Study Title: Implementing Enhanced Recovery After Surgery (ERAS) for Neonates Undergoing Major Surgery – A Prospective Multicenter Stepped-Wedge Cluster Hybrid Effectiveness-Implementation Study

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Prospective Observational Study

Implementing Enhanced Recovery After Surgery (ERAS) for Neonates Undergoing Major Surgery: A Prospective Multicenter Stepped-Wedge Cluster Hybrid Effectiveness-Implementation Study

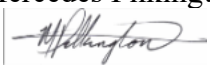
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Statement of Compliance

The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Research Ethics Board (REB) of Record, except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB of Record for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol or consent materials will require review and approval by the REB of Record before the changes are implemented to the study. All changes to the consent form will be REB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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List of Abbreviations

ACH	Alberta Children's Hospital
AIM	Acceptability of Implementation Measure
AIMS	Alberta Infant Motor Scale
AE	Adverse Event/Adverse Experience
BSID-IV	Bayley Scales of Infant and Toddler Development, 4th Edition
CDH	Congenital Diaphragmatic Hernia
CGA	Corrected Gestational Age
CRF	Case Report Form
CTU	Clinical Trials Unit
CRS	Clinical Research Services
DSMB	Data Safety Monitoring Board
ECMO	Extracorporeal Membrane Oxygenation
ERAS	Enhanced Recovery After Surgery
FETO	Fetoscopic Endotracheal Occlusion
FIM	Fidelity of Implementation Measure
GOSH	Great Ormond Street Hospital
HCP	Healthcare Provider(s)
HINE	Hammersmith Infant Neurological Examination
HSC	Hospital for Sick Children
IAM	Intervention Appropriateness Measure
LOS	Length of Stay
MME	Morphine Milligram Equivalents
NDI	Neurodevelopmental Injury
NEO	Neonatal ERAS Outcomes
nERAS	Neonatal Enhanced Recovery After Surgery
NICU	Neonatal Intensive Care Unit
OR	Operating Room
PDSA	Plan-Do-Study-Act
PFMA	Posture and Fine Motor Assessment
PI	Principal Investigator
PHI	Personal Health Information
PHIPA	Personal Health Information Protection Act
POMS	Peri-Operative Management Score
REB	Research Ethics Board
SAEs	Serious Adverse Events
SDM	Substitute Decision Maker
SSI	Surgical Site Infection
SOA	Schedule of Activities
TP	Treating Physician
TPN	Total Parenteral Nutrition

1. Protocol Summary

1.1 Synopsis

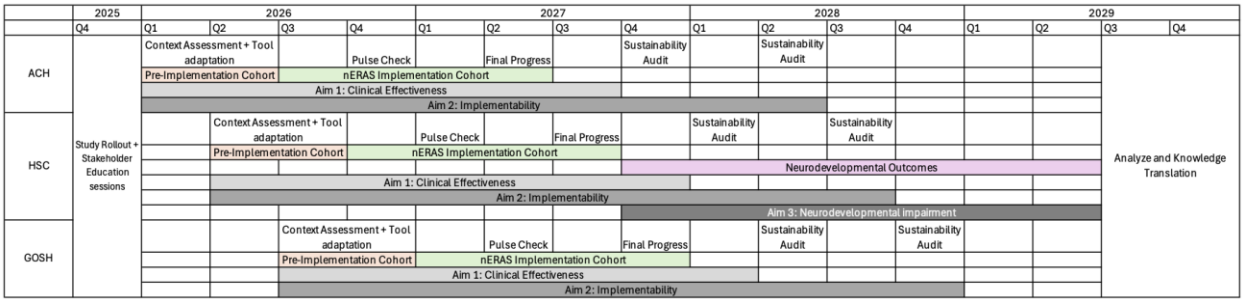
Title	Implementing Enhanced Recovery After Surgery (ERAS) for Neonates Undergoing Major Surgery: A Prospective Multicenter Stepped-Wedge Cluster Hybrid Effectiveness-Implementation Study
Short Title	Neonatal ERAS Outcomes (NEO) Study
Study Description	To address the study aims we will conduct a prospective multicenter stepped-wedge cluster effectiveness-implementation trial of a Neonatal ERAS Guideline. The effectiveness aims will a) evaluate the immediate and short- term clinical effectiveness of Neonatal ERAS (nERAS) for surgical neonates (Aim 1); and a nested cohort study will measure 18-month neurodevelopmental outcomes in a single cluster (Aim 2). The implementation aim will evaluate adoption, feasibility, and fidelity of a multifaceted implementation strategy of the guideline using mixed methods (Aim 3). We hypothesize standardizing care with a goal to minimize the physiologic stress following major surgery will have positive immediate- and short-term impacts on neonatal core outcomes. There are three clusters with staggered 6-month pre-implementation cohorts (n=140 neonates) and one-year active-implementation cohorts (n=280). All collected data will be collected retrospectively as components of standard of care during the perioperative period, 30-day surgical outcomes, and long-term follow-up at one year and 18-months (for neurodevelopment only). During the active-implementation phase, each study NICU will be supported with a multifaceted implementation plan to try to improve adherence to evidence-based practice.

Objectives	1. To measure the clinical effectiveness of nERAS implementation. We will use the Perioperative Management (POM) Score (temperature, pH, pCO_2, glucose, and unintended respiratory events) and core clinical outcomes to reflect perioperative stability and recovery pre-implementation and during active-implementation of nERAS. 2. To examine the feasibility of measuring the impact of nERAS on neurodevelopmental outcomes. We will conduct a nested sub-study that will determine whether Neonatal ERAS reduces the rates of adverse motor outcomes at 18 months corrected age. 3. To evaluate the implementability of nERAS using a multifaceted implementation strategy (to include Audit and Feedback, Modify and Tailor, and Internal-External Facilitation).
Study Design	An international multicenter stepped-wedge cluster hybrid type II effectiveness- implementation study will be conducted at three clusters: Alberta Children's Hospital (Calgary, Canada; ACH), The Hospital for Sick Children (Toronto, Canada; HSC; lead site), and Great Ormond Street Hospital (London, UK; GOSH). The trial will measure baseline perioperative and surgical outcomes and then actively implement a recently published Neonatal ERAS guideline that targets neonatal patients undergoing major non-cardiac surgical intervention during NICU admission. Each NICU will serve as a cluster and as its own control as there is variable existing ERAS implementation. To address effectiveness, the three clusters will collect the POM Score (temperature, pH, pCO_2, glucose, and unintended respiratory events) and 30-day clinical outcomes during a 6-month observation period (usual care unexposed cohort) and then during a subsequent 12-month active-implementation period (exposed cohort). A single center (HSC) will collect neurodevelopmental outcomes at 18 months from both cohorts. Mixed methods will be applied to address Implementability using a combination of validated surveys of healthcare professionals and patient families to measure acceptability and appropriateness. A retrospective chart audit will assess adoption, and feasibility and fidelity will be determined through validated questionnaires.

Participant Population, Selection Criteria	Effectiveness Aims: Inclusion: Consent provided by parent/legal guardian, infant aged ≥24 weeks gestational age at birth and <cGA 44 weeks at time of index surgery, requires major non-cardiac surgery requiring general anesthetic (e.g., thoracotomy, laparotomy, ventriculoperitoneal shunt, choanal atresia repair, etc.), and admitted preoperatively to a study NICU (HSC, ACH, or GOSH). Exclusion: Infants undergoing cardiac surgery as sole index surgical intervention, sole minor index surgery (e.g., central line placement, eye exam under anesthesia), born at less than 24 weeks estimated gestational age or greater than 44 weeks corrected gestation age on day of index surgery, intraoperative mortality, genetic anomaly associated with lethality (e.g., trisomy 13 or 18), preoperative ECMO (extra-corporeal membrane oxygenation) cannulation, or fetal intervention (e.g, FETO for CDH). Implementation Aim: Inclusion: Healthcare providers (surgeons, anesthesiologists, neonatologists, and nurses) who provide direct care for eligible infants described above, or caregivers of eligible infants described above (caregiver role to be defined by family and may include parent(s) and/or extended family members). Exclusion: Healthcare providers and/or caregivers who do not consent to participate in Implementation surveys or interviews.
Study Sites	The Hospital for Sick Children (Lead Site), Toronto ON, Canada Alberta Children's Hospital, Calgary AB, Canada Great Ormond Street Hospital, London, UK
Participant Duration	Patient outcomes will be tracked up to 1 year post-operatively in ACH and GOSH cohorts, outcomes will be followed until 18 months corrected gestational age for HSC cohort.
Number of participants	Approximately 400 infants are projected to be enrolled at all study sites over the course of the study. Healthcare providers and family caregivers will be recruited until qualitative analysis reaches data saturation (expect minimum of 15 HCP per site and 10 family caregivers per site).
Study Phases (Screening, Study Treatment, Follow-Up)	Screening for eligibility. Each cluster will have a pre-implementation phase in which standard of care is applied to surgical neonates without directed ERAS facilitation. Then each cluster will transition to an Active-Implementation Phase in which there will be cluster-level interventions to support implementation of ERAS guideline. Follow-up will include up to 18-month outcomes.

Efficacy Evaluations	Primary efficacy outcome is POM Score to reflect perioperative stability (composed of temperature, pH, pCO_2, glucose and unintended respiratory events). This is collected as part of routine care.
Implementation Evaluations	Primary implementation outcome is Adoption of ERAS recommendations.
Safety Evaluations	As this is an observational study, there are no study-related medical risks anticipated.
Statistical Analysis	POM scores will be compared pre-intervention to post-intervention using multivariable mixed-effects logistic regression models with random intercepts per site. An interrupted time series approach will be taken by standardizing time relative to implementation dates between sites. Changes in slope and intercept between pre and post implementation date will be assessed using interaction terms. Adjustment for potential confounders will be considered in the model. Odds ratios will be reported with 95% confidence intervals.
Data and Safety Monitoring Plan	The PI is responsible for data quality management and ongoing assessment of the study conduct.

1.2 Schedule of Activities (SOA)



Effectiveness Aims:

Activity	**Consent** [Up to 72 hours post-op]	**Immediate** [-3 to OR to +7 days]	**Short-Term** [OR + 30 days]	**Long-Term** [OR + one year]	**Neurodev't** [cGA 18 months]
Study team procedures					
Informed Consent	X				
Demographics	X	X			
Chart Review					
Preoperative Details		X			
Operative Details		X			
30 Day Outcomes			X		
One-Year Clinical Outcomes				X	
18-Month Neurodevelopment					SK

X- all patients
SK- only patients enrolled at The Hospital for Sick Children

Implementation Aim: Healthcare Team

Activity	Implied Consent	Pre-implementation	Active Implementation	Sustainment
Frontline Healthcare Providers	X			
Atlas Tools		X		
AIM, IAM, FIM		X	X	X
Healthcare Leaders	X			
Atlas Tools		X		
AIM, IAM, FIM		X	X	X
Implementation Team	X			
Atlas Tools – Pulse Checks		q2mon	q2mon	q3mon
Focus Groups		X	X	X

Implementation Aim: Parent/Legal Guardian

Activity	Consent	Early Feedback [OR + 7 days]	Late Feed-back [OR + >30 days]
Family Caregivers	X		
AIM, IAM, FIM		X	X
Focus Groups			X

1.3 Key Roles

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2. Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Neonatal surgery is a high-risk procedure

Children are not little adults, and neonates are not little children. Neonates requiring surgery represent one of the highest risk groups in the surgical population, presenting with unique physiologic, surgical, and anaesthetic challenges.[1] They are at increased risk of severe life-threatening cardiorespiratory complications both during and after surgery.[2,3] Surgical morbidity and mortality is further compounded when infants are born prematurely.[4] A recent Pediatric-NSQIP study revealed a staggering 22% thirty- day mortality for extremely premature infants undergoing surgery.[4] The overall thirty-day morbidity rate was 27% in preterm surgical infants and 18% in term surgical neonates; indicating that 1 in 4 preterm infants undergoing surgery will suffer a complication in the first 30 days after surgery.[5] In addition, nearly a quarter of patients undergoing non-cardiac surgery for congenital anomalies have cognitive or motor development delays measured at 12 and 24 months of age.[6] Complications, such as a surgical site infection (SSI), not only hinder immediate surgical recovery but also serve as an independent predictor of

length of hospital stay.[7] Neonatal surgical outcomes therefore have long- lasting impacts on patients, families, and society.[8]

Enhanced Recovery After Surgery guidelines are evidence-based tools to improve outcomes Enhanced Recovery After Surgery (ERAS) guidelines provide healthcare practitioners with evidence- informed recommendations designed to be implemented as a synergistic care bundle to standardise and improve perioperative care (ERAS pathways).[9] These guidelines are intended to minimise the physiological stress of surgery and the resultant catabolic state that contributes to adverse surgical outcomes.[10,11] ERAS guidelines currently exist for over 20 adult surgical procedures. Recommendations relating to preoperative optimization, intraoperative fluid management, and analgesia-related recommendations are similar across a number of specialty specific guidelines.[12–15] In adults, ERAS pathways have been shown to consistently reduce complications, postoperative length of stay (without increasing readmissions), and healthcare costs.[16–18]

ERAS implementation requires an integrated knowledge translation strategy ERAS guidelines are multifaceted tools that are composed of 15-25 evidence-based recommendations to incorporate into a patient's preoperative, intraoperative, and postoperative care.[12–15] When paired with an implementation strategy, an ERAS pathway effectively implements the relevant guideline. In Alberta, the implementation of multiple simultaneous adult ERAS pathways was demonstrated to improve guideline adherence[19] and multi-site implementation proved to be cost-saving.[18,20] Studies have demonstrated that patient and system outcomes improve with greater ERAS compliance.[21–23] Therefore, to maximise impact, a cohesive strategy to optimise implementation of ERAS guidelines is needed. This relies on multidisciplinary and multi-professional input during planning and their ongoing engagement to ensure fidelity.[24–26] Patient and caregiver buy-in is absolutely critical to ERAS development and implementation.[27,28] Family caregivers are particularly critical for neonatal patients as they are the patients' best advocates and are integral to the neonate's care team in the neonatal intensive care unit (NICU) and beyond discharge.[29] The NICU is a unique environment where quality improvement and care-bundles are utilised for a number of medical conditions.[30–32] It is unknown whether implementation strategies utilised for non-surgical populations in the NICU will translate well to the multidisciplinary continuum of perioperative care.[33]

Neonatal ERAS requires a paradigm shift to population-specific recommendations There are over 20 adult ERAS guidelines endorsed by the ERAS® Society (e.g., for colorectal surgery, liver surgery, and thoracic surgery).[34] However, there is a paucity of ERAS guidelines in the neonatal population. Our group developed the ERAS Guideline for Neonatal Intestinal Surgery in accordance with the structured standards laid out by the ERAS® Society in 2020.[14,35] If neonatal ERAS is to follow the specialty-specific paradigm utilised in adult ERAS, then separate guidelines would be required for a multitude of surgeries and diagnoses—intestinal

resection, hydrocephalus, esophageal atresia, bladder exstrophy. ERAS implementation is sub-optimal until a critical mass of patients are enrolled in the care pathway at a centre; procedure-specific pathways can therefore present a barrier in neonates.[23] Healthcare providers who implemented the Neonatal Intestinal Resection Guideline quoted infrequent use as a barrier to successful implementation.[36] Our team thereby undertook a rigorous process to develop the first of its kind ERAS Guideline that is intended to be utilised for *any neonate* requiring surgery as the recommendations remain agnostic to surgical intervention.[37] Our ERAS Society Recommendations for Neonatal Perioperative Care (Figure 1; Table 1) offer a unique opportunity to test whether simultaneous vertical and horizontal adoption of ERAS recommendations (within and across diagnoses) can bridge the knowledge to action gap by ensuring wide applicability and sustainability.[37]

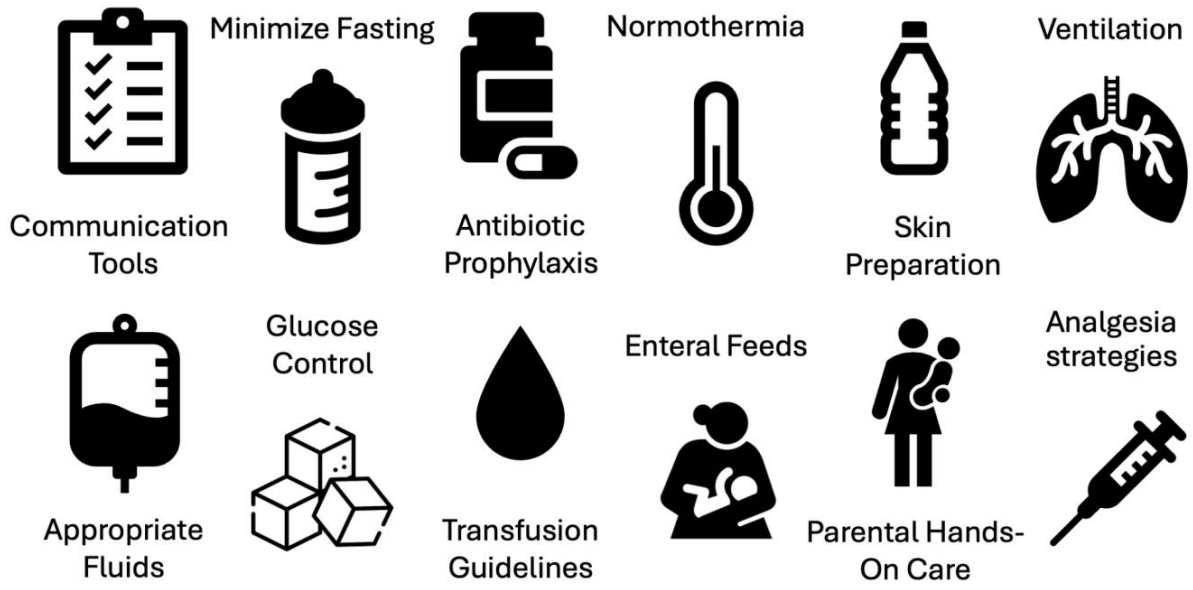


Figure 1: ERAS Society Recommendations for Neonatal Perioperative Care (Pilkington, et al., JAMA Surg, 2024)

Table 2. Consensus Guidelines for Neonatal Perioperative Care: Enhanced Recovery After Surgery (ERAS) Society Recommendations for Neonatal Intensive Care Units

Topic	Recommendation	Quality	Strength
Team communication	Implement perioperative multidisciplinary team communication using a structured process and protocol (eg, preoperative and postoperative huddles).	Moderate	Strong
Preop fasting	For neonates who are not otherwise nothing by mouth, offer formula or breast milk (with fortification removed) for up to 6 h and 4 h, respectively, preoperatively, and clear fluids up to 1 h preoperatively to minimize fasting.	Moderate	Strong
Temperature regulation	Continuously monitor intraoperative core temperature and take preemptive measures to prevent hypothermia (<36.5 °C) and maintain normothermia beginning before transfer from the NICU.	Moderate	Strong
Antimicrobial prophylaxis	Administer appropriate preoperative antibiotic prophylaxis within 60 min of skin incision for clean-contaminated, contaminated, and dirty cases.	Low	Weak
	Discontinue prophylactic postoperative antibiotics within 24 h of surgery unless ongoing treatment is warranted.	Low	Weak
Surgical skin site preparation	Use chlorhexidine-based skin preparation to prepare the surgical site in neonates and infants >35 weeks' gestation and >1500 g.	High	Strong
Perioperative ventilation	Use a lung-protective strategy (eg, 4-8 mL/kg, not >10 mL/kg and PEEP approximately 5). Ensure tidal volumes are measured intraoperatively and monitor carbon dioxide levels.	Low	Weak
	Consider using cuffed tracheal tubes for appropriately sized neonates to optimize ventilation and decrease the risk of reintubation. Consider the use of LMAs for appropriately sized infants for uncomplicated procedures where the anesthesia practitioner has access to the airway in case of need to rescue.	Low	Weak
	Aim for early postoperative extubation as soon as feasible, considering gestational age, risk for respiratory failure and type of surgical repair.	Moderate	Weak
Fluid management	Titrate perioperative fluids to maintain tissue perfusion and prevent hypovolemia, fluid overload, and hyponatremia.	Moderate	Weak
Perioperative glucose control	Ensure adequate perioperative glucose intake to avoid hypoglycemia which can be associated with adverse outcomes; tight glucose control with insulin infusions is not routinely recommended.	Low	Weak
Transfusion threshold	Restrict transfusions to maintain a hemoglobin level >90 g/L for a term neonate with no oxygen requirements. Term neonates within the first week of life, either intubated or with an oxygen requirement, should be transfused to maintain a hemoglobin level >110 g/L.	Low	Weak
	Use written transfusion guidelines that take into account the target hemoglobin threshold and coagulation profile as well as the clinical status of the neonate and local practice.	Low	Weak
Enteral feeds	Use breast milk as first choice for enteral nutrition.	High	Strong
	Use postoperative feeding protocols to promote early enteral feed introduction and advancement.	Low	Weak
Parental hands-on care	Facilitate hands on care and purposeful practice by parents that is individualized to meet the unique needs of parents and infants early during the admission. Build parental knowledge, skills, and confidence to take on a leading role and facilitate caregiver readiness for safe transition or discharge from the NICU.	High	Strong

Abbreviations: LMA, laryngeal mask; NICU, neonatal intensive care unit; PEEP, positive end-expiratory pressure.

SI conversion factor: To convert hemoglobin to grams per deciliter, divide by 10.

Table 1: Consensus Guidelines, and Associated Quality of Evidence and Strength of Recommendation, for Neonatal Perioperative Care: Enhanced Recovery After Surgery (ERAS) Society Recommendations for Neonatal Intensive Care Units (Pilkington et al., JAMA Surg, 2024)

Innovations are required to improve and measure neonatal surgical outcomes

Neonatal surgical outcomes must be improved, however, the clinical heterogeneity of neonates undergoing surgery makes it difficult to measure the clinical effectiveness of perioperative interventions. Complication rates frequently vary depending on specific procedures.[8,38] Many adult ERAS protocols measure length of hospital stay as a primary outcome as it is equated to '*enhanced recovery'* for elective procedures[16,17,39]; however, length of stay is much less relevant

to a preterm infant who requires hospital support that extends beyond their surgical recovery. nERAS requires new objective metrics to measure clinical effectiveness. The Children's Hospital Neonatal Consortium (CHNC) has designed a measure of neonatal physiologic stress using early postoperative pragmatic markers (temperature, pH, pCO2, glucose, and unintended respiratory events); although, it remains untested and unvalidated (*unpublished: CHNC*).[40] Neonatal core outcomes, such as survival, adverse events, and general cognitive ability, can measure short- and long-term outcomes but do not necessarily reflect the immediate perioperative period.[41] Validation work is required to determine if early stability of physiologic parameters can predict improved short- and long-term outcomes.

Neonatal ERAS requires tailored implementation to optimise neonatal outcomes
Neonatal ERAS implementation requires significant modification from most adult-ERAS pathways due to the critical role of the NICU during the perioperative period. The intensive care environment, role of neonatologists, and one-on-one nursing provide unique facilitators and barriers to ERAS implementation.[36] Neonatal ERAS integration is also reliant on parental engagement and parents have been and continue to be valuable partners in co-designing tools for implementation in the NICU.[29] Our team conducted an implementation pilot to introduce the Neonatal Intestinal Resection Guideline to a single NICU. Despite a light-touch facilitation strategy necessitated by the COVID-19 pandemic, a high level of feasibility and fidelity were successfully demonstrated (73% overall adherence to 17 recommendations).[42] Important facilitators to success included healthcare provider engagement and implementation tools developed by our group.[43,44] The pilot was unable to assess clinical effectiveness and generalizability of implementation strategies. Given the current uncertainties, our study team proposes a **multicenter prospective effectiveness-implementation study of the novel ERAS Guidelines for Neonatal Perioperative Care designed for any neonate undergoing major surgery**. This trial will measure the impact of nERAS on immediate- and short-term outcomes from surgery and test the generalizability of a multifaceted implementation strategy. For the first time, we will test the impact of nERAS on neurodevelopmental outcomes.

2.1. **Rationale**

It is well understood that there is a considerable lag between the development of evidence-based guidelines, and their implementation.[45,46] This implementation trial will seek to facilitate more rapid uptake of an evidence-based guideline and provide insight to its clinical effectiveness. A non-randomized stepped-wedge cluster trial is a pragmatic study design that ensures all three NICUs (clusters) will receive the intervention (multifaceted implementation of nERAS). The sequential roll-out will permit dedicated resources and centre-specific adaptation while permitting robust assessment of between- and within-cluster variability (accounting for any temporal trends). Study centres were selected to maximise generalizability by including a high-volume international cluster in addition to a moderate- and high-volume Canadian centre. This is reflective of the neonatal surgical community that relies upon collaboration to maximise impact.

This implementation study builds on our single centre implementation pilot of Neonatal ERAS for patients undergoing intestinal resection.[36,42] There have not been any studies to date that investigate the clinical effectiveness of ERAS for Neonates despite its well-documented outcomes for non-neonatal patients. In addition to immediate outcomes (using the POM Score as a proxy for stability) and short-term clinical outcomes, a nested single-centre cohort of prospectively enrolled infants undergoing major noncardiac surgery will examine whether nERAS implementation impacts NDI at 4, 8, 12, and 18-month corrected age. Evidence is building that infants who require surgery during the neonatal period are at increased likelihood of neurodevelopmental impairment (NDI).[6,47]

2.1.1. Potential Risks and Benefits

2.1.2. Potential Risks

2.1.2.1. Effectiveness Aims:

There are no known medical risks involved for the participants as there are no study-specific interventions or tests required. All data will be collected as part of routine care. The Neonatal ERAS Guideline contains recommendations based on best available evidence and is intended to standardize perioperative care while simultaneously allowing healthcare providers to deviate when clinically indicated. The risk of breach of confidentiality is a potential risk. Private health information (PHI) will be accessed during the initial chart review and access to PHI will be limited as much as possible. Each site will keep the file linking study IDs to patient MRNs that will not be shared with the data coordinating center or other study sites; each of these files will be password protected and stored separately from the rest of the study data. All information in REDCap will be protected.

2.1.2.2. Implementation Aims:

There are no known medical risks involved for the participants. Some of the topics or questions addressed in the surveys or focus group discussions during the study may be sensitive in nature, and participants may experience emotional distress while completing the questionnaire. Participants do not need to answer any question that causes discomfort and can conclude their participation at any time. The study research team can provide caregivers' resources if they express discomfort or distress related to the research or their child's hospitalization.

2.1.3. Potential Benefits

In adults, ERAS pathways have been shown to consistently reduce complications, postoperative length of stay (without increasing readmissions), and healthcare costs.[16–18] Given the novelty of ERAS for neonates, it is hypothesized but not yet proven that neonatal patients may experience similar benefits. If nERAS is proven effective, the results of this trial will help ensure there is dissemination of best practices to maximize guideline-concordant care. While there may be no direct benefit to current participants, the findings of this study have the potential to benefit future patients.

3. Objectives and Purpose

There are two primary objectives for the two primary effectiveness aims of the study. The first aim is multicenter whereas the second (neurodevelopmental) aim is only addressed by a nested sub-study at HSC only.

3.1. Primary Objective (Effectiveness)

Aim 1: To measure the clinical effectiveness of nERAS implementation. We will use the Perioperative Management Score (temperature, pH, pCO_2, glucose, and unintended respiratory events) to reflect perioperative stability and recovery pre-implementation and during active-implementation of nERAS. The POM Score was developed by the Children's Hospital Neonatal Consortium using relevant literature and expert review. It provides a pragmatic objective measure of neonatal physiologic status after surgery using investigations that are completed as part of routine clinical care. Hypo- and hyperglycemia, hypo- and hypercarbia, and acidosis have been associated with neonatal morbidity and mortality.[48-51] Failed extubations have been associated with lengthier NICU and hospital stays as well as increased mortality.[52,53] Many typical ERAS outcomes (e.g., length of stay, readmissions) are less relevant for neonatal surgical patients and composite complications vary widely by surgical intervention. The POM Score is calculated by the number of patients with all parameters within target (post-op temperature target 36.1-38°C within 30 minutes; post-op glucose target 2.6-11 mmol/L within one hour of NICU arrival; post-op pH target 7.2-7.5 within the first hour after surgery; post-op pCO2 target 31-75 mmHg within the first hour after surgery; and avoidance of unintended respiratory events within 24 hours (unplanned or failed elective extubation)). The score directly reflects at least 50% of the recommendations in nERAS (temperature regulation, perioperative ventilation, fluid management, perioperative glucose control, transfusion thresholds, and team communication).

Objective	**Brief Description / Justification of Outcome Measure**	**Outcome Measured By**	**Time Frame**
Measure the clinical effectiveness of nERAS implementation.	The objective is to improve physiological stability perioperatively as measured by the POM Score (temperature, pH, pCO2, glucose, and unintended respiratory events). ERAS recommendations are designed to minimize physiologic stressors; therefore, the POM Score has been chosen as the primary outcome.	Temperature: first recorded temperature post-operatively pH: first VBG/ABG collected post-operatively (as part of routine postop care) pCO_2: first VBG/ABG collected post-operatively (as part of routine postop care) Glucose: first glucose collected post-	The POM Score is derived from: blood tests (collected as part of routine care) within one hour after surgery, body temperature (measured within one hour of return to NICU from surgery), and unintended respiratory events within the first 24 hours post-operatively.

		operatively (as part of routine postop care) Unintended respiratory events: any reintubation or unplanned extubation within 24 hours post-operatively (determined from chart review)	

Aim 2: To assess the feasibility of measuring the impact on neurodevelopmental outcomes, a nested sub-study will assess if nERAS reduces the rates of adverse motor outcomes in patients before and after nERAS implementation. The primary adverse neurodevelopmental outcome is defined as cerebral palsy or motor composite scores below 2 standard deviations at 18 months corrected age, as measured by the Bayley Scales of Infant and Toddler Development, 4th Edition.[54] The neurodevelopmental outcomes will be compared between ERAS-exposed and usual care infants using regression analysis and adjusted for confounding variables.

Objective	Brief Description / Justification of Outcome Measure	Outcome Measured By	Time Frame
To assess whether nERAS reduces the rates of adverse motor outcomes related to neurodevelopment.	Evidence is building that infants who require surgery during the neonatal period are at increased likelihood of neurodevelopmental impairment (NDI).[6,47] A nested single-center cohort of prospectively enrolled infants undergoing major noncardiac surgery will examine whether nERAS implementation are measured (feasibility) and whether there is an impact on NDI at 18-month corrected age. All infants at HSC who undergo standardized neurodevelopmental follow-up as part of routine care after hospital discharge will be included.	The primary outcome of NDI is defined as any grade cerebral palsy or composite motor scores below 2 standard deviations as measured by the Bayley Scales of Infant and Toddler Development, 4th Edition (BSID-IV) at 18 months corrected age. BSID-IV is a comprehensive, standardized neurodevelopmental assessment tool with high reliability for evaluating developmental delays in infants and toddlers.[54]	The BSID-IV (cognitive, motor, and language subsets) will be administered at 18-months corrected age.

3.2. **Secondary Objectives (Effectiveness)**

Aims 1 and 2: To measure the clinical effectiveness of nERAS implementation. As secondary outcomes, we will use the core clinical outcome measures to reflect surgical recovery pre-implementation and during active- implementation of nERAS.

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
Surgical site infection	Core surgical complication with significant impact on length of stay and recovery.	Retrospective chart review using standardized definitions.	Within 30 days of surgery.
Sepsis	Core neonatal clinical outcome.	Retrospective chart review using standardized definitions.	Within 30 days of surgery.
Unplanned reoperation	Core surgical complication.	Retrospective chart review using standardized definitions.	Within 30 days and one year of surgery.
Opioid use	Neonates experience pain. Although opioids are effective, they have side effects and therefore opioid-minimizing strategies for pain management are best.[55-57]	Retrospective chart review documenting cumulative dose (in Morphine Milligram Equivalents [MME]), days on narcotics, narcotic prescription on discharge.	Cumulative dose of narcotics within first 7 days after surgery. Number of days of post-operative narcotic use (up to 30 days post-operatively).
Mortality	Core neonatal clinical outcome.	Retrospective chart review.	Within 30 days and one year of surgery.
Index NICU length of stay (LOS)	Number of days spent in the NICU (total and post-operatively).	Retrospective chart review documenting readiness for discharge to ward (regardless of bed availability).	Up to one year.

Total hospital LOS	Number of days spent in hospital (total and postoperatively).	Retrospective chart review.	Up to one year.
Readmission	Balancing measure for length of stay.	Retrospective chart review at hospital of index presentation.	Within 30 days of discharge.
Neurodevelopmental injury	Hammersmith Infant Neurological Examination (HINE).The HINE is an objective, standardized neurological examination tool with a high predictive value for the early detection of motor delay and cerebral palsy, which will be included to detect early motor impairments and infants at an increased likelihood of cerebral palsy. As a part of the secondary outcomes, gross and fine motor skills will also be assessed at 8 and 12 months of corrected age using the Alberta Infant Motor Scale (AIMS) and the Posture and Fine Motor Assessment (PFMA).[58-60] Information regarding post-neonatal seizures, pre-operative and post-operative head ultrasounds and head MRIs will also be collected retrospectively.	Retrospective chart review of standardized neurodevelopmental follow-up assessments.	4 months cGA (HINE) 8 and 12 months cGA (AIMS and PFMA) Head MRI and pre/post-operative head ultrasounds at term

Additional exploratory outcomes will include: Primary surgical diagnoses (pre-operative and post-operative), urgency, invasiveness and comorbidities at the time of surgery, surgical procedures performed, total surgery time, procedure and anesthesia length of time, intra-operative events, antibiotic regimen, blood culture results, temperature regulation pre-operatively/intra-operatively, pressor and maintenance fluids used, pre-operative/post-operative medications, sedatives and pharmacologic measures used, regional techniques used, post-operative paralysis, blood product transfusions and reactions, perioperative communications, parental involvement, pre-operative feeding, mucous fistula refeeding and stomas, breastmilk at

discharge, surgical site preparation, modes of ventilation, unplanned/planned reintubations and extubations, glucose monitoring, surgical complications at 30-days and 1-year post-operatively, emergency department visits/unplanned and planned re-admissions, central line days, days to full enteral feeds, days of supplemental respiratory support, growth parameters (raw values, percentiles, and z-scores), composition/tube feeding at discharge, and continuous electroencephalography (cEEG).

3.3. **Primary Outcome (Implementation)**

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
Adoption	Will assess concordance between care provided and evidence-based guideline recommended care.	Retrospective chart review using standardized definitions.	Within 30 days of surgery. Will be measured prior to structured implementation, during active implementation, and during sustainability audits at 6 and 12 months after active-implementation has been completed.

3.4. **Secondary Outcomes (Implementation)**

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
Implementation Readiness	To assess baseline readiness for nERAS implementation to enhance generalizability of results.	Atlas context surveys augmented by implementation team focus groups.[61]	Pre-implementation.
Appropriateness, Acceptability, and Feasibility of healthcare professionals	Healthcare provider perspectives on barriers and facilitators to care will shape implementation strategy and enhance generalizable implementation guidance.	IAM, AIM, and FIM validated surveys augmented by implementation team focus groups.[65]	Pre-implementation and during active-implementation.
Acceptability and appropriateness of caregivers	Family caregivers are an integral part of the healthcare team. Their	AIM and IAM survey and semi-	Active implementation.

	perspective will shape implementation to ensure family-centred care is enhanced at each step.	structured interviews	

4. Study Design and Endpoints

4.1. Description of Study Design

An international multicenter stepped-wedge cluster hybrid type II effectiveness- implementation study will be conducted at three clusters: Alberta Children's Hospital (Calgary, Canada; ACH), The Hospital for Sick Children (Toronto, Canada; HSC), and Great Ormond Street Hospital (London, UK; GOSH). The trial will measure baseline perioperative and surgical outcomes and then actively implement a recently published Neonatal ERAS guideline that targets neonatal patients undergoing major non-cardiac surgical intervention during NICU admission.[37] Each NICU will serve as a cluster and as its own control as there is variable existing ERAS implementation. Implementation of the guideline does not require any study-specific interventions as the guideline details evidence-based best practice and so the intervention is at the level of the cluster (NICU) to encourage adherence to best practices. The three clusters will collect the POM Score (temperature, pH, pCO_2, glucose, and unintended respiratory events) and 30-day clinical outcomes during a 6-month observation period (usual care unexposed cohort) and then during a subsequent 12-month active-implementation period (active-implementation exposed cohort).

A non-randomized stepped-wedge cluster trial is a pragmatic study design that ensures all three NICUs (clusters) will receive the intervention (multifaceted implementation of nERAS).[62-64] The sequential roll-out will permit dedicated resources and centre-specific adaptation while permitting robust assessment of between- and within-cluster variability (accounting for any temporal trends). Study centres were selected to maximize generalizability by including a high-volume international cluster in addition to a moderate- and high-volume Canadian centre. This is reflective of the neonatal surgical community that relies upon collaboration to maximize impact.

All eligible patients will be inpatients admitted to one of the study center's Neonatal Intensive Care Unit. All patients will require a major non-cardiac surgery and return to the NICU at least overnight post-operatively to be eligible. Neonates must be less than cGA 44 weeks at the time of surgery. See inclusion/exclusion for further details.

Each cluster will have a 6-month pre-implementation cohort and a 12-month active-implementation cohort. There is a one-year follow-up window for Clusters at ACH and GOSH. There is an 18-month follow-up window at HSC due to nested neurodevelopmental follow-up. Given the sequential on-boarding of active-implementation, the trial is intended to conclude in 4.5 years.

All effectiveness data collection will be performed retrospectively as no patient-level study-specific assessments are required; investigations collected as standard of care will be ascertained

from retrospective chart assessment. No masking of data collectors will be possible due to specified center-wide transition from baseline to active-implementation.

Implementation aim will be assessed through retrospective chart review (to measure adoption) and qualitative surveys/focus group discussions with healthcare providers and family caregivers.

4.2. Duration of Study Participation

There is a one-year follow-up window for clusters at ACH and GOSH. There is an 18-month follow-up HSC due to nested neurodevelopmental follow-up (which is conducted around 18 months of corrected gestational age and therefore may be up to 24 months post-surgery depending on gestational age at time of surgery).

4.3. Total Number of Participants and Sites

Recruitment will end when each center has a 12-month period of active-implementation participants enrolled (time frame selected as this will allow adequate enrollment at the lowest-volume center to meet the necessary sample size for quantitative assessment and will be sufficient in length to permit iterative implementation for implementation assessment). It is expected that approximately 555 participants will be screened in order to produce 400 evaluable participants. There are three sites (HSC, ACH, and GOSH). Based on pre-existing surgical volumes, we estimate there will be 300-350 screened patients at HSC in 18 months, 120-140 at ACH, and 135-150 at GOSH. We estimate ~80% of patients screened will meet our inclusion criteria. Pilot data suggested 90% of eligible patent/caregivers provided consent for enrollment for a final total number of 400 eligible patients.

4.4. Implementation Strategy

A multifaceted implementation strategy will be employed to include three components: Audit and feedback; Adapt and tailor; and Internal-external facilitation.[66] By design, the implementation strategy will be further shaped by the site-specific Implementation Readiness Assessments. At a minimum, Audit and feedback will provide each cluster with their monthly clinical and adoption outcomes (e.g., 3 SSI, 100% adherence with preoperative antibiotics within one hour of incision). Adapt and tailor will identify areas of need within and across clusters and mini-PDSA cycles for selected outcomes will be supported (e.g., development of a ‘extubation in the OR’ guideline if a cluster identifies they have unnecessary prolonged intubations). Finally, a research coordinator/assistant will provide implementation support at each cluster in conjunction with existing QI and clinical teams. Once a site transitions to Active-Implementation, they will be linked to other site’s facilitators for sharing of experience and resources (Internal-external facilitation).

5. Study Enrollment and Withdrawal

5.1. Effectiveness Participant Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Consent provided by substitute-decision maker

- Aged ≥24 weeks gestational age at birth and <44 weeks corrected gestational age (cGA) on day of index surgery
- Requires major non-cardiac surgery requiring general anesthetic (e.g., thoracotomy, laparotomy, ventriculoperitoneal shunt, choanal atresia repair, etc.)
- Admitted preoperatively to a study NICU (HSC, ACH, or GOSH)

5.2. Effectiveness Participant Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Infants undergoing cardiac surgery as sole index surgical intervention
- Sole minor index surgery (e.g., central line placement, eye exam under anesthesia)
- Aged less than 24 weeks estimated gestational age at birth or greater than 44 weeks corrected gestation age on day of index surgery
- Intraoperative mortality
- Genetic anomaly associated with lethality (e.g., trisomy 13 or 18)
- Preoperative ECMO (extra-corporeal membrane oxygenation) cannulation
- Prior fetal intervention (e.g, FETO for CDH)
- Immediate post-op destination is not NICU (e.g., surgical ward or PICU)

5.3. Implementation Participant Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Healthcare provider (surgeon, anesthesia provider, bedside NICU RN, neonatologist or relevant trainee) who provided care OR is a parent/caregiver to an eligible infant from the effectiveness arm

5.4. Implementation Participant Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Healthcare providers and/or caregivers who do not consent to participate in Implementation surveys or interviews.
- Healthcare provider who has already completed the relevant implementation survey >3 times (some healthcare providers will provide care for multiple infants in the study)

5.5. Strategies for Recruitment and Retention

Potential participants will be identified by the Treating Physician (neonatologist and/or surgeon). They (or a delegate within the circle of care) will introduce the study to substitute decision maker/parents and seek permission for a member of the research team to meet with them at bedside in the NICU or to discuss by phone the study (by parent/SDM preference).

Once a patient has been recruited, all further data collection will rely upon data collected as part of their perioperative and postoperative care. No explicit research-related reminders will be

provided. Reminders regarding follow-up appointments will follow existing protocols as the participating centers.

Once a patient has been recruited, their healthcare providers and caregivers will be separately approached to seek consent to participate in the qualitative implementation arm. If healthcare provide willingness to participate, they will provide implied consent form at the time of survey completion. For caregivers, they will be given the option to opt in or out of this qualitative arm during the consent process for the effectiveness arm. If they provide consent to participate, we will collect their contact information to provide the surveys and/or invitation to participate in the focus group discussion.

5.5.1. Compensation for Study Participation

This study involves implementation of a clinical care pathway (nERAS) within the existing standard of perioperative care in the NICU. Participation does not require any additional visits, procedures, or time commitment from families beyond routine clinical care. Data collection will be based on information already captured through the patient's medical record and standard follow-up assessments. However, there will be an honorarium provided to parents/SDMs for their participation in a virtual focus group. Reimbursements for child care and parking will be provided to Family Advisory panel for any in-person meetings.

5.5.2. Avoiding Undue Influence

Several steps will be taken to avoid any actual, apparent, perceived, or potential undue influence during recruitment and consent. First, recruitment and consent will not be conducted by any member of the participant's direct circle of care. Second, all study information will be presented in a neutral, non-coercive manner that emphasizes voluntary participation and the participant's right to decline or withdraw at any time without any impact on the care they receive. Third, adequate time will be provided for participants to review study materials, ask questions, and consider their decision without pressure (i.e. families will be approached based on their availability 72 hours before or up to 5 days after scheduled surgical procedure by a delegated study team member who will introduce and explain the study in more details, provide and review the appropriate consent form with the parent/guardian and obtain consent for participation.). Finally, the study team will follow a standardized consent procedure to ensure consistency and to minimize any perception of bias or influence.

5.6. Participant Withdrawal or Termination

5.6.1. Reasons for Withdrawal or Termination

Participants are free to withdraw from taking part in the study at any time upon request. An investigator may terminate participation in the study if:

- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Of note, NICU non-adherence with implementation of ERAS element(s) will NOT be a reason for exclusion or study termination.

- Participants may choose to withdraw from the Implementation arm without affecting their enrollment in the Effectiveness arm. They may also choose to withdraw from the Effectiveness arm while still providing feedback to the Implementation Arm.

5.6.2. Handling of Participant Withdrawals or Termination

Participant's parent/legal guardian are free to withdraw their child from taking part in the study at any time upon request (until data analysis is completed at which time data will be de-identified).

- If a participant withdraws, consent will be sought to include any previously collected data, but on request, the patient's study record can be destroyed up until the time of data analysis.

Patients will not be replaced if they discontinue or withdraw. Furthermore, given the duration of the study, minor protocol modifications may be required to incorporate emerging evidence or updates to ERAS best practices. Such adjustments will ensure continued alignment with current standards of care and will not require suspension of study enrollment or participant withdrawal unless specific criteria for withdrawal are met. Subsequent amendment to the REB will be made if there is any substantive change to the protocol. Additionally, participants will not be withdrawn from the study in the event of a protocol deviation made at the discretion of the healthcare provider to prevent or eliminate an immediate risk to the participant. Such deviations will be documented and reviewed as outlined in Section 13.

6. Study Assessments and Procedures

Potentially eligible infants will be identified by the Neonatal Surgical team (to include Neonatology and/or Surgery) at the time a surgical diagnosis is made and/or major non-cardiac surgery is planned. The inclusion criteria will be provided to the Neonatal Surgical team and if the infant is deemed potentially eligible, they will ask the parents for permission to be approached by the research team and then the Study Team will be notified who will contact caregivers to discuss informed consent in person or virtually. No deviations of care or specific medical assessments are required. The Informed Consent process will occur pre-operatively if possible, but can also be obtained up to 5 days post-operatively. If parents initially provide verbal consent by telephone, they will be provided the written consent documents at earliest convenience and provide signed written consent at that time. These procedures are reflected in the Schedule of Activities.

Once an infant has been enrolled, their treating surgeon, neonatologist, anesthesiologist, and perioperative bedside nurses will be identified from the clinical record and will be considered eligible for the Implementation Arm. The patient caregiver will also be asked at the time of providing consent for the Effectiveness arm if they are willing to be separately contacted to provide qualitative feedback. Refusal to participate in the Implementation Arm does not exclude a patient from the Effectiveness arm.

7. Study Procedures / Evaluations

7.1. Procedures / Evaluations

For the effectiveness assessment, all study data will be collected retrospectively from data within the patient's medical record that was ascertained as part of normal standard of clinical care. Retrospective chart review will occur at minimum on a biweekly basis to provide active disaggregated audit feedback to the Clusters (e.g., % of patients who had an unplanned extubation). No study-specific procedures or evaluations are necessary. No specimens will be collected for study purposes.

All data will be collected from Electronic Medical Records and be input into REDCap according to the study's variable list. In the event that any data is collected by paper, we will input into REDCap and destroy the paper record.

For the implementation arm, healthcare providers who have provided direct care to an eligible infant(s) in the past 90 days will be contacted to participate in the Implementation Surveys. These surveys will be online and performed using REDCap. A maximum of three invitations per provider will be offered to avoid excessive repeat evaluation. Caregivers will be contacted within one week post-operatively and reminded at three weeks post-operatively if the surveys are not completed. If they provide consent to participate in focus groups and/or semi-structured interviews, these will occur within 6 months of their child's surgery.

Audio recordings of focus groups/interviews will be captured using secure hospital Teams and/or Zoom recordings. Teams/Zoom recordings will be acquired using SickKids secure network and will be transcribed verbatim by SickKids' Microsoft Copilot, a protected platform. Transcription will occur on secure, password-protected computers connected to the SickKids network drive, accessible only to authorized study personnel. During transcription, all personal identifiers (e.g., names, locations, or other potentially identifying details) will be removed to produce de-identified transcripts. No third-party or online transcription services will be used. Once transcription and quality checks are complete, audio files will be permanently deleted from the device. Only de-identified transcripts will be retained for analysis and securely stored on the SickKids network drive, and no recordings or identifiable data will be stored on personal devices, cloud services, or external media outside SickKids' secure network.

8. Statistical Considerations

8.1 Study Hypotheses

We hypothesize that active-implementation of a Neonatal ERAS Guideline will improve the median POM Score by 15%. This means an additional 15% of infants will have early perioperative measurements reflecting physiologic stability. Additionally, we hypothesize that by improving perioperative stability, there will be improved short, medium, and neurodevelopmental clinical outcomes.

8.2 Sample Size Determination

The primary effectiveness outcome is perioperative physiologic stability as measured by the POM Score. This score reflects maintenance of normothermia, normoglycemia, appropriate ventilatory strategies, prevention of acidosis/alkalosis, and the absence of unintended respiratory events in the first 24 hours after surgery. A retrospective cohort of 766 patients at HSC had a mean monthly POM score of 60% (reflecting 60% of surgical neonates met all 5 criteria; unpublished data). Assuming a 1:2 ratio of unexposed to exposed patients, and an assumed increase of 15% in the POM score (from 60% in the unexposed window to 75% in the exposed window), 340 patients total are needed to achieve 80% power. This assumes 114 unexposed and 228 exposed patients. This calculation was done assuming a two-sample proportion test with unequal sample size, with an alpha of 0.05, with a two-sided alternative hypothesis.

8.3 Statistical Methods

POM scores will be compared pre-intervention to post-intervention using multivariable mixed-effects logistic regression models with random intercepts per site. An interrupted time series approach will be taken by standardizing time relative to implementation dates between sites. Changes in slope and intercept between pre and post implementation date will be assessed using interaction terms. Adjustment for potential confounders will be considered in the model. Odds ratios will be reported with 95% confidence intervals.

The primary neurodevelopment outcome measure (NDI) will be compared between pre-ERAS and ERAS-exposed infants using an interrupted time series and adjusted for potential confounders. Regression analysis will be used to relate perinatal, perioperative (POM Score), and short-term surgical outcomes to development of NDI. Univariable and multivariable random effect logistic regression models will be used to derive unadjusted and adjusted odds ratios and 95% CIs.

The Implementation primary outcome is Adoption (number of relevant nERAS recommendations followed for each patient). The sample size as determined for Aim 1 will detect a 10% improvement in adoption. Quantitative and qualitative analyses will be performed for implementation outcomes of feasibility, fidelity, adoption, acceptability, and appropriateness. Descriptive statistics will describe pre-implementation and progress surveys' quantitative results and will be compared using a paired t-test to describe changes over time. Focus group transcripts and implementation activity logs will be deductively coded on NVivo using the PARIHS Framework to describe the interplay of evidence, facilitation, and context for nERAS implementation. Purposive semi-structured interviews with neonatal perioperative healthcare providers and parent/family caregivers will be conducted until data saturation, and they will include sex and gender sampling.

9. Source Documents and Access to Source Data / Documents

Access to study records will be limited to REB-approved members of the study team. The PI will permit study-related monitoring, audits, and inspections by the REB and / or University compliance and quality assurance groups of all study related documents (e.g. source documents,

data collection instruments, study data etc.). The PI will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as a PI in this study implies acceptance of potential inspection by REB and / or applicable University compliance and quality assurance offices.

10. Ethics / Protection of Human Participants

10.1. Ethical Standard

The guiding clinical research ethical principles will be followed by the study team.

10.2. Informed Consent Process and Documentation

Patients will be identified by a team member from a primary circle of care (neonatal nurse/neonatologist/surgical fellow/nurse practitioner) during routine clinical care and will introduce the study. If the family is interested, parent/legal guardian will be approached by the study team to provide additional study information and obtain informed consent for participation in the effectiveness and/or implementation arm. An attempt will be made to obtain consent prior to the surgical procedure, however, if not successful, then a deferred consent model will be used in which there will be enough time for the family to review the information and to provide their fully informed consent. Families will be approached based on their availability 72 hours before or up to 5 days after scheduled surgical procedure by a delegated study team member who will introduce and explain the study in more details, provide and review the appropriate consent form with the parent/guardian and obtain consent for participation. If the family is interested and agrees to speak to a research team member, parent/legal guardian will be approached either in person or remotely. A delegated research team member will contact the parent/legal guardian via preferred method stated during the initial discussion with clinical team (i.e., Zoom Healthcare or MS Teams or OTN or telephone). The initial discussion by clinicians will be documented as per institutional requirements. Consent discussion will be conducted in person or remotely (video, telephone, etc.). For remote consent discussions, video conferencing (e.g. Zoom Health care or MS Teams) will be preferred to assess visual cues and ensure the parent/legal guardian understands the research study and the commitment required. The research team will provide the parent/legal guardian with a copy of REB approved informed consent either in person or will send it electronically (e.g., email, via REDCap link) before the scheduled meeting. If parent/legal guardian initially provide verbal consent remotely 24 to 72 hours before or after scheduled surgical procedure, they will be provided the written consent documents at earliest convenience and provide signed written consent at that time. Whether conducted in person or remotely, informed consent will be documented according to institutional policies and procedures. Electronic methods of documenting informed consent will be considered where physical signing of the informed consent document will not be possible and will include email or REDCap. Questions about their comprehension of the study will be asked during the conversation providing information about the study. Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study

participation. Extensive discussion of the risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be REB--approved and the potential participant will be asked to read and review the document. The delegated study team member will explain the research study to the potential participant and answer any questions that may arise. All potential participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Potential participant parents/legal guardians will have the opportunity to carefully review the written consent form and ask questions prior to signing. The potential participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The potential participant parents/legal guardians will sign the informed consent document prior to any procedures being done specifically for the study. The participant parents/legal guardians may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to the participant parents/legal guardians for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A paper copy of the signed informed consent document will be stored in the participant's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

Decision-making capacity refers to an individual's ability to understand information, appreciate relevant facts, and reason through their options, infer consequences, and apply values and beliefs. Capacity to consent will be assessed by the individual obtaining consent, which may be the PI or a delegated study team member. All delegated members who are not clinicians will receive appropriate training in capacity assessment prior to engaging in the consent process. These individuals will have access to the PI or a qualified clinician at any time if questions or concerns arise regarding a participant's decision-making capacity. This approach ensures that capacity assessments are conducted consistently, accurately, and in accordance with institutional and ethical standards. Training developed for non-regulated healthcare professionals will be compliant with SickKids' policies.

10.3. **Consent / Assent and Other Informational Documents Provided to Participants**

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant's parents/legal guardians. Written documentation of informed consent is required prior to starting data collection. The consent materials are submitted with this protocol.

Given the age of patients (neonates) there will not be any attempt to obtain participant assent as the study will have concluded prior to their reaching capacity for assent.

11. Data Handling and Record Keeping

11.1. Data Collection and Management Responsibilities

All data utilized in this study is de-identified, collected by the study delegated personnel. Patient data will be de-identified and coded. Study participants will be identified in research records with a unique study identification number. A template of the master linking log that will be used in this study will be submitted along with the study application. The code will be kept by the principal investigator of each participating center in a password protected file.

Furthermore, as dates (e.g. dates of birth, death, admission, discharge, etc.) are considered identifiable information, the study will implement a date-shifting strategy across all participating sites. All dates entered into REDCap will be automatically shifted by a predetermined number of days to prevent re-identification of individual participants. Each study site will use a different shift interval. The shifted dates will be used for all analyses and will not impact study procedures, timelines, or outcomes. This approach provides an added layer of protection while preserving the temporal structure necessary for research.

As per SickKids policies and procedures to safe-guard confidentiality, de-identified data will be stored in an encrypted file (a password protected excel spreadsheet available only to the PI and the study team member) on a locked/password protected computer.

Within the effectiveness arm, all data will be collected retrospectively from the patient's electronic medical record. Data collection will occur on an ongoing basis to allow for collation of adoption data for the Implementation Arm which will be presented back in a disaggregated monthly fashion. All data will be directly input into REDCap.

Data collection is the responsibility of the study staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents will be consistent with the source documents or the discrepancies will be explained and captured in a progress note and maintained in the participant's official electronic study record.

Study data will be entered into REDCap (Research Electronic Data Capture), a secure, web-based application designed exclusively to support data capture for research studies. REDCap is developed and maintained by a team at Vanderbilt University and licensed free of charge by the Research Institute at The Hospital for Sick Children. The application and data are housed on servers provided by The Hospital for Sick Children. These servers are located within SickKids secure data center. Local support for REDCap is provided by SickKids Research IT. The de-

identified information collected for the study purposes will be entered and maintained in a secure data sheet using the online platform REDCap designed for this project to centralize data entry and data maintenance. This secure database will be updated and maintained by the SickKids study coordinator, and only the main investigators will have access to the master spreadsheet in order to minimize any possible breach in confidentiality. The database will be accessible using a username and password from a password-protected hospital computer. Partnering institutions will be able to compile their local data onto our database and will only have access to their local institutions' data.

11.2. Study Records Retention

11.2.1. Data Storage

We will be very cautious about protecting patients' identification by restricting the access to the patients' information to only those key researchers who need this information to carry out one part of the study. All information and data for this proposed study will be carefully kept by key research personnel on password protected computers. Data will be entered into a centralized REDCap database located within SickKids secure data center. Data included and shared with the lead site for analysis will be aggregated and de-identified. Furthermore, identifiable information will be securely recorded in master linking logs separate from the remainder of the study documents (respective to the implementation and effectiveness phases of the study), which will only be accessible by delegated study team members/the PI.

Data will be retained for seven years from the last publication.

11.2.2. Data Retention and Destruction

De-identified data will be entered into a centralized REDCap database located within SickKids secure data center. Data included and shared with the lead site (SickKids) for analysis will be aggregated and de-identified. As required per the SickKids policy the PHI will be stored behind two locks and will be stored with two separate passwords/authentication methods. The physical safeguards that we will be using to securely maintain our data include locked offices, cipher/coded locks and access cards. The administrative safeguards that we will be using to securely maintain our data are: study data will be de-identified. A master linking log with identifiers will be password protected and kept and stored separately from the data; computer passwords only with research team; locked folder on SickKids shared drive and we will have a designated individual responsible for controlling who has access to data.

12. Protocol Deviations

The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without documented approval from the REB, except where necessary to eliminate an immediate hazard(s) to the study participants. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. All protocol deviations will be documented: the Principle Investigator will assess each protocol deviation to determine the impact to the patient's rights, safety, or welfare, study efficacy and data integrity. If there is any

uncertainty regarding the impact of the protocol deviation, the PI will consult with the Medical Monitor.

Protocol deviations will not exclude a patient; instead, they will be recorded as a part of the implementation assessment of adoption.

13. Publication and Data Sharing

An executive committee with representatives from the three study sites will be responsible for developing publication procedures and resolving authorship issues. This will be outlined in the study agreements. Furthermore, this study will be registered on *ClinicalTrials.gov* prior to participant recruitment. The registration will include study design and outcome details and will be updated as necessary to reflect any protocol amendments throughout the study period.

13.1. Communications and Deliverables

13.1.1. Participants and Substitute Decision-Makers (SDMs)

Individual participants or their substitute decision-makers will not receive personal health results, as study data are de-identified and analyzed in aggregate. Once the study is complete and results are published, publications will be available for review and a plain-language summary of the overall findings will be prepared and made available to participating sites. Families will be informed that they may request a copy of this summary through the study coordinator. Any summaries or communications for participants will be reviewed and approved prior to dissemination to ensure accessibility, accuracy, and compliance with institutional and privacy policies. We will work with our Family Advisory committee to develop appropriate knowledge translation strategies to empower families with relevant findings.

13.1.2. Scientific Community

13.1.2.1. Presentation and Publication Plan

Results from this study will be disseminated through presentations at national and international scientific meetings focused on neonatology, pediatric surgery, and perioperative care. The research team will also develop a knowledge translation strategy to share findings among participating NICUs, including presentations at departmental rounds and internal seminars.

De-identified data and aggregated results may be used in future analyses or guideline updates, consistent with participant privacy and institutional data-sharing policies. The study team also intends to provide summaries of key findings in lay language suitable for hospital communications and knowledge translation materials, with formal approval before any media release.

Study findings will also be submitted for publication in peer-reviewed journals relevant to neonatology, pediatric surgery, and perioperative medicine. Authorship will ensure contributions are accurately reflected. The research team plans to publish results describing study design and clinical/implementation outcomes as manuscripts. Publications will present only de-identified, aggregated data to protect participant privacy. All manuscripts will undergo internal review by the

study steering committee and approval processes prior to submission. Findings may also contribute to future guideline updates or secondary analyses in collaboration with the ERAS Society and other partner institutions.

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