PROTOCOL TITLE: Multicenter Randomized Control Trial of Bowel Ultrasound for Diagnosis of Necrotizing Enterocolitis

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
01	20MAY2022	Initial Creation	
02	22DEC2022	Changing inclusion criteria from preterm infants to include all infants concerned for NEC	
03	07MAR2023	Updating to increase enrollment numbers to 80 neonates and 80 neonatologists	
04	21JUL2023	Increasing enrollment numbers from 40 to 80 at KUMC	
05	25DEC2023	Increasing CMH enrollment numbers from 80 to 120	
06	17DEC2024	Adding UMKC as a study site	
07	15OCT2025	Adding this revision history table as it was missing initially	

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STUDY INFORMATION

1.0 Study Summary*

The diagnosis of necrotizing enterocolitis (NEC) – an acute and life-threatening intestinal disease that affects 5-10% of infants – can be challenging. Traditionally, neonatologists rely on abdominal radiographs (AXR) to evaluate infants with concern for NEC. In recent years, bowel ultrasound (BUS) has been proposed as a helpful adjunct to AXR for NEC evaluation. In centers where BUS expertise is available, clinicians now have the option of using BUS in addition to AXR in their diagnostic evaluation for NEC. However, significant variability remains on whether neonatologists would use or not use BUS in this clinical setting. An important reason for this variability is the lack of evidence regarding whether BUS improves patient outcomes or not. Additionally, BUS expertise generally is available only in highly specialized children's hospitals. Thus, in centers with limited BUS availability, AXR remains the standard imaging modality for NEC. ***The lack of rigorous and robust clinical trials conducted in diverse NICU settings is an important gap in knowledge that needs to be addressed before the routine use of add-on BUS for NEC evaluation.***

To help address these limitations, we propose to conduct comparative effectiveness research to evaluate the benefits of add-on BUS on patient outcomes. Our study design will be a pragmatic randomized clinical trial (RCT) of *AXR* versus *AXR + BUS* in infants with suspected NEC. We propose to conduct this study in two diverse sites. The first site will be the level IV NICU of Children's Mercy Kansas City (CMKC), which already has expertise in BUS for NEC. The second site will be the level III NICU of University of Kansas Medical Center (KUMC), an adult hospital with less experience in BUS. The rationale for this study is that infants at high risk for NEC are cared for in diverse settings including level III NICUs in adult hospitals that have little experience in using BUS to evaluate NEC. Our study has two specific aims.

> Specific aim #1: To determine the impact of add-on BUS for NEC evaluation on patient outcomes in two different NICU settings. We *hypothesize* that adding BUS to NEC evaluation changes differential diagnosis, therapy plan and patient outcomes.
> Specific aim #2: To determine the capability of implementing BUS for NEC evaluation in a level III NICU within an adult hospital. We *hypothesize* that BUS timeliness, quality, and inter-rater reliability are comparable between level III and IV NICUs.

The addition of BUS to the diagnostic repertoire of infants with suspected NEC is an important contribution to neonatology. Before widespread adoption can be realized, however, strong evidence is needed to determine whether the addition of BUS would lead to actual clinical benefits, *including in level III NICUs in adult hospitals*. We anticipate that our study will help address this critical gap in knowledge and provide important insights as to the safe and effective use of BUS for NEC.

2.0 Objectives*

2.1 Purpose, specific aims or objectives:

The overall objective of our study is to determine the clinical usefulness of BUS for NEC evaluation in diverse NICU settings. We plan to accomplish this overall objective by completing the following specific aims:

Specific aim #1: Determine the impact of add-on BUS for NEC evaluation on patient outcomes in two different NICU settings.
Specific aim #2: Determine the capability of implementing BUS for NEC evaluation in a level III NICU within an adult hospital.

2.2 Hypothesis:

Our hypothesis is that the addition of BUS to AXR can favorably change differential diagnosis, therapy plan, and patient outcomes of infants with suspected NEC; and that this beneficial impact extends to less specialized centers with little prior experience with BUS for NEC evaluation.

3.0 Background*

3.1 Gaps in knowledge.

In reviewing the evidence supporting the use of BUS in the diagnostic imaging evaluation for NEC, several important limitations need to be considered. **First**, the best level of evidence regarding BUS for NEC has been limited to diagnostic accuracy studies. While appropriate for early investigation, diagnostic accuracy studies are insufficient in demonstrating the clinical utility of new diagnostic tests. **Second**, most of these diagnostic accuracy studies are small, single-center cohort studies that retrospectively assessed the authors' experience with BUS following its adoption into the diagnostic pathway for NEC. Such studies have limited power, are subject to numerous confounders and biases, and are meant to generate hypotheses that can then be studied via larger, prospective studies. **Third**, most of the prior research on BUS has been conducted in the level IV NICUs of free-standing children's hospitals with pediatric sonographers and radiologists. Most infants at greatest risk for NEC, however, are cared for in level III NICUs within adult hospitals staffed by adult sonographers and radiologists with little to no experience in how to perform and interpret BUS for NEC evaluation. This limitation raises the important question of generalizability beyond specialized pediatric centers.

☒ Children/Minors (under 7 years of age)
☐ Children/Minors (7-17 years of age)
☒ Neonates (infants less than 30 days old)
☐ Neonates of Uncertain Viability (infants less than 30 days old)
☐ Non-Viable Neonates (infants less than 30 days old)
☐ Wards of the State
☐ Fetuses
☐ Pregnant Women

☐ Adults with impaired decision-making capacity

☒ CM Employees
☐ CM Students/Residents/ Fellows
☐ Economically or Educationally Disadvantaged Persons
☐ Prisoners

- Neonates (infants less than 30 days old) will be included in the study as the peak onset of NEC in preterm infants is around 2 to 4 weeks of life. Thus, there is no other means to study the impact of BUS on infants with suspected NEC without including neonates. To assess potential risks of BUS in this vulnerable population, we reviewed the published clinical studies on BUS for NEC evaluation and confirm that BUS is safe and well-tolerated in this population. Furthermore, BUS is already used in clinical practice for the evaluation of NEC, and thus no added risk to the neonate will occur because of the proposed research.

8.0 Local Number of Participants

	Site 1 (CMKC)	**Site 2 (KUMC)**	**Totals**
Enrollment Goal: (Neonates) *Number of participants to be enrolled = the number of participants to be consented or to be screened for chart reviews.*	120	80	200
Enrollment Goal: (Neonatologists) *Number of participants to be enrolled = the number of participants to be consented or to be screened for chart reviews.*	120	80	200

9.0 Identification and Recruitment of Potential Participants*

9.1 Identification of Potential Participants:

How will participants be identified? (Check all that apply)

☒ Chart reviews

☐ By their treating physician who will then provide the study team's contact information to the potential participant/family

☐ By their treating physician who will obtain patient/family permission to share contact information with the study team

☐ Self-refer in response to IRB approved advertisements or websites

☐ Through Cerner or other CM sources (e.g. databases, billing records, pathology reports, admission logs, etc.) May involve access of records by individuals not involved in the patient's care.

☐ List of candidates provided through the Data Report Request Form

☐ Registry of individuals interested in research opportunities

☐ Past participant list

☐ Participants will roll-over from another research study: Study #

☐ Other:

9.2 Pre-Screening prior to HIPAA Authorization

Will any of the identification methods checked above involve access to Protected Health Information (PHI) prior to obtaining HIPAA Authorization?

☒ Yes

☐ No

- *If yes, a "Partial Waiver of HIPAA Authorization" is required. Be sure to make this selection in the "HIPAA & Confidentiality" section below and complete* ***Addendum E: Waiver/Alteration of HIPAA Authorization***

9.3 Recruitment of Potential Participants:

- All consecutive infants admitted during the study period at the NICUs of CMKC or KUMC who meet eligibility criteria for the study will be automatically included in the study.

10.0 Procedures

10.1 Inclusion

Eligible infants who develop clinical concern for NEC for which the neonatologist decides to obtain imaging for further evaluation as part of usual clinical care will be included into the study.

10.2 Randomization

Infants who meet inclusion criteria of NEC concern as above will be randomized to either AXR arm or AXR + BUS arm based on the calendar month the infant was born. A pre-generated randomization calendar will be posted in the NICU workroom to inform the care team which arm the infant will be randomized to, and consequently which imaging test will be ordered.

10.3 Intervention: AXR or AXR + BUS

Infants randomized to AXR arm will have a portable abdominal x-ray ordered, performed, and interpreted per usual clinical workflow. Likewise, infants randomized to AXR + BUS intervention will have both a portable abdominal x-ray and add-on BUS ordered, performed, and interpreted per usual clinical workflow. Results of all imaging tests (AXR or AXR + BUS depending on randomization) will be available to the care team taking care of infants as per usual clinical care.

10.4 Post-AXR and Post-BUS Survey

Neonatologists will receive surveys to determine changes in their clinical diagnostic and therapeutic thinking after results of AXR or AXR + BUS.

10.5 Cross-over

Infants randomized to AXR only, but for whom the treating neonatologist deems a BUS is clinically warranted, will be allowed to cross-over and have BUS ordered. In our pilot study, only one infant randomized to AXR arm "cross-over" to AXR + BUS arm because of clinical concerns for an abdominal abscess (abdominal abscess is best evaluated by sonography). We had no instances in our pilot study of cross-over besides this isolated event, indicating clinical equipoise between AXR vs AXR + BUS. As such, although allowed in the study we anticipate cross-over to be rare.

10.6 Follow-up imaging

Infants with suspected NEC may need additional follow-up imaging for ongoing concerns of NEC. If the treating neonatologist deems follow-up imaging is needed, study infants will continue to have either AXR or AXR + BUS performed as determined by their randomization arm.

10.7 Multiple episodes of NEC concern

Infants may also develop more than one episode of NEC concern during their admission. For such instances, study infants will remain in the same randomization arm throughout the study.

10.8 Diagnosis and treatment decisions

All other diagnostic testing will be decided upon independently according to the treating neonatologist's clinical judgment. All treatment decisions, including length of bowel rest and length of antibiotic treatment, will also be at the discretion of the treating neonatologist.

10.9 Blood and Other Specimen Collection: NA

11.0 Surveys and Psychometric Testing:

- We will conduct two surveys to determine change in clinician's diagnostic and therapeutic thinking. The first survey (post-AXR survey), applicable to all infants, will be conducted after AXR is performed. The second survey (post-BUS survey), applicable only to infants randomized to AXR + BUS, will be conducted after BUS is performed. Surveys will be answered by the neonatologist taking care of the infants using a 5-point Likert scale from "not at all likely" to "extremely likely".

12.0 Follow-up

- All study infants will be followed throughout their course in the NICU, from admission to discharge. All data will be collected through clinical chart review. Follow-up will end once infants are discharged from the NICU. We will collect the following data points: (1) baseline characteristics (gestational age, birth weight, sex, race, mode of delivery, Apgar scores; (2) clinical characteristics at time of NEC concern (clinical presentation, age at time of NEC concern, results of diagnostic tests for NEC concern, information on treatment including days to full enteral feeds and days on antibiotics); and clinical outcomes at discharge (total length of stay, age at discharge, co-morbidities during NICU admission).

13.0 Genetic Analysis Information - NA

14.0 Sharing of Results with Participants

14.1 Results of all AXR and BUS will be uploaded in the electronic medical record as per usual standard workflow for any imaging test ordered in clinical practice. These results will be accessible by

neonatologists, radiologists, and other members of the clinical team authorized to view the infant's clinical chart as part of their duties in taking care of the infants in the study. Parents who are enrolled in the patient portal at CMH or KUMC will also have access to these results, just as they have access to all other results and health information of their infant.

15.0 Risks to Participants*

15.1 This study involves no greater than minimal risk to the subjects enrolled. BUS is a noninvasive imaging tool currently used in standard of care procedures for premature infants in the NICU. It has no radiation, does not require infants to fast or any other special preparation before the procedure, and is well-tolerated even by sick infants.

16.0 Potential Benefits*

16.1 There may be no direct benefit to the patient in the study. However, the BUS imaging done as part of the study will be available to any treating physician and may be helpful in medical management of the patient.

16.2 Knowledge gained from this study can potentially benefit future infants with NEC concern by providing strong evidence regarding the optimal use of BUS for NEC evaluation that is both safe and effective.

17.0 Investigator Assessment of Risk/Benefits Ratio*

17.1

Select as applicable:	**Pediatric Risk Category:**	
☒	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 participants. (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 participants, but likely to yield generalizable knowledge about the participant'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	

18.0 Payment, Reimbursement and Tangible Property provided to participants*

Is payment, reimbursement, or tangible property part of the study?

☐ Yes ☒ No *(If No, delete the following subsections)*

19.0 Compensation for Research-Related Injury - NA

20.0 Economic Burden to Participants

20.1 There will be no economic burden to participants of the study. All BUS imaging done as part of the study will be paid for by the study and will not be billed to participants.

21.0 Parental Permission and Adult Consent Process*

Written Informed Permission/Consent

☐ **Written informed permission of parent/LAR for pediatric participants**

Study group(s) to which this method applies:

☐ **Written informed consent of adult participants**

Study group(s) to which this method applies:

☐ **Written informed consent of participants turning 18**

This includes the continued access to and use of their PHI by the study team.

Study group(s) to which this method applies:

Waiver of Documentation of Permission/Consent

Permission/Consent form provided but signature will **NOT** be obtained (e.g. verbal consent)

Must complete *Addendum A: Waiver of Documentation of Permission/Consent*

☐ **Waiver of written documentation of permission of parent/LAR for pediatric participants**

Study group(s) to which this method applies:

☒ **Waiver of written documentation of consent of adult participants**

Study group(s) to which this method applies: Neonatologists taking part of the survey

☐ **Waiver of written documentation of consent of participants turning 18**

Study group(s) to which this method applies:

Waiver or Alteration of Permission/Consent

Parent/LAR permission/adult consent will **NOT** be obtained, or an alteration to an element(s) of consent.

Must complete *Addendum B: Waiver of Permission/Assent/Consent*

☒ **Waiver/Alteration of permission of parent/LAR for pediatric participants**

Study group(s) to which this method applies: AXR group and AXR + BUS group

☐ **Waiver/Alteration of consent of adult participants**

Study group(s) to which this method applies:

☐ **Waiver/Alteration of consent of participants turning 18**

Study group(s) to which this method applies:

Additional Methods

☐ **Obtaining permission/assent/consent of non-English speaking parents or participants**

Must compete *Addendum C: Non-English Speaking Participants*

Study group(s) to which this method applies:

☐ **Surrogate decision maker consent to be used when adults are not capable of consenting for themselves**

Must complete *Addendum D: Surrogate Decision Maker Consent*

Study group(s) to which this method applies:

22.0 Assent of Pediatric Participants

22.1 Select the option(s) that apply to the study:

☐ **Assent of pediatric participants WILL BE SOUGHT following assessment of ability to assent.**

☒ **Obtaining assent of pediatric participants is NOT POSSIBLE due to:**

☒ *The capability of the participants (considering the ages, maturity, physical and/or psychological state) is so limited that they cannot reasonably be consulted.*

☐ *The intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the participants and is available only in the context of the research.*

☒ **Obtaining assent of pediatric participants is NOT PRACTICLE given the context of this study** (e.g., minimal risk, no direct contact with participants).
Must complete *Addendum B: Waiver/Alteration of Permission/Assent/Consent*

23.0 HIPAA and Confidentiality

23.1 HIPAA Authorization

☐ Full Written HIPAA Authorization will be obtained (within the p/a/c form or standalone form)

☒ Partial Waiver of HIPAA Authorization (e.g. waiver for recruitment and pre-screening purposes only)
Must complete *Addendum E: Waiver/Alteration of HIPAA Authorization*

a) *Describe what PHI must be accessed for recruitment/pre-screening purposes prior to obtaining HIPAA Authorization.*

☐ Alteration of HIPAA Authorization (some but not all required elements of an Authorization are present, e.g. signature will not be obtained)
Must complete *Addendum E: Waiver/Alteration of HIPAA Authorization*

a) *Describe which proposed elements to be altered.*

☒ Waiver of HIPAA Authorization (authorization will NOT be obtained)

☐ If Other, explain:

23.2 Specify the PHI for which accessing ("viewing") or recording ("writing down") is necessary for the purpose of this research:

1. Name/Initials	☒ Accessed only	☐ Recorded
2. All elements of date (except year) directly related to an individual (e.g. date of birth, admission date, discharge date, date of death)	☐ Accessed only	☒ Recorded
3. Medical record number	☐ Accessed only	☒ Recorded
4. Account number	☐ Accessed only	☐ Recorded
5. Health plan identification number	☐ Accessed only	☐ Recorded
6. Social Security Number	☐ Accessed only	☐ Recorded

7. Device identifiers and serial number	☐ Accessed only	☐ Recorded
8. Certificate/License number	☐ Accessed only	☐ Recorded
9. Telephone number	☐ Accessed only	☐ Recorded
10. Fax number	☐ Accessed only	☐ Recorded
11. Email addresses	☐ Accessed only	☐ Recorded
12. Web addresses (URLs); Internet IP addresses	☐ Accessed only	☐ Recorded
13. Street address, city, county, precinct, zip code or equivalent geographical codes	☐ Accessed only	☐ Recorded
14. Full face photographic images and any comparable images	☐ Accessed only	☐ Recorded
15. Biometric identifiers, including finger and voice print	☐ Accessed only	☐ Recorded
16. Vehicle identifiers and serial numbers, including license plate number	☐ Accessed only	☐ Recorded
17. Any other unique identifying number, characteristic or code that may help identify individual participants including their initials (e.g. student or employee ID number)	☐ Accessed only	☐ Recorded
18. Elements of date, including year, for persons 90 years or older	☐ Accessed only	☐ Recorded
19. Other:	☐ Accessed only	☐ Recorded

23.3 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 login.

23.4 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.

23.5 A Certificate of Confidentiality has not been issued for this study.

24.0 Provisions to Protect the Privacy Interests of Participants*

24.1 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, which is password protected and encrypted. Additionally, study team members who are responsible for collected data only will be granted limited access to REDCap, allowing them to record data only.

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

25.0 Withdrawal of Participants*

25.1 A subject may be withdrawn from participation if they were transferred to another outside hospital or if they undergo exploratory laparotomy with ostomy and mucus fistula creation during the course of their admission as this procedure can preclude them from safely undergoing a BUS.

25.2 Subjects may also be discontinued from the study at the discretion of the site investigator as deemed appropriate for any reason.

25.3 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.

DATA MANAGEMENT

26.0 Data Collection*

26.1 The study will collect baseline clinical characteristics, lab test results, AXR and BUS results, clinical diagnosis, treatment data, and survey results.

- Clinical characteristics: gestational age at birth, weight at birth, sex, race/ethnicity, age at time of NEC concern,
- Lab test results: complete blood cell count (CBC), C-reactive protein (CRP), blood culture
- AXR and BUS results: time of order input in the chart, time of image acquisition, time of reporting, text of report and interpretation by radiologist
- Clinical diagnosis: NEC, no NEC, food protein-induced enterocolitis, clinical sepsis, other diagnosis

- Treatment data: medical treatment of NEC including days of bowel rest, days to full enteral feeds, days on antibiotics; surgical treatment of NEC including peritoneal drainage or exploratory laparotomy
- Survey results: post-AXR survey and post-BUS survey by neonatologists

26.2 Data will be obtained from the electronic medical record and surveys/questionnaires.

26.3 **Sensitive Data**: We will not be collecting or accessing sensitive data.

27.0 Adverse Events and Unanticipated Problems*

27.1 **Monitoring**: The study team will meet bi-weekly to monitor study progress, review participants and data, and troubleshoot any questions or problems related to the study. As all study interventions are standard of care, we do not anticipate any adverse events or problems related to the study protocol of add-on BUS.

27.2 **Reporting**: We confirm that Policy 5.11 Reportable Events of the CM Research Program Policies and Procedures will be followed in regard to reporting adverse events and other unanticipated problems to the CM IRB.

28.0 Statistical Analysis*

28.1 We will use two-tailed McNemar's test with paired measures to analyze differences in diagnostic thinking efficacy and therapeutic efficacy from pre- and post-BUS surveys. Comparison of duration of antibiotics, bowel rest, and days to full enteral feeds will be performed using Student's t-test. Kaplan-Meier curve will be used to analyze time to full feeds between the 2 groups, censoring for death, discharge/transfer out of the hospital, or 30 days following initial NEC concern. Analyses of patient outcomes (duration of bowel rest, duration of antibiotics, time to full feeds) will follow the intention-to-treat principle, with statistical significance set at a P value of < 0.05.

28.2 We will use t-test to analyze differences in mean time of BUS image acquisition and reporting. Chi-square test will be used to compare differences in proportion of BUS studies that were performed and reported per standardized protocol. Inter-rater reliability for BUS studies will be assessed by Cohen's kappa statistics.

28.3 Sample size was calculated based on our pilot study which demonstrated a mean ± SD of duration to full enteral feeds of 16 ± 9 days per episode of NEC concern. Using this information, we generated Table 1, which shows sample sizes for a range of possible means and standard deviations, with significance level of 0.05 and 80% power. For a 1-year study with 67 to 81 distinct episodes, for an SD of +8 days, we anticipate having sufficient sample size to detect a 5- to 6-day difference in mean duration to full feeds (highlighted in gray in Table 1).

Difference of means between groups	Expected Standard Deviation		
	±8	±9	±10
4 days	126	160	198
5 days	81	102	126
6 days	56	72	88

29.0 Data and Specimen Management*

29.1 Data Management:

- Data will be collected and stored in REDCap.
- Data will be stored for at least five years after final publication of results.
- Only IRB-approved study members will have access to the data.
- The Principal Investigator will be responsible for receipt or transmission of the data.
- Data will primarily be transferred via secure e-mail within CMH's internal email servers only. Data can also be transferred via password-protected, encrypted, CMH approved USB thumbdrives.

29.2 Specimen Management: NA

29.3 Biosafety Information

Will this study involve handling, transporting, or shipping any potentially hazardous biological material at/from a Children's Mercy location (e.g., blood, stool, saliva, tissue)?

☐ Yes

☒ No

Will this study involve processing any potentially hazardous biological material at a Children's Mercy location (e.g., blood, stool, saliva, tissue)?

☐ Yes

☒ No

If processing potentially hazardous biological materials, where will this work be conducted?

☐ Pediatric Clinical Research Unit (PCRU)

☐ Children's Mercy Research Institute Biorepository (CRIB)

☐ Children's Mercy Research Institute labs (mySafety ID#:_____)

☐ Other location

If "Other location," identify the location and mySafety ID# of the corresponding IBC protocol:

Location: _____

mySafety ID#: _____

30.0 Storing of Data and/or Banking of Specimens for Future Research

30.1 If this study involves storing of data or banking of leftover specimens for future research, indicate how the use will be managed:

☐ Contributing data and/or leftover specimens to an existing CM repository protocol (myIRB#_____)

☐ Contributing data and/or leftover specimens to an existing non-CM repository (Institution/Repository Name: _____)

☒ Not contributing to an existing repository for the management of data/specimens for future research use.

☐ Other:

30.2 If not contributing to an existing repository, describe:

- To maximize potential impact, de-identified clinical and imaging data collected from the study will be stored for potential use for for future research.
- De-identified data will be archived in Redcap and will be housed within the CMH Data Center by the Division of Biomedical Informatics as described before in section 23 (HIPPA) and section 29 (Data management).
- Data will be accessed through Redcap. Access will be restricted to only those persons specifically granted authorization by the Principal Investigator.
- Data will be stored for at least five years after final publication of study results.
- A formal request for release of de-identified data will be required, preferably by e-mail. Approval for release will be by the Principal Investigator. Both CM researchers and external researchers can request access for the data. Only de-identified data will be available.

31.0 Provisions to Monitor the Data to Ensure the Safety of Participants – NA (no more than minimal risk research)

STUDY MANAGEMENT

32.0 Setting & Locations*

32.1 The NICU at CMKC is an 87-bed level IV NICU. Majority of infants admitted at the NICU are born at other hospitals and are typically transferred to CMKC due to need for specialized care. Neonatologists are in-house 24/7. As a children's hospital, radiology staff at CMKC are composed of pediatric sonographers and pediatric radiologists. BUS for NEC evaluation has been available at CMKC since 2015. Despite its availability, current use of BUS for NEC evaluation at CMKC remains highly variable, often dependent upon the individual preferences of the treating neonatologist.

32.2 The NICU at KUMC is a 32-bed level III NICU. Majority of infants admitted at the NICU are born at KUMC. Neonatology coverage at KUMC is provided by CMKC neonatologists who are also in-house 24/7. As a general adult hospital, radiology staff at KUMC are composed primarily of adult sonographers and adult radiologists. Currently, only one radiologist at KUMC has the expertise to perform BUS for NEC evaluation. Because of this limited availability, BUS for NEC evaluation is infrequently performed at KUMC. However, as part of our study's aim of investigating

generalizability of BUS in NICUs of adult hospitals, pre-study training will be done to standardize performance and availability of BUS between CMKC and KUMC.

32.3 Close research collaboration exists between the NICUs of CMKC and KUMC. Several research protocols done at CMKC are also done at KUMC. In fact, KUMC is such an active site for collaborative research that a CMKC-employed neonatology research coordinator (Miah Ruffin) is dedicated solely for recruitment of participants at KUMC-NICU. Although KUMC has its own IRB, majority of the research done at KUMC NICU is approved via reliance on the IRB at CMKC.

33.0 Multi-Site or Collaborative Research

Choose ALL relationship types that apply:

☒ ***Multi-Site Research:*** *Multiple sites will be engaged in this human research project. Sites will use the **same** protocol to conduct the **same** human research activities (except for minor variations due to local context considerations).*

☒ ***Collaborative Research:*** *Multiple sites will be engaged in this human research project. Sites will **not** be performing the **same** research activities. The Site submission will specify the specific research activities each site will perform.*

☐ ***Student(s)*:** Student(s) will help with this project and will be engaging their home institution.

☒ **Visiting *Resident(s) /* Visiting *Fellow(s)*:** Visiting Resident(s) / Visiting Fellow(s) will help with this project and will be engaging their home institution.

Complete the Chart (*Add a new row for each site*):

Site Name	Enrollment Goal for Site(s) *Choose One*	Relying on CM IRB?
KUMC	☐ **Site will not rely on the CM IRB** ☒ **If relying on the CM IRB: Site Enrollment Goal:** *80* neonates and 80 Neonatologists ☐ **Site will not enroll**	☒ External Site will rely on the CM IRB as the IRB of Record using a reliance agreement. (**Required** for non-Exempt **NIH** or other **Federally Funded** research) ☐ External Site will utilize their home institution's IRB for IRB approval. A reliance agreement will **not** be sought. ☐ **Not Applicable**. Site will **not** interact or intervene with human participants or their identifiable data / identifiable biospecimens.
UMKC	☐ **Site will not rely on the CM IRB**	☒ External Site will rely on the CM IRB as the IRB of Record using a reliance

	☐ **If relying on the CM IRB: Site Enrollment Goal:** Click or tap here to enter text. ☒ **Site will not enroll**	agreement. (**Required** for non-Exempt **NIH** or other **Federally Funded** research) ☐ External Site will utilize their home institution's IRB for IRB approval. A reliance agreement will **not** be sought. ☐ **Not Applicable**. Site will **not** interact or intervene with human participants or their identifiable data / identifiable biospecimens.

34.0 International Research - NA

Addendum A: Waiver of Documentation of Permission/Consent

Regulatory Criteria: *To qualify for a waiver of documentation of parental permission or adult consent, the study must fit into at least one of the three scenarios below. Indicate which scenario(s) applies.*

☐ **The only record linking the participant and the research would be the permission/consent form and the principal risk is potential harm resulting from a breach of confidentiality.** Each parent/LAR or adult participant will be asked whether they want documentation linking the participant with the research, and the parent/LAR's or adult participant's wishes will govern.

OR

☒ **The research presents no more than minimal risk of harm to participants and involves no procedures for which written parental permission or adult consent is normally required outside of the research context.**

OR

☐ **The parent(s)/LAR or adult participants are members of a distinct cultural group or community in which signing forms is not the norm**, the research presents no more than minimal risk of harm to participants and an appropriate alternative mechanism for documenting that informed parental/LAR permission or adult consent was obtained will be provided. Describe the alternative mechanism provided:

Addendum B: Waiver/Alteration of Permission/Assent/Consent

What's the difference between a "waiver" and an "alteration" of parental permission, child assent, or adult consent?

- A "waiver" of parental permission, child assent, or adult consent is when **all 9 required elements of permission/consent are waived.** If the IRB approves a waiver then the study team does not need to obtain the parental permission or adult consent in order to include a participant in the study.

- An "alteration" of parental permission, child assent, or adult consent is when **one or more of the 9 required elements are waived** because they are not relevant to the research activity. If the IRB approves an alteration, then the study team must still obtain parental permission or adult consent in order to include a participant in the study, but certain elements may not be required in the form/discussion.

NOTE: *If requesting a waiver of parental/LAR permission because parental permission is not a reasonable requirement to protect the participants [e.g. research on neglected or abused children], contact irb@cmh.edu to discuss additional regulatory requirements.*

Regulatory Criteria: *To qualify for a waiver or alteration of parental permission or adult consent,* ***ALL*** *of the following must apply. Explain how the study meets each of the regulatory criteria below.*

Criteria	Explain how the study meets the criteria
The research involves no more than minimal risk to the participants	Add-on BUS involves no more than minimal risk to participants for the following reasons: (1) BUS is non-invasive, free from radiation, does not require any special preparation before the procedure, and is well tolerated even in sick, infants. (2) BUS is an accepted imaging option for the diagnostic evaluation of infants with suspected NEC. (3) The workflow for obtaining BUS in the study will be the same as the workflow for obtaining BUS in routine clinical care. Thus, the BUS images acquired by the sonographer and the report provided by the radiologist will be securely stored in the infant's electronic medical record.

	(4) There is clinical equipoise for the diagnostic imaging evaluation of NEC (AXR vs AXR+BUS). This is evidenced by the fact that the diagnostic imaging algorithm for neonates for whom there is NEC suspicion is more based on the staff present that day than any other factor.
The research could not practicably be carried out without the requested waiver/alteration (i.e., explain why the study could not be done if permission/assent/consent were required)	We initially conducted a pilot study to determine the feasibility of a RCT study design of BUS for NEC evaluation. While the RCT study design itself was feasible, we found that the process of obtaining consent was not practicable. The reasons why the proposed research could not be practicably carried out without the requested waiver are detailed below and in **Fig 3**: (1) **NEC is an emergency, making traditional parental consent at time of NEC concern impossible**. Because NEC can rapidly deteriorate, infants with suspected NEC require "stat" evaluation with imaging and other laboratory tests. Families approached for research during emergency situations are often unable to give proper informed consent because of physical and emotional distress. Obtaining consent at time of NEC concern would also increase the risk of delaying evaluation. For these reasons, traditional parental informed consent at time of NEC concern is not possible for our study. (2) **Obtaining consent prior to NEC concern will require impractically large numbers to meet sample size demands.** To overcome the emergency nature of NEC, we elected in our pilot study to seek consent from all infants who meet eligibility criteria, follow consented infants over time, and randomize only consented infants who develop concern for NEC. The problem with this approach is that only 36% (20/56) of consented infants developed NEC concern for randomization into the study. Based on these numbers, we will need to successfully consent 222 infants to achieve our target sample size of 80 infants. Although mathematically possible, it would require implausibly high approach and consent rates to successfully enroll 222 infants over the 2 years of the proposed study, making this approach of obtaining consent prior to NEC concern impracticable. This approach would also intrude on many families who would not need and may not

	want the information provided. A secondary concern would be the excessive personnel time and cost requirements to consent 222 families to meet the targeted enrollment of 80 infants. (3) **The inherent differences in families able to be consented versus not consented in the study may result in underrepresentation, selection bias, reduced generalizability, and erroneous conclusions**. In our pilot study, majority of infants were unable to be consented for two reasons. The first reason (40% of infants) was that the infants were very sick at the time of transfer and their NEC concern episode happened very early in their hospitalization, resulting in very limited time to consent the parents. The second reason (also 40% of infants) was that infants were transferred from faraway hospitals. As a level IV NICU, infants admitted at CMH are referred from the whole of Kansas and western half of Missouri. Similarly, as a tertiary referral hospital for high-risk pregnancies, KUMC admits and delivers pregnant moms from all over Kansas. Such families who live farther away from Kansas City are often not able to be present as often in the NICU to be approached for research. Thus, because of these two reasons for limited availability to obtain consent, we believe our pilot study sample was biased by overrepresentation of healthier infants and infants from the Kansas City metropolitan area. Limited availability to consent for research is also known from prior studies to be higher among families that have transportation issues, speak a different language other than English or Spanish, unable to pay their phone bills, etc. Together, these barriers can systematically prevent the inclusion of at-risk families in research studies, decreasing generalizability of our results. If this selection bias were to persist in our larger study, it would weaken the scientific validity of our research by increasing the likelihood of missing important benefits or hazards and reaching erroneous conclusions.

(4) **Complexity of following consented infants for development of NEC concern result in missed randomization, loss of study participants, and insufficient power**. In our pilot study, 20% of consented infants who developed concern for NEC (4/20) were not randomized into the study. The complexity of following consented infants prospectively for development of NEC concern is a major contributing factor for missed randomization. This is because NEC concern, which by itself is already a relatively rare event, can occur at any time of the day or night, and can occur several weeks from the time of informed consent. The loss of even a few subjects from complex consent process and missed randomization would negatively impact the power and validity of our proposed study. Instead, we propose including all consecutive infants who develop NEC concern into the study with waiver of consent to simplify the study process, eliminate errors related to missed randomization, and maximize sample size and power for the study.

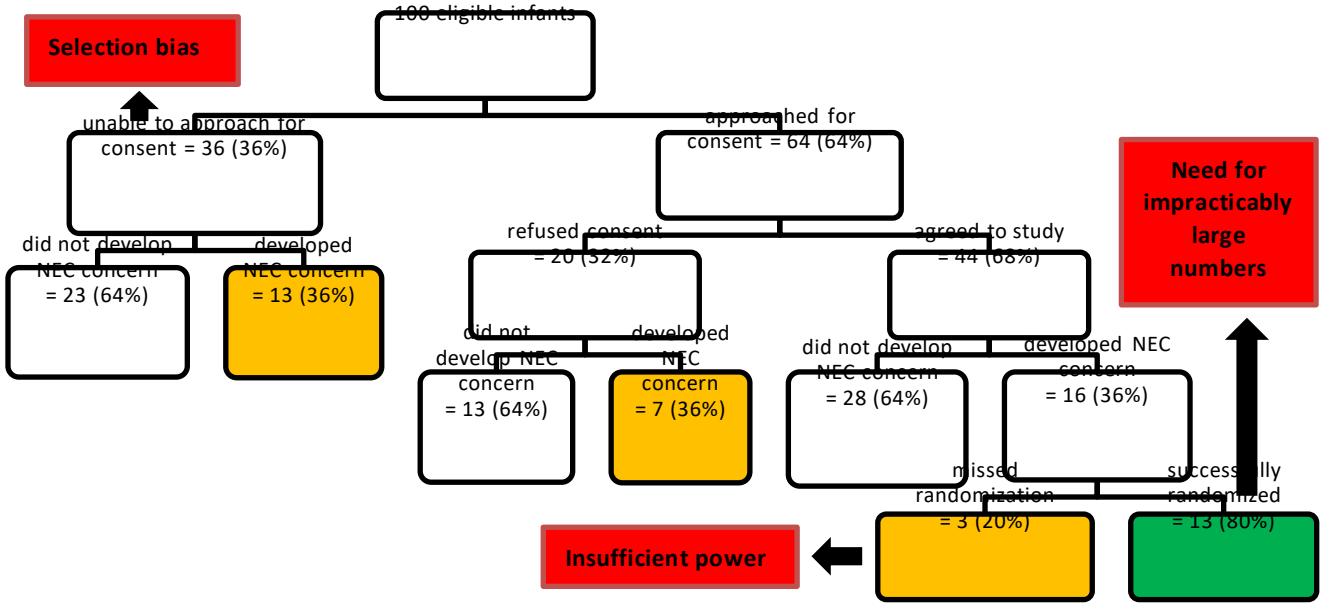

Figure 3. A hypothetical example of 100 eligible patients to demonstrate how traditional consent process prior to NEC concern is not practicable. Using estimates based on our pilot study, the traditional consent process would have only successfully randomized 13 infants (**green box**). The **red boxes** indicate reasons why the traditional consent process would not be practicable for our study. In contrast, a waiver of informed consent would have successfully randomized 36 infants (**green box** + **yellow boxes**).

If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format	PHI is required to identify subjects and data from all participants is needed to describe aims of the study.
The waiver/alteration will not adversely affect the rights and welfare of the participants	The waiver will not adversely affect subjects for the following reasons: (1) The allowance of cross-over in the study ensures that participants will not be deprived from obtaining BUS should the treating neonatologist deem it is clinically warranted to do so. Thus, the availability of BUS as an option remains the same regardless of research participation or not. (2) BUS will be performed for proper clinical indication of NEC concern and not for research purposes only. Results of BUS will be available to clinical care team per routine clinical care. Thus, research participation will not affect the regular care of infants with NEC concern, nor will it negatively affect infant's welfare. (3) BUS results will be performed per routine clinical workflow, ensuring information from BUS will be kept secure and confidential in the patient's electronic medical record. Thus, research participation will not affect patient confidentiality.
Whenever appropriate, the participants or legally authorized representatives will be provided with additional pertinent information after participation	NA – no additional disclosure of information is needed as families will be updated and provided with the information from BUS during family-centered patient care rounds as part of routine care. Additionally, results of BUS will be freely available in the infant's electronic medical record.

Proposed Alteration (if applicable):

Select which required elements of permission are to be omitted.

☐ A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the participant's participation, a description of the procedures to be followed, and identification of any procedures that are experimental;

☐ A description of any reasonably foreseeable risks or discomforts to the participant;

☐ A description of any benefits to the participant or to others that may reasonably be expected from the research;

☐ A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant;

☐ A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained;

☐ For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

☐ An explanation of whom to contact for answers to pertinent questions about the research and research participants' rights, and whom to contact in the event of a research-related injury to the participant;

☐ A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled; and

☐ One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

  ☐ A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the participant or the legally authorized representative, if this might be a possibility; or

  ☐ A statement that the participant's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

Provide the rationale for omitting the item(s) selected:

Addendum C: Non-English Speaking Participants

There are special considerations that must be made when obtaining permission/assent/consent from participants who prefer to communicate in a language other than English. To ensure that adequate processes are in place to obtain effective permission/assent/consent from these participants address each of the items below.

Indicate which language(s) other than English are understood by prospective participants or representatives.

☐ Spanish
☐ Arabic
☐ Burmese
☐ Somali
☐ Vietnamese
☐ Other:_____

Describe the plan for enrolling non-English speaking participants (e.g. fully translated consent forms, use of Qualified Bilingual Study Staff or interpreters):

If providing fully translated consent forms, explain if the ORI Translation Program for internally and/or federally funded studies will be used, or if translation services will be obtained through the study sponsor or some other service.
NOTE: If using ORI Translation Program services for an industry sponsored study, contact Research Business Operations staff to get this negotiated in the study agreement/contract.

Addendum D: Surrogate Decision Maker Consent

Assessment of Decision-Making Capacity:

- *Describe the process to determine whether an individual is capable of consent. See CM Research Policy 9.10 Incapacity, Temporary or Fluctuating Decision-Making Capacity for more information on the proper procedures for enrolling adults who are not able to consent for themselves.*

Identification of Surrogate Decision Maker

- *List the individuals from whom permission will be obtained in order of priority, e.g. durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child.*
- *For research conducted in the states of Missouri and/or Kansas, review CM Research Policy 9.10 Incapacity, Temporary or Fluctuating Decision-Making Capacity to be aware of which individuals in the state meet the definition of "legally authorized representative."*
- *For research conducted outside of Missouri and/or Kansas, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective participant to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel review the protocol.*

Assent of Adult Participant

- *Describe the process for assent of the adult participants who are unable to consent for themselves. Indicate whether:*
    - *Assent will be required of all, some, or none of the participants. If some, indicate which participants will be required to assent and which will not.*
    - *If assent will not be obtained from some or all participants, an explanation of why not.*
    - *Describe whether assent of the participants will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents or require participants to sign assent documents.*
    - *Describe how participants will be closely monitored.*
    - *Describe whether participants will be withdrawn if they appear to be unduly distressed.*

Addendum E: Waiver/Alteration of HIPAA Authorization

What's the difference between a "waiver" and an "alteration" of HIPAA Authorization?

- A "waiver" of HIPAA Authorization is when **the requirement to obtain authorization is completely waived.** If the IRB approves a waiver then the study team does not need to obtain HIPAA Authorization in order to include a participant in the study.

- An "alteration" of HIPAA Authorization is when **one or more of the required elements of authorization are waived.** If the IRB approves an alteration then the study team must still obtain HIPAA Authorization in order to include a participant in the study, but certain elements may not be required in the form/discussion.

Regulatory Criteria: *To qualify for a waiver/alteration of HIPAA Authorization,* ***ALL*** *of the following must apply to a study. Explain how the study meets each of the regulatory criteria below.*

Criteria	*Explain how the study meets the criteria*
The use or disclosure of PHI involves no more than minimal risk to the privacy of individuals based upon the following: a. Plan to protect PHI from improper use and disclosure: b. Plan to destroy PHI at the earliest opportunity, unless there is a health or research justification for retaining the PHI: c. Assurance that PHI will not be reused or disclosed to any other person or entity:	a. We plan to protect identifiers by the following plan: - Only trained research personnel who have been educated on HIPAA regulations and who have been given password-protected access to clinical health systems and medical records will have access to this information. - All databases into which the data will be stored will be housed on secure networks with password-protection.

	- The electronic data will be stored on a server managed by Children's Mercy. Access to the server is restricted to only those with IRB approval for the study, and it is password protected. b. All PHI collected during the study will be removed once complete research data has been collected and validated through quality assurance review. We will only maintain de-identified data for potential use in future research. c. PHI will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.
The research cannot practicably be conducted without the waiver/alteration, i.e. explain why a signature for HIPAA Authorization cannot be obtained.	A signature for HIPPA Authorization cannot practically be obtained because we are requesting to waive parental consent for the study. Without a corresponding HIPPA waiver, we would have to approach the families of every single patient treated in the NICU at the time of the study, which would be contrary to our request for waiver of parental consent. See ***Appendix B*** for reasons why a waiver of parental consent is requested for the study.
The research cannot practicably be conducted without access to and use of the PHI, i.e. explain	Access to and use of PHI is needed for the study for the following reasons:

why access to PHI is needed for this study.	(1) The month of birth will be used to determine randomization. Other elements of date will be used to calculate duration of antibiotic treatment and days to full enteral feeds. (2) Name and MRN will be used to track infant's course throughout NICU admission and access electronic medical records for data collection.