

## Cover Page

We are submitting the protocol and statistical methods for the below study:

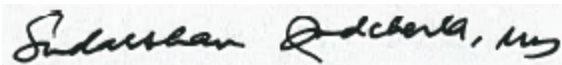
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Brief Title:  
Neonatal Gastro-Esophageal Reflux Disease (GERD) Management Trial (GMT)

This includes the manuscript published in Pediatric Research with a copy of the IRB protocol included.

The date of the most recent IRB protocol with all revisions listed is 6/6/2019.

Sincerely,



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**TITLE: Role of Feeding Strategy Bundle with Acid-Suppressive Therapy in Infants with Esophageal Acid Reflux Exposure: A Randomized Controlled Trial**

**RUNNING TITLE:** Infant GERD Management and Therapy Trial

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**AUTHOR CONTRIBUTIONS:** Dr. Sudarshan R. Jadcherla obtained funding, conceptualized and designed the study, performed procedures and data acquisition, supervised data analysis, interpreted data, drafted the initial manuscript, and reviewed and revised the manuscript. Ms. Kathryn A. Hasenstab performed data acquisition, analysis, and interpretation of data, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. Lai Wei designed the study, performed statistical analysis, interpreted data, and reviewed and revised the manuscript. Ms. Erika K. Osborn performed data acquisition, analysis, and interpretation of data, and reviewed and revised the manuscript. Drs. Sreekanth Viswanathan and Ish K. Gulati performed procedures and data acquisition, interpretation of data, and reviewed and revised the manuscript. Drs. Jonathan L. Slaughter and Carlo Di Lorenzo provided additional intellectual input, interpreted data, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## KEY POINTS

- Conservative feeding therapies are thought to modify GERD symptoms and its consequences. However, in this randomized controlled trial in convalescing neonatal ICU infants with GERD symptoms, when controlling for preterm or full-term birth and severity of esophageal acid reflux index, the effectiveness of acid suppression plus a feeding modification bundle (volume restriction, intra- and post- prandial body positions, and prolonged feeding periods) vs. acid suppression alone, administered over a 4-week period was not superior in improving symptom scores or feeding outcomes.
- Restrictive feeding strategies are of no impact in modifying GERD symptoms or clinically meaningful outcomes. Further studies are needed to define true GERD and to identify effective therapies in modifying pathophysiology and outcomes.
- The improvement in symptoms and feeding outcomes over time irrespective of feeding modifications may suggest a maturational effect. This study justifies the use of placebo controlled randomized clinical trial among NICU infants with objectively defined GERD.

## **ABSTRACT**

**OBJECTIVE:** To test the hypothesis that a feeding-bundle concurrent with acid-suppression is superior to acid-suppression alone in improving gastroesophageal reflux disease (GERD) attributed-symptom scores and feeding outcomes in neonatal ICU infants.

**METHODS:** Infants (N=76) between 34-60 weeks' postmenstrual age with acid reflux index >3% were randomly allocated to study (acid suppressive therapy + feeding bundle) or conventional (acid suppressive therapy only) arms for 4 weeks. Feeding bundle included: total fluid volume <140 ml/kg/day, fed over 30 min in right lateral position, and supine postprandial position. Primary outcome was independent oral feeding and/or  $\geq 6$ -point decrease in symptom score (I-GERQ-R). Secondary outcomes included growth (weight, length, head circumference), length of hospital stay (LOHS, days), airway (oxygen at discharge), and developmental (Bayley scores) milestones.

**RESULTS:** Of 688 screened: 76 infants were randomized and used for the primary outcome as intent-to-treat, and secondary outcomes analyzed for 72 infants (N=35 conventional, N=37 study). For study vs conventional groups, respectively: a) 33%(95% CI, 19%-49%) vs 44%(95% CI, 28%-62%),  $p=0.28$  achieved primary outcome success, and b) secondary outcomes did not significantly differ ( $p>0.05$ ).

**CONCLUSIONS:** Feeding strategy modifications concurrent with acid suppression are not superior to PPI alone in improving GERD symptoms or discharge feeding, short-term and long-term outcomes.

## **INTRODUCTION**

Differentiating gastroesophageal reflux (physiological, GER) from GER disease (pathological, GERD) remains a challenge in ICU infants (1-5). Troublesome symptoms (6) often trigger a battery of empiric therapies, such as acid-suppression, feeding modifications, and positional changes (7-10). Prevalence of GERD ranges from 2–30% across neonatal intensive care unit(NICU)s in the United States, along with a 13-fold variation in therapies, imposing an additional economic burden of over \$70K per admission and 30 hospital days (9-13).

The infant GER questionnaire-revised (I-GERQ-R) is a survey of parental/provider perception of symptom burden thought to be due to GERD, with a 6 point decrease indicating clinical improvement (14). Although, prior clinical trials for GERD pharmacotherapy have used symptom-based criteria (15-18), few have evaluated the effectiveness of a bundled holistic approach, i.e., a combination of pharmacologic-, feeding-, and positional approaches in NICU patients. Improvement of parental perception of symptoms and total GER events with left lateral position and proton pump inhibitor (PPI) (8), reduction of GER events with infants in prone or left lateral post-prandially (19), and conservative strategies for 2 weeks showed improvement with I-GERQ-R scores among one to ten months age (20). We observed that decreased feeding volume and prolonged feeding duration were associated with reduced GER events (21). However, a bundled approach combining targeted acid suppression (limited duration), feeding modifications (volume, position, duration) and postprandial positions has not been rigorously examined in infants with proven esophageal acid reflux index (ARI) severity.

Based on this *rationale*, we have undertaken this clinical trial to determine the effective therapeutic strategies on the clinically meaningful primary outcomes in infants presenting with GERD symptoms who have qualifying ARI criteria. The *objective* of this RCT was to examine the

short- and long-term clinical outcomes among infants treated concurrently over 4 weeks with PPI with randomly assigned feeding strategy modifications while controlling for gestational maturity (pre-term or full-term at birth) and severity of esophageal ARI (3-7%, >7%). Our *hypothesis* was that the study approach (acid suppression, modified feeding volume, duration, and position) was superior in achieving independent oral feeding or a 6-point reduction in I-GERQ-R vs the conventional (acid suppression alone) feeding approach.

## **PATIENTS AND METHODS**

### **STUDY DESIGN AND EXPERIMENTAL PROTOCOL**

This is a single center, single blinded RCT (Clinicaltrials.gov: [NCT02486263](https://clinicaltrials.gov/ct2/show/study/NCT02486263)) comparing the effectiveness of two feeding strategies combined with the use of a PPI (omeprazole) to manage acid-GERD [GERD Management and Therapy trial (GMT trial)]. This study was approved by the Institutional Research Board (IRB) at Nationwide Children's Hospital, Columbus, OH (IRB # 11-00734). Omeprazole is commonly used off-label in this population within the standard of care (9). Data safety monitoring plan was implemented and monitored quarterly by the Data Safety Monitoring Board (DSMB). Written, signed, and informed parental consent was obtained. Health Insurance Portability & Accountability was followed. Study PI and RN coordinator were available 24/7.

Twenty-four-hour pH-impedance studies were performed (6, 22, 23) (Laborie Medical Technologies, Mississauga, ON, Canada). ARI (duration of esophageal acid exposure, %) was calculated (24). I-GERQ-R symptom score (14, 17, 25) was collected. Demographic and clinical outcomes were managed using research electronic data capture tools (REDCap) tools (26) for up to 2 years from subject enrollment.

### **PARTICIPANT SELECTION, RANDOMIZATION AND ALLOCATION**

Inclusion criteria were: a) infants admitted with clinical symptoms of GERD between 34-60 weeks postmenstrual age, with physician's intent to treat with acid-suppressive therapy, b) an intake volume of full enteral feeds  $\geq 150$  mL/kg/day, c) room air or supplemental oxygen  $\leq 1$  liter per minute, and d) ARI  $\geq 3\%$  (6, 22-24). Exclusion criteria were: a) infants with known genetic, metabolic or syndromic diseases; b) neurological diseases including  $\geq$  grade III intraventricular hemorrhage or perinatal asphyxia, c) GI malformations or surgical GI conditions, and d) infants on acid suppressive medication at initial evaluation. Randomization was performed among consented subjects who were stratified 1:1 ratio by ARI severity (3%-7%: indeterminate acid reflux and  $>7\%$ : severe acid reflux) and by birth gestation (preterm, full term) into study feeding approach or conventional approach. Permuted Block Randomization with block sizes of 2, 4, 6, and 8 was undertaken by the study statistician (OSU Center for Biostatistics) using a computer-generated allocation and implemented in REDCap. Nurse coordinator enrolled subjects by verifying eligibility, obtaining parental consent, and entering demographic data into REDCap. PI and study staff who evaluated subject clinical outcomes were blinded to study allocation.

## **STUDY INTERVENTIONS**

### **Interventions**

Providers employ uniform feeding and nutritional practices in our NICU infants as per our standardized guidelines, which applies to nutrient and volume modifications. However, upon randomization and allocation, individual protocols are complied with. Upon completion of screening, enrollment and randomization, the assigned feeding management strategy was relayed to parents and the medical team. Subjects in both arms received omeprazole off label, as a therapeutic choice (27, 28) at a recommended dose of 0.75 mg/kg/dose BID (15, 27, 29). The conventional approach was to not adjust provider recommended feeding strategies (i.e. fed in any



position, duration, volume, and postprandial position). The study approach utilized a modified feeding strategy including: a) feeding in the right lateral position to facilitate intra-prandial gastric emptying (30), b) feeding duration of at least 30 min utilizing pacing when orally fed to ensure completion of prescribed volumes or via pump to ensure steady delivery of milk if gavage-fed (21), c) supine postprandial position (31), and d) limiting total feeding volume to  $\leq 140$  ml/kg/day (21).

## OUTCOME MEASURES

The *a priori primary end-point* was achieving independent oral feeds and/or a six-point decrease in I-GERQ-R score at 5 weeks or sooner, whichever was earliest at discharge. *To clarify further, there were 2 scenarios:* 1) Among infants who were transitioning to oral feeds (gavage fed) at inception: success was defined as achieving full oral feeds or a  $\geq 6$ -point decrease from baseline I-GERQ-R. 2) Among infants who were on full oral feeds at inception, success was determined if full oral feeds were maintained plus a  $\geq 6$ -points decrease from baseline I-GERQ-R. *Secondary end-points* included growth metrics (weight, length and head circumference), supplemental oxygen, economic metrics (LOHS), long-term feeding outcomes at 6 months and 1 year, and developmental outcomes at 2 years (32, 33).

## STUDY OVERSIGHT

Compliance to protocol and Data Integrity were maintained. Patient care data were stored and secured. Study recruitment criteria were reported to DSMB quarterly and IRB annually. Compliance measurements were documented as intake volumes, feeding durations, feeding positions, postprandial positions and symptom scores, growth metrics and nutritional status. Compliance to administration of omeprazole was confirmed using electronic medical records

(Epic, Epic Systems Corporation, Verona, WI, USA) and or parental validation. Trial protocol and important changes to methods after trial commencement are listed in **Supplement 1**.

## **STATISTICAL METHODS**

Based on our preliminary data, we had planned to enroll 100 patients (50 per group) to detect 27% or higher increase in proportion of success of study group compared to the conventional group with 80% power and overall one-sided  $\alpha$  level of 0.025. One interim futility analysis was planned at about 50% information prior to the final analysis at 100% information, corresponding to 50 and 100 evaluable patients, respectively. The boundary was determined using Lan-DeMets spending functions to simulate O'Brien-Fleming boundaries(34). Using the target proportion of success, the boundary at the futility analysis was  $p > 0.297$ .

Seventy-six infants were randomly assigned till the end of funding for this study and were included in the analysis of demographics and clinical characteristics (**Fig 1, Table 1**) and primary outcome by intent-to-treat. If a patient dropped out before the end of study and no symptom score was evaluable, we treated the patient as a failure for the primary outcome by intention-to-treat. Secondary outcome analysis was performed for 72 subjects (**Fig 1**). Futility boundary was not reached at interim analysis of 50 patients ( $p = 0.1 < 0.297$ ) and accrual was continued with DSMB approval. Summary statistics were calculated for patient demographics and clinical characteristics for final analysis. Success rate in achieving PO or reduction in the I-GERQ-R by 6-points was calculated with 95% confidence interval and compared using chi-square test between the conventional and study groups (primary outcomes) for the intention-to-treat and treat-as-treated analyses. Fisher's exact or chi-square test were used to compare other categorical secondary outcomes including feeding method and supplemental oxygen between the groups. Shapiro-Wilk test for normality was used for the continuous outcomes. Paired t-tests or Wilcoxon signed-rank

tests were used to assess changes in growth velocity and feeding therapy characteristics between time-1 and time-2. Two sample t-tests or Wilcoxon rank-sum tests were used to compare these continuous outcomes between conventional and study groups. Median (interquartile range [IQR]), mean (SD), or % was reported, unless stated otherwise. *P* values <0.05 were considered statistically significant, and SAS version 9.4 (SAS, Inc, an IBM Company, Chicago, IL) was used.

## **RESULTS**

### ***Participant Characteristics***

Screening, recruitment and follow-up of subjects occurred between August 2012 to October 2018, and data was locked May 2019. Recruitment ended to allow for clinical outcome analysis. *From the 688 infants assessed for eligibility, ARI was: normal (<3%) in 246 (36%), indeterminate (3-7%) in 169 (25%), and abnormal (>7%) in 273 (40%). Study enrollment, randomization, and primary outcome analysis are described in the CONSORT diagram (Fig 1). Demographic and clinical characteristics at allocation were not significantly different in both groups (Table 1).* Frequency (%) of GERD referral reasons were for respiratory concerns (apnea/bradycardia/desaturation, airway management, or suspected aspiration) in 54%, feeding concerns (poor oral feeding or intolerance) in 47%, and GERD type symptoms (arching/irritability or emesis) in 25% (note proportions do not add to 100 due to providers being able to list multiple reasons for referral). Reasons for referral did not differ between conventional and study groups (all *P*>0.05). Proportion of milk types (exclusive breast milk: exclusive formula: combination of formula and breast milk, %) were not different between groups: 19: 67: 14 in conventional vs 18: 53: 3 in study groups (*P*=0.24). Of those formula fed (28 in conventional group, and 29 in study group) proportion of formula types (hydrolyzed: gentle: low lactose: preterm: standard, %) were: 4:7:4:75:10 in conventional vs 10:10:0:69:10 in study groups (*P*=0.84). Caloric density ranged

from 19 cal/oz to 30 cal/oz, and the proportions (%) (19: 20: 22: 24: 27: 30 cal/oz) for conventional (11: 31: 33: 19: 6) and study groups (8: 20: 30: 35: 3) did not differ ( $P = 0.47$ ). Breast milk intake in both groups was 40% at inception ( $P=1.0$ ), and the caloric density (cal/oz) for the conventional vs. study groups was 24 [22-25] and 24 [22-27] respectively ( $P=0.41$ ) For conventional and study groups respectively, acid suppressive dose (mg/kg/dose BID) was 0.75 [0.75 – 0.75] vs 0.75 [0.75 – 0.75],  $p=0.27$  upon initial dose, and 0.75 [0.75 – 1.0] vs 1.0 [0.75 – 1.0],  $p=0.09$  at follow-up.

## **STUDY OUTCOMES**

### **Primary and Secondary Clinical Outcomes**

The clinically meaningful primary and secondary outcomes did not differ significantly between groups (**Table 2**). I-GERQ-R scores for study and conventional groups are shown (**Fig 2**). At inception: positive I-GERQ-R was 19/35 (54%) in the conventional group vs 24/37 (65%) in the study group,  $p=0.36$ . At Time-2: positive I-GERQ-R prevalence was 9/31 (29%) in the conventional group vs 13/34 (38%) in the study group,  $p=0.43$ . In the study group vs conventional group, respectively: a) primary outcome achieved in 33% (95% CI, 19% - 49%) vs 44% (95% CI, 28% - 62%) ( $p=0.28$ ), b) secondary outcomes: independent oral feeding in 65% (95% CI, 48% - 80%) vs 77% (95% CI, 60% - 90%),  $p=0.26$ ,  $\geq 6$ -point I-GERQ-R decrease in 38% (95% CI, 22% - 56%) vs 35% (95% CI, 19% - 55%),  $p=0.82$ , length of stay was 98 [81-132] days vs 108 [83-125] days,  $p=0.89$ , and oxygen requirement at discharge in 19% (95% CI, 8% - 35%) vs 26% (95% CI, 13% - 43%),  $p=0.49$ . There were no significant differences in growth metrics (all  $p>0.05$ ) or developmental scores at 2 years (all  $p>0.05$ ). Feeding outcomes or I-GERQ-R scores did not significantly differ between conventional vs study groups based on feeding method at inception (**Table 3**). Individual I-GERQ-R questions relating to vomiting, regurgitation, and crying (i.e. frequency of emesis, volume of emesis, symptoms with emesis, and crying more than usual in the

past week) had no differences ( $P > 0.05$ ) within the group or between the groups across maturation for these individual symptoms, except for symptoms with emesis (never: rarely: sometimes: often: always, %) was 16:16:42:19:6 for conventional group at Time-1 vs 18:18:29:0:35 for study group at Time-1,  $p < 0.01$ .

### **Compliance measures, side effects and adverse events**

Compliance to randomization, allocation and interventions, and drop outs are reported (**Fig 1, Table 2**). Total fluid volume was identical at inception but both groups showed a reduction compared to baseline at time-2. However, as per the trial design, the study group showed significantly (all  $p < 0.05$ ) lower volume intake, feeding in right side lying position, and postprandial supine position. Feeding duration of actual feeding was increased in the study group but not statistically different from the conventional group. No side effects or adverse events were reported in either group.

## **DISCUSSION**

In this RCT, while controlling for birth gestation and severity of acidity, we compared the effectiveness of acid suppression with or without a systematic feeding modification bundle in modifying feeding outcomes and I-GERQ-R scores. We found no differences in our *a priori* primary outcome or pre-assigned secondary outcomes. Important clinical and research implications can be noted despite the non-superiority of the feeding bundle.

Diagnostic conundrums and management issues with GERD in the NICU setting persist. Prior studies (8, 19, 20) used perceived clinical symptoms as a basis for acid-suppression, but studies have shown lack of benefit on symptom improvement (35, 36). Recent work by us (6, 21, 22), suggests that such symptoms are often due to pharyngo-esophageal provocation or cross-systems activation of reflexes, and can occur during non-acid events or swallowing events, or

during transient relaxation of lower esophageal sphincter (30). However, the inability to handle the refluxate determines the ‘troublesomeness of the symptoms’ rather than the esophageal acid exposure. Clinical practice varies when pathophysiological reasoning is not commonly applied. Clinical practices can have unintended consequences (1, 37-40) resulting from acid suppression, undernutrition, delays with feeding milestones, decisional conflicts, discharge outcomes and prolonged hospitalization, all of which can escalate burden (9, 27).

*Salient features of our study include:* 1) Allocations were unbiased and appropriately distributed between groups. 2) Among those presenting with GERD symptoms at inception, about 36% of infants had normal esophageal acid exposure, while 40% had abnormal acid exposure, and the rest in the indeterminate range. 3) The study bundle was not superior to acid suppression alone in improving primary outcomes or secondary outcomes. 4) Restricted feeding volume, body positions (intra- and post-prandial), oral or gavage feeding methods, supplemental oxygen, birth gestation and postnatal maturation did not influence the primary or secondary outcomes. 5) Reliability of compliance among those discharged was based on parental trust and available information. 6) There were no reported adverse events. No differences in long term developmental outcomes or economic burden measures, such as, LOHS, feeding methods and respiratory support at discharge were noted. 7) Symptom scores (I-GERQ-R) were significantly lower in both groups, suggesting that maturation may play a role in symptom modification, and not the bundled approaches. 8) Feeding outcomes improved in both groups.

*GMT Trial strengths and clinical implications are several:* 1) Random allocation, study design and protocol adherence were robust and rigorous. Although our strict inclusion criteria may have led to lower eligibility, our approach resulted in identifying infants carefully with true ARI as a marker of esophageal acid exposure. Objective determination of GERD based on ARI >7%

is justifiable in future trials, as nearly 40% of infants are in this severe range, and it is possible to study such a group in larger clinical trials based on pH and impedance criteria, while employing placebo for equipoise. Since time-limited PPI therapy concurrent with feeding strategies was neither shown to be beneficial or associated with adverse effects, we believe that, it is safe to include a completely untreated placebo group in future trials that enroll patients with objectively determined acid-GERD. 2) The management strategies were tightly regulated, as were feeding and testing guidelines, and the treatment was uniformly delivered across the two groups. The patient population was homogeneous and constituted a fair representation from the convalescing NICU population. In addition, the randomized controlled allocation accounted for premature or full-term birth, and the indeterminate or determinate acid-GERD per ARI. Furthermore, the prevalence of oxygen requirement or tube feeding at discharge was not different between groups. 3) Our study trial has many elements of objectivity. Determination of I-GERQ-R and ARI, as well as monitoring feeding methods during the trial are strengths. Thirty-six percent of those with aerodigestive and or cardiorespiratory symptoms perceived by their clinicians to be due to GERD prior to trial consent, were not randomized and were also never treated with a PPI as the esophageal acid exposure was normal ( $ARI < 3\%$ ). In a purely symptom-based clinical trial, all those 688 infants screened would have likely been treated for presumed GERD. In the current study, only those that had true ARI exposure have been randomized and treated. Therefore, the symptom-based approach alone is not the solution to diagnose and treat GERD. Interestingly, perception of symptoms (IGERQR scores) decreased across time regardless of treatment group allocations (**Fig 2**). These findings strongly support maturational effect. As both groups were treated with PPI, placebo-included RCTs are needed to determine if maturation alone will improve objectively determined acid- and non-acid-GERD. 4) Absence of pH-impedance testing to confirm true acid-GERD prior

to randomization would have resulted in all patients being treated based on subjective, non-specific symptoms alone. Owing to the strict inclusion and exclusion criteria of this RCT, those with indeterminate and abnormal ARI were treated with a PPI. In the future, a careful RCT that tests the utility of PPI treatment for confirmed acid-GERD by allocating patients to either limited PPI treatment or placebo is indicated to determine whether PPI treatment is needed. The effectiveness of our short-term use of PPI for 4 weeks to improve GERD-attributable symptoms should be tested in future trials. Effect of esophageal acid exposure and therapies on primary mechanistic outcomes of esophageal motility and symptom causation will be addressed in future reports. 5) In routine clinical practice, feeding volumes are modified and alterations in feeding positions are used to manage symptoms. Our study did not show any differences in the outcomes with feeding- and position modifications. Furthermore, volume restriction had no influence on the study outcomes. The improvement in symptoms and feeding outcomes over time irrespective of PPI or feeding modifications may suggest a maturational effect.

It is important to note that major mechanisms of GER, i.e. transient LES relaxation is the major reason for any reflux events- both acid or non-acid substrate. Our therapeutic target was acid reflux index in this study via PPI, feeding volumes, and positional changes. Given that acid GER can also have weakly or non-acid either before or after PPI therapy, and that there were no differences in outcomes between the two groups, we speculate that neither PPI, feeding volume, or positional changes modify the studied indices or symptoms. Maturation under optimal conditions of good nutrition along with placebo-controlled trials are needed to answer the importance of weakly acid or non-acid GER, which would require a multicenter trial with a large group of infants with appropriate physiologic diagnostic testing.



*Our study has limitations.* 1) Parental and physician biases appeared to be a barrier to recruitment. Recruitment was slow despite the high prevalence of GERD-associated symptoms and a high eligibility rate. This is concerning, as many parents refused clinical trial participation. Many infants did not have true acid-GERD, and fluid restriction often occurred before testing. Interestingly, in some cases, parents and providers did not want to stop the PPI use. These barriers to recruitment can be mitigated in future larger trials with better parent-provider education, as no major effects on the primary or secondary outcomes were noted in our study with or without our allocated bundled GERD treatment. 2) Owing to the higher screening to eligibility ratio, rigorous inclusion criteria, and strict study protocols, we could not complete the recruitment as originally planned of 100 evaluable patients. Seventy-six infants were randomly assigned during the funding period. However, using this cumulative sample size of 72 patients for interim monitoring, we found that we would stop for futility at this time point even if the funding period was not ended. 3) Further studies are needed to correlate parental/provider perception of symptoms (I-GERQ-R) with true symptoms and symptom indices examined during pH-impedance testing. Such studies should also address the severity of acid exposure index in relation to changes in symptom indices.

## **CONCLUSION**

We addressed the current practice controversies in this clinical trial: 1) Screening and identifying acid-GERD objectively is possible in symptomatic infants prior to any pharmacotherapy. 2) Feeding strategy modification (fluid restriction, positional changes, prolonged feeding duration) has no role in decreasing reflux-type symptoms or in improving the primary outcome of achieving independent oral feeds and/or a six-point decrease in I-GERQ-R score. 3) No difference in the prevalence of chronic lung disease was noted between the groups. 4) I-GERQ-R scores decreased across time regardless of treatment group allocations that strongly

support maturational effect. However, we did not detect an effect on *a priori* short-term or long-term outcomes following randomized allocations. As restrictive feeding strategies do not make a difference, placebo-controlled clinical trials in a larger cohort of convalescing NICU infants with objectively determined newer GERD criteria must be addressed in future trials.

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Table 1. Baseline Demographic and Clinical Characteristics of Enrolled Participants

Variable	Overall Subjects (N = 76)	Conventional Group (N = 36)	Study Group (N = 40)
<b>At Birth</b>			
Gender, Female – n (%)	37 (49)	18 (50)	19 (48)
Race – n (%)			
African American	11 (15)	3 (8)	8 (20)
Asian	1 (1)	0 (0)	1 (3)
Other	6 (8)	2 (6)	4 (10)
Unknown	1 (1)	1 (3)	0 (0)
White	57 (75)	30 (83)	27 (68)
Ethnicity – n (%)			
Hispanic or Latino	2 (3)	2 (6)	0 (0)
Non Hispanic or Latino	71 (93)	32 (89)	39 (98)
Unknown	3 (4)	2 (6)	1 (3)
Gestational Age (GA) – wks	29.3 [27 - 32.9]	29.3 [28 - 32.2]	29.2 [27 - 33.1]
Preterm birth – n (%)	68 (90)	34 (94)	34 (85)
Birth Weight – kg	1.23 [0.9 - 1.9]	1.2 [0.9 - 1.9]	1.3 [0.9 - 2.1]
Size for Gestational Age – n (%)			
Small (< 10th %)	9 (12)	5 (14)	4 (10)
Average (10th - 90th %)	58 (76)	26 (72)	32 (80)
Large (> 90th %)	9 (12)	5 (14)	4 (10)
Cesarean Delivery – n (%)	50 (66)	22 (61)	28 (70)
<b>At Inception</b>			
Postmenstrual age – wks	41.1 (2.5)	41.3 (2.2)	40.9 (2.7)
Chronologic age – wks	10.9 (4.3)	11.1 (4.5)	10.7 (4.3)
Weight – kg	3.5 (0.8)	3.5 (0.8)	3.5 (0.8)
O2 Requirement at 36 wks PMA – n (%)	36 (47)	17 (47)	19 (48)
O2 Requirement at 28 days age – n (%)	46 (61)	21 (58)	25 (63)
Feeding Method – n (%)			
Gavage	2 (3)	0 (0)	2 (5)
Transitional	37 (49)	18 (50)	19 (48)
Oral	37 (49)	18 (50)	19 (48)
Nasal Cannula Oxygen – n (%)	23 (30)	11 (31)	12 (30)
Total Intake Volume – mL/kg/day	150 [149 - 154]	150 [148 - 152]	150 [150 - 157]
Total Oral Intake Volume – mL/kg/day	112 [45 - 150]	112 [57 - 150]	112 [22 - 148]
Acid Reflux Index (ARI) – %	9.3 [6.0 - 17.1]	10 [6.0 - 16.7]	9.1 [5.0 - 17.8]
ARI Category – n (%)			
Indeterminate (ARI 3 - 7%)	26 (34)	12 (33)	14 (35)
Abnormal (ARI > 7%)	50 (66)	24 (67)	26 (65)

Data presented as n (%), Median [IQR], or Mean (SD).

**Table 2. Primary and Secondary Clinical Outcomes and Compliance Measures**

Primary Outcome (intent-to-treat analysis)	Overall (N = 76)	Conventional (N = 36)	Study (N = 40)	P-value
<i>A priori</i> clinical outcome Success, n (%)	29 (38)	16 (44)	13 (33)	0.28
Secondary Outcomes	Overall (N = 72)	Conventional (N = 35)	Study (N = 37)	P-value
I-GERQ-R decrease by 6 – n (%)	24/65 (37)	11/31 (35)	13/34 (38)	0.82
Feeding Outcome at Time 2 – n (%)				0.26
PO	51 (71)	27 (77)	24 (65)	
Transition (PO + Tube)	18 (25)	8 (23)	10 (27)	
Tube	3 (4)	0 (0)	3 (8)	
Length of hospital stay – days	108 [82 - 129]	108 [83 - 125]	98 [81 - 132]	0.89
Hospital stay Inception to Discharge – days	25 [11 - 45]	23 [3 - 39]	27 [16 - 47]	0.26
Weight Growth Velocity (GV) – g/day	27.1 (9.4)	26.5 (7.2)	27.6 (11.1)	0.64
Length GV – cm/day*	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.88
Head Circumference GV – cm/day*	0.1 [0.0 - 0.1]	0.1 [0.0 - 0.1]	0.1 [0.0 - 0.1]	0.87
Feeding Method at Discharge – n (%)				0.32
PO	54 (75)	29 (83)	25 (68)	
Transition (PO + Tube)	14 (19)	5 (14)	9 (24)	
Tube	4 (6)	1 (3)	3 (8)	
Oxygen Requirement at discharge – n (%)	16 (22)	9 (26)	7 (19)	0.49
<b>Compliance to Feeding Methods</b>				
<b>Total Fluid Volume (TFV)</b>				
TFV at Inception- #	N/A	150 [147, 152]	150 [149, 156]	0.8
TFV at Time 2- #	N/A	143 [134, 148]*	133 [126, 137]*	<0.001
# days TFV ≤ 140 / kg / day	N/A	10 [2, 26]	22 [11, 31]	0.005
TFV compliance (TFV <140/kg/d for >75% of time)	N/A	9 (26)	27 (73)	<0.001
<b>Position</b>				
Feeding Position, RSL, %	N/A	5 [1, 17]	78 [12, 94]	<0.001
Feeding in RSL >75% of the time, %	N/A	0 (0)	21 (57)	<0.001
Supine Position Post-Prandial, %	N/A	50 [40, 66]	87 [74, 96]	<0.001
Supine Position Post-prandial >75% of the time, %	N/A	7/34 (21)	27/36 (75)	<0.001
<b>Feeding Duration</b>				
% time feed duration >30 min, %	N/A	4 [0, 37]	15 [0, 69]	0.15
Feeding Duration at Inception, min	N/A	23 [17, 41]	30 [19, 34]	0.64
Feeding Duration at Time 2, min	N/A	23 [19, 28]	26 [20, 30]	0.15
<b>Long-term Follow-up†</b>				
Feeding Method at 6 months – n (%)				0.65
PO	36/50 (72)	21/27 (78)	15/23 (65)	
Transition (PO + Tube)	10/50 (20)	4/27 (15)	6/23 (26)	
Tube	4/50 (8)	2/27 (7)	2/23 (9)	
Feeding Method at 1 year – n (%)				0.11
PO	37/44 (84)	20/22 (91)	17/22 (77)	
Transition (PO + Tube)	4/44 (9)	0/22 (0)	4/22 (18)	
Tube	3/44 (7)	2/22 (9)	1/22 (5)	
<b>CCA BSID-III</b>				
Cognitive Score <80 – n (%)	9/44 (21)	5/23 (22)	4/21 (19)	1.00
Cognitive Score – #	95 [90 - 105]	100 [90 - 105]	90 [90 - 100]	0.11
Receptive Communication <80 – n (%)	14/42 (33)	8/23 (35)	6/19 (32)	0.83
Receptive Communication Score – #	90 [77 - 103]	91 [74 - 103]	89 [77 - 103]	0.75
Expressive Communication <80 – n (%)	11/25 (44)	7/14 (50)	4/11 (36)	0.69
Expressive Communication Score – #	86 [71 - 100]	81 [71 - 94]	89 [71 - 103]	0.66
Fine Motor <80 – n (%)	11/41 (27)	5/23 (22)	6/18 (33)	0.49
Fine Motor Score – #	94 [79 - 103]	97 [82 - 110]	88 [70 - 97]	0.13

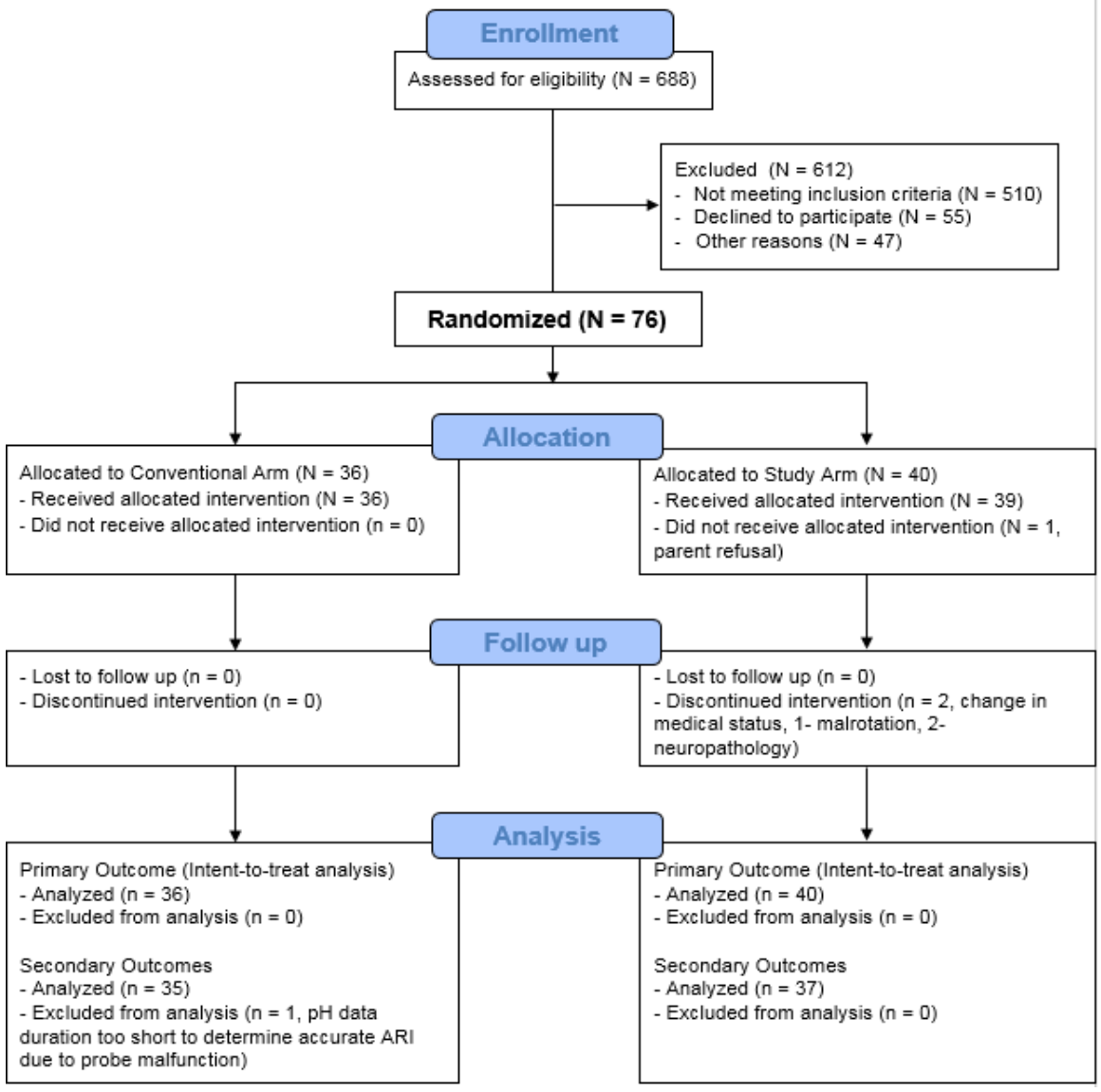
Data presented as n (%), Median [IQR], or Mean (SD). \*1 value missing from both conventional and study groups. †Data was not available for all subjects for long-term follow up outcomes, n values are reported.

**Table 3. Feeding and I-GERQ-R Outcomes by Feeding Method at Inception**

Outcome	Conventional	Study	P-value
<i>Among those Tube fed at Inception</i>	<b>N = 18</b>	<b>N = 20</b>	
Achieved exclusive oral feeding	11 (61)	7 (35)	0.11
Achieved I-GERQ-R decrease $\geq 6$	7/17 (41)	8 (40)	0.94
Achieved PO or I-GERQ-R decrease $\geq 6$	14 (78)	13 (65)	0.39
Achieved exclusive oral feeding + I-GERQ-R decrease $\geq 6$	4/17 (24)	2 (10)	0.38
<i>Among those PO fed at Inception</i>	<b>N = 17</b>	<b>N = 17</b>	
Maintained PO	16 (94)	17 (100)	1.0
Achieved I-GERQ-R decrease $\geq 6$	4/14 (29)	5/14 (36)	1.0
Maintained PO or I-GERQ-R decrease $\geq 6$	16 (94)	17 (100)	1.0
Maintained PO + I-GERQ-R decrease $\geq 6$	4/14 (29)	5/14 (36)	1.0

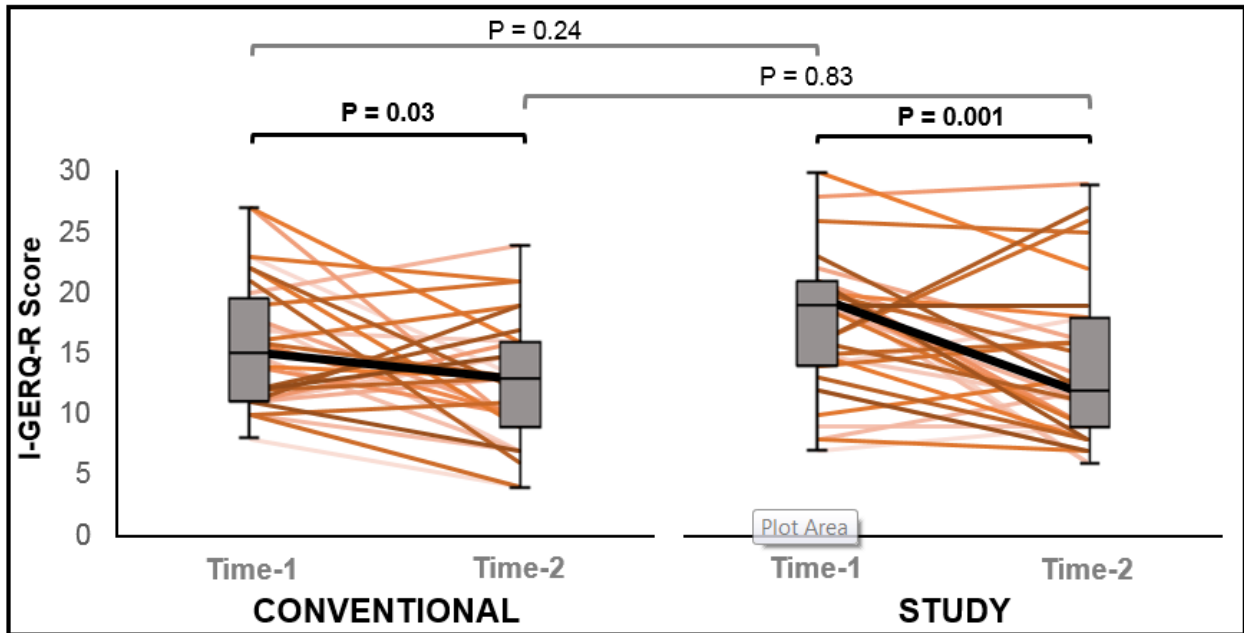
Data presented as n (%).

**FIGURE 1.**



**Figure 1. Study Enrollment and Randomization.** Depicted is the CONSORT diagram describing participant flow and randomization into the conventional or study bundles, and subjects analyzed for outcomes.

**FIGURE 2**



**Figure 2. I-GERQ-R Outcomes.** Depicted is a combination plot by group (boxplots) and individual I-GERQ-R scores (black line represents median). Note that parent perception scores (I-GERQ-R) significantly decreased in both groups at Time-2.

**PROTOCOL TITLE:**

Pathophysiology of the Aerodigestive Reflex in Infants: GERD Management and Therapy Trial  
[GMT Trial]

**PRINCIPAL INVESTIGATOR:**

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**VERSION NUMBER/DATE:**

Version 9.0 6/6/2019

**Nationwide Children's Hospital IRB REVISION HISTORY**

Revision #	Version Date	Summary of Changes	Consent Change?
1	11/30/2012	Because NICU infants have lower fluid prescriptions in general, revised allowable total fluid volume from $\geq 170$ ml/kg/day to $\geq 150$ ml/kg/day at inception to be eligible for screening	No
2	2/15/2013	Because convalescing NICU infants with lung disease can have varying supplemental oxygen requirements, revised allowable respiratory support from Room air or $\leq 0.3$ LPM via nasal cannula to $\leq 1.0$ LPM or Room air at inception to be eligible for screening	No
3	12/9/2013	Because parents and providers did not permit stopping the PPI at 4 weeks for clinical reasons, allowed the subject to remain on medication at the follow up evaluation	No
4	3/24/2014	Allowed Practitioners to increase permissible study medication dose as clinically indicated	No
5	7/29/14	Added the use of swallowing motility measurements to the mechanistic study protocol	Yes
6	9/19/2014	Convalescing subjects with Neonatal Abstinence syndrome admitted to NICU have feeding difficulties masquerading as GERD symptoms.	No

		Changed inclusion criteria to permit these infants to be screened for eligibility into the study	
7	5/1/2015	To examine sucking, swallowing and motility measures, sucking-swallowing rhythms were measured for the mechanistic study protocol	Yes
8	1/12/2018	Added reciprocity with The Ohio State University and included biostatistician, Wei Lai into the study staff	yes

## 1.0 Study Summary

<b>Study Title</b>	Pathophysiology of Aerodigestive Reflex in Infants: GERD Management Trial
<b>Study Design</b>	Single center randomized control trial
<b>Primary Objective</b>	To compare two feeding approaches and their effect on clinical outcomes in infants with proven Gastroesophageal Reflux Disease (GERD)
<b>Secondary Objective(s)</b>	To determine the pathophysiological mechanism of success or failure to either therapy, we will test the hypothesis and validate results from the preliminary data by utilizing our diagnostic tools to identify differences between the two study arms in regards to: aerodigestive reflexes, esophageal clearance mechanisms, neuromotor markers of swallowing, and pH-Impedance-symptom indices.
<b>Research Intervention(s)/ Investigational Agent(s)</b>	Both groups will have esophageal manometry studies followed by randomization into two groups, Conventional and Study. The <b>conventional group</b> allows for unrestricted feeding volumes with no time limit, feeds given in any position and random post prandial feeding positions. <b>The study group</b> will have permissive feeding volume restrictions, feeding duration of at least 30 minutes, feeding given in right side lying, and supine post prandial position. Both groups will be treated with omeprazole per NCH NICU guidelines

<b>IND/IDE #</b>	N/A
<b>Study Population</b>	Infants admitted to the NICU at NCH and referred to the Neonatal and Infant Feeding Disorders program for evaluation of Gastroesophageal reflux Disease (GERD)
<b>Sample Size</b>	120
<b>Study Duration for individual participants</b>	5 weeks
<b>Study Specific Abbreviations/ Definitions</b>	GMT (GERD Management and Therapy Trial) RSL- right side lying ARI –Acid reflux index PMA= (Gestational age at birth + chronologic age)

## 2.0 Objectives

### 2.1 Purpose, specific aims or objectives

- Clinical trial based on objective evaluation of symptoms scored by blinded independent rater during pH-Impedance studies (Aim 1).
- Investigates the neuro-physiological aspects of the reflexes involved with GERD and its complications (Aim 2).
- Unique to this proposal, we will apply physiologically rational, and safe, therapeutic strategies that have the real potential to ameliorate GERD symptoms/complications. If the proposed aims are achieved, we anticipate:
  - Finding that not only acid, but also feeding volume, position and maturational changes in adaptation underlie the pathogenesis of GERD, and in this way clearly identifying relevant new therapeutic targets for this disease.
  - Understanding the various stimulus-targets and provoked reflexes that lead to sensitization of afferents, and thereby symptoms associated with GERD.
  - Understanding the mechanism(s) underlying functional esophageal disorders in infants, thereby clarifying the pathophysiology of symptoms presumed to be GERD related.
  - Development of cost effective, efficacious methods for the diagnosis and management of GERD in infants.
  - Establishing objective criteria for evaluating the need for anti-reflux surgical procedures in infants.

### 2.2 Hypothesis



- Aim 1
  - The innovative feeding strategy provided over 4 wks is more effective than standard therapy for the acquisition of safe feeding skills by improved symptom scores (Primary), improved individual I-GERQ-R measures, growth measures, reduced lengths of stay and resource utilization (Secondary).
- Aim 2
  - The sensory-motor characteristics of aerodigestive reflexes evoked with induced esophageal stimulation or upon spontaneous esophageal provocation as in GER, improve in the innovative therapy group with regards to: sensory thresholds, response latency and duration, frequency and magnitude of reflexes, TLESRs, spatial-temporal-physical- chemical characteristics of GER events with associated symptom indices.

### **3.0 Background**

#### **3.1 Relevant prior experience and gaps in knowledge**

- The NASPGHAN-2009 guidelines define GERD as reflux of gastric contents in the presence of troublesome symptoms and/or complications. The prevalence of GERD in premature infants is estimated to be 10.6 %. Premature infants have pathologic reflux with esophageal manifestations (e.g. irritability, feeding refusal, arching, dysphagia) and extra- esophageal manifestations (e.g. arousals, cardiorespiratory-, sensory-, and physical symptoms, chronic lung disease, impaired growth). Such high risk infants suffer chronic morbidity, longer hospitalizations, re- admissions, and account for an unacceptable health care burden.
- Current treatment approaches in infants are likely to fail because of lack of clear therapeutic targets. Furthermore, GERD symptoms are non-specific and heterogeneous such that designing effective approaches to symptom based management is very difficult.
- Exact economic burden of premature infant GERD is lacking. 12.7% (525,000) out of 4,131,019 births in 2009 were born at < 37 wks. Assuming that half (263,000) of these infants are in NICUs, and given our estimated prevalence of GERD as 10.6% (27,900) and the estimated cost per admission attributable to GERD was \$76,796; we project an estimated economic burden attributable to GERD as over \$2.1 billion. Others have estimated that 48% of ICU discharges are treated for presumed GERD. Clinical significance of GERD is also evident from the 7-fold increase in the use of acid suppressive medications, and indeed about 45% of anti-reflux procedures are performed in infants (15). These numbers ignore the quality of life issues for both the patients and the parents.
- Extensive developments with the mechanisms, physiology, pharmacotherapy and clinical approach to GERD in the human adult, as well as therapeutic limitations in infants are well recognized. Specifically for infants, there are no available safe or FDA-approved prokinetics that regulate esophageal motility and suppress transient lower esophageal sphincter (LES) relaxations.

#### **3.2 Relevant Preliminary Data**

- In an observational study in infants (N=35) referred for GERD management, we studied the impact of feeding methods (volumes, duration, flow rates, caloric density, osmolality) on pH-Impedance variables of GER. The conclusions were: longer feeding duration, less feeding volume, and slower flow rate led to less total GER events, fewer nonacid GER events and shorter bolus clearance time; whereas, caloric density and osmolality of feeds has no impact on the characteristics of GER.
  - Jadcherla SR, Chan CY, Moore R, Malkar M, Timan CJ, Valentine CJ 2011 Impact of Feeding Strategies on the Frequency and Clearance of Acid and Nonacid Gastroesophageal Reflux events in dysphagic Neonates. JPEN J Parenter Enteral Nutr.
  - Malkar M, Chan CY, Peng J, Moore R, Jadcherla SR 2011 Effect of osmolality and caloric density of feeds on the frequency and characteristics of gastroesophageal reflux in infants. Neurogastroenterol Motil.
- The effect of right lateral position on accelerated gastric emptying has been described by others (107, 108, 114), and the effect of supine posture in the prevention of ALTEs or SIDS is recognized in the AAP guidelines.
  - 2003 Apnea, sudden infant death syndrome, and home monitoring. Pediatrics 111:914-917.
  - Omari TI, Rommel N, Staunton E, Lontis R, Goodchild L, Haslam RR, Dent J, Davidson GP 2004. Paradoxical impact of body positioning on gastroesophageal reflux and gastric emptying in the premature neonate. J Pediatr 145:194-200.
  - Corvaglia L, Rotatori R, Ferlini M, Aceti A, Ancora G, Faldella G 2007 The effect of body positioning on gastroesophageal reflux in premature infants: evaluation by combined impedance and pH monitoring. J Pediatr 151:591-596, 596 e591.
  - Van Wijk MP, Benninga MA, Dent J, Lontis R, Goodchild L, McCall LM, Haslam R, Davidson GP, Omari T 2007 Effect of body position changes on postprandial gastroesophageal reflux and gastric emptying in the healthy premature neonate. J Pediatr 151:585-590, 590 e581-582.
- We used state-of-the-art methods including, multimodal esophageal sensory provocation concurrent with video, pH-Impedance and symptom indices in the investigation of sensory-motor aspects (sensory thresholds, reflex frequency, response latency, duration and magnitude) of Vago-vagal reflexes (Primary and Secondary Peristalsis, Upper esophageal sphincter contractile reflex-UESCR, Lower esophageal sphincter relaxation reflex-LESRR and Pharyngeal reflexive swallowing) that facilitate swallowing and esophageal clearance to maintain airway protection in neonates. Twelve pharyngo esophageal motility studies were done in 6 subjects, 3 in each group, at inception (test-1) and again at completion of therapy (test-2). With innovative strategy, the response onset to esophageal stimulation induced LESRR is decreased at T2 in addition to a greater LES relaxation magnitude compared to T1; in contrast, response onset to LESRR and LESRR magnitude are similar at T1 and T2 for standard therapy. This finding supports the hypothesis that LES relaxation governed by inhibitory vagal effects mediated by nitrergic neurons is rapidly restored with innovative feeding strategy, similar to those changes tested during maturation.
  - Pena EM, Parks VN, Peng J, Fernandez SA, Di Lorenzo C, Shaker R, Jadcherla SR 2010 Lower esophageal sphincter relaxation reflex kinetics: effects of peristaltic reflexes and maturation in human premature neonates. Am J Physiol Gastrointest Liver Physiol 299:G1386-1395.
- Clinical outcomes from 44 subjects that had reflux index >3% were measured; 24 infants had lower feeding volumes, longer feeding duration, greater compliance to supine postprandial posture (innovative feeding strategy); 20 infants had standard feeding

therapy, all received acid suppressive therapy. This trial supported the hypothesis that the innovative feeding strategy is superior to standard feeding therapy.

### 3.3 Statistical procedures

- Statistical Analyses:
  - Aim I: Outcomes: We will test the hypothesis that the innovative feeding strategy provided over 4 wks is more effective than standard therapy for the acquisition of safe feeding skills by improved symptom scores (Primary), improved individual I-GERQ-R measures, growth measures, reduced lengths of stay and resource utilization (Secondary). Linear mixed models will be used to study the associations between the primary endpoints for Aim 1 (symptom scores) and treatment, and trend across time. The interaction term “group x time” will be included in the model to study whether the two treatment groups have different “behavior” across time. Confounder variables, such as medications, feeding position or volume, will be included in the models. Logistic regression models will be used to assess success of the treatment vs. standard of care. Also, potential confounders (e.g. feeding method: oral vs. tube) will be included and studied in these models. Holm’s method will be used to adjust for multiple comparisons (150). All the secondary variables listed above, will be analyzed using either linear mixed models or logistic regression models. Model goodness of fit tests and residual analyses will be performed to assess the models. Interaction terms and potential confounder variables will be included.
  - Aim II: Mechanistic Hypothesis: We will test the hypothesis that the sensory-motor characteristics of aerodigestive reflexes evoked with induced esophageal stimulation or upon spontaneous esophageal provocation as in GER, improve in the innovative therapy group with regards to: sensory thresholds, response latency and duration, frequency and magnitude of reflexes, TLESRs, spatial-temporal-physical- chemical characteristics of GER events with associated symptom indices. Based on the preliminary data, we will have at least 80% power to detect the above differences of pre and post therapy between the two groups. Linear mixed models or logistic regression models (depending on the nature of the outcome variable) will be used to study the associations of interest within sensory motor components of aerodigestive reflexes within and between study groups and their outcomes. Potential confounders as well as interaction between groups and type of infusion will be included in the models. We have utilized similar models previously. Correlation between symptom indices (SI, SSI, SAP) and reflexes will be calculated.
- Sample Size Determination:
  - From the more recent preliminary data analysis, 83.3% (20/24, 95% CI: 62.6%-95.2%) of patients had success based on symptoms and feeding methods in the innovative strategy group, while only 35% (7/20, 95% CI: 15.4%-59.2%) had success in the standard therapy group. In order to provide greater assurance than afforded by comparing to historical control of the standard therapy, a total of evaluable 100 patients will be randomized into the innovative feeding strategy or standard therapy group. The chi-square test yields 80% power to detect 27% or higher increase in proportion of success while maintaining an overall one-sided  $\alpha$  level of 0.025. This conservative power calculation is supported by the preliminary data and assumes the proportion of success for the standard therapy is around 40% and a group-sequential design with O’Brien-Fleming error spending function.
- Interim Analysis:

- One interim futility analysis will be undertaken at about 50% information prior to the final analysis at 100% information, corresponding to 50 and 100 evaluable patients, respectively. The boundary is determined using Lan-DeMets spending functions to simulate O'Brien-Fleming boundaries with an overall one-sided  $\alpha$  level of 0.025. Using the target proportion of success, the boundary at the futility analysis expressed as a p-value is 0.297. We plan to enroll 120 patients to allow for 20% of attrition.
- Intention to treat analysis:
  - Every patient who had been randomized will be included in the analysis. If a patient drops off before end of study and no symptom score has been measured, we will treat the patient as a failure. Beside the intention to treat analysis, we will also perform the analysis with only those patients that complete the study. Linear mixed models will be used to study the associations between the primary endpoints for Aim 1 (symptom scores) and treatment, and trend across time. The interaction term "group x time" will be included in the model to study whether the two treatment groups have different "behavior" across time. Confounder variables, such as medications, feeding position or volume, will be included in the models. Logistic regression models will be used to assess success of the treatment vs. standard of care. Also, potential confounders (e.g. feeding method: oral vs. tube) will be included and studied in these models. Holm's method will be used to adjust for multiple comparisons. All the secondary variables listed above, will be analyzed using either linear mixed models or logistic regression models. Model goodness of fit tests and residual analyses will be performed to assess the models. Interaction terms and potential confounder variables will be included.
  - The proposed projects will focus on esophageal provoking stimuli in designing multi-faceted innovative therapies, that will be studied in a prospective single center randomized blinded controlled trial. The pH- Impedance data with associated symptom indices will be analyzed. This trial will advance our knowledge of GER and GERD in infants. These studies will likely mandate the development of infant-specific diagnostic and treatment paradigms to manage not only GERD but also other diseases where GERD is a co-morbidity.

### **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 R01 and is built on Novel Concepts, and State-Of-The-Art Methods. Previously we have developed, validated, and safely used the approaches and equipment necessary to assess GER and GERD in infants including: a) novel multimodal esophageal sensory-motor testing using manometry provocation methods, b) respiratory inductance plethysmography, c) ultrasonography of glottal motion, d) video-manometry, e) pH-Impedance with direct observation/video correlation of symptoms, and f) robust analytical and statistical paradigms. We are translating these methods to improve outcomes in infants with feeding problems, e.g., improving successful feeding outcomes and avoidance of gastrostomy in those referred for G-tube placement.
- We will explore the sensory-motor mechanisms leading to symptoms in infants with GERD. GERD symptoms can be attributed to: a) refluxate properties:

physical (gas, mixed, liquid), chemical (acid, non-acid), spatial (high or low) or temporal (acid or bolus clearance time); or b) luminal clearance mechanisms: esophageal mechano-distention and chemo-sensitive stimulation induced aerodigestive reflexes. The mechanisms for symptoms may underlie in stimulus thresholds, response-frequency, response-latency and response-magnitude of the aerodigestive protective reflexes. Therefore, to test the effects of different treatment strategies on these aerodigestive reflexes, we will interrogate the sensory-motor components before and after proposed therapies.

- Publication history and references pertinent to this proposal are as follows:
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#### 4.0 Study Endpoints

- Primary Outcome
  - **Clinical outcome of feeding success for those infants transitioning to oral feeds at inception.**
    - The primary endpoint is the feeding success defined as achieving full oral feeds (defined as no need for tube feeds to maintain hydration and nutrition) and/or a  $\geq 6$ -point decrease from baseline I-GERQ-R. The time frame is up to 5 weeks after enrollment.
  - **Clinical outcome of feeding success for those infants on full oral feeds at inception.**
    - The primary endpoint is the feeding success defined as maintaining full oral feeds and a  $\geq 6$ -point decrease from baseline I-GERQ-R. The time frame is up to 5 weeks after enrollment.
- Secondary Outcomes
  - Clinical Outcomes
    - Length of hospital stay
    - Growth outcomes during the study period and up to 1 year
    - Independent feeding skills over time up to 1 year
    - Respiratory support during the study period and at discharge
    - Developmental outcomes with Bayley's scores at 2 years
    - Individual differences in I-GERQ-R questionnaire
  - Motility Outcomes
    - Mechanisms of aerodigestive clearance and esophageal provocation are evaluated based on esophageal motility studies at inception and after 5 weeks.
  - pH Impedance outcomes
    - 24-hour pH impedance results at inception of study and then 5 weeks later after treatment completed

## **5.0 Study Intervention/Investigational Agent**

- Those subjects randomized into the study group will follow innovative feeding strategy for 5 weeks. The innovative feeding strategy is as follows:
  - Feeding Volume  $\leq 140$  ml/kg/d
  - Feeding duration over 30 minutes
  - Right lateral feeding position
  - Supine position postprandial

## **6.0 Procedures Involved\***

### **6.1 Study design:**

- Study design and setting: This is a Single Center Prospective Randomized, Blinded Controlled Trial. Consented subjects will undergo 1:1 randomization into either innovative feeding strategy and standard therapy arms.
- Patient Population: Potential study subjects are those that are referred by their attending physician for evaluation and management of potential GERD, the key symptoms being irritability and arching, gagging, choking, coughing, aspiration, life threatening events, swallowing problems, and/or failure to thrive. I-GERQ-R questionnaire will be completed as per guidelines. Each patient must have a signed consent from parent/legal guardian prior to initiation of screening for the trial.
- Inclusion Criteria: Hospitalized convalescing infants with aerodigestive symptoms or admitted for GERD symptoms, < 42 weeks GA. Infants will be included if PMA at time of study is  $\geq 34$  wks age and  $\leq 60$  wks. Subjects must be on full enteral feeds defined as  $\geq 150$  mL/k/day. Infants must be breathing unaided, and nasal cannula oxygen up to 1 LPM is allowed. In subjects receiving empiric prokinetics or acid suppressive agents, the medications need to be stopped for  $\geq 72$  hr prior to evaluation.
- Exclusion Criteria: Infants with known genetic, metabolic or syndromic disease, neurological diseases such as Grade III or IV intra ventricular hemorrhage or perinatal asphyxia, GI malformations and surgical GI conditions.
- Tests and procedures
  - Twenty-four-hour pH and impedance ordered diagnostically for suspected GERD
  - If RI >3 and infant meets all above criteria, infant randomized into conventional or study group
  - Esophageal manometry performed
  - 4 weeks of the study intervention for the study group and standard treatment for the conventional group while collecting data on symptoms, feeding position, duration and volume

- Omeprazole stopped after 4-week course.
- Repeat esophageal manometry and pH impedance testing done after 1 week off omeprazole (at week 5). If the providers/parents are resistant or refuse to stop the medication, repeat testing will still be done, and the alteration will be noted.
- Overall Study Endpoints: Primary clinical outcome occurs at time 2 study or at discharge if time 2 study not completed. Secondary study outcomes occur at time 2 studies. Secondary clinical outcome measures (growth characteristics, development and long term feeding outcomes) will be collected up to 24 months.
- Methods to overcome potential confounders: Data will be collected from EPIC documentation, feeding diaries, parent interviews and follow up appointments. While inpatient, these are documented regularly. After discharge, we will be dependent on parents to provide the data.
- 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 completely withdrawal from the study will be encouraged to follow the standard of care; wherein, response failures are followed for secondary outcomes until 18 months.
- Secondary Outcome Measures: (up to 24 months, for Bayleys developmental score) Secondary outcome measures (growth characteristics, development and long term feeding outcomes) will be collected up to 12 months.

## 6.2 Describe:

- 24-hour Esophageal pH/impedance testing and calculation of acid reflux index (ARI) is a standard clinical test. Subjects will be monitored 1:1 by trained staff not associated with the study for the duration of the test. This allows us to quantify the components of refluxate and associated symptom indices while assuring subject safety.
- 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.
- Manometry and pH/impedance testing are both performed on a routine basis for clinical diagnostic purposes. The catheters needed to perform these studies are placed under strict guidelines by, in the instance of pH/impedance testing, a trained Registered Nurse or, in the case of manometry testing, a trained physician. The pH/impedance catheter placement is confirmed by x-ray.



- For the duration of both of these procedures, the subject is monitored by a trained RN, and vital signs (heart rate, breathing and oxygen saturation) are monitored by both visualization of subject and electronic monitoring.
- Equipment used to perform these procedures are commonly used in clinical diagnostic testing and are being used for FDA approved purposes.
- Omeprazole is prescribed to both groups and is the standard of care in the NICU.
- The source records that will be used to collect data about subjects will be EPIC records, patient diary logs for symptoms, I-GERQ-R questionnaires, feeding process, medication compliance, physician visits and clinical data.

### **6.3 Data to be collected**

- Patient diary logs for symptoms, feeding process, medication compliance, physician visits and clinical data.
- 24-hr pH data will be collected to characterize the frequency, acid reflux index, Vandenplas score, longest reflux event duration, and number longer than 5 min
- Basal manometry data will be collected to assess swallow frequency, resting UES and LES pressure, swallow propagation types, peristaltic velocity, frequency of symptoms and the causative mechanisms.
- 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 pertinent to secondary peristalsis or deglutition response, esophago-UES contractile reflex, LES-relaxation reflex, and symptoms during the stimulation. This protocol will be performed in both experimental and standard therapy groups at time-1 and time-2 (where feasible).
- Basal and adaptive pharyngeal reflexes with air and water infusions are measured at time-1 and time-2 (where feasible).
- Subjects will be monitored up to one year through electronic medical records (EPIC) for number of hospital readmissions, number of clinic visits, growth metrics and medication use.

### **6.4 Long term follow up**

- Long term follow-up will include feeding method, growth characteristics and development up to 18 months of age.

## **7.0 Sharing of Results with Subjects\***

Results of pH/impedance testing will be shared with care team and/or parents at the time of testing. Results of manometry testing will be conveyed verbally to

parents and/or the care team at the time of testing along with any incidental findings that may impact subject's care.

## **8.0 Study Timelines\***

The study procedures (pH/impedance and manometry) will be performed two times with 5 weeks between.

Omeprazole will be given for 4 weeks, with a 1-week washout period prior to the performance of the second studies.

## **9.0 Inclusion and Exclusion Criteria\***

Inclusion criteria:

- Hospitalized infants with aero-digestive symptoms or were admitted for GERD symptoms
- $\geq 34$  weeks PMA and  $\leq 60$  weeks PMA (PMA= GA+ Chronological age)
- Enterally fed infants (PO or NG)
- Average daily fluid of 150 to 170 ml/kg/day at time of study
- Supplemental oxygen of  $\leq 1$  LPM by nasal cannula
- Subjects receiving empiric prokinetics or acid suppressive agents, the medications will be stopped for  $\geq 72$  hr prior to evaluation

Exclusion criteria:

- Known genetic, metabolic or syndromic disease
- Grade III or IV IVH or intra-cranial hemorrhage, perinatal asphyxia
- GI malformations or surgical GI conditions

Infants who are hospitalized in the NICU at NCH main campus and have undergone pH/impedance testing will be screened for the above inclusion and exclusion criteria. 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**

- N=120 subjects
- This is a single center trial, all subjects will be recruited at Nationwide Children's Hospital

### **12.0 Recruitment Methods**

- 6.4 Infant's referred to the Neonatal and Infant Feeding Disorders Program at Nationwide Children's Hospital who have a pH/impedance study will be screened.
- 6.5 RN Coordinators will identify and screen potential subjects
- 6.6 Parents of infants will be offered \$20.00 for each study visit completed. Payment is made in the form a debit card with payment loaded to it following the visit.

### **13.0 Withdrawal of Subjects\***

- If a subject develops any condition outlined in the exclusion criteria (i.e. surgical or neurological conditions) they will be withdrawn
- Subjects will be withdrawn if there are any safety concerns
- Parents can choose to withdraw their infant at any time during the study period, but some data collection will continue.

### **14.0 Risks to Subjects\***

This study includes the risk associated with the nasal placement of the manometry probe and pH/impedance 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\***

Infants can benefit from evaluation careful observation of GERD feeding and breathing problems. The esophageal manometry may provide added information about the infant's feeding problem and those results will be reported to the parents and providers.

### **16.0 Data Management\* and Confidentiality**

**16.1 Data analysis plan:** See above statistical analysis

**16.2 Data safety plan:**

- All data will be stored on password protected computers accessible by trained Research assistants within the lab. Redcap will be used to store data. All paper CRFs are stored in locked cabinets with access limited to lab staff.
- Data will be verified by at least two specially trained study team members.

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

- Subjects are monitored throughout study procedures by a trained Registered nurse
- Meetings of the Data Safety Monitoring Board will take place on a quarterly basis.
- The study is overseen by the IRB at NCH and annual reports will be submitted
- A Data safety monitoring plan will be implemented with reports given to the DSMB and the IRB and NIDDK when appropriate.
- Subjects who remain hospitalized throughout the study period will be monitored by lab staff via review of their electronic medical record and review of bedside documentation
- Subjects who have been discharged to home will be monitored by weekly telephone communication with parents and caregivers
- Parents will be told whom to contact in case of concerns

#### **18.0 Provisions to Protect the Privacy Interests of Subjects**

- Parents will have the choice of whether to participate and share information about their child.
- The research team will access electronic records for follow up data.

#### **19.0 Compensation for Research-Related Injury**

- Research related injury will not be compensated
- Language from consent:
  - If your child is hurt by the procedures that are part of the Study, you should seek medical treatment for the injuries and tell the Study Doctor as soon as possible at the number on the first page 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**

- None

## **21.0 Consent Process**

- 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 can be obtained from one parent only as this study is level 2 risk.
- Consent will not be obtained from individuals other than parents (i.e. foster parents, custodial agencies)
- Consent will be obtained in person

## **22.0 Process to Document Consent in Writing**

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

## **23.0 Setting**

- This research will be conducted at Nationwide Children’s Hospital, Columbus, Ohio
- Research procedures will be performed at Nationwide Children’s Hospital
- Safety monitoring will be conducted through the NCH IRB

## **24.0 Multi-Site Research\***

24.1 This is a single site study with collaboration from The Ohio State University Department of Biostatistics for assistance with data analysis. 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.

## 24.0 Protected Health Information Recording

### 1.0 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?**

**3.1 Throughout the study period and 18 months of follow up follow up, plus 10 years.**

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

Each subject will be given a code known only to study staff and identifiable information will be kept separate from study data. Both will be stored in a secure area in a locked cabinet or in a computer database accessible only by study staff.

**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**

**X 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**

**5.0 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.)**

**25.0 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 18 months 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