Contemporary Clinical Trials 72 (2018) 8–15

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

# Design and rationale of the "Sedation strategy and cognitive outcome after critical illness in early childhood" study

Martha A.Q. Curley[a,b,c,*], R. Scott Watson[d,e], Amy M. Cassidy[a], Cheryl Burns[f], Rachel L. Delinger[e], Derek C. Angus[g], Lisa A. Asaro[h], David Wypij[h,i,j], Sue R. Beers[f], for the RESTORE-cognition Study Investigators[1]

[a] From the School of Nursing, University of Pennsylvania, Philadelphia, United States
[b] Perelman School of Medicine, University of Pennsylvania, Philadelphia, United States
[c] The Children's Hospital, Philadelphia Research Institute, Philadelphia, United States
[d] Department of Pediatrics, University of Washington, Seattle, United States
[e] Center for Child Health, Behavior, and Development, Seattle Children's Research Institute, Seattle, United States
[f] Department of Psychiatry, University of Pittsburgh School of Medicine, United States
[g] Clinical Research, Investigation, and Systems Modeling of Acute Illness Center, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, United States
[h] Department of Cardiology, Boston Children's Hospital, Boston, United States
[i] Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, United States
[j] Department of Pediatrics, Harvard Medical School, Boston, United States

ARTICLE INFO

*Keywords:*
Healthcare outcomes
Respiratory failure
Pediatric
Post-intensive care syndrome

ABSTRACT

There is increasing concern that sedatives commonly used during critical illness may be neurotoxic during the period of early brain development. The *Sedation strategy and cognitive outcome after critical illness in early childhood* (*RESTORE-cognition*) study is a prospective cohort study designed to examine the relationships between sedative exposure during pediatric critical illness and long-term neurocognitive outcomes. We assess multiple domains of neurocognitive function 2.5–5 years post-hospital discharge, at a single time point and depending on participant and clinician availability, in up to 500 subjects who had normal baseline cognitive function, were aged 2 weeks to 8 years at pediatric intensive care unit admission, and were enrolled in a cluster randomized controlled trial of a sedation protocol (the *RESTORE* trial; U01 HL086622 and HL086649). In addition, to provide comparable data on an unexposed group with similar baseline biological characteristics and environment, we are studying matched, healthy siblings of *RESTORE* patients. Our goal is to increase understanding of the relationships between sedative exposure, critical illness, and long-term neurocognitive outcomes in infants and young children by studying these subjects 2.5 to 5 years after their index hospitalization. This paper highlights the design challenges in conducting comprehensive neurocognitive assessment procedures across a broad age span at multiple testing centers across the United States. Our approach, which includes building interprofessional teams and novel cohort retention strategies, may be of help in future longitudinal trials.

## 1. Introduction

Ensuring the safety and comfort of the > 100,000 critically ill infants and children supported on mechanical ventilation (MV) in the U.S. each year is integral to the practice of pediatric critical care [1–3]. Humane care of these young patients requires the use of sedating medications, most commonly combinations of opioids and benzodiazepines [2, 3]. Unfortunately, sedative use also carries risk. Animal studies found that even transient administration of benzodiazepines and other sedatives during periods of developmental synaptogenesis [4] caused widespread neuronal apoptosis and residual learning and memory deficits [5–9]. Sedation can be administered for days to weeks to > 90% of acutely-ill, ventilated infants and children [2, 3]. Thus, a commonly used treatment in critically ill young children may itself have detrimental, age-dependent long-term effects [10].

Most studies on this topic have analyzed large, existing databases to

* Corresponding author at: School of Nursing, University of Pennsylvania, Claire M. Fagin Hall, 418 Curie Boulevard - #425, Philadelphia, PA 19104-4217, United States of America.
*E-mail address:* curley@nursing.upenn.edu (M.A.Q. Curley).
[1] The *RESTORE-cognition* study investigators are listed at the end of the paper.

https://doi.org/10.1016/j.cct.2018.07.004
Received 4 April 2018; Received in revised form 25 June 2018; Accepted 9 July 2018
Available online 11 July 2018
1551-7144/ 

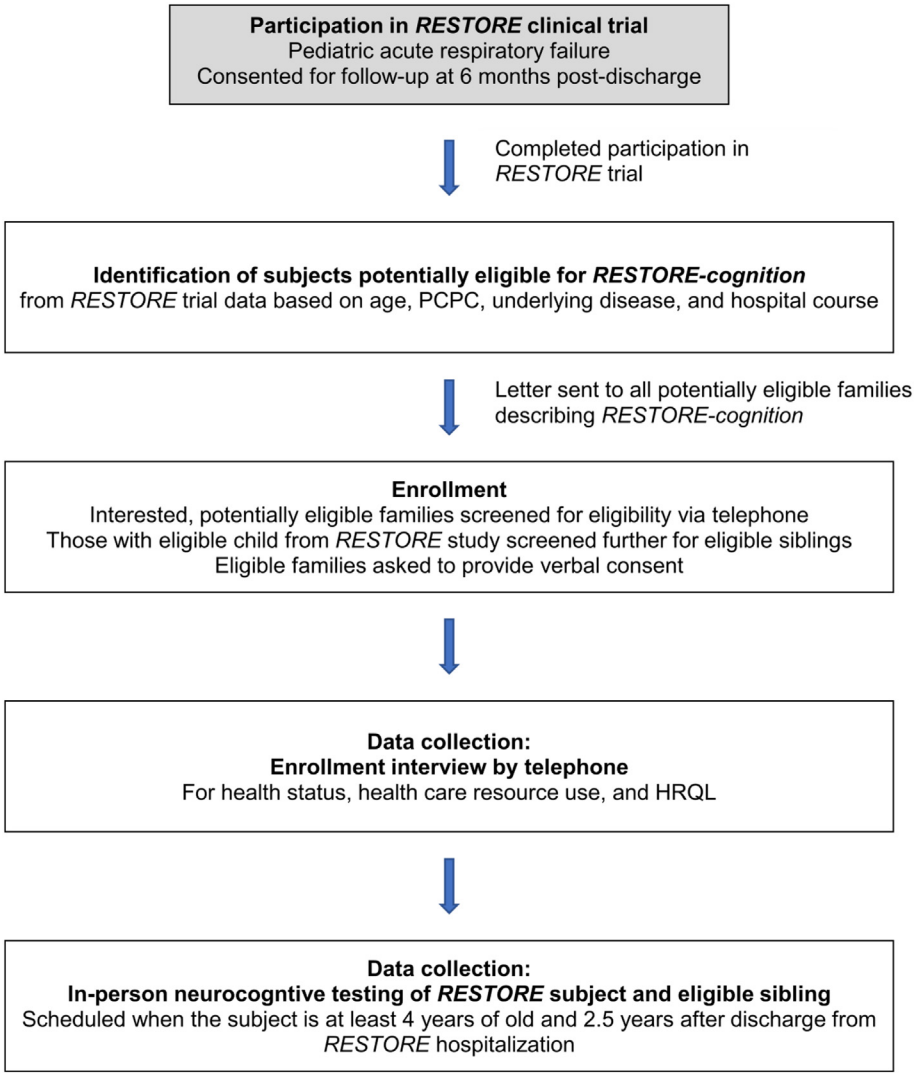


**Fig. 1.** Study recruitment and flow. HRQL – Health-related quality of life; PCPC – Pediatric Cerebral Performance Category.

explore relationships between exposure to anesthesia in infancy or early childhood and subsequent school-related learning problems or academic achievement [11–16]. In a population-based retrospective birth cohort study in Olmsted County, MN, children younger than 4 years receiving multiple anesthestics had higher than baseline rates of learning disabilities, with the risk increasing with anesthetic duration [14]. Using the same database, but comparing outcomes after vaginal vs. cesarean delivery and exposure to general vs. regional anesthesia, no relationship was found between anesthesia exposure and subsequent learning disabilities [13]. To our knowledge, there are no studies investigating neurocognitive outcomes after prolonged exposure to sedatives as used in the pediatric intensive care unit (PICU) in older infants and children.

An opportunity to increase our understanding of the long-term neurocognitive effects of sedation during pediatric critical illness was provided by the cluster randomized controlled trial (RCT) of a sedation protocol, *Randomized Evaluation of Sedation Titration for Respiratory Failure* (*RESTORE*, U01 HL086622 and HL086649). This trial enrolled 2449 patients at 31 sites across the U.S. to determine whether a sedation protocol used at intervention sites decreased MV duration and sedative exposure among children with acute respiratory failure (vs. usual care at control sites) [17]. The protocol did not change the duration of MV but did allow patients to be more awake while intubated and exposed to fewer sedative and analgesic medications. Detailed data were collected on doses and durations of sedative medications and in-hospital course.

In this study, *Sedation strategy and cognitive outcome after critical illness in early childhood (RESTORE-cognition)*, we are assessing multiple domains of neurocognitive function 2.5 to 5 years post-hospital discharge in a subset of *RESTORE* subjects and matched, healthy siblings. The purpose of *RESTORE-cognition* is to determine the relationships between sedative exposure during pediatric critical illness and long-term neurocognitive outcomes. The study is funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (R01 HD074757; Multiple Principal Investigators: Curley and Watson) and is being coordinated at the University of Pennsylvania (Philadelphia, PA) and Seattle Children's Research Institute (Seattle, WA).

## 2. Materials and methods

### 2.1. Objectives and hypotheses

*RESTORE-cognition* has two primary objectives/aims:

- To determine if the **magnitude of exposure to specific sedative medications** is associated with neurocognitive outcomes when controlling for severity of illness, hospital course, and baseline