risk infants also suffer chronic morbidity, longer hospitalizations, re-admissions, and account for an unacceptable health care burden. Designing effective symptom-based management is very difficult.

3.2 Relevant preliminary data.

- Three references are attached below in this section that lend support to our investigations, difficulties with strict protocols and need for personalization and parent preferred pragmatic therapies. Complimentary protocols (feeding outcomes in dysphagia, mechanisms of dysphagia, outcomes in gastrostomy bound infants) will address the original study aims as well. Updated statistical procedures based on the advice of our statistician, Dr. Lai Wei, PhD, DSMB team, and our Program Project Group is shown below.

3.3 **Updated statistical procedures:**

- The design of the Patient Preferred Trial has been modified to a single arm observational study with patients who have not achieved PO at the time of study or PO with feeding difficulties, comparing VFSS and manometry vs VFSS only (the historical control) on feeding outcomes. The primary outcome is success rate at discharge. We will prospectively follow 60 infants who are not fully PO or PO and symptomatic at the time of study. Based on our Feeding Outcomes of Dysphagia Study (vs. historical control), the success rate at discharge is around 60%. With 60 patients enrolled, we will have 90% power to detect an absolute increase of 20% from 60% for those who do not have treatment informed by manometry (historical control) to 80% in those in the manometry informed group with two-sided type I error of 0.05. Achievement will be assessed by tracking feeding methods at discharge or 4 weeks whichever is earlier and then at 1 year.

- Jadcherla SR, Peng J, Moore R, Saavedra J, Shepherd E, Fernandez S, Erdman SH, DiLorenzo C. Impact of personalized feeding program in 100 NICU infants: pathophysiology-based approach for better outcomes. J Pediatr Gastroenterol Nutr. 2012 Jan;54(1):62-70.

- Jadcherla SR, Stoner E, Gupta A, Bates DG, Fernandez S, Di Lorenzo C, Linscheid T. Evaluation and management of neonatal dysphagia: impact of pharyngoesophageal motility studies and multidisciplinary feeding strategy. J Pediatr Gastroenterol Nutr. 2009 Feb;48(2):186-92

- Jadcherla SR, Khot T, Moore R, Malkar M, Gulati IK, Slaughter JL. Feeding Methods at Discharge Predict Long-Term Feeding and Neurodevelopmental Outcomes in Preterm Infants Referred for Gastrostomy Evaluation. J Pediatr. 2017 Feb;181:125-130

3.4 **Scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge**

- This proposal is a logical extension of our current P01 and is built on Novel Concepts, and State-Of-The-Art Methods [1-14,15-20], and the field will be changed if the proposed aims are achieved: In the previous funding period, we characterized the reciprocal physiology between the esophagus and aerodigestive tract in premature infants. The studies indicated airway protective reflexes undergo maturation through the early stages of life and their absence or aberrance is associated with dysphagia and its complications. We will extend this knowledge to test diagnostic yield as well as novel feeding management strategies for dysphagia.
- The central unifying hypothesis supported by our preliminary data is that VFSS with the addition of Manometry along with parent preferred feeding strategy is more effective in preventing long term feeding tubes in infants with aerodigestive problems and feeding difficulties.
- We will investigate the sensory-motor mechanisms relevant to dysphagic infants. Dysphagia may be attributed to luminal clearance mechanisms and failure of airway protective mechanisms: esophageal mechano-distention and chemo-sensitive stimulation induced aerodigestive reflexes. The mechanisms for symptoms may lie in stimulus thresholds, response-frequency, response-latency and response-magnitude of the aerodigestive protective reflexes. In those with persistent failure, a time 2 study is undertaken where feasible to ascertain dysfunctional mechanisms. Unique to this proposal, we will apply physiologically rational, safe, therapeutic strategies that have the potential to ameliorate dysphagia We anticipate finding that feeding methods underlie the pathogenesis of dysphagia and reveal relevant new therapeutic targets.
- Publications History and References Pertinent to this Proposal are as follows:
    - Jadcherla SR, Hasenstab KA, Shaker R, Castile RG. Mechanisms of cough provocation and cough resolution in neonates with bronchopulmonary dysplasia. Pediatr Res. 2015 Oct;78(4):462-9. doi: 10.1038/pr.2015.131. Epub 2015 Jul 7. PubMed

PMID: 26151491; PubMed Central PMCID: PMC4800483

- Babaei A, Venu M, Naini SR, Gonzaga J, Lang IM, Massey BT, Jadcherla S, Shaker R. Impaired upper esophageal sphincter reflexes in patients with supraesophageal reflux disease. Gastroenterology. 2015 Nov;149(6):1381-91. doi: 10.1053/j.gastro.2015.07.007. PubMed Central PMCID: PMC4628603
- Jadcherla SR, Shubert TR, Malkar MB, Sitaram S, Moore RK, Wei L, Fernandez S, Castile RG. Gestational and postnatal modulation of esophageal sphincter reflexes in human premature neonates. Pediatr Res. 2015 Nov;78(5):540-6. doi: 10.1038/pr.2015.149. PubMed PMID: 26270576; PubMed Central PMCID: PMC4628557
- Madhoun LL, Siler-Wurst KK, Sitaram S, Jadcherla SR. Feed-Thickening Practices in NICUs in the Current Era: Variability in Prescription and Implementation Patterns. J Neonatal Nurs. 2015 Dec 1;21(6):255-262. PubMed PMID: 26664251; PubMed Central PMCID: PMC4671396. (PO1 DK 068051, R01 DK 068158)
- Jadcherla SR. Dysphagia in the high-risk infant: potential factors and mechanisms. Am J Clin Nutr. 2016 Feb;103(2):622S-8S. doi: 10.3945/ajcn.115.110106. Review. PubMed PMID: 26791178; PubMed Central PMCID: PMC4733255
- Jadcherla SR, Hasenstab KA, Sitaram S, Clouse BJ, Slaughter JL, Shaker R. Effect of nasal noninvasive respiratory support methods on pharyngeal provocation-induced aerodigestive reflexes in infants. Am J Physiol Gastrointest Liver Physiol. 2016 Jun 1;310(11):G1006-14. doi: 10.1152/ajpgi.00307.2015. PubMed PMID: 27012774; PubMed Central PMCID: PMC4935482. (PO1 DK 068051)
- Lang IM, Medda BK, Jadcherla SR, Shaker R. Characterization and mechanisms of the pharyngeal swallow activated by stimulation of the esophagus. Am J Physiol Gastrointest Liver Physiol. 2016 Nov 1;311(5):G827-G837. doi:

10.1152/ajpgi.00291.2016. PubMed PMID: 27634013; PubMed Central PMCID: PMC5130554.

- Jadcherla SR. Advances with Neonatal Aerodigestive Science in the Pursuit of Safe Swallowing in Infants: Invited Review. Dysphagia. 2017 Feb;32(1):15-26. doi: 10.1007/s00455-016-9773-z. Review. PubMed PMID: 28044203; PubMed Central PMCID: PMC5303645.
- Mei L, Jiao H, Sharma T, Dua A, Sanvanson P, Jadcherla SR, Shaker R. Comparative effect of the sites of anterior cervical pressure on the geometry of the upper esophageal sphincter high-pressure zone. Laryngoscope. 2017 Nov; 127(11): 2466-2474. doi: 10.1002/lary.26642. Epub 2017 May 23. PubMed PMID: 28543926. (PO1 DK 068051, R01 DK 025731, T32 DK 061923)
- Hasenstab KA, Sitaram S, Lang IM, Shaker R, Jadcherla SR. Maturation Modulates Pharyngeal-Stimulus Provoked Pharyngeal and Respiratory Rhythms in Human Infants. Dysphagia. 2018 Feb; 33(1): 63-75. doi: 10.1007/s00455-017-9833-z. Epub 2017 Aug 21. PubMed PMID: 28828751
- Lang IM, Medda BK, Shaker R, Jadcherla SR. The effect of body position on esophageal reflexes in cats: A possible mechanism of SIDS? Pediatr Res. 2017 Dec 20. doi: 10.1038/pr.2017.302. [Epub ahead of print] PubMed PMID: 29166377.
- Jadcherla SR, Prabhakar V, Hasenstab KA, Nawaz S, Das J, Kern M, Balasubramanian G, Shaker R. Defining pharyngeal contractile integral during high-resolution manometry in neonates: a neuromotor marker of pharyngeal vigor. Pediatr Res. 2018 Jul 6. doi: 10.1038/s41390-018-0097-6. [Epub ahead of print] PMID: 29976974
- Levy DS, Osborn E, Hasenstab KA, Nawaz S, Jadcherla SR. The Effect of Additives for Reflux or Dysphagia Management on Osmolality in Ready-to-Feed Preterm Formula: Practice Implications. JPEN J Parenter Enteral Nutr. 2018 Jul 10. doi: 10.1002/jpen.1418. [Epub ahead of print] PMID: 29992586

4.0 Study Endpoints

4.1 The study endpoint will be independent oral feeding without symptoms requiring intervention by 4 weeks or sooner.

4.2 The study will be ended with any safety concerns for the subject

5.0 Study Intervention/Investigational Agent

5.1 The intervention will be the addition of either concurrent or sequential high resolution esophageal manometry with the VFSS as well as a follow up esophageal manometry as needed. This is an accepted diagnostic tool used in infants with feeding difficulties.

6.0 Procedures Involved*

6.1 Study Design

- Study design and setting: Eligible subjects (study) will undergo diagnostic VFSS in combination with manometry, either concurrent or sequential. They will have parental choice of preferred feeding therapy. The data is from single center prospective observational study. The controls are those who had VFSS alone with provider recommendations from the same single center.
- Patient population and characteristics: (i) Study and control infants have oral feeding difficulties with symptoms requiring interventions/monitoring. (ii) They have diagnostic need for VFSS due to aerodigestive and feeding difficulties. (iii) Study subjects must have a signed informed consent from parent/legal guardian prior to manometry study. Control subjects did not require consent as they were historical controls.
- Inclusion criteria: Infants with feeding-related aerodigestive symptoms who are $\leq$ 60 wks PMA (both pre-term and full-term) who are orally feeding $\geq$ 25% of at least 50% of their feeds who are on full enteral feeds with no more than 1LPM NC respiratory support. All infants will have a diagnostic VFSS scheduled.
- Exclusion criteria: Genetic or metabolic syndromes, grade III or greater, moderate to severe HIE, craniofacial, airway or foregut malformations or ENT or neuro surgeries. Infants who are exclusively breastfeeding are also excluded.
- Test-1: VFSS with concurrent or sequential pharyngo-esophageal manometry along with standard safety metrics. Esophageal and pharyngeal provocation induced

aerodigestive reflexes will be tested. Oral feeding challenge test is performed during manometry. The same procedures without VFSS will be repeated at Time-2 where feasible and relevant.

- Overall Study Endpoints: Primary endpoint is therapeutic success defined as full oral feeding without symptoms requiring intervention at 4 weeks (for outpatient studies and those still admitted at 4 weeks) or discharge, whichever is earlier. Secondary clinical end points include growth velocity and feeding outcomes at 1 year.
- Methods to overcome Potential Confounders: It is NICU standard to document in EPIC: i) Daily documentation of symptoms, medication use, feeding methods and duration, feeding volume and weight, ii) Weekly documentation of growth velocity (weight, length, head circumference).
- Removal and management of subject(s) from protocol: The investigator and/or the parent(s) have the right to withdraw from study at any time and opt for the standard of care. Parent(s) that withdraw their infants from the study therapy will be encouraged to continue to remain in the study for all follow up evaluations. Those who choose complete withdrawal from the study will be encouraged to follow the standard of care; wherein, response failures are followed until 1st birthday in the multidisciplinary developmental follow-up clinic.
- Intermediate outcome measures (up to 1 yr age): Acquisition of feeding and GI milestones during first year of life.

6.2 Describe:

- Manometry methods have been used concurrent with video, submental EMG, RIP, ECG, pulse-oximetry and nasal air flow to test basal and adaptive pharyngo-esophageal reflexes and sensory-motor characteristics of motility and to monitor safety. Concurrent synchronized video recordings will be performed to further validate symptoms based on objective definition of the esophageal reflexes. Documentation of symptom markers can be validated by integrating manometry with respiratory inductance plethysmography and video.
- Multimodal esophageal and pharyngeal sensory-motor testing protocols: We have developed and extensively used these protocols to measure sensory-motor characteristics of

reflexes, and these testing protocols will be performed as validated and reported
- The source records that will be used to collect data about subjects will be EPIC records, patient diary logs for symptoms, feeding process, medication compliance, physician visits and clinical data.

6.3 **Data to be collected**
- Patient demographics, feeding and growth outcomes, length of hospital stay and comorbidities will be collected from parents and from medical records. Basal manometry data will be collected to assess the mechanisms of normal or abnormal swallowing. Multimodal sensory motor testing involves mid-esophageal provocation with graded infusions (0.1 to 5 ml) of air (to stimulate mechanoreceptors), apple juice (pH 3.7, to stimulate acid-sensitive receptors), and sterile water (pH 7.0, as control stimulus), and examine the changes in sensory-motor characteristics of aerodigestive reflexes. Basal and adaptive pharyngeal reflexes with air and water infusions are measured.

6.4 Long term follow-up will include feeding method, growth characteristics and development up to 1 year of age.

7.0 Sharing of Results with Subjects*

7.1 Manometry results are shared with the parents at the time of the study. Parents decide on their preferred feeding approach (flow change, thickener change, no change) and if the patient is inpatient, this is shared with the medical team.

8.0 Study Timelines*

8.1 Describe:

- The individual subject's participation in the study will last $\leq$ 4 weeks. Data will be collected for the first year of life.
- The duration anticipated to enroll all study subjects is between 2/16 until 7/20.
- The estimated date to complete this study (complete primary analyses) is 12/20.

9.0 Inclusion and Exclusion Criteria*

9.1 All infants < 6 months PMA who are scheduled for a VFSS will be screened for the above eligibility criteria.

9.2 All subjects who consent and receive a concurrent or sequential VFSS and esophageal manometry will be included in the analysis.

9.3 Our population will include individuals who are not yet adults (infants)

10.0 Vulnerable Populations*

10.1 This research complies with 45 CFR 46, as it includes only human infants up to 6 months old. As this study involves slightly greater than minimal risk, as regulated in 45 CFR 46 Subpart D, all subjects for this study will have consent of at least one parent.

- The Neonatal and Infant Feeding Disorders (NIFD) Program is directed by the PI, Dr. Sudarshan Jadcherla who is a Neonatologist with Pediatric GI experience and is a recognized GI motility expert. The NIFD program is a nationally recognized clinical program supported by the NIH and is well equipped to conduct clinical studies such as proposed in this application. In addition, there is a team of dedicated trained nurse coordinators who are competent and comfortable with performing these procedures on preterm infants as well as a neonatal nurse practitioner. The team also includes trained technical personnel affiliated to this program who perform these studies on a regular basis for diagnostic purposes in this same population.

11.0 Local Number of Subjects

11.1 60 subjects

12.0 Recruitment Methods

12.1 Parents of infants scheduled for a VFSS who meet the eligibility requirements will be approached

12.2 Subjects will be recruited from the VFSS schedule at NCH.

12.3 RN Coordinators will identify and screen potential subjects.

12.4 There will be a $20 payment for each study completed.

13.0 Withdrawal of Subjects*

13.1 Patients will be withdrawn if there are any safety concerns with continuing.

13.2 . If a parent decides to withdraw their infant, follow up data will continue to be collected.

14.0 Risks to Subjects*

14.1 This study includes the risk associated with the nasal placement of the manometry probe and the infusion catheter. These risks are similar to the risks associated with the placement of a nasogastric feeding tube in infants which is frequently done for tube feeding infants both in the hospital and sometimes at home.

15.0 Potential Benefits to Subjects*

15.1 The addition of the esophageal manometry to the VFSS will provide added information as to the etiology of the infants feeding problem. This can be used to improve treatment options and possibly improve outcomes.

16.0 Data Management* and Confidentiality

16.1 Data Analysis Plan

- Descriptive statistics will be reported as median (IQR), mean ± SD or total number and percentage for demographics and clinical characteristics. For PPG vs FOD historical control comparisons, two-sample t-test or ANOVA will be used for the continuous variables and chi-squared or Fischer's exact tests will be used for the categorical variables, whichever is appropriate. Non-parametric method (e.g. Wilcoxon) might be used if the data is not normally distributed. Normality will be assessed using Shapiro-Wilks test and visually inspection of the data. For other Normal vs Abnormal VFSS and the effect of parent preferred therapy -flow modification or thickener use) comparisons, due to the nature of the repeated measure of the data, repeated measure ANOVA for continues measured variables and Generalized estimating equation (GEE) for categorical variables, to predict the likelihood of the specific response, will be used as to make the between group comparisons. Compound symmetry (CS) will be specified for the covariance structure of the repeated data. Bonferroni correction will be used to conserve the overall type I error at □=0.05. To characterize the association between the disease comorbidities and feeding success, simple and multiple logistic regression analysis will be performed. Statistical Analysis Software, version 9.4 (SAS Institute Inc., Cary, NC, USA)

16.2 Data will be stored in RedCap and each subject will have a file which is kept in a secured locked location.

16.3 Data will be verified by at least two individuals on the study team

17.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

17.1 *Describe:*

- The study is overseen by an IRB at NCH where safety is reviewed on a quarterly basis for the enrolled subjects

18.0 Provisions to Protect the Privacy Interests of Subjects

18.1 Parents will have the choice of whether to participate and share information about their child.

18.2 The research team will access electronic records for follow up data.

19.0 Compensation for Research-Related Injury

19.1 Research related injury will not be compensated

19.2 Language from Consent:

- If your child is hurt by the procedures that are part of the Study, they will be monitored and treated as needed by the study team which includes a physician and a nurse. If there is concern for injury after the procedure, you should seek medical treatment for the injuries and call the study team as soon as possible at the number on page1 of this form. If it is an emergency, call 911 or go to the nearest emergency department. In most cases, this care will be billed to your health insurance company or whoever usually pays for your health care at the usual charges, but some insurance companies will not pay for care related to a study. If the care is provided at Nationwide Children's Hospital, we make no commitment to pay for the medical care provided to you. No funds have been set aside to compensate you in the event of injury. If no one else pays for your care, you may have to pay for the cost of this care. This does not mean that you give up any of your legal rights to seek compensation for your injuries.

20.0 Economic Burden to Subjects

20.1 None

21.0 Consent Process

21.1 Consent

- Consent will take place in person with one parent (risk level 2) prior to the study taking place.
- We will be following "SOP: Informed Consent Process for Research (HRP-090)."

Non-English Speaking Subjects – if known, skip if not known

- If subjects do not speak English are enrolled, the consent form will be translated in person by an interpreter speaking the language of the parent.

Subjects who are not yet adults (infants, children, teenagers)

- All subjects enrolled in this study will be infants.
- Parental permission will be obtained from one parent only as this study is level 2 risk.
- Consent will not be obtained from individuals other than parents.

22.0 Process to Document Consent in Writing

22.1 We will be following "SOP: Written Documentation of Consent (HRP-091)."

23.0 Setting

23.1 The research will be conducted at Nationwide Children's Hospital, Columbus, Ohio.

- Subjects will be recruited from the VFSS schedule at NCH.
- Research procedures will be performed at NCH.

We will be monitoring safety through an IRB at NCH.

24.0 Multi-Site Research*

24.1 Dr. Wei is a Research Assistant Professor at the Department of Biostatistics at The Ohio State University College of Medicine and Public Health. She has expertise in clinical statistical modeling techniques. She has worked with the PI with sample size and statistical design for this study. She will provide consultation with analysis and design support. Dr. Wei works with the PI closely with regards to statistical outputs and manuscript writing.

24.2 Data is stored in RedCap where all of the study staff including Dr. Wei can access the data. Subject identifiers include Names, Birth Date, Discharge Date and Medical Record Numbers as identified in the consent form.

25.0 Protected Health Information Recording

Indicate which subject identifiers will be recorded for this research.

☒ Name
☐ Complete Address
☐ Telephone or Fax Number
☐ Social Security Number (do not check if only used for ClinCard)
☒ Dates (treatment dates, birth date, date of death)
☐ Email address, IP address or url
☒ Medical Record Number or other account number
☐ Health Plan Beneficiary Identification Number
☒ Full face photographic images and/or any comparable images (x-rays)
☐ Account Numbers

☐ Certificate/License Numbers
☐ Vehicle Identifiers and Serial Numbers (e.g. VINs, License Plate Numbers)
☐ Device Identifiers and Serial Numbers
☐ Biometric identifiers, including finger and voice prints
☐ Other number, characteristic or code that could be used to identify an individual
☐ None (Complete De-identification Certification Form)

2.0 Check the appropriate category and attach the required form* on the Local Site Documents, #3. Other Documents, page of the application. (Choose one.)

☒ Patient Authorization will be obtained. (Include the appropriate HIPAA language (see Section 14 of consent template) in the consent form OR attach the HRP-900, HIPAA AUTHORIZATION form.)
☐ Protocol meets the criteria for waiver of authorization. (Attach the HRP-901, WAIVER OF HIPAA AUTHORIZATION REQUEST form.)
☐ Protocol is using de-identified information. (Attach the HRP-902, DE-IDENTIFICATION CERTIFICATION form.) (Checked "None" in 1.0 above)
☐ Protocol involves research on decedents. (Attach the HRP-903, RESEARCH ON DECEDENTS REQUEST form.)
☐ Protocol is using a limited data set and data use agreement. (Contact the Office of Technology Commercialization to initiate a Limited Data Use Agreement.

***Find the HIPAA forms in the IRB Website Library, Templates.**

Attach the appropriate HIPAA form on the "Local Site Documents, #3. Other Documents", page of the application.

3.0 How long will identifying information on each participant be maintained?

4.0 Describe any plans to code identifiable information collected about each participant.

5.0 Check each box that describes steps that will be taken to safeguard the confidentiality of information collected for this research:

X Research records will be stored in a locked cabinet in a secure location
X Research records will be stored in a password-protected computer file
The list linking the assigned code number to the individual subject will be maintained separately from the other research data
X Only certified research personnel will be given access to identifiable subject information

6.0 Describe the provisions included in the protocol to protect the privacy interests of subjects, where "privacy interests" refer to the interest of individuals in being left alone, limiting access to them, and limiting access to

their information. (This is not the same provision to maintain the confidentiality of data.)

Confidential Health Information

1.0 Please mark all categories that reflect the nature of health information to be accessed and used as part of this research.

- ☒ Demographics (age, gender, educational level)
- ☒ Diagnosis
- ☒ Laboratory reports
- ☒ Radiology reports
- ☒ Discharge summaries
- ☒ Procedures/Treatments received
- ☒ Dates related to course of treatment (admission, surgery, discharge)
- ☐ Billing information
- ☐ Names of drugs and/or devices used as part of treatment
- ☐ Location of treatment
- ☐ Name of treatment provider
- ☐ Surgical reports
- ☒ Other information related to course of treatment
- ☐ None

2.0 Please discuss why it is necessary to access and review the health information noted in your response above.

2.1 We will be looking at outcome variables for the first year of life

3.0 Is the health information to be accessed and reviewed the minimal necessary to achieve the goals of this research? ☒ Yes ☐ No

4.0 Will it be necessary to record information of a sensitive nature? ☐ Yes ☒ No

5.0 Do you plan to obtain a federally-issued Certificate of Confidentiality as a means of protecting the confidentiality of the information collected? ☐ Yes ☒ No