ABSTRACT
DEFINING THE DIFFICULT-TO-SEDATE CLINICAL PHENOTYPE IN CRITICALLY ILL CHILDREN
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Each year thousands of critically-ill children receive sedation to help them tolerate intensive care therapies. A significant number of these children do not respond as expected to appropriately dosed sedation and remain agitated for some period, leading to iatrogenic injury and increased stress, as well as increased resource use. Children who remain under-sedated despite optimal therapy are considered “difficult-to-sedate”, but, to date, little data have been available to support an accurate description of this group of children. Recent attention to heterogeneity of treatment effect has spurred the development of clinical phenotypes that describe subgroups of patients within a disease process who differ in their clinical attributes and responses to therapy. Defining the difficult-to-sedate clinical phenotype in critically ill children is important because it will allow the use of sedation therapy targeted to the unique clinical, physiological, and developmental characteristics of the child.

The three papers developed in this dissertation study explored the concept of the difficult-to-sedate child clinical phenotype. A comprehensive review of the literature identified the lack of an operational definition and identified factors contributing to the clinical phenotype. These factors were used to develop an initial operational definition and construct a conceptual model. Expert critical care clinicians validated the elements of the operational definition through an assessment of face and content validity and proposed additional factors for inclusion in the model. A refined definition was tested using data from the RESTORE study. Characteristics identified through latent class and classification and regression tree analysis were consistent with the conceptual model proposed.
Decreasing the ambiguity that currently exists around the concept of the difficult-to-sedate child clinical phenotype is a major achievement of this study. A clear operational definition of the concept promotes its consistent measurement and facilitates future investigation, and allows useful comparisons across studies. The conceptual model and operational definition require further investigation and refinement, as well as validation by other investigators. This study suggests that a clinically meaningful population of difficult-to-sedate children requiring mechanical ventilation for a critical illness exists. Documentation of this phenotype promotes the development of evidence on the best way to support these children.