The Canadian Neonatal Network™/Le Réseau Néonatal Canadien™

2025 CNN-CPTBN Annual Meeting

Research Proposal

Digital Twins to Mimics the Control Arm of a RCT: a "Proof-of-Principle" Feasibility and Appropriateness Study

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Background/Rationale

Digital twins (DT) are virtual replicas of physical entities or systems that can be used for various purposes, including simulation, testing, and prediction, gaining momentum in health care with its application in personalized medicine, hospital management, and medical device development. A digital twin (DT) in healthcare is used to simulate, justify, and optimize various aspects of healthcare delivery and patient outcomes using a virtual representation of a patient, organ, medical device, or healthcare system.

Despite RCTs being the gold standard for drug and device development research, more than half are underpowered for sample size or are based on calculations of unreal effect size such that they could not be replicated. This, in addition to certain RCT terminated halfway due to recruitment issues or funding challenges, makes it very difficult to conclude efficacy of any studies with high certainty. DT concept can potentially address these challenges by reducing the number of physical (real) participants required for trials, lowering cost, shortening duration, increasing diversity of included population (potentially), allowing use of standardized virtual controls and removing ethical concerns regarding use of placebo. This will be a "Proof of Concept" study using one completed RCT to assess feasibility and applicability of DT as a control arm for a RCT. The results of this study will have a significant impact in informing future trials to potentially reduce costs related to patient enrollment and lead to early completion, accelerate drug development, and increase access to experimental treatments.

Objectives and Hypotheses

Primary objective:

To assess the feasibility and appropriateness of using DTC to generate a mimicked control arm of a completed multicenter RCT utilizing the Canadian Neonatal Network (CNN) Database.

Primary null hypothesis: There would be significant difference between DT Controls generated from CNN database and actual controls enrolled in MOBYDICK RCT for baseline characteristics and outcomes.

Primary alternate hypothesis: There would be no significant difference between DT Controls generated from CNN database and actual controls enrolled in MOBYDICK RCT for baseline characteristics and outcomes.

Secondary objectives:

(i) To analyze the scientific validity (outcomes comparison) of DT-based control arm neonates, and
(ii) To evaluate the technical, operational, and economic feasibility of implementing DT in RCTs.

Secondary null hypothesis: Even by increasing the number of control DT (1:2 or 1:3 or 1:4), we cannot increase validity of DT selection as measured by differences in characteristics and outcomes.

Secondary alternate hypothesis: By increasing the number of control DT (1:2 or 1:3 or 1:4), we can increase the validity of DT selection as measured by differences in characteristics and outcomes.

Study Design and Datasets

In this "Proof of Feasibility" study, we will use the MOBYDICK trial dataset from an already completed and published RCT control population as a reference set, and generate DT using the Canadian Neonatal Network (CNN) dataset. The base cohort will be identified from the CNN database using the inclusion criteria of MOBYDICK RCT on 1:1 basis. Our aim is to identify at least one but up to four DT control. If more than four DT controls are identified, the selection will be random via computer. There were 255 control infants in the original MOBYDICK RCT. Since this a "proof of concept" study, our sample size is limited by what controls we find. It could be 255 if we find 1:1 matched DT only or up to 1020 DT if we find 4 control DT for one real control neonate.

Outcomes

Our primary outcome for the study is to assess feasibility and appropriateness of DT to be used as control arm of RCT. Feasibility will be assessed by identifying whether we are able to find suitable DT and how many suitable DTs are identified per control patient. Appropriateness will be assessed by comparing outcomes of DT and real control arm patients.

Analyses and Reporting of results

Please see below for detailed analytical plan. By systematically applying these statistical methods, we will provide a comprehensive comparison of DT with actual controls. This approach allows for a nuanced understanding of where each model excels or falls short in generating DT that reflects real-world patient populations.

Analyses

Comparison between actual controls and DT controls will be made using covariate distribution comparison, correlation structure preservation, overall similarity metric, and UMAP visualization to evaluated differences and similarities between the cohorts. Secondarily, we will evaluate how increasing the control group size reduces the differences in baseline characteristics of DT controls and actual controls using standardized differences (or standard errors) as a matrix. By systematically applying these statistical methods, we can provide a comprehensive comparison of DT with actual controls, assessing various aspects of synthetic data quality, utility, and efficiency. This approach allows for a nuanced understanding of generating DTC that reflects real-world patient populations.

Timeline

-3 months to 0 month: REB approval and approval from trial committee of MOBYDICK
0-2 months: Complete data sharing agreements
2-3 months: Preparation of CNN database
3-6 months: Identification of DT from CNN
6-9 months: Analyses and review of results
9-11 months: Preparation of report, presentation of results, preparation of publication
12 months: Investigator meeting, preparation of KT and Development of proposal for multi-RCT evaluation and simultaneous live RCT identification of DT.