Study Title	**Predictive Modelling for sepsis and necrotizing enterocolitis in preterm infants**
Study Intervention	Develop, test, and validate predictive models for sepsis and necrotizing enterocolitis in preterm infants
Indication Studied	Late onset sepsis and necrotizing enterocolitis
Sponsor	NICHD
Sponsor Protocol	NICHD: RO1 HD072071
Number	UVA IRB #:21237
Development Phase of Study	Observational
Release Date	Protocol Version 4.0 Version Date: March 10, 2025
GCP Statement	This study is to be performed in full compliance with acceptable Good Clinical Practices (GCP) as required by U.S. Code of Federal Regulations applicable to clinical studies (45CFR46), ICH GCP E6 and completion of Human Subjects Protection Training. All required study documentation will be archived as required by regulatory authorities.
Principal Investigator	**Brynne Sullivan MD,**
Participating Institutions	University of Virginia, Charlottesville, VA Washington University, St. Louis, MO Columbia University, New York, NY University of Alabama, Birmingham, AL
Biostatistician	Douglas Lake, PhD

SIGNATURE PAGE

Signature:	DocuSigned by: Brynne Sullivan 3C509A7871A2445...	3/13/2025
Name:	Brynne Sullivan, MD Role: PI	Date

INVESTIGATOR'S AGREEMENT

I confirm that I have read this protocol and I agree to conduct the study as outlined herein. I agree to conduct the study in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices as outlined in ICH E6 and the applicable laws and regulations.

Site Investigator:	DocuSigned by: Brynne Sullivan 3C509A7871A2445... (Signature)	3/13/2025 (Date)
	Brynne Sullivan (Name)	

Instructions to the Site Investigator: Please sign and date this signature page. File the original signature page in the study file at the site and send a copy of the signed and dated page to the UVA Study PIs or designee.

STUDY DESIGN

This is a multicenter observational study to develop predictive models for sepsis and necrotizing enterocolitis in preterm infants, using clinical, laboratory, and bedside monitor data.

- No interventions are involved.
- Clinical, laboratory, and imaging data will be collected from the medical record.
- Vital sign data will be collected from the bedside monitors.
- Machine learning will be used to develop, test, and validate predictive algorithms

SYNOPSIS

Title: Predictive Modeling for sepsis and necrotizing enterocolitis in preterm infants
Investigators: Karen Fairchild, M.D.; Brynne Sullivan, M.D.
Planned Study Initiation: November 2018
Study Duration: 10 years
Length of subject participation: Study data are collected from birth until NICU discharge. Neurodevelopmental follow-up data will be collected until age 2.
Objective: To test the hypothesis that validated algorithms combining cardiorespiratory metrics from NICU bedside monitors with clinical, demographic and laboratory variables can provide early warning for sepsis and NEC in VLBW infants in the NICU.
Outcomes: Primary: • Late-onset (>3d of age) sepsis • Other late-onset infections • Necrotizing enterocolitis Secondary: • Mortality • Days on mechanical ventilation • Preterm morbidities including but not limited to brain injury, retinopathy, acute kidney injury, and bronchopulmonary dysplasia • Days on antibiotics • Length of NICU stay • Neurodevelopmental outcomes at routine NICU follow-up visits

Methodology: Observational study with data collection from electronic health record
Total Number of infants planned: 8500
Inclusion criteria: • Birthweight <1500 grams **Exclusion criteria:** • None
Investigational intervention: None (data collection only)
Other study intervention(s): None
Statistical methods: Descriptive statistics, logistic regression, decision tree, neural network, deep learning and others will be utilized. **Efficacy:** Algorithms for sepsis and NEC risk will be developed and externally validated and cross-validated. **Safety:** Patient data will be linked and coded within sites (with PHI stored on research drives behind fire walls). Only data with limited HIPAA identifiers (dates and study IDs but no key to the code) will be shared between sites.

LIST OF ABBREVIATIONS

Abbreviation or specialist term	Explanation
BPD	Bronchopulmonary Dysplasia
CBC/Diff	Complete Blood Count and differential
Corrected Age	Chronologic age in months, minus #months premature (used after NICU discharge)
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRP	C Reactive Protein
GA	Gestational Age
HUS	Head ultrasound
IRB	Institutional Review Board
IVH	Intraventricular Hemorrhage
MOP	Manual of Procedures
NEC	Necrotizing Enterocolitis
NICU	Neonatal Intensive Care Unit
PMA	Postmenstrual age (gestational age plus chronologic age in weeks, used during NICU
cPVL	Cystic Periventricular Leukomalacia

REDCap	Research Electronic Data Capture
ROP	Retinopathy of Prematurity
UVA	University of Virginia
VLBW	Very Low Birth Weight (<1500 grams)

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1. BACKGROUND AND RATIONALE

Study Synopsis

In a multi-NICU study, we are developing, testing, and validating predictive modeling algorithms for early detection of sepsis and NEC in VLBW infants.

Disease Background

The number of very low birthweight (VLBW, <1500 g) infants born in the US each year remains about 60,000(1). Their course of post-natal development in the NICU centers on support of ventilation and nutrition while systems mature. There are, however, interruptions by the apparently sudden onset of inflammatory illnesses such as sepsis and necrotizing enterocolitis (NEC), occurring in approximately 15% and 8% of VLBW infants, respectively. The mortality is high and there is substantial short- and long-term morbidity(2)(3)(4). These illnesses are not really sudden, though – clinical signs of illness occur relatively late, when the systemic inflammatory response is well-developed. Effective detection systems would allow earlier recognition and treatment.

Many have postulated that new analysis of existing data from standard-of-care bedside monitors should give clues that are useful in early diagnosis(5)(6)(7). The University of Virginia group has reduced one such analysis to clinical practice. We found abnormal heart rate characteristics (HRC) of reduced variability and transient decelerations in the heart rates of septic infants for 12 to 24 hours and more prior to clinical suspicion(8). We developed mathematical tools to detect abnormal HRC, validated them externally, demonstrated their relationship to clinical data such as lab results and other findings, and performed a large randomized trial to assess impact on VLBW outcome(9). The results were important – a more than 20% mortality reduction when HRC monitors were displayed to clinicians with no other intervention mandated. Since then we have shown that adding other vital sign data, such as oxygen saturation, as well as other demographic and clinical data, including laboratory values, might improve on heart rate characteristics monitoring for predicting sepsis, NEC, and other outcomes(10)(11).

Rationale for Study Design

- Routinely monitored cardiorespiratory signals hold much physiologic information that is not synthesized in such a way as to alert clinicians to subtle changes that occur very early in the systemic inflammatory response.
- The combined efforts of clinicians, mathematicians and engineers can lead to effective new monitoring strategies that allow early diagnosis of otherwise invisible clinical deterioration.
- Adding clinical, demographic, and laboratory data to bedside monitor cardiorespiratory data will improve prediction and early detection of sepsis and NEC over any of these data alone.
- Improved analytics will favorably impact patient outcomes by assisting clinicians in decisions about initiation of antibiotics and other therapies early in the course of illness.

2. STUDY OBJECTIVES

2.1 Hypothesis

Validated algorithms combining bedside monitor cardiorespiratory-based metrics along with clinical, demographic and laboratory variables can provide early warning for sepsis and NEC in VLBW infants in the NICU.

2.2 Specific Aims

- For all VLBW infants, collect baseline demographic and clinical data.
- Characterize, categorize, and catalogue events of sepsis and NEC, and associated clinical and laboratory variables, as well as ventilator status at the time of illness
- Identify metrics of heart rate, respiratory rate, and combined cardiorespiratory characteristics that change in the preclinical phase of sepsis and NEC
- Develop new or optimally adapted mathematical measures that report on abnormal waveforms in the ECG, chest impedance, and/or pulse oximetry signals
- Construct predictive models to predict or detect sepsis or NEC, combining clinical, laboratory, and physiologic monitoring data using standard techniques such as (but not limited to) logistic regression, and using novel approaches from the field of Big Data analytics such as deep neural networks
- Develop and externally validate algorithms on VLBW infants at the other participating NICUs over the course of the study.

3. SUBJECT ELIGIBILITY

Inclusion Criteria

- Birthweight <1500 grams

Exclusion Criteria

- None

4. Study Plan

Clinical Data Collection

REDCap will be used by all sites for electronic data entry. All data required for this study should be documented in the infant's medical record as part of routine care. Data entry guidelines are specified in the Manual of Procedures (MOP). Both retrospective and prospective data will be collected and analyzed.

Bedside Monitor Data Collection

At all sites, digital waveforms (3 EKG leads, chest impedance, and the O2 saturation) along with q2sec vital signs are stored using BedMasterEx software (Excel Medical), Philips Data Warehouse Connect, or other similar data storage systems. These data are labeled by bed number and a coded timestamp. Retrospective and prospective data will be used for this study.

Clinical data and bedside monitor data will also be collected and shared between sites via UVA Box.

5. STATISTICAL CONSIDERATIONS

Statistical Methods

Clinical, demographic, and cardiorespiratory parameters are combined using multivariate statistical methods, such as logistic regression, k nearest neighbor analysis, random forests, neural nets, and other techniques(12)(13). The period of interest is the 24 hours prior to the event. Thus the output of the model is the probability of an event in the next day. We divide by the average probability of the event, and present the clinician with the fold-increase in risk of an upcoming event. We will have a development/test cohort and validation cohort both within and between centers to account for differences in clinical practices that may impact vital sign patterns.

Study Size Considerations

We anticipate enrolling at least 1667 VLBW infants per site over a 4-year period. With incidence of late-onset sepsis and NEC being approximately 15% and 7% respectively, we anticipate having about 200 episodes of culture-positive sepsis and 100 episodes of NEC with bedside monitor data available for analysis. Generally, 50 events allow for a predictive model with 5 predictive variables and (based on our experience with bootstrapping) 95% CI of 0.3 around the ROC area, so we will have sufficient numbers of infants with events to develop and validate models.

6. STUDY MANAGEMENT

Institutional Review Board (IRB) Approval and Consent

This is a purely observational study. Bedside monitor data are currently collected and stored at all sites. Routine clinical data are annotated in the electronic health record. For purposes of this study, waiver of consent is appropriate since there are no interventions, data are considered de-identified under the Privacy Rule since they have only the limited HIPAA identifiers of date and Study ID , (Limited Data Set) and securely stored, and requiring consent would impact the study results since the consented population would be smaller and may differ from the entire VLBW cohort in ways that could impact the validity of the sepsis and NEC algorithms we develop. Data will collected either prospectively or retrospectively.

7. Study Records and Record Retention

Study documentation includes all electronic case report forms in REDCap, source documentation, Sponsor-Investigator correspondence, regulatory documents (e.g., protocol and amendments, IRB correspondence and approval) and the like.

Source documentation will be captured in electronic format and include information from patient's electronic medical records and / or data obtained from various bedside vitals monitoring equipment e.g., using BedMasterEx software (Excel Medical), Philips Data Warehouse Connect and include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Study documentation will be kept on file for the length of time that is required by each participating sites IRB.

8. REFERENCES

1. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S, et al. Births: final data for 2005. Natl Vital Stat Rep. 2007 Dec 5;56(6):1–103.
2. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002;110(2 Pt 1):285–91.
3. I. A-C, B.J. S. Neonatal infection and long-term neurodevelopmental outcome in the preterm infant. Curr Opin Infect Dis. 2006;19(3):290–7.
4. Greenberg RG, Kandefer S, Do BT, Smith PB, Stoll BJ, Bell EF, et al. Late-onset Sepsis in Extremely Premature Infants. Pediatr Infect Dis J. 2017 Aug;36(8):774–9.
5. Sullivan BA, Fairchild KD. Predictive monitoring for sepsis and necrotizing enterocolitis to prevent shock. Semin Fetal Neonatal Med. 2015;20:255–61.
6. Lloyd R, O'Toole J, Livingstone V, Hutch W. Predicting 2-y outcome in preterm infants using early multimodal physiological monitoring. Pediatr Res. 2016;80(3):382–8.
7. Doheny KK, Palmer C, Browning KN, Jairath P, Liao D, He F, et al. Diminished vagal tone is a predictive biomarker of necrotizing enterocolitis-risk in preterm infants. Neurogastroenterol Motil. 2014;26(6):832–40.
8. Fairchild KD, O'Shea TM. Heart rate characteristics: physiomarkers for detection of late-onset neonatal sepsis. Clin Perinatol. 2010 Sep;37(3):581–98.
9. Moorman JR, Carlo WA, Kattwinkel J, Schelonka RL, Porcelli PJ, Navarrete CT, et al. Mortality reduction by heart rate characteristic monitoring in very low birth weight neonates: a randomized trial. J Pediatr. 2011;159(6):900–6.e1.
10. Fairchild KD, Lake DE, Kattwinkel J, Moorman JR, Bateman DA, Grieve PG, et al. Vital signs and their cross-correlation in sepsis and NEC: A study of 1,065 very-low-birth-weight infants in two NICUs. Pediatr Res. 2017;81(2):315–21.
11. Sullivan BA, Wallman-Stokes A, Isler J, Sahni R, Moorman JR, Fairchild KD, et al. Early Pulse Oximetry Data Improves Prediction of Death and Adverse Outcomes in a Two-Center Cohort of Very Low Birth Weight Infants. Am J Perinatol. 2018 Nov;35(13):1331–8.
12. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: Seven steps for development and an ABCD for validation. Vol. 35, European Heart Journal. Oxford University Press; 2014. p. 1925–31.
13. Collins GS, Reitsma JB, Altman DG, Moons K. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): The TRIPOD Statement. Ann Intern Med. 2015 Jan 6;162(8):600.