

Pilot randomized trials in pediatric critical care: A systematic review

Duffett M, Choong K, Cupido C, Hartling L, Menon K, Thabane L, Cook DJ

epicc.mcmaster.ca

Background

Randomized controlled trials (RCTs) in pediatric critical care are challenging to conduct for numerous reasons. Pilot trials can be used to evaluate the feasibility of, and inform the design and conduct of, larger RCTs.

Objectives

To systematically identify pilot RCTs in pediatric critical care and describe:

1. key elements of their methods and reporting
2. their impact, measured by citations and the number leading to larger trials

Methods

Searching: To identify pilot trials we searched the Evidence in Pediatric Intensive Care Database (epicc.mcmaster.ca) from inception to April 16, 2013. This is a database of published pediatric critical care RCTs found by searching MEDLINE, EMBASE, LILACS and CENTRAL.

To identify publications that cited these pilot trials we used Web of Science®. To identify published and ongoing trials informed by these pilot RCTs we searched the EPICC database and the World Health Organization's Clinical Trials Registry Platform (www.who.int/ictrp).

Inclusion criteria: Published trials that were explicitly described as pilot, feasibility, proof-of-concept, phase 2, vanguard or preliminary RCTs.

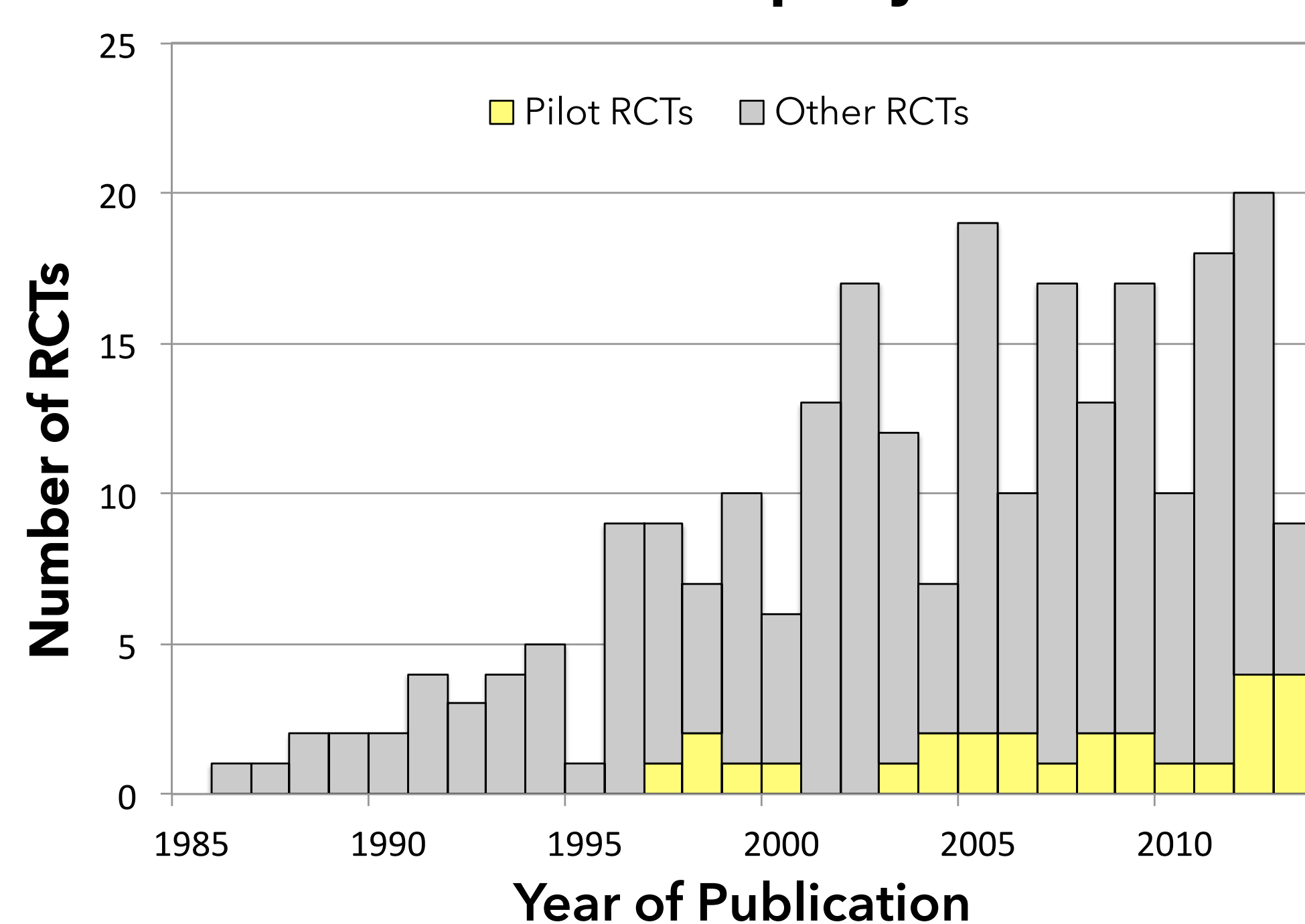
Data extraction and analysis: Pairs of reviewers screened studies for eligibility and abstracted data independently. Discrepancies were resolved by consensus. We used the Mann-Whitney U test and Fisher's Exact test to compare pilot trials to other pediatric critical care RCTs.

Results

Pilot trials comprised 27 (11%) of a total of 248 pediatric critical care RCTs.

The earliest pilot trial was published in 1997 and 13 (48%) since 2009.

Number trials per year



Characteristics of critical care trials

Characteristic	Pilot Trials (n=27)	Other Trials (n=221)	p value
Children randomized	30 (20 to 43) min=6, max=156	50 (32 to 98) min=8, max=4947	<0.001
Multi-centred	6 (22)	39 (18)	0.60
Studied medications	15 (56)	140 (63)	0.53
Blinding	13 (48)	112 (51)	0.84
Commercial funding	5 (19)	35 (16)	0.78
Any funding reported	18 (67)	123 (56)	0.31
Stopped early	3 (11)	29 (13)	1.00
High risk of bias	15 (56)	93 (42)	0.22

Data are reported as median (IQR) or number (%).

Terms used to describe trials

Terms	Number (%)*
pilot	18 (67)
feasibility	4 (15)
preliminary	3 (11)
exploratory	3 (11)
phase	2 (7)
proof-of-concept	1 (4)
vanguard	1 (4)

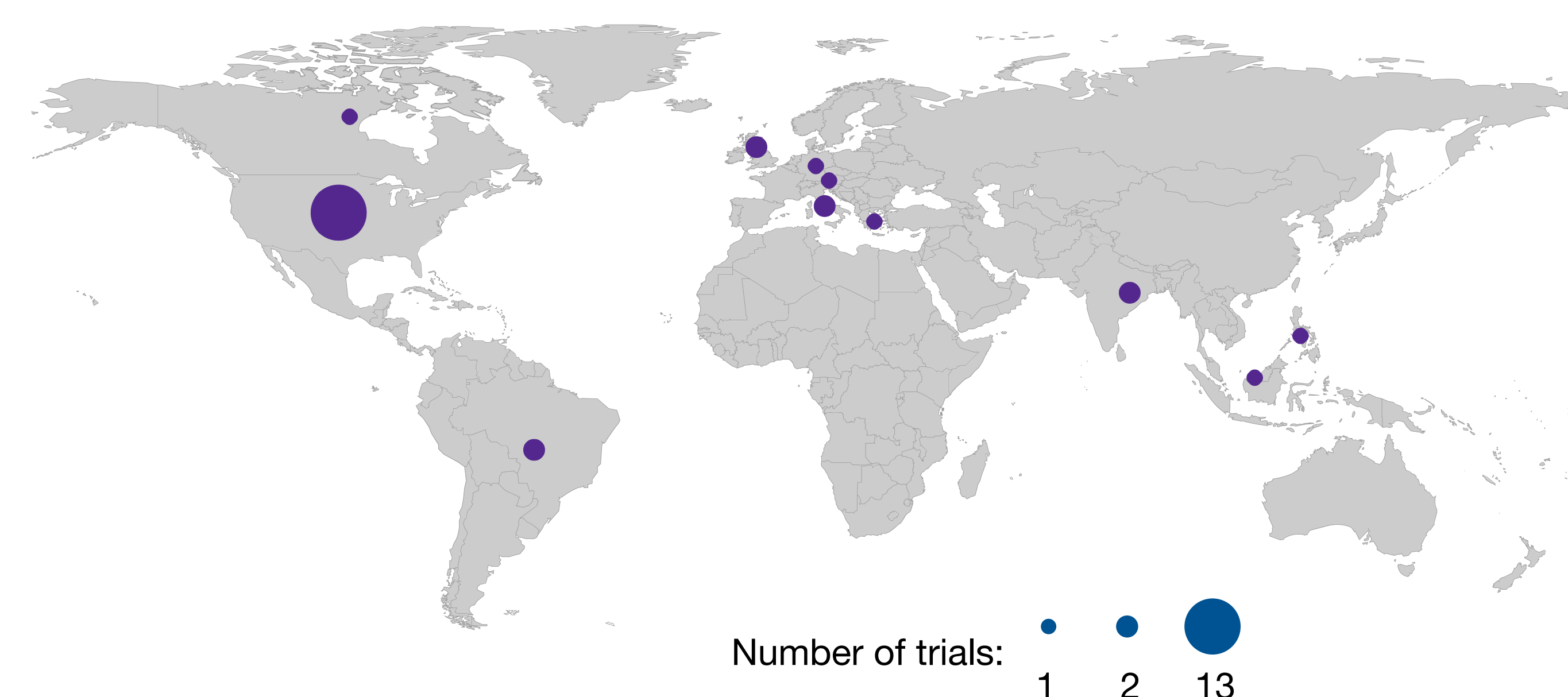
*some trials used more than 1 term

Location of pilot trial description in publication

Pilot Trial	Section of publication						
	Title	Abstract	Introduction	Methods	Results	Discussion	Conclusions
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13/14*							
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							
25							
26							
27							

Results

Number of pilot trials per country



Characteristics of pediatric critical care pilot trials

Year	Indication	Intervention	Centres	Children
2013	Ventilation weaning	Computerized weaning	1	30
2013	Anemia	Cell saver salvaged blood	1	110
2013	Acute lung injury	Nutritional immunomodulation	1	26
2013	Cardiac arrest	Hypothermia	15	84
2012	Post cardiac surgery	Levosimendan or milrinone	1	40
2012	Post cardiac surgery	Levosimendan	1	63
2012	Asthma	NIPPV	1	20
2012	Acute lung injury	Surfactant	36	165
2011	Pulmonary hypertension	Nitric oxide or iloprost	1	15
2010	Hyperglycemia	Exanatide	1	24
2009	Sepsis/shock	Vasopressin	1	24
2009	Cardiomyopathy	Nesiritide	1	20
2009	Sepsis/shock	Hydrocortisone	1	40
2008	VAP	Cefepime or ceftazidime	1	30
2007	Traumatic brain injury	Magnesium sulfate	2	6
2006	Traumatic brain injury	Creatine	1	39
2006	Diarrhea	Probiotics	1	56
2005	Traumatic brain injury	Hypothermia	6	48
2005	Traumatic brain injury	Hypothermia	1	27
2004	Candidemia	Fluconazole or Itraconazole	1	43
2004	Traumatic brain injury	CPP or ICP targeted therapy	1	17
2003	Sepsis/shock	Hydroxyethyl Starch	1	27
2000	Bronchiolitis	Surfactant	1	19
1999	Nutrition	Glutamine	1	9
1998	Bronchiolitis	Surfactant	1	20
1998	RSV infection	Palivizumab	6	35
1997	Parental coping	Support program	1	30

*1 publication reported 2 trials: a multicentre and a single-centre trial with different inclusion criteria

Methods and reporting of pilot trials

Publication: Trials were published in 17 different journals. Pediatric Critical Care Medicine published the highest number, 9 (33%), of these pilot trials. 4 (15%) were registered.

Type of primary outcome: 18 trials (67%) reported the primary outcome. Of these:

- 2 (7%) used feasibility
- 9 (33%) used intermediate outcomes (e.g. laboratory or physiological measurements, severity of illness scores or measures of the process of care)
- 7 (26%) focused on clinical outcomes

1 trial reported criteria for considering the pilot trial a success.

Sample size: 8 trials (30%) reported how their sample size was determined:

- 4 (15%) were calculated to detect a specified difference in participant outcomes
- 3 (11%) used a fixed time period for enrollment
- 1 (4%) used 10% of the calculated size for the expected larger trial

Authors' Conclusions: 12 (46%) publications made explicit conclusions or recommendations about the design or feasibility of future larger trials; 1 trial concluded that a larger trial was not appropriate because of safety concerns. 8 (31%) publications made clinical recommendations based on the results of the pilot trial.

Impact of pilot trials

Citations: 18 (78%) of the 23 publications indexed in Web of Science® were cited at least once. These were cited a median (IQR) number of 9.5 (2.5-27) times in total and 2.3 (0.7-4.8) times per year since publication. 3 trials were cited by at least 1 pediatric critical care RCT, none by the same researchers.

Informing future trials: We found no published trials based on these pilot RCTs. We found 5 subsequently registered trials based on these pilot trials: 4 recruiting and 1 stopped early.

Conclusions

Published pilot trials in pediatric critical care are smaller than other RCTs, but they are not different with respect to other key features. There are important opportunities to improve the conduct and reporting of pilot RCTs.

These RCTs are explicitly labeled as pilot trials yet they often focus on clinical outcomes. They uncommonly report explicit feasibility outcomes, criteria for success or rationale for the sample size. We may have underestimated the use of pilot trials as some RCTs intended by the investigators as pilot trials may not have been explicitly labeled as such.

Pilot trials in pediatric critical care do not often lead to larger trials. Understanding and addressing the reasons for this are an important next step for the pediatric critical care research community.