PROTOCOL TITLE:

Pilot Randomized Control Trial of Necrotizing Enterocolitis Screening Abdominal Radiograph versus Bowel Ultrasound plus Abdominal Radiograph in Premature Neonates

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REVISION HISTORY

This Revision History table is provided for the benefit of study team version control. If this table will not be useful to your team, you do not need to include it.

Revision #	Version Date	Summary of Changes	Consent Change?

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1.0 Study Summary

Study Title	Pilot Randomized Control Trial of Necrotizing Enterocolitis Screening using Abdominal Radiograph versus Bowel Ultrasound plus Abdominal Radiograph in Premature Neonates
Study Design	Pilot Randomized Controlled Trial
Primary Objective	To establish the feasibility and pilot the design and delivery of a diagnostic randomized controlled trial (RCT) of BUS for NEC evaluation.
Secondary Objective(s)	• Explore whether the addition of BUS to the NEC diagnostic and monitoring pathway will change: 1. The rates of medical versus surgical management 2. The days between NEC diagnosis and surgical intervention for those that need it 3. The days NPO for those that get medical management • Develop a predictive model for NEC diagnosis • Develop a predictive model for medical versus surgical management • Explore the usefulness of serial fecal calprotectin levels as a predictive biomarker for NEC
Research Intervention(s)/ Investigational Agent(s)	N/A
IND/IDE #	n/a
Study Population	Premature NICU babies under 32 weeks gestational age
Sample Size	160 subjects enrolled
Study Duration for Individual Participants	From enrollment until discharge or transfer from CMH
Study Specific Abbreviations/ Definitions	NEC – Necrotizing Enterocolitis BUS – bowel ultrasound AXR – abdominal radiographs FC – fecal calprotectin NICU – Neonatal Intensive Care Unit CMH – Children's Mercy Hospital MRN – medical record number OSH – outside hospital LAR – legally authorized representative P/A/C – permission/assent/consent

	RCT – randomized controlled trial NPO – nothing by mouth VLBW – very low birth weight

2.0 Objectives

2.1 The overall primary objective is to establish the feasibility and pilot the design and delivery of a diagnostic randomized controlled trial (RCT) of BUS (bowel ultrasound) for NEC evaluation which will lead to a successful application for a larger, multi-center clinical trial in the future. This program of research is anticipated to have a significant positive impact in the timely and accurate diagnosis of NEC in preterm infants.

We plan to accomplish our overall objective for this project by pursuing the following *specific aims*:

1. Explore whether the addition of BUS to the NEC diagnostic and monitoring pathway will change:
   (a) The rates of medical versus surgical management
   (b) The days between NEC diagnosis and surgical intervention for those that need it
   (c) The days NPO for those that get medical management
2. Develop a predictive model for NEC diagnosis
3. Develop a predictive model for medical versus surgical management

2.2 A secondary exploratory objective is to determine the usefulness of serial fecal calprotectin levels as a predictive biomarker of NEC. We hypothesize that tracking changes in fecal calprotectin levels from baseline can identify preterm infants with and without NEC.

3.0 Background

Necrotizing enterocolitis (NEC) is the most common bowel disease in premature and low birth weight neonates. NEC is defined by the loss of mucosal integrity of the bowel wall enabling bacteria and other toxins to permeate into the bowel causing ischemia and necrosis which can lead to bowel perforation and sepsis (*1, 2*). NEC can result in substantial morbidity and mortality and prolonged hospital stay.

In the past, abdominal radiography has been scored on a standard scale that correlated with outcomes. Duke University Medical Center developed a standardized ten-point radiographic scale, the Duke Abdominal Assessment Scale (DAAS) (Appendix B) and was proven to be directly proportional to the severity of NEC on patients that underwent surgery (*3, 4*). Abdominal radiographs are assessed for gas pattern, bowel distention, location and features, pneumatosis (gas in bowel wall), portal venous gas, and pneumoperitoneum (free air in peritoneal cavity) to indicate the level of suspicion of NEC (*3, 4*). The use of abdominal radiographs is the most common assessment for suspected NEC in infants, however, there have been recent studies done on the utility of bowel ultrasound to aid in early diagnosis of NEC due to the ability to evaluate peristalsis, echogenicity and thickness of bowel wall, pneumatosis and the capability of doing color Doppler to evaluate blood perfusion(*2*). A University of Toronto study used ultrasound to assess bowel perfusion with color Doppler in neonates and found a correlation between absence of bowel wall perfusion and the increased severity of NEC on surgical pathology (*5*). Although there are similar signs found between abdominal radiography and bowel ultrasound, some of the more severe features

such as, pneumoperitoneum, were found to be more sensitive on bowel ultrasound, thus potentially leading to more definitive treatment (*5*). Currently, there is no good study evaluating whether the use of bowel ultrasound affects clinical outcomes in VLBW patients over the use of abdominal radiography alone.

The use bowel ultrasound has yet to be adopted in the setting of suspicion for NEC at our institution. This is primarily due to the lack of expertise of the ultrasound technologists, radiologists and clinicians. With literature dating back to 2005(*5, 6*) supporting the use of bowel ultrasound in diagnosis of severity of NEC, we would like to see if a regimen involving combined ultrasound and radiograph screening for NEC would make a difference in clinical outcomes (morbidity, mortality, and length of stay (LOS)) compared with radiograph screening alone.

Calprotectin is a protein found in the stool that, at elevated levels, indicates gastrointestinal inflammation. The addition of fecal biomarkers to the diagnostic work up for NEC also has promising impact. It has been suggested that fecal calprotectin levels obtained at the time of suspicion of NEC may be a useful noninvasive indicator to determine the severity of inflammation in the intestine and whether it is related to NEC or other forms of inflammation. (*8*) Correlation of the fecal biomarkers with findings on BUS may be helpful to more definitively diagnose NEC.

4.0 Study Endpoints

4.1 The primary endpoint for this study will be feasibility of recruitment into a diagnostic RCT and implementation of BUS intervention in infants with suspected NEC. Feasibility parameters to be assessed include recruitment, randomization, retention, and crossover. Recruitment will be measured as proportion of eligible infants who are enrolled, while randomization will be proportion of enrolled infants who develop NEC suspicion and undergo randomization. Retention will be defined as proportion of infants who complete the study. Crossover will be measured by proportion of infants randomized to standard of care who crossover to BUS arm. Successful implementation of intervention will be assessed by (1) proportion of properly completed BUS studies by sonographers; (2) proportion of adherence to standardized reporting template by radiologists, and (3) timeliness of stool collection in proximity to the BUS. For the secondary endpoint measures, time to achieve full enteral feeds will be defined as days to reach enteral feeds of 120mL/kg/day following suspension of feeds due to suspected NEC; and total antimicrobial days will be defined as days treated with empiric antibiotics due to suspected NEC. For the exploratory aim, the primary endpoint will be changes in serial fecal calprotectin levels and its association with NEC diagnosis.

5.0 Study Intervention/Investigational Agent

5.1 Patients who consent for this study will undergo a series of BUS and noninvasive fecal calprotectin tests over the course of their enrollment. There are no known adverse effects of BUS.

6.0 Procedures Involved

6.1 Experienced research coordinators will screen for potentially eligible infants daily. NICU staff may notify someone from the study team about potential subjects. Infants successfully enrolled in the study will be clearly identified by signage at the bedside and updated lists in the work room. All enrolled subjects will have a baseline fecal calprotectin level obtained at the time of enrollment or with next stool. If an enrolled infant develops concern for NEC (as determined clinically by treating neonatologist), a sealed envelope will be opened to reveal to which arm the infant is randomized: **(A)** AXR only (***standard of care***) or **(B)** AXR and BUS (***intervention***).

Intervention. Infants randomized to the ***AXR only arm*** will obtain an AXR as per standard of care (see **Figure**). Repeat AXR, if any, will be left to the discretion of the treating neonatologist. In this arm, no BUS study will be performed *unless* the attending neonatologist decides it is clinically indicated. This situation is expected to be exceedingly rare, as BUS is not part of the standard of care for NEC evaluation. Infants randomized to the ***AXR and BUS arm*** will also get an AXR, with repeat AXR left to the discretion of the treating neonatologist. In addition to this standard of care, infants randomized to this arm will receive a BUS as the intervention. This BUS will be ordered at the same time as the initial AXR and will be performed within six hours of the order being placed. Since CMH has overnight and weekend sonographers, BUS can be done performed 24/7. An additional BUS and fecal calprotectin level will be performed once every 24-hours until clinical suspicion is no longer warranted. Enrolled patients who may undergo multiple "suspected NEC" encounters during the course of their admission will remain in the same arm throughout the study.

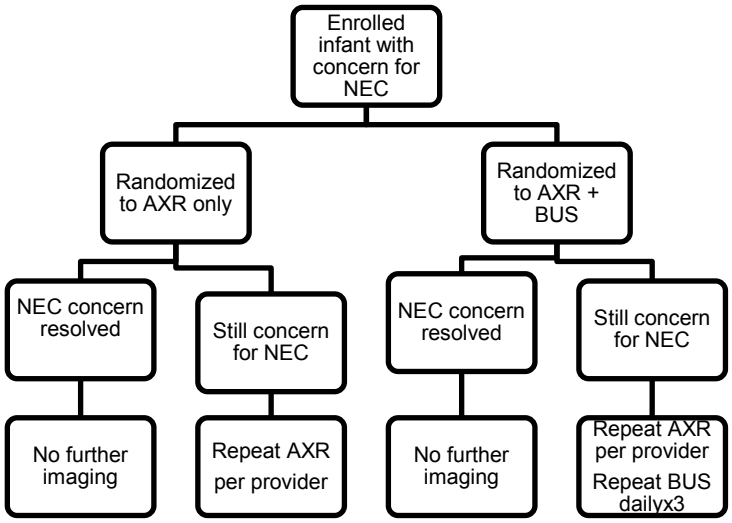

Figure: Flow diagram of study following randomization.

Management. All AXR and BUS exams will be interpreted by board-certified pediatric radiologists, and all imaging results will be available for clinicians to review as part of the subject's medical record. Fecal calprotectin levels will be documented in the patient's research data, but not included in the subject's medical record. All laboratory tests and treatment, including antibiotics or bowel rest, will be left to the discretion of the treating neonatologist. Participation in the study will end at the time of discharge or transfer.

BUS performance and interpretation. US performance and interpretation will be performed by a sonographer and radiologist, respectively, as per standard clinical work-flow. All BUS results will be available to the study team (i.e. no blinding). Variability in performance of US by sonographers will be minimized by pre-study training and quick reference cards in each US machine as detailed above. Likewise, variability in US interpretation will be minimized by the pre-study training as well as the use of a standardized template for reporting US results (see **Appendix**). All study US exams will be over-read by the study radiologists to ensure accurate interpretation. In cases of differences in their readings, final interpretation will be made by the study radiologists and these results will be communicated to the clinical team.

Fecal calprotectin measurement. Stool will be collected from a diaper following study enrollment regardless of rate of feeds. We will do an additional collection of stool after five weeks of life to get a baseline calprotectin level. "Baseline" is defined as an infant who is greater than or equal to five weeks of age and is tolerating full enteral feeds of at least 120 mL/kg/day. All stool samples will be collected by the NICU nurse or study staff. Stools can be stored for up to 72 hours if needed and then processed using the Fecal Calprotection High Range Quantitative Quantum Blue assay. All results will be recorded in Redcap. If a baby develops a concern for NEC, the next three stool samples at least a day apart will be collected for FC analyzation. An additional stool sample will also be collected at the resolution of NEC watch, which is defined by tolerance of $\geq$ 120mL/kg/day of enteral feeds for at least two days. Infants who have repeated concern for NEC will again have the first three stool samples collected with each event, with another stool also collected at resolution of NEC. The stool samples will be kept suspended in a buffer in a test tube for the duration of the study in the event a sample needs to be retested.

6.2 Protected health information (PHI) to be collected for the purpose of this study alone will include: DOB, gender, race, MRN, account number, dates of abdominal radiographs, ultrasound examinations, lab and vital signs. All data will be collected and kept in a password protected database (REDcap) that only CMH study personnel will have access to. A master linking list between MRN and study-ID numbers will be kept separately in REDcap and will be destroyed upon completion of the study. The research record generated will consist of an excel spreadsheet from the data dictionary within REDcap. Security measures include: storage of the

data on a password protected computer in a restricted access departmental folder limited to only study personnel.

7.0 Data and Specimen Banking

7.1 By consenting to the study, patients will allow the collected stool samples to be stored for future research in Dr. Venkatesh Sampath's laboratory (IBC protocol 18-28).

7.2 The Premature Infant Stool Microbiome Repository will be comprised of stool samples that will prospectively be used to study NEC and/or the microbiome of the bowels in premature infants. The purpose of this database is to provide a CMH-wide bank of specimens that will be used for future research for projects involving the study of NEC and/or bowels of premature infants.

7.3 Repository Director – The Director is responsible for the design, development, implementation, and management of the repository. The Director is the person ultimately responsible for repository's compliance with all applicable federal, state, local laws and CMH institutional policies. The Director is responsible for ensuring: 1) the Repository operates within budget; 2) Informed consent is obtained, documented, and stored in compliance with IRB regulations and institutional policies; 3) Repository personnel are appointed, trained, and supervised by the Director to ensure there is an adequate number of staff with adequate experience and assigned responsibilities commensurate with capabilities; and 4) employ a quality assurance system to ensure the Repository's operation is in compliance with the SOP, IRB approval, regulations, and institutional policies.

7.3.1 Repository Manager – The Repository Manager maintains the operation of the day-to-day activities of the Repository, such as submitting accurate and timely information for continuing review, reporting to the IRB any adverse events, unexpected problems, or protocol deviations/violations, and maintaining repository records appropriately.

7.3.2 Technical staff – Responsible for implementation of policies and procedures established by Director. Duties of each staff member are commensurate with their job description.

7.3.4 Contributing Investigators – Persons who provide data/specimens to the repository for storage.

7.3.5 Recipient Investigators – Persons who query or extract data/specimens from the repository for use in future research projects.

Sample size is approximately 80 donors per year from CMH in accordance with inclusion/exclusion criteria to the NEC and Preemies study. (Section 11.0). Stool will be collected by the bedside ICN RN directly from the diaper into a specimen cup. A small amount of stool will be taken in order to complete the calprotectin testing, the unused stool will be stored in the repository.

Time-Line: Stool samples should be stored at 4 degrees C. For microbiome analysis, stools should be transferred to Eppendorf tubes and stored at -80 degrees C preferably within 24-36 h.

Procedure:

* Wash your hands thoroughly before beginning the collection.

* Collect pre-weighed Eppendorf tubes from Sampath Lab (note weight).

* Open the Eppendorf tubes.

* Using the wooden stick, collect a small amount of feces from the specimen cup.

* Weigh the tube with feces.

* Discard the rest of the feces after completing Calprotectin studies in the usual way.

* Firmly screw the lid on the specimen container (taking care that it is not cross-threaded).

* Please ensure the specimen jar is correctly labelled with your de-identified study code number and samples number (ex., ID-Stool 1, Stool 2), date & time sample was collected. Please record the weight of stool in the tubes.

* Place the sealed specimen jar in the plastic hazard bag provided and immediately store -80 0C.

INFANT STOOL SAMPLE LABEL

Participant ID #: ----------

Date of collection: ___/___/___

Stool sample id:

Day of life stool was collected:

Time Collected: ___:___ am/pm

Weight of stool:----------

7.3 The stool samples will be labeled with the study ID of the enrolled patient in the NEC and Preemies study. The stool samples will be labeled with a letter in alphabetical order for subsequent stool samples (i.e. 1-a, 1-b, etc.).
7.4 Repository Personnel will view and record PHI for inclusion into the Repository: [Manager, Staff, etc.]. Medical information is protected under federal, state, local privacy laws and under the terms of the consent process. CMH employees with access to the repository may not disclose information in

accordance with the Administrative Policy, Confidentiality. Database is password protected and accessible only by Repository personnel.

7.5 Only projects researching NEC or bowel microbiome in premature infants will be considered for use of the Premature Infant Stool Sepository. The recipient investigator must have a protocol approved by an IRB for this purpose or an approved Exemption from the IRB. This documentation must be provided before samples/data are distributed.

Recipient investigators include CMH investigators and non-CMH investigators.

7.6 A written 1-2 page request summarizing the project for which the samples are requested must be submitted to the Repository Director. The request must contain the following details: number of samples, ethnicity of donors, amount and concentration of DNA in addition to a brief project summary (abstract), the specific aims/goals, significance and experimental design and methods (Appendix 5).

Only recipient investigators authorized by the Repository Director will have direct access to the Repository. The Repository will not release any direct identifiers to any recipient investigators (see Form X: Recipient investigator query form).

Information accessed by non-CMH employees may also be bound under non-disclosure or confidentiality agreements. Confidentiality Disclosure Agreement (CDA) will be signed and kept on file for persons not bound by CMH Administrative Policy, Confidentiality in order to protect the sensitive information that they have access to. See Administrative Policy, Confidentiality Agreement.

Sample:

Data	Repository Personnel	CMH Recipient Investigators	Non-CMH Recipient Investigators
Identifiable data set (Form A)	All/Manager only	Available upon request and IRB approval	Not released
De-identifiable data set (Form B)	All	Available upon request and IRB approval	Available upon request and IRB approval

8.0 Genetic Analysis Information

8.1 N/A

9.0 Sharing of Results with Subjects

9.1 N/A

10.0 Study Timelines

10.1 The duration of participation of patients that enroll in the study will be from time of enrollment to discharge or transfer from CMH

10.2 The study timeline is as follows:
Stage 1, patient accrual - 10/1/2018 – 12/31/2020
Stage 2, data analysis - 1/1/2021 - 3/31/2021
Stage 3, grant applications- 3/1/2021
Projected start date is upon IRB approval. Projected start date 10/1/2018
Total length of time: 3 years

11.0 Inclusion and Exclusion Criteria

Inclusion Criteria

- Neonates born prior to or at 32 weeks gestation admitted to NICU at CMH

Exclusion Criteria

- Infants with chromosomal or multiple congenital anomalies
- Unable to ultrasound the bowel (e.g. gut in silo, omphalocele, gastroschisis)
- Infants who are greater than 36 corrected weeks upon admission
- Infants who have had recent abdominal surgery
- Infants who have had a previous bowel perforation

12.0 Vulnerable Populations

12.1 This study involves no greater than minimal risk to the subjects enrolled. BUS is a noninvasive imaging tool used in standard of care procedures often for premature infants in the NICU currently. Fecal calprotectin sampling is also noninvasive and would only involve a stool sample obtained from a diaper. Consent will be obtained from the patients LAR after a full explanation of the study is given and any questions the LAR has are answered. Assent will not be obtained due to age.

13.0 Local Number of Subjects

13.1 This pilot study will enroll 80 NICU patients per year, aiming to randomize 40 patients a year with suspected NEC.

14.0 Screening and Recruitment Methods

14.1 Potential subjects will be screened and recruited in the NICU at Children's Mercy Hospital upon admit. Screening will be done by a

CMH NICU fellow or research coordinator on the study and consent will be obtained shortly after eligibility is confirmed.

14.2 The source of subjects will solely come from the CMH NICU.

14.3 Potential subjects will be identified by the NICU staff and a member of the study team will be notified to confirm eligibility and approach the subject and LAR to obtain consent if desired.

14.4 A pre-screening log will be maintained for the purpose of tracking enrollment. This will include DOB, MRN, eligibility, and choice to participate. This will ensure a patient is not approached more than once.

15.0 Reimbursement, Payment and Tangible Property provided to subjects

15.1 N/A

16.0 Withdrawal of Subjects

16.1 A subject may be withdrawn without their consent if they undergo any medical procedure during the course of their admission that excludes them from safely undergoing a BUS.

16.2 Subjects may choose to discontinue study participation at any time, for any reason, specified or unspecified, and without prejudice. Subjects may be discontinued from the study for any of the following reasons:

- At the subject's or their parent's/LAR's request
- At the discretion of the site investigator as deemed appropriate for any reason

Procedures for orderly termination will include a discussion with the parents or LAR for the reasons behind early termination.

16.3 If a subject withdraws from the research study, data that has already been collected may still be used; however, no new information will be collected except information related to adverse events or other safety issues.

17.0 Risks to Subjects

17.1 This study involves no greater than minimal risk to the subjects enrolled. BUS is a noninvasive imaging tool used in standard of care procedures often for premature infants in the NICU currently. Fecal calprotectin sampling is also noninvasive and would only involve a stool sample obtained from a diaper.

18.0 Potential Benefits to Subjects

18.1 There may be no direct benefit to the patient in the study, however, imaging done as part of the study will be available to any treating physician and may be helpful in medical management of the patient. Any procedures or treatments performed as a result from the imaging will be the financial responsibility of the patient.

19.0 Investigator Assessment of Risk/Benefits Ratio: (IRB makes the final determination)

Select as applicable:	**Pediatric Risk Category:**	
X	Category 1	Research not involving greater than minimal risk (45 CFR §46.404 and 21 CFR §50.51)
	Category 2	Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. (45 CFR §46.405 and 21 CFR §50.52)
	Category 3	Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. (45 CFR §46.406 and 21 CFR §50.53)
	Category 4	Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. (45 CFR §46.407 and 21 CFR §50.54)
Select if applicable:	**Adult Risk Category:**	
	Not Greater than Minimal Risk	
	Greater than Minimal Risk	

20.0 Data Management and Confidentiality

20.1 This is a pilot study only to evaluate feasibility of a larger clinical trial. We will use the pilot data in the future to perform a power analysis for the larger study.

20.2 We anticipate having to approach ~100 patients/year to achieve the 40 patients/year needed for our pilot study. We are assuming a NEC suspicion incidence rate of 50% and approximately 20% of parents/patients declining to consent for the study (e.g. 100 patients * 80% consent rate * 50% with NEC suspicion = 40 patients/year).

20.3 With a target of 80 patients randomized, we anticipate the enrollment period to last ~2 years. We will stop consenting patients as soon as we meet our desired enrollment**.**

20.4 A certificate of confidentiality will not be sought for this study.

20.5 Study data will be evaluated by the PI throughout the duration of the study for QA.

20.6 Patient information will be maintained in a REDCap application and will be housed within the CMH Data Center by the Division of Biomedical Informatics. The hosting server has an internal failover two-node cluster. The CMH Data Center is constantly staffed by qualified personnel and physical access is limited to authorized personnel. The

Center has optimized conditions for the servers and stabilized electrical supply. The database has a full backup. The database server is located inside the CMH corporate firewall. A person must have CMH system access to loin. Additional security for the study patient database restricts access to only those persons specifically granted authorization by the Principle Investigator. It is possible for data to be downloaded from REDCap. Individuals who lack authority to see confidential data can download reports with non-identifiable data only. The core research group will have the ability to download sensitive fields and if such a download occurs, REDCap maintains a record of who, what, when, and to where copies of the database were imported.

21.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

N/A

22.0 Provisions to Protect the Privacy Interests of Subjects

22.1 Privacy interests for subjects will be maintained by limiting interaction with subjects and LAR to only study personnel at the discretion of the treating physician.

22.2 This study is voluntary, the physicians involved do not have any financial gain or interest with the study. Subjects may withdraw participation at any time and their care and treatment at CMH will not be compromised. Subjects and their families will be told that there participation is voluntary and that they may stop at any time.

22.3 Only IRB approved members of the study team will be granted access to the study folder located on the network drive or the REDCap database. Additionally, study team members who are responsible for collected data only will be granted limited access to REDCap, allowing them to record data only.

22.4 PHI to be accessed and/or recorded for this research study includes: DOB, MRN, dates of service (BUS exams, FC results, HSCT, lab dates and dates of severity milestones and death if applicable) will be recorded.

22.5 HIPAA authorization will be wrapped into permission/assent/consent form.

23.0 Compensation for Research-Related Injury

23.1 There is no more than minimal risk to subjects.

24.0 Economic Burden to Subjects

24.1 There will be no cost to patients for participating in this study. All BUS imaging and Fecal Calprotectin tests will be the covered by study funds. However, patients will be charged for any standard of

care imaging, procedures, or treatments that coincide with their diagnosis (i.e. AXR, antibiotics, surgery).

25.0 Permission/Assent/Consent Process

25.1 Permission/Assent/Consent will be obtained by a LAR from all patients wishing to participate.

- The p/a/c process will take place in the CMH NICU at the patient's bedside.
- The patient's LAR will be given time to review materials and ask any questions.
- We will be following CMH research policies on informed consent.
- We will have the option to obtain consent via telephone in the event a parent or guardian is unavailable at the bedside or only comes on weekends.
- We will follow CMH policy 10.05 Telephone and Telemedicine Consent Process.
- Parental permission will be obtained from one parent or LAR.
- This study will only occur in Missouri at the Children's Mercy Hospital – Adele Hall.
- Other than biological parents, LARs such as an adoptive parent will be allowed to consent for a child's participation in this study.

Consent at 18 years of age, when minor subjects become adults

N/A

Waiver or Alteration of Parental Permission or Child Assent Process (permission and/or assent will not be obtained, required information will not be disclosed, or the research involves deception)

N/A

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

N/A

Non-English Speaking Subjects

- P/A/C forms will be translated into Spanish by ORI Translations program.

Cognitively Impaired Adults

N/A

Adults Unable to Consent

N/A

26.0 Process to Document Permission/Assent/Consent

26.1 Study staff will be following CM Research Policy 10.04 Obtaining Permission/Assent/Consent.

26.2 We request a waiver of documentation of P/A/C for patients in which phone consent was obtained since the study involves no more than minimal harm.

27.0 Setting

27.1 Potential subjects will be recruited from the NICU at CMH Adele Hall. NICU staff may notify study team members of an eligible patient and eligibility will be confirmed upon screening. Once eligibility is confirmed, the subject will be approached for consent.

All procedures (BUS, AXR, and fecal calprotectin testing) will take place at the patient's bedside in the CMH NICU.

28.0 Resources Available

28.1 The facilities and other resources available to the research team include everything needed to undertake and complete the proposed pilot study successfully. The NICU at CMH provides clinical care to over 150 preterm infants ≤ 28 weeks gestation per year and thus provide access to sufficient patients. The culture of clinical research is vibrant in the NICU with high recruitment rates for current studies. US services at CMH are also robust. CMH has in-house sonographers to perform US and radiologists to interpret these studies 24/7. Each member of the collaborative team has strong commitment from their departments for this study in the form of (1) protected research time, (2) cost sharing of salaries, (3) administrative support, and (3) research coordinator effort. In summary, the outstanding facilities, strong intellectual environment, and abundant resources available to the team are strongly supportive of the proposed research and overall success of the project.

There are 20 sonographers which are all registered diagnostic medical sonographers (RDMS). 18 of the sonographers have also passed their pediatric sonography boards.

All imaging will be performed portable in NICU by standard portable radiography (GE) and ultrasound equipment (GE Logiq E9 and Zonare Z-One Smartcarts) already in practice at our institution.

Fecal calprotectin tests will be performed on Quantum Blue Reader testing devices that utilize Fecal Calprotectin fCAL high range tests and CAKEX Cap Devices to obtain calprotectin levels.

Dr. Alain Cuna, one of the Co-Investigators, will present the proposed study at a CMH NICU Conference held monthly to ensure all NICU physicians are aware of the upcoming process and logistics of the study.

29.0 Multi-Site Research

29.1 N/A

30.0 International Research

30.1 N/A

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