



The Canadian Neonatal Network™/Le Réseau Néonatal Canadien™

2025 CNN-CPTBN Annual Meeting

Research Proposal

Multi-strain Probiotics to Prevent Necrotizing Enterocolitis in Very Preterm Infants: A Stepped-Wedge Cluster Randomized Trial

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Necrotizing enterocolitis (NEC) remains a devastating disease among Canadian preterm infants. Probiotics have emerged as an effective measure to prevent NEC. The effectiveness of probiotics is disease- and strain-specific. The discontinuation of the most used multi-strain probiotics in Canada presents an opportunity to systematically evaluate a new probiotic product before clinical implementation. Canadian NICUs, supported by the Canadian Neonatal Network (CNN), are eager to conduct this trial, leveraging CNN's robust infrastructure for multicenter studies.

A stepped-wedge cluster randomized trial (SW-CRT) design will address cross-contamination challenges seen in previous probiotic trials. This study will examine the efficacy of the probiotic combination of *one billion Bifidobacterium animalis subsp. DSM 15954lactis* and *Lactocaseibacillus rhamnosus GG*.

Research question

In preterm infants of <32 weeks' gestation, does multi-strain probiotics decrease NEC compared to no treatment?

Study Design

Stepped-Wedge Cluster Randomized Trial (SW-CRT). Each participating NICU will serve as a cluster, transitioning from the control phase (no probiotics) to the intervention phase (administration of multi-strain probiotics) at pre-specified time points.

Study Plan

1. Trial Population

- **Inclusion Criteria:**
 - Preterm infants <32 weeks gestational age.
 - Birth weight <1500 g.
 - Receiving enteral feeds within 72 hours from birth.
- **Exclusion Criteria:**
 - Major congenital anomalies.
 - Conditions affecting gastrointestinal systems that prohibit infants from starting feed in the first 72 hours after birth.

2. Randomization and Intervention

- **Cluster Randomization:** NICUs will be randomized to transition from control to intervention at designated intervals.
- **Intervention:** Multi-strain probiotic combination will be administered once daily (0.5 g sachet) within 24 hours of starting enteral feeding.

3. Control Phase

- No probiotics will be administered. Outcomes will be recorded to establish baseline incidence rates of NEC and related parameters.



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4. Intervention Phase

- Probiotics will be introduced, and the same outcomes will be monitored. Individual consent will be sought before giving probiotics to the study subject.

5. Sample Size Calculation

The trial will be powered to detect a clinically significant reduction in NEC incidence, with adjustments for clustering and the SW-CRT design. Preliminary estimates suggest a sample size of approximately 2160 infants across 12 NICUs (preliminary calculation).

6. Data Collection and Management: RedCap and CNN unique identifier. This RedCap is to monitor safety outcomes and patient enrolment. CNN will be used for main data collection. Additional data will be collected for the study using standardized data forms. A central coordinating center will oversee data monitoring, quality assurance, and analysis.

7. Ethical Considerations and Health Canada approval

- Individual consent will be sought to use probiotics and collect data for the study in the intervention arm. The consent will be taken to collect data only in the control arm.
- Health Canada approval for the study produced will be submitted prior to presentation.