

## **The Promise of Pragmatic Trials for Critically Ill Neonates and Children**

Luregn J. Schlapbach<sup>1,2</sup>, MD, PhD, FCICM, ORCID 0000-0003-2281-2598

Mark J. Peters<sup>3,4</sup> PhD, ORCID 0000-0003-3653-4808

<sup>1</sup> Department of Intensive Care and Neonatology, and Children`s Research Center, University Children`s Hospital Zurich, Zurich, Switzerland

<sup>2</sup> Child Health Research Centre, The University of Queensland, Brisbane, Australia

<sup>3</sup> University College London Great Ormond Street Institute of Child Health, London, U.K

<sup>4</sup> Paediatric Intensive Care Unit, Great Ormond Street NHS Foundation Trust, London, U.K

### ***Correspondence:***

Luregn Schlapbach

Head, Department of Intensive Care and Neonatology

University Children's Hospital Zurich – Eleonore Foundation

Steinwiesstrasse 75

CH-8032 Zurich

phone +41 44 266 71 11

email: [luregn.schlapbach@kispi.uzh.ch](mailto:luregn.schlapbach@kispi.uzh.ch)

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Over 100,000 infants and children are admitted to neonatal and paediatric intensive care units in the UK annually. Infections and sepsis remain a leading cause of admission, short- and long-term morbidity, and mortality in this patient group<sup>1,2</sup>. Yet, the majority of diagnostic and therapeutic practices in these patients lack high grade evidence. This exposes children to suboptimal decision-making and ineffective or even harmful interventions. The cost to patients, families, and society of this evidence deficit is unknown. Is this simply attributable to the innate challenges of performing clinical trials (cost, time and availability of appropriately trained staff) or rather to the specific critical care setting (time-sensitive interventions, safety concerns, acceptability to staff and parents and the complexity of consent under acute stress)?

Encouragingly, the gap may be starting to close as the rate of neonatal and paediatric critical care randomized controlled trials (RCTs) has increased considerably over the past decade.

While recruiting critically ill children into RCTs may not yet be a standard of care, the availability of deferred consent options, the National Institute for Health and Care Research Health Technology Assessment programme (NIHR HTA) funding focus on real world effectiveness, the creation of research networks, and access to electronic health records have contributed to this development<sup>3,4</sup>. Of key importance was the push for pragmatic trials, aiming to resolve day-to-day uncertainties in clinical practice, addressing common questions and simple interventions through a design promising greater generalizability and feasibility.<sup>5</sup>

At the heart of the RCTs lies the intention to compare the performance of two or more interventions in a clinical setting which prohibits a fully controlled laboratory experimental setup. Explanatory RCTs attempt to demonstrate *efficacy* with less ‘noisy’ designs. These include ensuring the intervention is optimally delivered amongst carefully selected patients and sites. In contrast, pragmatic RCTs are more suited to test the *effectiveness* of the

intervention in real-world settings, accepting heterogeneity and clinician- and site-related variability. Recently, the COVID-19 pandemic unleashed the potential of this approach, generating high grade evidence across anti-infective, immunomodulatory, and diagnostic strategies over a short period of time thanks to highly agile pragmatic trial platforms such as RECOVERY<sup>6</sup>.

In this context, the work by Marshall et al on behalf of the NeoCLEAR Collaborative Group (REFERENCE) in *The Lancet Child Adolescent Health* highlights the promise of pragmatic trials. The authors used a 2x2 factorial design to test the effectiveness of lumbar puncture techniques, comparing sitting versus lying position, and early versus late stylet removal. They reported highest success rate in the sitting position (63.7% compared to 57.6%); notably, adverse events such as cardiorespiratory deterioration were uncommon with this technique. 1082 infants were recruited across 21 UK centers over only 24 months which is impressive. The authors acknowledge that the impact of the measured outcome improvement (6.1% absolute increase, indicating a number needed to treat of 16) on clinical practice remains to be proven, and a number of limitations such as inability to blind for the interventions, or controlling for operator experience.

While it is difficult to ascertain to what degree the findings are generalizable to other patients groups such as older children and other healthcare settings, this study points towards the aptness of pragmatic trials to improve practice for the most vulnerable children. First, the authors tackled a very common population (neonates with suspected infection undergoing a septic-work up) exposed to a common intervention (lumbar puncture) which has an every day failure rate of as high as 1:1. Second, they demonstrate the feasibility of generating high quality evidence for ‘point-of-care’ decisions that may have been considered unanswerable

by many, and which until now represented “trial orphans”<sup>7</sup>. Third, the intervention is cost-neutral and is setup in a way (online education) which lends itself to rapid implementation. Finally, although the outcome (successful first pass lumbar tap) may not impress as patient-centered, it is directly related to risks of missing meningitis if unsuccessful, unnecessary prolonged antibiotic therapy and hospital duration all of which are of considerable relevance to families and the healthcare system.

The experience from RECOVERY, and trials such as NeoCLEAR permit to shape opportunities and risks related to pragmatic trials for critically ill neonates and children (Table). The general benefits that follow participation in research are well-documented<sup>8</sup> creating further rationale to enhance enrolment of critically ill children in trials. It would be highly desirable if international research networks<sup>9,10</sup> in this field join forces to develop a framework which will enhance capacity, capability, and timely delivery of such trials to globally diverse populations, designed to maximize the chances of rapid progress of best care implemented at the bedside.

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**Table. Comparison of strengths and potential weaknesses of pragmatic trials in critical care patients.**

<b>Domain</b>	<b>Strengths</b>	<b>Weaknesses/Risks</b>	<b>Comments</b>
<b>Cost</b>			
<b>Feasibility</b>			
<b>Population</b>	<b>Inclusive</b>	<i>Risk of heterogeneity of treatment effect</i>	<b>Risk of underestimating maximum value of an intervention in a more selected population</b>
<b>Intervention</b>	<b>Adherence may be variable</b>		<b>Likely to reflect real world application of any trial finding</b>
<b>Control/Comparison</b>	<b>Treatment as usual</b>	<b>Can be highly variable and difficult to specify</b>	
<b>Outcome</b>	<b>Patient centred clinical and cost effectiveness</b>	<b>Effect size may have to be large to be detectable in feasible population</b>	

<b>Interpretation</b>	Effectiveness (relevance for clinical practice)	Efficacy	
<b>Generalisability</b>	High in comparable real-world settings; Reflects imperfect delivery to heterogenous populations		
<b>Impact and implementation</b>			