SPECIAL ARTICLE

The United Kingdom Paediatric Critical Care Society Study Group (UK PCCS-SG): the 20-year journey towards pragmatic, randomized clinical trials

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Over the past two decades, pediatric intensive care research networks have been formed across North America, Europe, Asia and Australia/New Zealand. The United Kingdom *Paediatric Critical Care Society Study Group* (PCCS-SG) has over a 20-year tradition of fostering collaborative research leading to the design and successful conduct of randomized clinical trials (RCTs). To date, the PCCS-SG network has delivered 13 different multicenter RCTs covering a spectrum of study designs, methodologies and scale.

Lessons from the early years have led PCCS-SG to now focus on the entire process needed for developing a RCT, starting from robust preparatory steps such as surveys, data analysis and feasibility work through to a definitive RCT. Pilot RCTs have been an important part of this process as well. Facilitators of successful research have included the presence of a national registry to facilitate efficient data collection; close partnerships with established Clinical Trials Units to bring together clinicians, methodologists, statisticians and trial managers; greater involvement of transport teams to recruit patients early in trials of time-sensitive interventions; and the funded infrastructure of clinical research staff within the National Health Service to integrate research within the clinical service.

The informal nature of PCCS-SG has encouraged buy-in from clinicians. Greater international collaboration and development of embedded trial platforms to speed up the generation and dissemination of trial findings are two key future strategic goals for the PCCS-SG research network.

Conducting randomized clinical trials (RCTs) in pediatric critical care is challenging. Over the past two decades, research networks have been formed across North America, Europe, Asia and Australia/New Zealand to promote a systematic, collaborative approach to the successful design and conduct of RCTs in pediatric intensive care units (PICUs). In the United Kingdom (UK), the Paediatric Critical Care Society (PCCS, formerly the Paediatric Intensive Care Society, https://pccsociety.uk) Study Group (SG) had its first national research collaborators meeting in Cambridge, 2005. Its aim was to foster collaborative studies that would lead to the design and successful conduct of clinical trials.

As past and present Chairpersons of the UK PCCS-SG, we have had the privilege of being part of a journey covering observational studies through to pragmatic, multicenter RCTs (**Figure 1**). To date, the SG has led 13 different multicenter studies and RCTs, spanning a variety of study designs, methodologies and scale (**Table 1**) [1-12]. In this Special Article for *Pediatric Critical Care Medicine*, we outline the successes and challenges faced by the PCCS-SG since 2005. Some of the lessons we learned are specific to the UK research environment but most will be relevant to other PICU research group. The potential for future collaborations between pediatric critical care research networks is exciting.

DEVELOPMENT OF PCCS-SG CLINICAL TRIALS

The trajectory from recognizing an important clinical question and formulating a study to producing generalizable findings is never straightforward. Two examples from the inaugural SG meeting might help to illustrate this point.

Conducting a RCT of hypothermia therapy for severe traumatic brain injury (TBI) was considered infeasible because analysis of data from the UK Paediatric Intensive Care Audit Network (PICANet, https://www.picanet.org.uk), the national registry, suggested that it

would take many years to complete in UK PICUs [13, 14]. However, this analysis was instrumental in the SG's decision to join international collaborations on TBI such as the Approaches and Decisions for Acute Pediatric TBI (ADAPT comparative effectiveness study, 2014-2017) [15]. Second, an idea for a RCT of glycemic control in PICU (the CHiP trial, 2008-2011) was taken through to completion (recruiting 1369 children from 13 UK PICUs) [1, 16]. It was supported by robust PICANet data confirming trial feasibility, and there was a commitment from SG members to retain clinical equipoise during the trial. Notably, CHiP was the first RCT to leverage PICANet to reduce the burden of trial specific data collection. Such efficient 'registry trials' have now become popular with funding agencies because they reduce the principal cost of large trails: site staff time associated with data collection.

In the more recent years of the PCCS-SG, the template for successful completion of collaborative RCTs has become established using a survey of PCCS-SG members regarding opinions and current practice as the first step. This qualifies the level of support from clinicians willing to maintain equipoise and participate in a trial of therapy. It also more formally records current practice. When combined with a thorough analysis of high-quality population-based PICANet registry data describing the expected patients of interest (sometimes supplemented by custom prospective data collection) we can reduce much of the uncertainty about feasible recruitment and control group outcomes. Formal testing of feasibility in small pilot RCTs maybe required either prior to or during the early phases of a multicenter definitive RCT (see next section).

The importance of these preparatory steps is illustrated by two salutary examples of PCCS-SG RCTs where it was not possible to model patient recruitment adequately in advance. The SLEEPS (safety profile, efficacy and equivalence in pediatric intensive care sedation) RCT (November 2009 to May 2012), which compared intravenous clonidine with

midazolam, recruited only 129 patients of a needed sample size of 1000 [2]. The investigators concluded that the "reluctance of clinicians to allow sedation to be studied in unstable critically ill children" was a factor, and that there was more to learn about parents providing consent to research studies during critical illness. The Randomised Study of early Continuous positive airways pressure in Acute Respiratory Failure in children with impaired immunity ("SCARF trial" January 2013 to January 2016) recruited only a third of the anticipated sample size of 148 children [4]. Absence of data about ward-level oxygen use (before PICU admission) to base sample size and recruitment calculations was a key factor; modeling using the more readily available PICANet data was an oversight since it did not reflect the pre-PICU problem of interest.

Pilot trials

All RCTs have inherent uncertainties in the assumptions about recruitment and protocol adherence. Pilot trials provide evidence for the likely number and mixture of PICUs needed to recruit patients for a trial, and give a contemporary estimate of outcomes to base sample size calculations on. As such, the 2-3 years spent doing a pilot trial before the main RCT can be considered time well spent.

The FIRST-ABC master protocol, which compared high flow nasal cannula [HFNC] with continuous positive airway pressure [CPAP] in both acutely ill children (step-up RCT) and in the post-extubation setting (step-down RCT), provides some valuable insights [9, 10]. FIRST-ABC was conducted only after survey data and assessment of current practice confirmed equipoise from clinicians and showed widespread variability in standard care [17]. The stringent test of feasibility was applied in the pilot RCT, and data on anticipated recruitment rates, acceptability of the consent model and point estimates of outcome measures were

obtained [18]. Informative pilot work was also a key factor behind the successful recruitment of 2040 children to the Oxy-PICU trial (conservative versus liberal oxygenation targets in PICU) from September 2020 to May 2022, including during the Coronavirus disease 2019 (COVID-19) pandemic [12, 19].

RESEARCH PRIORITIZATION AND THE "LESS IS MORE" THEME

Research prioritization is an important function of the PCCS-SG. In the UK, there are just 28 PICUs, for a child population of approximately 14 million; they admit between 16,000 and 20,000 children annually, of whom 65% are invasively ventilated (**Figure 2**). Now consider, first, the size of recently completed pragmatic RCTs, including: SANDWICH (effect of a sedation and ventilator liberation protocol vs usual care on duration of invasive mechanical ventilation; 8843 patients from 18 PICUs) [8]; FIRST-ABC Step-up and Step-down trials (1200 patients from 24 PICUs) [9, 10]; and Oxy-PICU trial (2040 patients from 15 PICUs) [12]. Add two other planned RCTs: the PRESSURE trial (protocolized evaluation of permissive blood pressure targets versus usual care, ISRCTN20609635), which opened in September 2021 and aims to recruit 1900 intubated patients receiving vasoactive infusions for shock in 17 PICUs; and, the GASTRIC-PICU (no routine gastric residual monitoring to guide enteral feeding in PICU; ISRCTN pending) trial that will open in 2023 and aims to recruit 4700 patients from 19 PICUs in the UK and 1500 patients from 6 PICUs in Australia and New Zealand [7]. It is self-evident from the scale of UK PICU practice and the sample size needed for a RCT that the SG needs to exercise openness and justice in its research priorities. The SG cannot hope to support all ideas at the same time.

The selection of topics for study deserves comment. As a community, there was an increased understanding of the inherent heterogeneity in disease syndromes such as sepsis

or pediatric acute respiratory distress syndrome. In the UK setting, more targeted interventions would likely struggle either to recruit sufficient patients when specifying a detailed phenotype, or would be challenged by the risk of heterogeneity of treatment effect, e.g., if we considered all septic shock cases as candidates for corticosteroid therapy [20]. This response was further informed by the "less is more" concept, which proposes that the greatest advances in recent years have been achieved by defining and removing, or reducing harmful interventions (e.g., more conservative use of transfusion or parenteral nutrition [21, 22]). Therefore, many SG studies have tried to determine if less of a particular intervention is safe and clinically effective, such as: FiSh, the restricted fluid bolus versus current practice in children with septic shock [5]; FEVER, permissive versus restrictive temperature thresholds in critically ill children with fever and infection [6]; and others about oxygen use, gastric feeding, and blood pressure targets [ISRCTN20609635]. This strategy enables a higher proportion of patients to participate in studies, which in turn means that most UK PICUs have a track record in collaborative research and have become familiar with research delivery processes. It also allows the design of pragmatic clinical trials: a "pragmatic RCT" mimics usual PICU practice and is designed to inform real-world decision-making with available interventions or treatments, rather than investigational therapies. And, of course, this inclusive and pragmatic approach is aligned with that of the UK National Institute of Health and Social Care Research Health Technology Assessment (NIHR HTA) program – the principal funder of UK PCCS-SG studies.

PARENT PARTNERSHIP

The most recent PCCS-SG prioritization exercises sought opinions on research priority and perspectives from medical, nursing and allied health professional practitioners working

within UK PICUs as well as from parents, patients and families [23, 24]. Genuine public and patient involvement in developing an area for study, in trial design, wording of information sheets, and delivery as RCT steering group committee members and named applicants is now usual practice in SG studies. Although this process is required by UK funding agencies, the SG's experience is that every project has been improved by the involvement of families and past patients.

The partnership with parents also extends into other areas of research practice; that is, supporting families in which their child recruited to a RCT has died, and the use of the deferred consent (or "research without prior consent") model. Regarding bereavement, planning of SG trials has been informed by the methodological BRACELET (death, bereavement and RCTs) study of policy and practice in UK neonatal and pediatric intensive care trials carried out from 2002 to 2006 [25]. BRACELET included parents involved in six PICU trials and concluded that in order to respond to bereavement in a fair and sensitive way, as well as to better inform the design of RCTs, it is crucial that investigators listen to bereaved parents and evaluate new methods for doing so.

Deferred consent

In the PCCS-SG trials, deferred consent was first used in the CATCH (impregnated central venous catheters for prevention of bloodstream infection in children trial) [3], and subsequently used in the FIRST-ABC step-up and step-down trials [9, 10] and the Oxy-PICU RCT [12]; and it is now being used in the PRESSURE trial. Children eligible for these trials most often need an intervention started in a life-threatening emergency, where any delay in commencing treatment could be detrimental. The purpose of the deferred consent model is to minimize additional distress and burden on families during the emergency, and defer a

detailed discussion about consent to the RCT after randomization. This model was developed using the CONseNt methods in pediatric Emergency and urgent Care Trials (CONNECT) guidance [26] and it has been found acceptable to parents/guardians and PICU clinicians involved in the CATCH, FiSh, the FIRST-ABC and Oxy-PICU pilot studies [3, 18, 19, 26]. In this process, once a patient is identified as being eligible for such a trial, they are randomized and the randomly assigned treatment commenced as soon as possible. Following randomization, a trained, delegated member of the local research team approaches the parents/legal guardians as soon as practically and appropriately possible (usually within 24–48 hours of randomization) to discuss the trial and provide a participant information sheet detailing the purpose of the trial; what participation involves; confidentiality and use of data; and availability of trial results. A consent form is also provided indicating that: the information given has been read and understood; consent is given for continuation in the trial, access to medical records for data collection, receipt of follow-up questionnaires, and for anonymized data to be shared in future.

ORGANIZATION AND COLLABORATION

One of the characteristics of the UK PCCS-SG is that it is an open organization, one without a formal membership list. This openness has many advantages including welcoming clinicians who may wish to support research but do not consider themselves clinical academics, and the low threshold for participation also means that a high proportion of UK PICUs contribute to SG studies.

The SG is heavily dependent on working in collaboration with Clinical Trials Units and the PICANet registry. The availability of high quality, contemporary epidemiological data from PICANet allows access to PICU population diagnostic codes, case mix and severity-

adjusted short-term outcome data on more than 350,000 admissions, along with data on daily interventions for organ support [27]. The registry provides two essential functions for designing RCTs: i) an estimate of the available population for a potential study, and the likely number and mixture of PICUs needed to recruit these patients; ii) point estimates and distributions of potential outcomes or endpoints. The most recent use of the PICANet registry in determining RCT feasibility has been for the GASTRIC-PICU study: analysis of admissions from 2016 and 2017 showed that over 16,000 children met inclusion criteria, and over 12,500 stayed on the PICU for >3 days [7].

WIDER RESEARCH CONTEXT

Context is everything. In the UK, PICU-related clinical research has benefited from healthcare reorganization, with the development of regional centralized units within a coordinated national health system of subspecialty medical and surgical practices. This reorganization includes the formation of emergency transport services that act as the first point of PICU contact for sick children transported from district general hospitals, who account for a third of all UK PICU admissions. Involvement of transport services as part of PCCS-SG has allowed the randomization and initiation of interventions such as central venous access (CATCH), fluid therapy (FiSh), oxygen targets (Oxy-PICU) and blood pressure targets (PRESSURE) in the pre-hospital setting, much earlier than would have been possible if only PICUs were involved in recruitment.

At the same time, PCCS-SG has benefited from a national research agenda prioritizing *Medicines for Children*. In addition, the creation of regional NIHR Clinical Research Networks, research infrastructure funded to facilitate recruitment to studies, has allowed PICUs to recruit patients at much lower costs than previously. A network of Clinical Trials Units (CTUs)

with specialist teams of biostatisticians and trial methodologists has also developed to support the study of effective clinical trials in the health service. In this new landscape, UK PCCS-SG clinical researchers have learnt much from this unique partnership between clinicians and CTU staff.

FUTURE DIRECTIONS FOR THE UK PCCS-SG

Even though the UK PCCS-SG has more pragmatic RCTs in various stages of implementation, and plans for international collaboration, it is exploring ways to improve the efficiency of translating ideas into a trial results. The current track record seems too long from idea to RCT publication: the CHiP trial took 10 years, and the recent FIRST-ABC trials took 8 years. Is there a way to make such programs more efficient? The recently funded PERMIT (paediatric early rehabilitation and mobilization during intensive care feasibility) study may be one type of solution [28]. PERMIT will use a structured program to developing a trial intervention package for rehabilitation starting in the PICU. One hundred and fifty patients will be observed in 15 UK PICUs, on day 3 of admission, with the plan to develop and subsequently pilot an as yet unknown intervention package. We will need to see what unfolds over the next years, but hopefully it will be more efficient than the past 18 years. Another solution is the adoption of "randomized, embedded, multifactorial, adaptive platform trials", as is currently underway in critically-ill adults with community-acquired pneumonia [29]. Such a design also has application to international collaboration, as demonstrated by trial participation during the COVID-19 pandemic [30]. Perhaps, as a worldwide PICU community, we should now be following our adult critical care colleagues in the development of harmonized multi-region platform trials to address the most pressing research priorities in our field.

FINAL THOUGHTS

The key principles by which UK PCCS-SG has moved ideas from conception to successful completion of RCTs are summarized in **Table 2**. A number of successful (and unsuccessful) RCTs exist in the SG portfolio (Table 1 and Figure 1). These studies would not have been possible without the national reorganization of PICU healthcare in the UK, changes in national research priorities, and unique enablers such as the development of CTUs, PICANet and the NIHR CRNs. Also, RCTs of emergency treatment are possible because there is wide acceptance of the deferred consent model amongst healthcare professionals and UK patients and families. Last, given the limited number of PICUs in the UK, SG clinicians are prepared to work collectively, particularly on the issue of retaining clinical equipoise.

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The growth and achievements of the UK PCCS-SG since first national collaborators meeting in 2005 is the result of many friends, colleagues and leaders in our field. Along with all members of the UK and Ireland PCCS we are immensely proud of the collaborative work of all PICUs in the network.

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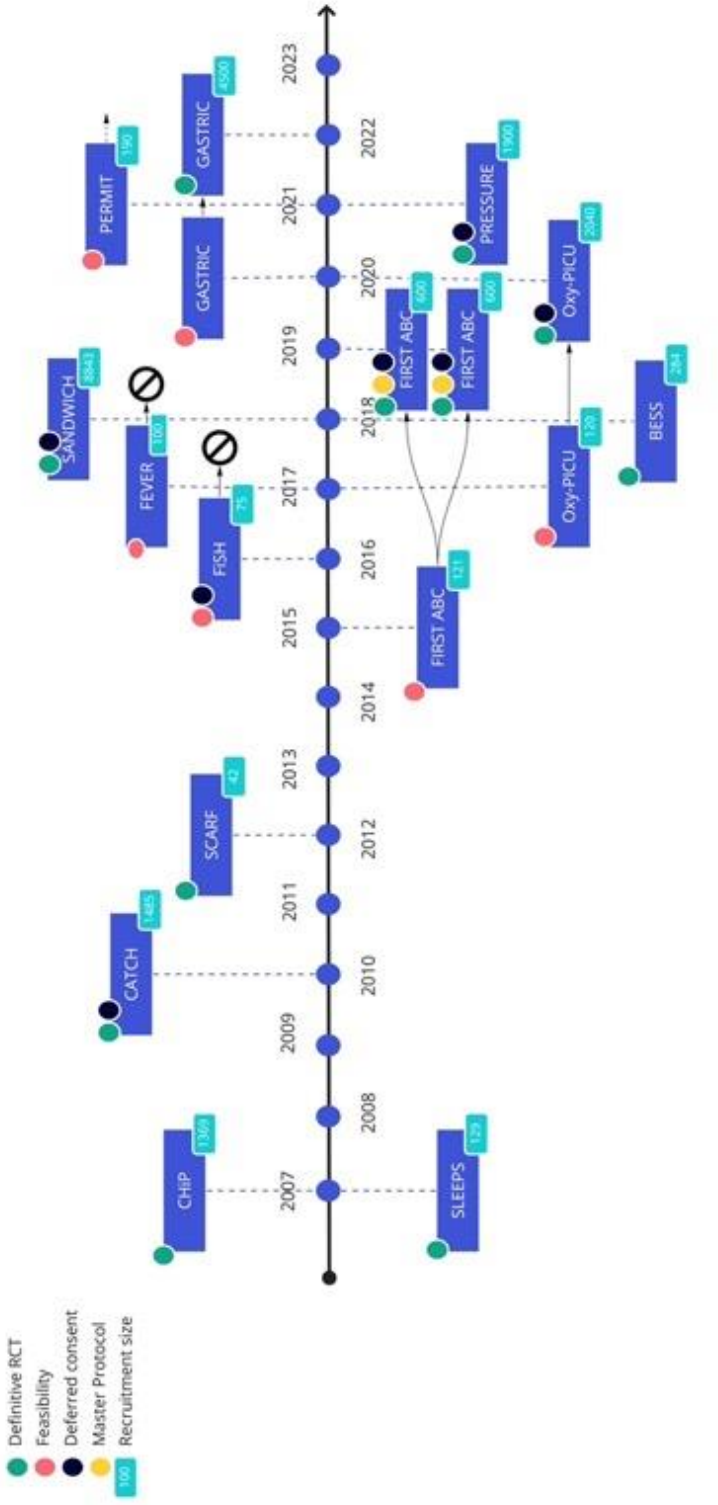

Figure 1. Time line of pilot and full RCTs. Dotted lines indicate timing of trial registration.

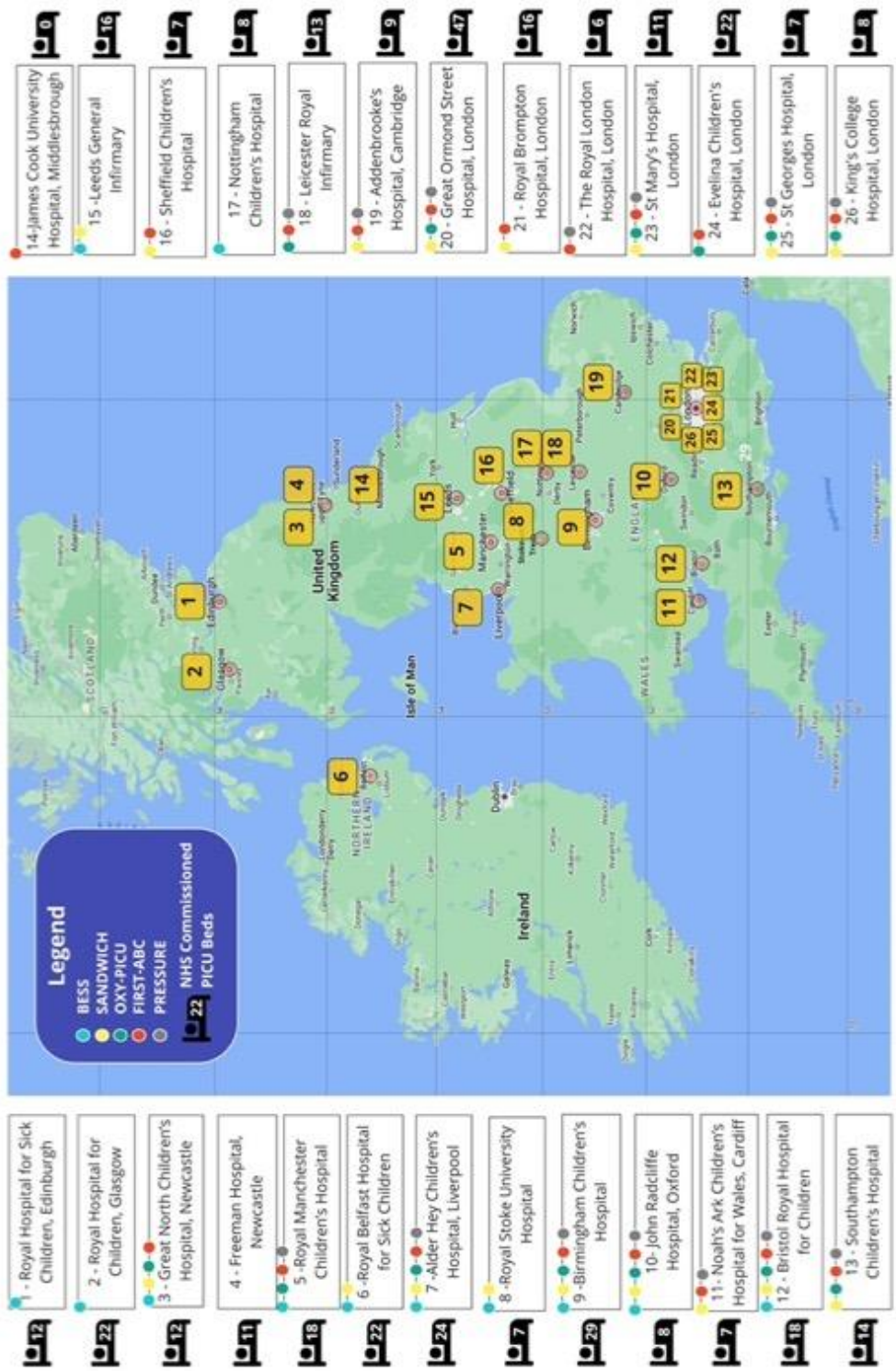

Figure 2. Map of PCCS-SG contributing PICUs.

Table 1

Trials	Population	Feasibility →	Definitive RCT
Vital sign homeostasis and test of "less is more"			
Glucose: glucose control of 72-126 or <216 mg/dL (CHiP)	Children on IMV and vasoactive agents	Population estimate from PICANet registry	**2008-2011:** 1369 children recruited in 13 PICUs [1]
Oxygen: SpO_2 target of 88-92% or >94% (Oxy-PICU)	IMV with supplemental oxygen	**Pilot RCT (2017):** 119 recruited in 3 PICUs [19]	**2020-2022:** 2040 recruited in 15 PICUs [12]
Temperature: antipyretic use for fever ≥ 37.5 °C or ≥ 39.5 °C (FEVER)	Temperature ≥ 37.5 °C within the first 48 of unplanned PICU admission	**Pilot RCT (2017):** 100 recruited in 4 PICUs [6]	[redacted]
Fluid status: Use of restricted fluid strategy during resuscitation (FiSh)	Emergency admission with suspected infection and shock after 20 mL/kg bolus	**Pilot RCT (2016-2017):** 75 recruited in 13 emergency departments [5]	[redacted]
Blood pressure: usual care of mean arterial blood pressure or >5th centile for age (PRESSURE)	IMV and receiving vasoactive agent for shock	Population estimate from PICANet registry	**2021-ongoing:** 1900 needed from 17 PICUs [ISRCTN20609635]
PICU respiratory therapies			
Surfactant: treatment for bronchiolitis (BESS)	Infants <6 months on IMV for acute bronchiolitis	Population estimate	**2018-ongoing:** 284 needed from 15 PICUs [ISRCTN11746266]
CPAP for ARF: early or late (SCARF)	Impaired immunity and new onset of ARF	**Pilot RCT (2013-2016):** 42/148 recruited in 3 PICUs [4]	[redacted]
CPAP or HFNC: used as support for breathing (FIRST-ABC)	After extubation (Step-down) or acutely ill children (Step-up)	**Pilot RCT (2015-2016):** sample, 121 recruited in 3 PICUs [18]	**2019-2021:** step-up, 600 recruited in 24 PICUs [10] **2019-2020:** step down, 600 recruited in 22 PICUs [9]
Other PICU therapies			
Sedation: clonidine versus midazolam (SLEEPS)	PICU admissions expected to require IMV for >12 hours	Population estimate from PICANet registry	**2009-2012:** 129/1000 recruited in 10 PICUs – RCT stopped [2]
Sedation and MV liberation: Effect of liberation protocol (SANDWICH)	PICU admissions expected to require IMV for >48 hours	Population estimate from PICANet registry	**2018-2019:** Cluster RCT - 8843 recruited from 18 PICUs [8]
CVC: Effect of antibiotic or heparin impregnated CVC and CLABSI (CATCH)	PICU admissions expected to require a CVC ≥3 day.	Population estimate from PICANet registry	**2010-2012:** 1485 recruited from 14 PICUs [3]
Infection control: Effect of SDD enhanced control on HCAIs (PICnIC)	All PICU admissions	**Pilot RCT (2021-ongoing):** 324 needed from 6 PICUs [11]	**Unknown, pending outcome of Pilot**
Enteral feeding: use of GRV monitoring to guide feeding (GASTRIC-PICU)	PICU admissions expected to require IMV for >48 hours who can be fed via stomach	Population estimate from PICANet database (2016-2017) analysis and surveys [7]	**Expected start 2023:** 6200 needed; 4700 from 19 UK PICUs and 1500 from 6 PICUs in Australia and New Zealand

Table 2

Lessons from the UK PCCS SG trials portfolio
The national healthcare research environment: • Context of healthcare organization and research infrastructure and priorities • Infrastructure with national registry of PICU cases (PICANet) so that consideration of trial with sample size and outcomes are realistic • Working with professional Clinical Trials Units • Acceptance of the deferred consent model for RCTs of emergency treatments
The special interest PICU study group organization: • Open organization with broad engagement of PICUs and their practitioners so that as many PICUs as possible are involved; the strength and volume of the organization determines what is feasible • Maximize what is possible to study in your population; the UK PCCS SG strategy is focused on "less is more" pragmatic RCT research questions
Developing research priorities: • Select research priorities based on feasibility, consensus, and justice • Engage all stakeholders including families and patients • Ensure that during the life-time of a priority project, there remains clinician equipoise
Moving forward with a research protocol: • Base the trial feasibility on the correct data for the population of interest, at a time at which they would be eligible, e.g., pre- versus post-PICU admission • Carry out efficient and timely pilot studies before embarking on full RCT • Recognize that RCTs can be a long Journey – it took 10 years for the first RCT from concept to publication