Building Global Collaborative Research Networks in Paediatric Critical Care: a Roadmap

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On behalf of

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Word count: 3721

Tables: 4

Figures: 1

Key words: child; collaboration; critical care; evidence; intensive care; trial

Key messages

- Although critical illness in children often leads to death, morbidity, and long-term disability with high associated societal costs, the burden imposed by critical illness on child health globally contrasts with the paucity of evidence based on randomized controlled trials for interventions, practices and policies applied to critically ill children.
- This gap is widening as the number of paediatric intensive care facilities expand globally, especially in lower and middle income country settings, highlighting the need to match the design and conduct of paediatric critical care trials to the needs of stakeholders around the globe.
- A diverse group of 32 international experts in paediatric critical care trials representing trial networks across North and South America, Europe, Asia, Oceania, and Africa was convened to review the current state of conducting international trials in paediatric critical care, and to formulate recommendations to overcome associated barriers and limitations.
- Challenges identified include i) lower patient numbers, ii) heterogeneity related to cognitive development, unique co-morbidities such as congenital conditions and rare diseases, and illness or injury, iii) consent by proxy, iv) lack of appropriately funded paediatric specific research, and v) poor infrastructure in resource limited settings.
- The expert group recommends an action plan designed to advance international paediatric critical care trials, through enhancing international collaboration and exchange in trial prioritization and planning, education, and trial conduct, standardisation of data collection and core outcomes, patient and public involvement and engagement, paediatric funding advocacy, novel platform trial designs, coupled with a nested implementation program.

- Building on existing paediatric regional trial networks, the action plan serves to outline key strategic steps which should be put into practice over the coming decade with the goal of increasing the conduct and global reach of paediatric critical care trials.

Abstract

Paediatric critical care units care for children at a vulnerable stage of development, yet the evidence-base for the field remains scarce. The evidence gap is accentuated in less lower and middle income country settings despite the rapid increase in provision of global paediatric critical care. Thus, we aimed to develop a roadmap providing strategic guidance for international paediatric critical care trials. We convened a multi-disciplinary, globally representative group of 32 paediatric critical care experts from 6 continents representing paediatric critical care research networks and groups which was tasked to review the changing landscape and current evidence of paediatric critical care, identify key challenges towards paediatric critical care trials, and propose solutions. In iterative group meetings, a strategy to address the current gaps was formulated and voted on. The group identified key challenges to paediatric critical care research including lower patient numbers compared to adult critical care, heterogeneity related to cognitive development, co-morbidities and illness or injury, consent challenges, lack of appropriately funded research, and poor infrastructure in resource limited settings. To enable the generation of timely evidence through clinical trials, a 7-point action plan was proposed, including: 1. Formation of an international paediatric critical care research network; 2. Development of a web-based paediatric critical care trial toolkit library accessible to all networks; 3. Establishment of a global paediatric critical care trial repository including systematic prioritization which involves key stakeholder groups, patients, and families; 4. Development of a harmonised trial minimum data elements and data dictionary; 5. Building of infrastructure and capability to support platform trials; 6. Funder advocacy; and 7. Development of a collaborative implementation programme. In summary, building on the achievements in regional paediatric critical care trials from the past decade, international collaboration in the field should concentrate efforts on the implementation of this

action plan. This will contribute to the successful design and conduct of trials which match the needs of globally diverse paediatric populations.

Background

Paediatric critical care (PCC) involves the care of critically ill children ranging from newborns to young adults who require enhanced monitoring and specialised technologies to treat life-threatening illnesses and injuries, and recovery from major interventions[1]. Increasing specialisation of PCC requires advances in innovation and coordinated research efforts which address the complexity and vulnerability of the patients[2,3]. Over the past decade, paediatric critical care has witnessed considerable development - notably related to increasingly complex patient comorbidities, technological advances, improved survival rates, ethical and funding challenges, and expansion of paediatric intensive care units (PICUs) in lower and middle income country (LMIC) settings.

However, the growth of paediatric critical care (PCC) across the world has not been adequately matched by an increase in research outputs, widening the gap between evidence and practice[4]. More recently, the COVID-19 pandemic research experience, the formation or consolidation of regional, national and international PCC research networks, and a trend towards adopting novel trial designs and developing associated infrastructure, provide a unique window of opportunity to develop a framework for a sustainable international PCC research collaboration.

The need for international collaboration in PCC research has been highlighted at several recent scientific meetings[5]. To address this need, a Working Group was formed across existing PCC research networks and groups from six continents to formulate a position paper on International PICU Research Collaboration. The aim was to describe the current landscape of PCC trial research,

define barriers, and identify potential solutions to build a roadmap towards effective, impactful, international collaboration on PCC trials.

A leadership group consisting of representatives of the Canadian Critical Care Trials Group (CCCTG; KM), the United Kingdom Paediatric Critical Care Society Study Group (PCCS-SG; PR), and the European Society of Paediatric and Neonatal Intensive Care (ESPNIC; LJS) was formed. Each of the major regional PCC research networks across the globe, defined as networks with a track record in publishing multi-site PCC research, was contacted, covering six continents. Each network was asked to identify two to four representatives with a track record in conducting PCC research to join an international Working Group. Due to the absence of a PCC clinical or research network in Africa, internationally renowned investigators were tasked to nominate African representatives. The preliminary submitted list of proposed members was reviewed and alternate suggestions for names requested to ensure adequate diversity of gender, professional background, and career stage of the final Working Group. This resulted in a total of 32 members (**Supplement**), including medical, nursing, allied health, research coordination, and data science experts from 20 countries. The need to include people with lived experience as patients or parents was discussed in the foundational meeting; given barriers pertinent to culture, language, and lack of patient and public representation structures in several of the networks, the panel decided to restrict the present foundational work to healthcare staff representatives from the respective networks.

Key topics were identified in iterative rounds during three virtual meetings of the Working Group (**Supplementary Methods** and **Supplementary Figure 1**), which led to the formation of four

subgroups focusing on: a) the changing landscape of PCC, b) the evidence base of current PCC management, c) challenges of PCC research, and d) potential solutions. Each of the subgroups were tasked to explore available literature on the topic using narrative literature searches and expert consensus opinions. Subsequently, a roadmap for future PCC research collaboration was iteratively formulated. Items prioritized for the roadmap were voted on by the Working Group. Acceptance was defined as agreement by at least >80% of votes, by at least 26 (>80%) of the Working Group members[6].

The changing landscape of paediatric critical care

Outcome trends

Clinically important outcomes of critical illness in children include mortality, and longer-term measures such as health-related quality of life, functional status, and neurodevelopment for survivors and their families[7]. Over the years, mortality in PCC has gradually decreased, especially in high-income countries (HICs), from 2.3%-6.5% in 2000-2015 to 1.8-4.4% in 2016-2018[1,2], but remains substantially higher in LMIC settings (21.1%-40% in 2008-2017 to 6.7%-29.3% in 2020-2022) [8,9]. The changes in mortality rates highlight the need for clinical care improvements and research outcomes to shift focus from simply increasing survival to also decreasing longer-term morbidity caused by physical, cognitive, emotional, and behavioural sequelae of critical illness in children. [10,11].

Increasing complexity and technology dependence

The increased survival rates in both neonatal and paediatric critical care have been accompanied by an increase in the proportion of children admitted to PICU with underlying comorbidities and

technology dependence[12]. Chronic critical illness incorporates an overlap between technological dependence, illness chronicity, and complexity. Medically complex children are commonly admitted to intensive care because of lower physiological reserve during acute illness or to support post-operative care and represent a disproportionately high utilisation of specialist intensive care resources[13]. Prior to admission, many of these children already manifest altered indicators of health-related quality of life and functional status and are at increased risk of deterioration subsequent to acute critical illness, for example due to sepsis [14]. This trend is accentuated by improved prevention of common paediatric illnesses and accidents, rapidly advancing therapeutic options for previously fatal rare diseases[15], as well as societal changes in relation to ethics and parental preferences affecting decision-making.

Development of paediatric intensive care services in LMIC settings

Historically, the cost effectiveness of PCC in areas where resources are scarce has been considered insufficient to justify major investment in PCC services in LMIC. However, this landscape has undergone considerable changes over the past two decades, most pronounced in South America and South-East Asia where thousands of PICUs have emerged[16,17]. While detailed longitudinal epidemiological data on the evolution of critical illness and its management in LMIC settings are lacking, in the group`s experience, there is wide variability in provider models and a substantial proportion of children are managed outside dedicated intensive care units. Critical care services can improve outcomes if combined with a focus on community recognition of serious illness, early access to care, referral, and safe transport[18]. However, most hospitals in LMIC settings do not have a designated PICU with paediatric trained nursing staff, adequate registered nurse to patient ratios to care for critically ill patients, appropriate equipment, monitoring capabilities, or ancillary

support. PICUs that are established in LMICs are typically staffed by general paediatricians and many lack specialized services[17]. In addition, there are sometimes profound disparities in paediatric critical care capabilities even within the same country[3]. In some LMIC settings, particularly large cities in China, India, South Africa, South America and the Middle East, university and private hospitals are capable of providing PCC services with invasive monitoring, and life support therapies, including extracorporeal support, comparable to PICUs in HICs. However, until recently, PICUs in LMIC settings were rarely included in large clinical trials, despite caring for a rapidly growing proportion of the global population of PCC patients.

The COVID-19 pandemic and its impact on PCC research

The COVID-19 pandemic, coupled with the urgency to deliver rapid high-grade evidence to advance the management of the associated conditions, boosted the conduct of interventional trials in adults, particularly in critical care (REMAP-CAP, RECOVERY)[19]. In comparison, conduct of research in the PICU was affected by the COVID-19 pandemic in numerous ways. Research within academic medical centres was paused as available staff were redirected to clinical care and some PICUs began admitting and caring for adult patients[20,21]. Due to the limitations of family presence and research staff in the PICU[22], novel models of telephone and video consent were developed which have been recognized as more efficient and have persisted post COVID-19. Some existing observational registries within established networks were able to rapidly begin including COVID-19 specific information which then became available for patient screening for clinical trials[23]. We witnessed rapid international collaboration to describe the emergence of a new, uniquely paediatric disease, Multisystem Inflammatory Syndrome in Children (MIS-C) through agile national and international, often multidisciplinary collaboration[24]. However, only two interventional trials of

MIS-C have been published to date, with enrolment limited to two European countries[25,26]. At this stage, it remains unclear how well the international PCC research community is prepared to deploy agile and effective trials in a future pandemic emergency which may affect children more frequently than COVID-19 did.

The current evidence base for paediatric critical care practice

Despite an increase in the number of published randomised clinical trials (RCTs) in PCC since the 1990s[27] (**Figure 1**), the evidence base for most interventions and practices in this field remains limited[28]. Most recent clinical practice guidelines incorporating systematic reviews and meta-analyses demonstrate that much of clinical practice is based on low level or absent evidence[29-31]. Many recommendations are based on expert consensus or are inferred from adult data. Many paediatric pilot studies never progressed to larger definitive trials, one reason being the difficulties in accessing infrastructure, expertise, funding, and collaboration to mount fully powered trials[32]. In addition, many of the currently published RCTs are single-centre, often underpowered and may overestimate treatment effects. The inconsistent and inadequate reporting of primary outcomes used in PCC trials makes comparability and pooling of data difficult in a meta-analysis. Compounding this, event rates (especially mortality) are relatively small in PCC, and robust intermediate outcome measures that could allow a reduction of sample size are lacking[33]. Much of the published evidence in PCC also does not include term babies (37 weeks to 44 weeks gestational age), a subset of patients that form a substantial proportion of the PCC population. Finally, adolescents are inconsistently included in both paediatric and adult ICU based studies as a result of varying local practice and absence of a biological understanding of when a paediatric ICU patient should be considered comparable to an adult ICU patient in terms of physiology and

management[34]. While approaches such as extrapolations from other populations, systems biology evidence, inference from other subtype populations, and causal inference from observational studies[35] may be scientifically robust and acceptable to regulators, the paucity of large, adequately powered PCC-specific RCTs remains a major contributor to the use of off-label medication.

Further affecting the availability of high-quality PCC evidence is the limited amount of intra- and inter-continental collaboration for research[36]. Previous international collaborations have mainly focused on guideline recommendations which relied predominantly on consensus opinion (**Table 1 PLACEHOLDER FOR REFERENCES HERE**)[37-44]. Additionally, trials were predominantly conducted in HICs[45], with a different critical care population and healthcare system to that of LMIC, limiting the generalizability and relevance to an international population.

Despite the enormous potential of paediatric critical care innovation to impact on societal burden given the long life expectancy of children, and the augmentation of paediatric healthcare costs by effects on their parents and future dependants[46], we lack robust models on whole-of-life and whole-of-society costs which can be averted by improvements in paediatric critical care.

Challenges

Research in the paediatric critical care environment poses manifold challenges. The heterogeneous population, coupled with relatively low mortality rates (in HIC)[1], and overall lower numbers compared to adult or neonatal ICUs, impose fundamental restrictions to conducting adequately powered trials. Moreover, most critically ill children are cared for outside of affluent countries, where multiple systematic, socioeconomic, and infrastructure-related barriers to high quality research exist[47]. PCC research is even more complex when undertaking collaborative trials across

international borders. Systematic challenges for international PCC research are numerous, and extend to methodological, operational, ethical, cultural and funding aspects, as well as collaboration (**Table 2)**. Three factors particularly relevant for PCC trials that consistently impact collaboration in a range of global settings relate to heterogeneity of patients, paediatric infrastructure, and consent.

Heterogeneity of patient cohorts

PCC trials include patients across a range of age-groups from neonates, preschool children to prepubertal school age children, adolescents and to young adults, with associated age-specific variability in vital signs, organ function, neurodevelopment, immune, endocrine, and metabolic function. These factors are unique compared to the adult critical care population, represent important confounders which may affect a spectrum of aspects such as drug formulation, interaction and dosing requirements, responses to therapy, and require adjustment in interpretation of clinical trial data. A second source of paediatric heterogeneity – potentially resulting in distinctive phenotypes - relates to comorbidities, with up to 50% of children admitted to PICUs suffering from chronic diseases unique to this age group, such as congenital conditions, and rare diseases manifesting during early childhood[12]. In adult patients, studies are increasingly deciphering host response patterns to identify subgroups of patients more likely to benefit, or suffer harm, from interventions such as immunomodulation[48]. While it appears plausible that such subphenotypes are similarly relevant for PCC cohorts, transferability to paediatric age groups has not been extensively investigated. In addition, the previously listed paediatric sources of heterogeneity in combination affect epidemiology, disease dynamics, and host response.

Unfortunately, trials of small sample sizes, as often seen in the PCC setting, will continue to be ill-equipped to allow for analysis that accounts for these numerous confounders.

Lack of infrastructure and resources

PCC research continues to be highly fragmented. LMIC settings remain severely underrepresented, and the lack of investment, infrastructure and resources even in HIC settings is sometimes prohibitive to facilitate robust clinical research[27,36]. Researchers face a high clinical workload and often insufficient options for training, collaboration, and mentorship. Challenges still exist in HICs, such as disproportionally less research funding available compared with adult research, smaller numbers of trials to reach a critical mass, and dearth of industry funding; these challenges are magnified in LMIC settings. Clinical Trial Units are lacking in many parts of the world, and where they exist, their familiarity with paediatric specific needs, particularly related to critical care, is deficient. Research and collaborative networks are emerging as facilitators for carrying out clinical trials[49]. Although the number of trials conducted by PCC research networks is still small, these studies are generally multicentre, international, larger and have greater impact in terms of citations and publication in journals[50].

Consent

In the PCC setting, the challenges associated with obtaining informed consent for acute care trials are intricate and multifaceted. Specifically, important barriers to obtaining consent include limited enrolment windows due to time-sensitive research interventions, parental anxiety compromising the ability to understand and provide informed consent, and unavailability of legal guardians, particularly when children are transferred to a hospital distant from the referring facility[51]. Notably,

a scoping review revealed consent rates as low as 43% in PCC trials, posing challenges to study feasibility and funding, although more recent pragmatic trials often report consent rates of over 70%[52]. However, alternate consent models such as research without prior consent (consent-to-continue), which have been increasingly used in pragmatic trials[53], are often not approved by IRBs in LMICs and even in certain HICs. The potential for selection bias associated with consent also threatens the generalisability of trial results. Parents of sicker patients, and socioeconomically more disadvantaged parents, may be more likely to decline consent, resulting in underrepresentation in the study population. Importantly, cultural factors, such as the ability of mothers to provide consent without the father's involvement, require unique consideration[54-56].

Proposed solutions

To address challenges of inequality in research activity and relevance, global collaboration is paramount and may assist with optimising the use of limited research resources, whilst being cognisant of universal and regional ethical, regulatory and operational requirements and governance (**Table 2**).

Prioritisation of research within the PCC community

Collaborative research endeavours can help choose research priorities according to the potential impact to the community, enhance efficiency of PCC research by minimising duplication, and appropriately target efforts to areas with differing capacity and need[57]. Such exercises have been completed by some regional or national networks[57], and demonstrate that stakeholder involvement in priority setting is key to improving acceptance and uptake of research by healthcare professionals, potential participants (patients and families) and community end-users[58]. A global

PCC "research observatory" listing current and planned projects across PCC networks, with regular updating, could allow the collection of harmonised data on PCC research priorities, capacity and activity mapping as a prerequisite to address the clinical and moral imperativeness of generating evidence for critically ill populations which is generalisable and which can result in the highest impact at global scale. At the same time, as evidenced for example by strikingly different effect sizes observed in trials on therapeutic hypothermia for neonatal encephalopathy[59], populations from LMIC settings may differ in terms of epidemiology, comorbidities, presentation modes including survival bias, and available treatment and management which may necessitate trials specifically designed to these settings.

Funding

Research capacity mapping is an important mechanism to tackle current inequalities in PCC research funding, by allowing funding resources to be specifically targeted to sites with limited research capacity such as in LMIC settings. Large international funding bodies for PCC are scarce, creating a need for PCC trial funding through global organizations such as the Wellcome Trust or the Gates Foundation. This warrants emphasis to regularly demonstrate current disease burden for example related to critical illness and mortality due to communicable disease, as well as on the potentially preventable fraction as a result of improved PCC delivery. National funders should develop strategies to direct more funding to support research relevant to health issues in lower socio-economic settings[60], capable of rapidly mobilising resources for new or emerging health priorities. In addition, grant calls should permit collaboration and coordination across novel funding strategies internationally or enable open calls in multiple jurisdictions (for example, partnership of Australian National Health and Medical Research Council with Horizon EU or UK

National Institute of Health Research). The World Health Organisation's ESSENCE (Enhancing Support for Strengthening the Effectiveness of National Capacity Efforts) on Health Research initiative is a good example of such a harmonised international approach[61].

Traditionally, compared to oncology, paediatric critical care research has rarely built on industry funding, even though multiple exciting opportunities such as devices, digitalisation, biomarkers, and medicine development exist. Emphasis on public private partnerships (for example under the Innovative Health Initiative in Europe; https://www.ihi.europa.eu/) will require readiness of paediatric critical care research for industry collaboration.

Networks and partnerships

Developing and strengthening strategic regional, national and international networks can enhance capacity and mitigate the impact of current global inequities in PCC research, for example by providing wider access to research resources[62], additional opportunities for funding, resource sharing, mentorship and research capacity development, and recruitment of larger, more diverse participant numbers in reasonable timeframes to improve the external validity of findings. Although several PCC research networks exist currently (**Table 3**), there are no structured regular cross-network meetings nor can members easily gain access to specific PCC trial resources. Thus, there is a need to develop an open access resource on PCC research consortia mapping available PCC networks, and provision of information on topics such as prioritization, as well as of educational and trial materials. This would facilitate the prioritisation, coordination, and implementation of future collaborative research geared towards adequately powered trial cohorts.

Patient and public involvement and engagement

Wide differences in research practices, support systems, and requirements pertaining to the involvement of persons with lived experience of the paediatric critical care setting were noted across the panellists. In some countries, such as the U.K. and Australia, structured patient and family involvement has been included as a mandatory element of competitive funding assessment and ethical reviews. The systematic integration of the experiences and perspectives of paediatric critical care survivors and their families through co-design of trial setup, conduct, and dissemination for example enables more meaningful prioritization of diseases, interventions, and paitent- and family-centered outcomes including safety outcomes[63]. In addition, patient and public involvement and engagement (PPIE) is particularly relevant for paediatric critical care given inherent challenges with research consent for procedures and practices where patients are mostly unable to provide consent due to disease as well as age[64]. Persons with lived experience represent a key stakeholder group and therefore can be effective drivers towards policy change as well as justification of funding priorities.

Standardization and harmonization

Standardization of terminology, definitions and outcome measures, including safety endpoints increases the translatability of research. Relevant initiatives in this regard include development of Core Outcome Sets and Core Outcome Measurement Sets for PCC research[7,65,66], deriving consensus research definitions (for example, acute paediatric critical illness[67]), standardisation of key variables and data collection methods (e.g., REDCap[68]) through low-technology interfaces such as mobile phones and tablet devices, and transparent reporting. The recent Phoenix Sepsis Criteria, resulting from an international data-driven process of over 3.5 million paediatric

encounters across high, middle, and lower income (LMIC) settings, may serve as a model for future large scale internationally diverse collaborations in the field of PCC[6,69]. While the Phoenix Sepsis cleaned and harmonised data from diverse settings centrally, a shift towards shared data models (such as the Observational Medical Outcomes Partnership [OMOP] Common Data Model) in the future may yield greater efficiencies of scale and facilitate federated analyses as well as findable, accessible, interoperable and reusable data. Harmonized minimal data collection may also allow the prospective accumulation of safety and efficacy data needed for medicines for which conditional approvals were obtained as well as post-marketing progression.

PCC research education, training and mentorship

Building research capacity is essential to ensuring sustainability. Until now, this has not played a key role in the formation of the PCC workforce, with well-documented shortages in LMIC areas[62]. Where possible, training and educational programs to build research capacity should be delivered through partnerships and networks between institutions in high income countries (HICs) and LMICs. Such programs may take the form of short, focused courses with standardized content (e.g. research methods, protocol development) using a variety of platforms (face to face, online) and pedagogical approaches, as well as longer-term training. The era of virtual meetings provides ample opportunities to develop and implement more innovative mentorship and training models to prepare and expand the clinical and research workforce which will develop and conduct future international PCC trial workforce across the globe.

Ethical considerations

While there are internationally accepted frameworks for ethics conduct of clinical research, such as the Nuremberg and Helsinki convention, particular ethical considerations may apply to PCC research in resource-limited contexts[70], with considerations given to the key principles of collaborative partnerships, social value, scientific validity, justice, assessment of the risk benefit ratio, independent review, informed consent and respect for participants.

Study design and impact

Pragmatic trials represent a promising strategy allowing research to be conducted in sites with less established infrastructure[71]. As evidenced by a number of recent large PCC trials[45,53,72-74], pragmatic trials may help overcome barriers relating to a) patient recruitment, with heterogeneity as present in daily practice being accepted; b) individual informed consent, which might be deferred in emergency situations in comparative effectiveness studies where both interventions are standard of care or waived, for example in pragmatic trials with cluster randomization; c) safety concerns, with interventions allowed to be flexibly applied and embedded into standard clinical care; d) outcome measurement, as outcomes are clinically meaningful and patient-centred requiring minimal training to evaluate; and e) cost[75]. Yet, the potential drawbacks of pragmatic trials require careful attention in design and conduct, in particular variable application of interventions to broad heterogenous patient groups, uncontrolled standard treatments, and use of opportunistic rather than biomarker or surrogate end-points related to the intervention[71].

Newer study designs, many of which originated in paediatric oncology, yet remain rarely used in PCC trials[76], provide renewed impetus to improve research efficiency and may be more suitable to iteratively build evidence; this may become particularly relevant under the perspective of future precision medicine trials. Adaptive platform trials are able to study multiple interventions in a

disease or condition in a perpetual manner, with interventions entering and leaving the platform on the basis of a predefined decision algorithm[77] – these features make platform trials particularly important for paediatric critical care where research evidence needs to be generated rapidly on many interventions. The large sample sizes required for adequately powered pragmatic, adaptive trials are achievable through international collaboration (for example, https://clinicaltrials.gov/study/NCT03896763) but need time, money and expertise to implement especially in resource limited settings. However, these designs promise higher efficiency in conduct and are more suited to address a range of heterogeneity sources such as income level, comorbidities, or phenotypes. Trials should endeavour to estimate the impact on societal disease burden, such as lost lives or disability adjusted years in addition to direct and indirect healthcare costs. To ensure sustainability of impact, trials should be coupled with implementation studies.

Foundational research nested within or compementary to trials

While RCTs represent the gold standard of evidence generation, trials rely on additional research strategies to improve their design and which can advance understanding of disease susceptibility, disease progression, causality of interventions with outcomes, and identify novel treatment targets. Where feasible, basic and observational research can be seamlessly nested within trials, which offers advantages in terms of efficiency and access to high quality representative cohorts[78]. This permits selection of patients for more costly investigations such as -omics or pharmacokinetic modelling, which may not be feasible in larger numbers or outside specialized and appropriately funded centers. Nested mechanistic or molecular studies and observational studies are required to optimise dosage regimens and can reveal potential effect sizes in pilot studies. Furthermore, data-driven or biology-driven investigations are necessary to enable personalized approaches through

the identification of treatable traits. Finally, for paediatric critical care, given inherent limitations due to patient numbers, understanding how knowledge on biology, treatments, and treatment responses generated in neonatal and adult populations can be extrapolated to paediatric age groups is of paramount importance. For example, a better understanding of transferability of subphenotypes identified in adult ARDS and sepsis cohorts towards children, with particular notion of the adolescents age group, will boost evidence generation for children and can inform inclusion of children in adult trials, as well as specific cross-age group trial designs[79]. With the rapid increase of Artificial Intelligence in healthcare, age specific validation of algorithms as well as demonstration of their impact through trials will become increasingly important for the PCC field[80].

Publication barriers

By improving the capacity to conduct high quality PCC research globally, through the initiatives recommended above, it is hoped that some of the current inequality of publications between high-income and other settings can be mitigated[81]. While open access publication allows free dissemination of knowledge, expensive article processing fees (APCs) are often prohibitive to researchers, particularly from resource limited settings[82]. Journals should consider how to support publication of important papers with global impact from all settings. Editorial policies should consider, as an ethical imperative, the need for stakeholder representation and ownership in published research. In addition, equal consideration should be given to trials with negative findings so as to ensure unbiased publication of available results.

Conclusions and roadmap for the future

PCC is a rapidly growing speciality with the potential to transform the lives and health of future generations. Current clinical practice in this discipline remains however mostly based on low-quality evidence. The paediatric critical care community has recognized the limitations grown from historic practice, lack of collaboration, and siloed research and needs to embrace structured and complimentary measures towards sustainable and effective international collaboration powered and designed to overcome the current limitations. This journey can greatly learn from decades of research excellence driving practice in paediatric oncology. To fundamentally advance generation of actionable knowledge over the next decade, we propose a 7-point action plan (**Table 4**). First, the creation of an international research network from existing regional and national networks to catalyse a step-change in collaborative research. The current working group could form an ideal starting point for this future international network and will benefit from central administrative support. Second, developing a web-based toolkit library to share research methods, templates, educational materials, and practical experience of delivery, particularly related to novel clinical trials. As part of this work, it is imperative to foster exchange on patient and public involvement and engagement (PPIE) strategies and provide access to toolkits facilitating the integration of persons with lived experience and their families at all stages of the study (design, conduct, interpretation and dissemination). This will require the development of a patient- and parent-led community that can both support families involved in research and researchers.

Third, conducting harmonised research prioritisation exercises across existing research networks to identify important research questions that are best tackled through international collaboration. Such prioritization work should include a diverse representation from medical, nursing, allied health, academia, as well as patient, family, and industry representatives. A global PCC "research observatory" could allow sharing of these research priorities as well as capacity and activity

mapping. Fourth, harmonisation of minimal datasets and core outcome sets to permit interoperable, more efficient data collection and trial conduct. Fifth, through exchange with neonatal and adult trialists, funding bodies, and research institutions such as NIHR, work towards the design and kick-off of a platform trial infrastructure capable to support international PICU trials. Sixth, a programme of funder advocacy focusing on creating sustainable funding models for PCC that cut across international boundaries. Seventh, a collaborative approach to implementation research to study how best to facilitate rapid uptake of evidence into clinical practice. The ability of the PCC research and clinical community to mount a global research ecosystem for PCC trials, modelled on the success story of paediatric oncology, can expand thanks to new partnerships between regional research networks, stakeholders ranging from patients to industry, with the aim of delivering improved care at the bedside resulting in decreased short- and long-term burden to patients, families, and society as a crucial metric by which the success of collaborative research can be measured.

Acknowledgements:

We thank Trish Gilholm and Renate Le Marsney, University of Queensland, Australia, for their work on the trials database.

This work was supported by a grant to PR, MC, KM, LJS by the UK Academy of Medical Sciences Networking Grant (NGR1\1903). LJS received support from the NOMIS Foundation and the Thomas and Doris Ammann Foundation. KSG is the recipient of a National Health and Medical Research Council (Australia) Investigator Grant. JH Lee received research funding from National Research Medical Council, Singapore and Thrasher Foundation, United States. Ben Gelbart received a grant from Murdoch Children's Research Institute. The funders had no role in the development of this manuscript.

Author contributions:

LJS, PR, and KM jointly conceptualized and initiated the study, reached out to trial networks, and wrote the first draft, and revised the manuscript after peer review. AA, NN, JHL, KG, AA, MP, LY, BM led subgroups. All authors contributed to sections of the manuscript, iterative discussions, revision of the manuscript, and approved the final manuscript.

Declaration of interests:

LJS received grants from Swiss Personalized Health Network; Personalized Health-Related Technologies Switzerland; NOMIS Foundation; Thomas & Doris Ammann Foundation; NIH; NHMRC; Medical Research Future Funds. KG receives support from a National Health and Medical Research Council Emerging Leader Fellowship. BM received grants from received grants

from EuroQoL, Society of Critical Care Medicine, and serves as president of the World Federation of Pediatric Intensive and Critical Care Societies and the Critical Care Society of South Africa. NN received grants from Actuated Medical, and Philips Respironics. AA received travel support from the World Health Organisation. JHL received grants from the Thrasher Foundation and the National Research Medical Council, Singapore. MP received grants from NIHR HTA and RfPB and serves on the NIHR HTA general funding committee. JFS received grants from the Universidad de La Sabana. HF received a grant from NIH. PF received grants from CIHR. MK received a grant from NIH and consultancy fees from Metran and is the medical president of ESPNIC. KM received funding from the CHEO Foundation, and is Chair of the Canadian Critical Care Trials Group.

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Table 1. Table of recent international paediatric critical care guidelines

Guidelines	Year published	Networks Involved	Total Number of Recommendations	Number of Strong Recommendations
Pediatric Ventilator Liberation[37]	2023	PALISI, ATS, SCCM	15	0
Bronchiolitis PICU Guidelines[38]	2023	GFRUP	40	3
PANDEM[39]	2022	SCCM	44	14
ESPNIC Intravenous Fluids[40]	2022	ESPNIC	16	2
Surviving Sepsis[41]	2021	SCCM, ESPNIC, AAP, AACN, ACEP, CHEST, PIDS, SSAI, SIDP, UKST WFPICCS	77	6
ESPNIC Nutrition[42]	2020	ESPNIC	32	0
Traumatic Brain Injury[43]	2019	BTF, CNS	22	0
PALICC2[44]	2023	PALISI, WFPICCS	146	1

Abbreviations: PALISI - Pediatric Acute Lung Injury and Sepsis Investigators; ATS - American Thoracic Society; SCCM - Society of Critical Care Medicine; GFRUP - Groupe Francophone de Réanimation et Urgence Pédiatriques; ESPNIC - European Society of Pediatric and Neonatal Intensive Care; AAP - American Academy of Pediatrics; AACN - American Association of Critical-Care Nurses; ACEP - American College of Emergency Physicians; PIDS - Pediatric Infectious Diseases Society; SSAI - Scandinavian Society of Anaesthesia and Intensive Care Medicine; SIDP - Society of Infectious Diseases Pharmacists; UKST - United Kingdom Sepsis

Trust; WFPICCS - World Federation of Pediatric Intensive and Critical Care Societies; BTF - Brain Trauma Foundation; CNS - Congress of Neurological Surgeons

Table 2: Overview of challenges impacting international collaboration in paediatric critical care trials and potential solutions.

Category	Challenges	Potential solutions
Methodological	Heterogeneity in patients and treatment within and between PICUs	Pragmatic clinical trials, with embedded predictive and prognostic enrichment strategies
	Selection of an appropriate primary outcome	Development and use of core outcome sets
	Competition in relation to research questions within and across countries with lack of coordination	Prioritization of research questions within and across countries
	Pre-PICU comorbid and functional status not or variable assessed across different institutions	Obtaining pre-PICU baseline assessments of functional status
Operational	Variability in the capacity for research delivery within and between countries, including access to appropriate statistical and technical support	Centralisation of operational capacity 'hub' sites providing assistance to 'spoke' sites in terms of trial logistics and access to trial statistics and technical expertise
	Greater availability of research funding in HICs versus LMICs, and for adult versus paediatric ICU	Advocacy for paediatric research funding in LMICs given its whole-of-life and whole-of-society impact
	Lack of research infrastructure in LMICs	Partner with adult trials where possible to share infrastructure
	Differences in regulatory requirements across jurisdictions and protracted processes and timeframes to negotiate international contracts	Standardized international contracts and data sharing processes using experience from precedent trials
	Lack of protected time and training for research for clinicians	Develop training resources through global collaboration; support research efforts, staff (including protected time), and infrastructure through HIC funding
	Differences in routine clinical data collection and challenges related to data protection and sharing across jurisdictions	Standardize and harmonize data collection across patient journey in trials and into follow-up
	Challenges obtaining international grant funding	Promote pragmatic designs to enhance feasibility of international collaboration

	Lack of infrastructure and support to administer multinational grants	Develop clinical trial hubs for PCC in partnership with existing centres (such as global research centres) which have infrastructure and experience in the administration of multinational grants
	Practical follow-up of patients for any length of time in geographically remote, poorly accessible areas; exacerbated in areas of conflict or affected by natural disasters	Explore harmonisation of data extraction from electronic health records to reduce manual data entry workload
Ethical and consent	Variability in Institutional Review Board approval processes within and between countries	Knowledge exchange between networks, and between IRBs
	Obtaining informed consent and assent	Develop culturally appropriate consent procedures for different settings
	Variability in acceptability of alternate consent models such as consent-to-continue (research without prior consent)	Advocacy for the development of alternate consent models for LMICs
	Cultural considerations, language differences, literacy barriers	Develop accessible audio and video materials to facilitate understanding of consent to families
Cultural	Cultural attitudes and distrust of research and medical care	Promote understanding of importance of research in improving care
	Differences in consent patterns across cultures	Develop clinician-research curricula
	Perspectives of clinical staff that research is a burden	Education of the clinical workforce about the contribution of research to patient outcome improvement
	Low prioritization of research in areas focused on providing basic services	Enhance award mechanisms
Funding	Region or country specific funding	Joint funding calls between funders, parallel funding submissions
	Lack of infrastructure funding beyond specific research projects	Seek infrastructure funding from global funders
	Most funding sources available for researchers in high income settings	Reducing Article processing fees to reduce publication bias

	Larger funding bodies for low-income settings tend to prioritize preventive and community health rather than critical care	Advocate for global foundations to fund international trials, including in LMIC settings
Collaboration	Competition as a cause of lack of collaboration among researchers/research networks	Exchange and strategic planning between research networks

Table 3. Overview of current paediatric critical care networks. Note: In Africa, no formal paediatric critical care research network exists currently.

Trial Networks (Year of Creation); website	Location	Number of PICUs (N Member)	Structure; Funding	Member Occupations	Initial Purpose	Focus
PCCS-SG (2005) https://pccsociety.uk/research/pccs-study-group/	United Kingdom	28 (120)	Registered UK Charity; unfunded	Nurses; Physicians; AHPs	A multi-disciplinary group of PCCS members interested in, and leading, research in paediatric critical care	MCRCTs; multi-center observational studies
CCCTG (1989) https://www.ccctg.ca/	Canada	17 (400)	Not-for-Profit; CIHR	Nurses; MD; RTs; OT; PT; PharmD; RCs; Patient and Family Partners	To conduct clinical research, translate knowledge into practice, and mentor future investigators	MCRCTs; multi-center observational studies
PALISI (2002) https://www.palisi.org/home	United States	157 (710)	Not-for-Profit; self-funded through memberships	Nurses; MDs; PTs; RTs	To identify preventive, therapeutic, and preventive strategies for acute respiratory distress syndrome, sepsis, multi-organ failure, and other acute, life-threatening pulmonary or systemic inflammatory syndromes that affect infants and children.	16 subgroups (including RCTs, Epidemiological, Biomarkers, etc)
ESPNIC (1980) www.espnic.eu	Europe	Unknown (779)	Not-for-Profit; self-funded through memberships	Nurses; MDs; AHP; Trainees	To encourage the development of new treatments and technologies; To promote collaboration among PCCU and NCCU healthcare providers across Europe	MCRCTs; multi-center observational studies; surveys; creation of guidelines

ANZICS PSG (2003) https://www.anzics.com.au/psg/	Australia, New Zealand	15 (N/A)	Not-for-Profit; some society support (ANZICS)	Nurses; MDs; RCs; AHPs	To work with healthcare providers, government agencies, and key decision makers to support diverse service portfolios including clinical quality registries, research and facilitation of health initiatives in resource limited locations.	Working groups on PCCU research coordinators (PIRCIG), consumer engagement, long-term follow-up, data science, education
SLACIP/ LARED (2014)/ BRnet PIC (2018) https://www.la-red.net/ https://www.brnetpic.org/	Argentina, Bolivia, Chile, Perú, Colombia, Brazil, Ecuador, Uruguay, Honduras, Suriname	50 (ca. 500)	Independent Organizations (Combined Executive and Scientific Committee); unfunded	Nurses; MDs	To collaborate across paediatric emergency and intensive care disciplines to improve the management and health care of critically ill children	Acute respiratory failure; Sepsis; NeuroTrauma; Transport; Post-PCCU
PACCMAN (2015) https://www.scri.edu.sg/paccman/about-paccman/	Indonesia, Philippines, Vietnam, Thailand, Singapore, South Korea, India, Pakistan, Saudi Arabia, Malaysia, Japan, China and Hong Kong	48 (84)	unfunded	Nurses; MDs	To promote collaboration and share experiences to develop best practices	Multi-center observational studies; Registry-based studies
African PICUs	Ghana, South Africa, Kenya, Namibia, Zimbabwe, Tanzania, Uganda, Nigeria, Malawi, Zambia, Morocco, Ethiopia.	Unknown (N/A)	Informal; unfunded	Unknown	To advocate for SDGs for health, recognising social determinants of health; early recognition and timely intervention at all levels (including primary care).	Social determinants of health, observational studies

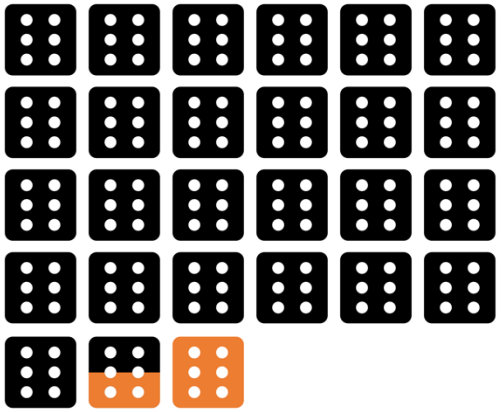
Table 4. Action plan for Global Paediatric Critical Care Collaborative Research Networks

Action 1: Create an international paediatric critical care research network (a network of networks) by end of 2024
Representation from all major regional and national research networks
Regular meetings and interactions with regional networks to minimise competition and to plan joint research studies
Action 2: Develop a web-based toolkit library for sharing across international boundaries by end of 2025
Share materials for research training through webinars and provide access to trial expertise through international advisory boards, exchange scholarships and studentships
Knowledge exchange to facilitate rapid adoption of pragmatic and novel platform trials recruiting across HIC and LMIC settings
Action 3: Establish a global paediatric critical care research 'observatory' by end of 2026
Initiate and share stakeholder-led research prioritisation exercises within and across networks
Establish patient and public engagement to ensure research priorities address needs of patients and families
Identify common research priorities that are amenable to global collaborative clinical trials
Action 4: Develop re-usable harmonised minimum datasets and core outcome sets for paediatric critical care trials by end of 2027

Define minimum dataset and data dictionary for standardised data collection for eligibility, baseline characteristics, interventions, and short- and long-term outcomes
Build on existing core outcome set work and define minimum criteria for follow-up
Action 5: Build a platform trial infrastructure in at least 2 regions by 2028
Define a strategy for international platform trial infrastructure with the regional PICU trial networks, and adult and neonatal patient focussed trial hubs
Define governance for international recruitment into platform trial hubs
Start recruiting in at least 1 region.
Action 6: Build an active programme of funder advocacy by 2027
Pitch PCC topics to international funding bodies (Wellcome Trust, Gates Foundation) and philanthropic organisations
Work with national funders to advocate for novel funding approaches including joint funding calls across international boundaries, as well as targeted support of exchanges such as PhD and scholarschips across regions.
Action 7: Plan a collaborative approach to implementing research evidence into practice by 2027
Develop co-ordinated research dissemination strategies, working with all stakeholders including patients, voluntary sector and industry

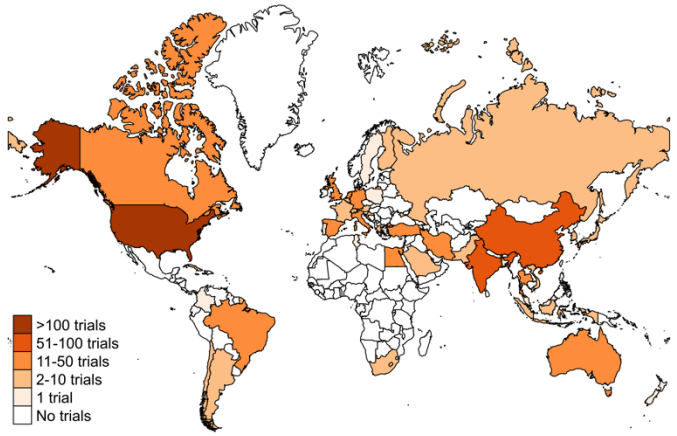
Figure 1: Characteristics of PICU trials conducted between 1986 and June 2023: a) 572 PICU trials published, 34 multi-national [each die represents 22 trials]; b) Distribution of country of PICU trial lead site; c) Bubble graph demonstrating number (y-axis) and median sample size (bubble) of PICU trials, grouped into two-year periods (excluding cluster trials; number of trials = 562); d) Stacked bar graph demonstrating percent (y-axis) and sample size (bars) of PICU trials (excluding cluster trials; number of trials = 562), grouped into two-year periods .

a)

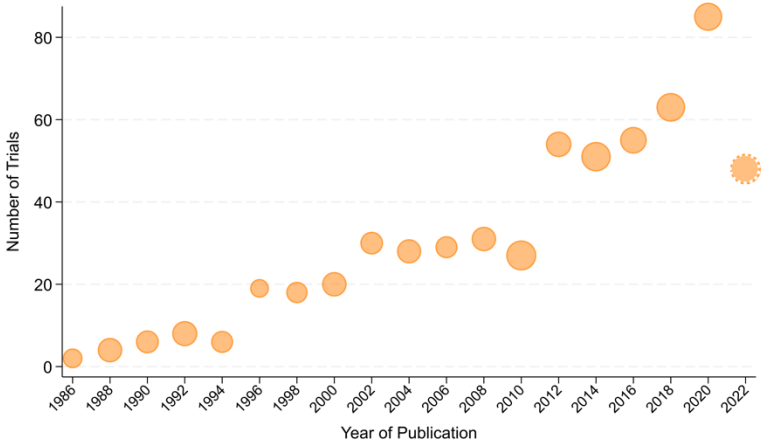


583 PICU Trials, 6% multi-national

b)



c)



Median Trial Sample Size 60 (Interquartile Range 37, 100)

d)