International perspective on research priorities and outcome measures of importance in the care of children with acute exacerbations of asthma: a qualitative interview study

Charmaine S Gray,1,2 Yao Xu,3,4 Franz E Babi,5,6 Stuart Dalziel,7,8 Colin V E Powell,5,10 Shu-Ling Chong,11 Damian Roland,12,13 Mark D Lyttle,14,15 Ricardo M Fernandes,16,17 Javier Benito,18 Mike Johnson,19 Adriana Yock-Corrales,20 Indumathy Santhanam,21 Suzanne Schuh,22,23 Baljit Cheema,24 Jenny Couper,1 Simon Craig,1,4,25 On behalf of the Pediatric Emergency Research Network (PERN)

ABSTRACT

Background Acute exacerbations of asthma are common in children, however, treatment decisions for severe exacerbations are challenging due to a lack of robust evidence. In order to create more robust research, a core set of outcome measures needs to be developed. In developing these outcomes, it is important to understand the views of clinicians who care for these children in particular, views that relate to outcome measures and research priorities.

Methods To determine the views of clinicians, a total of 26 semistructured interviews based on the theoretical domains framework were conducted. These included experienced clinicians from emergency, intensive care and inpatient paediatrics across 17 countries. The interviews were recorded, and later transcribed. All data analyses were conducted in NVivo by using thematic analysis.

Results The length of stay in hospital and patient-focused parameters, such as timing to return to school and normal activity, were the most frequently highlighted outcome measures, with clinicians identifying the need to achieve a consensus on key core outcome measure sets. Most research questions focused on understanding the best treatment options, including the role of novel therapies and respiratory support.

Conclusion Our study provides an insight into what research questions and outcome measures clinicians view as important. In addition, information on how clinicians define asthma severity and measure treatment success will assist with methodological design in future trials. The current findings will be used in parallel with a further Paediatric Emergency Research Network study focusing on child and family perspectives to develop an internationally agreed core outcome set for future research in trials of acute severe asthma.

INTRODUCTION

An acute exacerbation of asthma, in children, is a common reason for emergency department (ED) presentation and subsequent admission to hospital.1 Hospital admissions for asthma are increasing and are associated with a significant economic burden.2–4 While many children have mild to moderate exacerbations and are discharged home, a recently published study of 14029 children presenting to Australasian EDs found that 36% of children with acute asthma are admitted to hospital, with 1.1% requiring paediatric intensive care unit admission (PICU).5 In addition, recent studies document increasing PICU admission for severe acute asthma worldwide.6 Despite this concerning scenario, the evidence base informing treatments for these high-risk patients with severe presentations is weak.6 Current knowledge is limited due to
a lack of adequate sample size in existing trials, a wide range of treatment options and variation in both clinical management practice and outcome measures use.2–7,8

As such, there is a need to develop a core outcome set for trials in this population to enable collation and systematic review of high-quality and comparable trial results. The process to define core outcomes for a specified study population has been outlined by the Core Outcome Measures in Effectiveness Trials initiative.9 A working group within the Paediatric Emergency Research Network (PERN), an international umbrella collaborative acute care research network, has been established to determine a core outcome set for acute severe asthma in children.10 The primary aim of this paper is to describe the views of clinicians in identifying important outcome measures. The secondary aim is to understand important research priorities and explore the underlying behaviours and knowledge used by clinicians to define, treat and reassess asthma.

Findings from this study will allow the development of a comprehensive list of outcome measures relevant to research in this field. These outcomes will be aligned with those identified by parents and children and will be combined to inform a future Delphi study to generate a core outcome set. This will enable the development of consensus guidelines and standardised protocols for randomised controlled trials in this important condition.10

METHODS

Study design
We conducted clinician interviews across multiple hospitals and countries and included multiple specialties. The focus was to understand how and why clinicians treat asthma in the way they do, including identifying what clinicians perceive as important in both research questions and outcome measures.

Theoretical framework

Methodological orientation and theory

In order to change behaviour, there is a need to explore the underlying drivers of current practice. The theoretical domains framework (TDF), underpinned by behavioural change theories, provides a structured and comprehensive framework to understand the different elements of behavioural change, thus allowing for more effective implementation research.11 Broadly speaking, the TDF covers the following domains: knowledge, skills, social/professional role and identity, belief about capabilities, belief about consequences, motivation and goals, memory, attention and decision process, environmental context, social influences, emotion and behavioural regulation.12 Based on this framework, interview questions were formulated according to each domain to ensure a breadth of understanding of why clinicians assess and manage asthma in the way they do. The questions were formulated initially by the research working group to cover what was identified as the key questions for understanding asthma and research and outcome priorities. This was then compared with the outline of the TDF to ensure all components were covered. This was then refined by the initial research working group; including researchers (CG, SC, FB and SD) with final interview questions based on consensus. For each interview, to allow for comprehensive data collection at the end of each interview an open-ended question was asked ‘is there anything else on this topic or thoughts around this topic you would like to add or ask?’. This component was also transcribed and used in analysis of the data as per the rest of the data set.

The semi-structured interview allowed flexibility within the components of the interview and included collection of demographic features of participants. The questions (online supplemental appendix 1) explored how clinicians define an acute severe exacerbation of asthma in children, the relative clinician-perceived importance of different outcomes and aspects of clinical care, and opinions on priorities for future research. The interview format was not modified during the interview process.

Participant selection and sampling

Experienced clinicians in paediatric emergency medicine, intensive care and inpatient paediatrics across 17 countries were recruited through convenience sampling from the PERN asthma group by email. The total number of recipients of the initial email was 27. Each member from the group was asked to either participate or invite another clinician (such as intensive care paediatric physicians, emergency physicians, general and respiratory paediatricians) within their local health network to participate. In order to have a diverse view, a maximum of five clinicians in one country and no more than two clinicians from the same hospital were included. This recruitment process commenced to ensure adequate diversity both geographically across the globe and to ensure representation, where possible, across both high-income and low-middle income countries (table 1). Once this was ensured we continued with interviews, until thematic saturation was reached. Interview data were analysed after the first 10 interviews, and after then every 5 interviews thereafter. Each participant received an invitation letter with a participant information sheet from the principal investigator (CG). A total of twenty-six interviews were conducted; twenty one interviews were conducted using Zoom videoconferencing12 and recorded, two interviews which were conducted face to face at the primary researcher’s own hospital. Three interviews were completed with the exchange of written questions and answers: two participants preferred written documentation due to English as a second language, and one due to unreliable internet service. All interviews were recorded and transcribed by a professional transcription service. The interviewees with each type of interview method are denoted in Table 1. Verbal consent was obtained at the
commencement of each interview. No potential interviewees refused consent and no interviewees withdrew from the study.

Two of the interviewees were colleagues of the principal investigator working in the same healthcare system. To mitigate interview bias a general email was sent to all emergency physicians, intensive care physicians and general paediatric clinicians. The two interviewed were those that expressed interest and availability to participate. The same set of questions was asked as was done for all other interviewees and the interview recorded and transcribed verbatim. All other interviewees were unknown to the investigator prior to this study.

**Researcher characteristics and reflexivity**

The research team has reflected on our sociodemographic, cultural and educational backgrounds and the influence on our data collection and interpretation. The lead author (CG) is an Australian medical specialist having completed both her medical degree and specialist qualifications in paediatrics. This study comprised part of her PhD and she is experienced in contributing to multicentre research in the field of acute, severe asthma. During the data collection and analysis for this study, the lead author worked as a paediatric emergency physician at a major hospital in Adelaide Australia and was a PhD candidate at University of Adelaide. The second author is a bicultural (Chinese/Australian), PhD qualified researcher with 10 years’ experience in triangulation research combining quantitative and qualitative methods. The rest of the authors represent a geographically diverse group of clinicians across the globe, all working clinically within paediatric emergency medicine and collectively with extensive experience in both qualitative and quantitative research. Interviews were only conducted by the lead author and data analysis was conducted by the first and second authors.

<table>
<thead>
<tr>
<th>Country</th>
<th>Specialty</th>
<th>Practice setting</th>
<th>Years of experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>America</td>
<td>Emergency physician</td>
<td>Tertiary</td>
<td>&gt;15</td>
</tr>
<tr>
<td>Argentina</td>
<td>Paediatrician</td>
<td>Tertiary</td>
<td>5–10</td>
</tr>
<tr>
<td>Australia</td>
<td>Paediatric emergency physician*</td>
<td>Tertiary</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Australia</td>
<td>General paediatricist*</td>
<td>Tertiary</td>
<td>5–10</td>
</tr>
<tr>
<td>Australia</td>
<td>Intensive care physician</td>
<td>Tertiary</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Australia</td>
<td>Emergency physician</td>
<td>Tertiary</td>
<td>0–5</td>
</tr>
<tr>
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<td>Paediatric emergency physician</td>
<td>Tertiary</td>
<td>&gt;10</td>
</tr>
<tr>
<td>China</td>
<td>Paediatricist†</td>
<td>Tertiary</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>Paediatricist</td>
<td>Tertiary</td>
<td>5–10</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>Paediatric respiratory physician</td>
<td>Tertiary</td>
<td>5–10</td>
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<tr>
<td>India</td>
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<td>Tertiary</td>
<td>5–10</td>
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<tr>
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<td>0–5</td>
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</tr>
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<td>Paediatric allergist†</td>
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<td>Tertiary</td>
<td>5–10</td>
</tr>
<tr>
<td>Uruguay</td>
<td>Paediatric intensivist</td>
<td>Tertiary</td>
<td>5–10</td>
</tr>
</tbody>
</table>

All other interviews these were conducted via ZOOM conference software.

*These interviews occurred in person at researcher’s primary place of work.
†These occurred via written correspondence.
‡Tertiary and secondary refers to the capacity of the hospital to either be a specialist paediatric hospital, with access to a wide range of medical and surgical specialties and most commonly a paediatric intensive care unit or secondary where a paediatric patient would be seen in ED but if unwell or requiring complex care would need to be referred. For this study, the interviewees denoted themselves as working at a tertiary or secondary hospital.

ED, emergency department.
Data analyses

The recordings of interviews were deidentified and transcribed by a central secure academic transcription service (www.gotranscript.com). The transcripts were then sent to the interviewer for review. Once checked and approved, transcripts were uploaded into NVivo V.12 to assist with data analysis (18 March 2020, QSR International, London, UK).

Detailed inductive analysis occurred on raw data. Data were then categorised into themes that were then mapped to the TDF. The two researchers (CG/YX) independently reviewed the transcribed interviews. Text relevant to more than one theme were cross-indexed. Coding was discussed after the first five interviews to ensure consistency. Discrepancies were identified, discussed and consensus was reached.

Within themes, all subthemes were defined, and reported as the number of times the thematic concept was coded. Verbatim quotation for themes are highlighted in results and online supplemental appendix 2.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

This paper is reported according to the Standards for Reporting Qualitative Research.

RESULTS

Interviews were conducted between December 2018 and August 2020. Demographic characteristics, location of clinical practice and method of interviewing for each participant are outlined in table 1. The average interview duration was 33 min (range from 15 to 60 min). Interviews conducted via written communication were excluded from the timing range reported. Overall themes are outlined in table 2 and are reported with reference to the TDF which they are mapped. Several dominant themes were identified and the subthemes within each have been outlined. The results outlined below report the dominant themes with regard to the primary aim of this study, to explore outcome priorities and the secondary aims of
both identifying research questions and how clinicians define asthma and severity in response to treatment.

**Dominant theme: defining asthma and severity of asthma (knowledge)**

The subthemes identified in defining an asthma exacerbation in descending order of frequency were history, clinical examination, age, excluding differential diagnosis, use of local guidelines and response to treatment. A peak flow meter was only mentioned in one interview as being in routine use. There was variation in the age range from when an asthma exacerbation was considered, with age ranging from 2 to 5 years old. No interviewee considered asthma exacerbation as a diagnosis in children younger than 2 years old. While asthma severity was viewed as a combination of features, the dominant subtheme associated with severe or life-threatening asthma exacerbation was the level of consciousness.

*A child that’s agitated, distressed or drowsy makes me more concerned that I’m dealing with severe asthma.* Uruguay, Paediatric Intensivist

Other subthemes included oxygen saturations, observations and the number of an asthma score. The value of oxygen saturations considered as a sign of severe exacerbation ranged from 90% to 94%. Three asthma scoring systems were identified, the Pulmonary Respiratory Assessment Measure (PRAM)\(^\text{15}\) the Pulmonary Index score\(^\text{16}\) and the Wood and Downe’s score.\(^\text{17}\) The use of the scores was identified as both guiding treatment choices and measuring success and clinical response to treatments.

*It’s throughout our whole department and it’s part of our EMR. It has a direct order entry. It’s all based on PRAM scoring and then automatic order-filling based on that.* Switzerland, Emergency Physician

**Dominant theme: drivers of treatment decisions (knowledge)**

There were similarities among providers in the first-line treatments for children with non-severe asthma, with all clinicians mentioning supplemental oxygen and short-acting beta agonists. There was some variability regarding the indication for steroids in mild-moderate asthma. There was considerable variation in the management of severe asthma: when discussing the use of a particular intravenous agent, the drivers of using escalated therapy and how the outcomes of treatment were measured (Knowledge, Motivation and Goals). Reasons for variation were attributed to personal clinical experience and knowledge of the existing literature.

*My experience with magnesium is [that] it seems to be [a] safe and effective therapy.* Australia, Paediatric Emergency Physician

*I’m probably using aminophylline more in the last one to two years for the severe critical asthma that’s going to ICU.* Australia, Emergency Physician

*Changed threshold of using IV/Oral corticosteroids. In the past reserved them only for patients who did not respond initially to therapy. Nowadays prescribe them to any patient with an exacerbation needing a hospital visit. Based on some research I had read at some point.* Tanzania, Emergency Physician

The complexity of treatment decisions was highlighted as outlined below.

*I would say that the decision is probably influenced by the time of the shift, whether it’s day or night, whether there’s a space where … [in] the ward or they’re going to be needing ED for a long time, what the feeling of the nurses is.* Costa Rica, Respiratory physician

There were different opinions on when respiratory support therapies such as the use of high flow nasal cannulae and non-invasive ventilation were used. (Skills/belief about capabilities)

*We give high flows or at least more flows of oxygen, that might improve their oxygenation. Helping them with some PEEP, might help them decrease, at least, their work of breathing.* Costa Rica, Paediatrician

*Then as far as non-invasive ventilation like BiPAP or CPAP, those are usually applied if we continue to have a child that shows signs of poor ventilation.* South Korea, Paediatric allergist

A dominant theme was the need for admission and the likelihood of Intensive Care admission if the children required IV therapy. (Emotion/motivation, goals and social influences)

*If you are on an infusion of whatever your choice of the day is, in our hospital, that means you go to intensive care.* New Zealand, General Paediatrician

*It’s very [very] hard to discharge a child who I’ve given intravenous treatment to because fear of judgment by my peers.* Australia, Emergency Physician

The theme of limited access to resources, particularly in availability of high flow or access to intensive care, was more apparent in low-income and middle-income countries (Environmental context and resources).

*The circuit we use is a single-use circuit. That is the only problem with high-flow nasal cannula, but being a third-world country, the problem in certain patients, it won’t be affordable.* India, Paediatric Emergency Physician
Dominant theme: measurements of successful treatment (motivation and goals)

There were three subthemes that encapsulated the way clinicians identified treatment success by: Improvement in the clinical status during an observational period, minimisation of the need for invasive ventilation and meeting patient-centred goals. With respect to clinical improvement, the most common goal was the work of breathing, although this measure was often combined with general improvement in mental status and hypoxia.

The work of breathing in terms of respiratory rate, use of accessory muscles is lessening. Then I think the treatment is successful. Australia, Emergency Physician

In contrast, physicians in less-well resources regions expressed an opinion that escalation of therapy was usually instituted to avoid respiratory failure requiring mechanical ventilation, respiratory arrest and death.

All we are trying to prevent is the cardiac arrest ultimately. India, Paediatric Emergency Physician

Patient-centred goals emphasised the importance of making the child feel more comfortable and diminishing the concern of staff and parents.

Makes the child feel more comfortable. They feel calmer, and their look and their symptoms settle down. Australia, General Paediatrician

Dominant theme: research goals and outcome measures (goals and skills)

Participants outlined several research themes and outcome measures outlined in Table 3. In addition, figure 1 reflects the dominant themes of outcome measures by years of experience. The more experienced clinicians all highlighted length of stay as an outcome measure, with the less experienced clinicians focusing more on disposition from ED. All clinicians across the years of experience highlighted the importance of including patient-related outcome measures. Table 4 provides suggestions for future research questions and important trial outcome measures are listed in Table 5. Verbatim examples of each research question are provided in online supplemental appendix 2.

In addition, clinicians have emphasised the importance of a consensus for key core outcome measures, including factors perceived as important by children and families. This also included the need to consider how core outcomes would differ in different economic and social settings. It was commented on that higher mortality rates and severity at presentation in lower socioeconomic countries would affect the outcome and research goals identified.

Well, they die before we can take care of them. They die. They just simply die... If you make a trial in that country or in that country, outcomes are different than I guess in Australia or in Uruguay. Uruguay, Paediatric Intensivist

Table 3 Outcome measures and research questions mapped to the domain of goals and skills from the TDF and ordered by number of interviews in which theme was mentioned

<table>
<thead>
<tr>
<th>Outcome priorities</th>
<th>Length of stay parameters</th>
<th>Patient disposition from ED</th>
<th>Patient-related outcomes</th>
<th>Rate of complications</th>
<th>Using a validated score</th>
<th>Length of non-invasive ventilation (NIV) and invasive ventilation (IV)</th>
<th>How much treatment was needed</th>
<th>Death and respiratory arrest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entrance into studies</td>
<td>Understanding different phenotypes</td>
<td>Defining severity for an acute exacerbation</td>
<td>How asthma is defined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research questions</td>
<td>Diagnosis and classification</td>
<td>Peak flow usefulness</td>
<td>Aligning guideline</td>
<td>Identifying those with secondary pneumonia</td>
<td>Point of care US</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment goals</td>
<td>Respiratory function</td>
<td>Target oxygen level</td>
<td>Prevention of exacerbations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment options</td>
<td>Best IV therapy</td>
<td>Nebulised magnesium/heliox/intramuscular epinephrine/ketamine</td>
<td>Steroids</td>
<td>NIV and high flow</td>
<td>Use of IV therapy on the ward</td>
<td>Role of Ipratropium Bromide</td>
<td>Efficacy of asthma care plan</td>
<td></td>
</tr>
</tbody>
</table>

ED, emergency department; TDF, theoretical domains framework.

Dominant themes around future research from clinician’s perspective were categorised into three main areas: defining entrance into studies, identifying important outcome measures for clinical trials and determining important research questions.

With regard to entrance into studies, dominant themes included an understanding of different asthma phenotypes, the clinical diagnosis of asthma and defining severity of an acute exacerbation.

Figure 1 Dominant outcome measures identified by years of experience of clinician. ED, emergency department.
Table 4  Research questions in each of the dominant themes with examples

| 1. Treatment options | What is the best IV bronchodilator therapy and in what order should the IV options be given?  
| | What is the utility of NIV and high flow?  
| | Which steroid is ‘best’ for exacerbations of asthma, what dosing?  
| | What are the risks of giving IV therapy on the ward?  
| | What is the role of nebulised magnesium?  
| | What is the role of ketamine?  
| | How does ipratropium help prevent admission or escalation of care in an acute exacerbation of asthma?  
| | What is the role of IM epinephrine?  
| | What is the role of Heliox? |
| 2. Diagnosis and classification | What is the usefulness of peak flow in diagnosis and classification of severity?  
| | How do you identify those with secondary pneumonia? What is the utility of point of care ultrasound?  
| | What should an international clinical practice guideline look like and what are the research goals? |
| 3. What are reasonable treatment goals? | For clinical parameters including respiratory function?  
| | What should be the target oxygen level? |
| 4. Questions related to families and children | What are ways in which you can prevent asthma exacerbations?  
| | How do you ensure knowledge translation of asthma care plans? |

IV, invasive ventilation; NIV, non-invasive ventilation.

You have the severe obese asthmatics that have a completely different phenotype to significant severe eosinophilic asthmatic. I guess you need to rule out which group of asthmatic[s] you want to study and what is your aim of the study. Costa Rica, Paediatrician

Is getting a clear definition of what asthma is and that’s probably the biggest challenge in these studies is like what are we calling asthma and making sure that, that’s defined, then the people running the trials are getting the same groups of kids in. Australia, General Paediatrician

DISCUSSION

This study explored the priorities in research questions and outcome measures for children with acute exacerbations of asthma. This was examined by using the TDF to gain an understanding of how clinicians diagnosed asthma, classified severity management decisions and measurement of success (or otherwise) of the treatment administered. Findings from this study can now be used to help us prioritise specific research areas in paediatric acute asthma and inform investigators about the use of relevant patient populations and how to best assess treatment response.

Diagnostic criteria for acute exacerbation of asthma in children varied between clinicians. It is common that individuals have different understanding or interpretation of a concept however, without internationally recognised criteria to diagnose the severity of acute asthma in the ED setting, it is challenging to systematically examine the quality of practice including treatments, outcomes and costs.

Respondents have suggested some common features useful in defining entry criteria for future asthma studies. These include a minimum age of 2 years, and the need for definitions of asthma to include components from medical history (such as a previous salbutamol responsive wheeze episode) and examination findings such as respiratory distress or work of breathing.

Further, for trials in severe asthma exacerbations, it is important to standardise the assessment of severity. Asthma scores were a popular choice, as they allow for both measurement as study entry criteria and a way to measure change. The use of asthma scores is widespread in some regions (particularly North America and Europe) however, robust validation is lacking. Experienced clinicians described the utility of altered conscious state as a marker for critical illness; however, this is not routinely captured in most asthma scores. In
addition, the measurement properties of this symptoms/sign are not well explored.

It was more common that clinicians from low-income and middle-income countries (LMIC) reported need to manage more severe or life-threatening disease and how treatment decisions may be influenced by cost. This is likely multifactorial and reflects accessibility and affordability of high-quality timely healthcare. It is clear that there needs to be better understanding of how cost impacts families or clinicians’ choices of treatment and that treatment choices that are more readily used in low-income and middle-income countries, for example, subcutaneous or intramuscular epinephrine need to feature in trial design.

This study has reiterated the variability of treatment options outlined in previous research\(^6\)\(^7\) and provided some depth of understanding for it. It has been found that the clinicians often relied on their clinical guidelines as their knowledge basis, along with their colleagues’ opinions to guide their treatment decisions. A presumption was made by the clinicians that these guidelines were based on evidence although this was not verified and there continues to exist significant disparity in guidelines both within countries and internationally.

Hospital length of stay was the most commonly suggested outcome measure, and has been regularly used in paediatric asthma studies.\(^8\) As an outcome parameter, the length of stay is easy to measure, impacts families and hospitals, and has clear fiscal implications. However, length of stay may not necessarily reflect the outcome from treatment only, but also may be influenced by historical factors, time of day, or local hospital policies (eg, requiring hospital admission and/or PICU admission after IV therapy) and affordability in countries without easily accessible free healthcare for children. Important considerations relevant to patients and families include the impact of treatment and hospitalisation on a child and their family unit.

LIMITATIONS
It is recognised that there is a small number of respondents per region and the representation from low-income and middle-income countries and non-English-speaking participants was small. It would be important when defining research questions to consider how these would be useful or transferable to low-income and middle-income families. However, data saturation was reached adding confidence to these findings. This study is also limited to the view of professionals and further work is required to refine findings and include the view of families and children.

CONCLUSION
This study has gathered opinions and priorities of experienced clinicians from different geographical regions on which children with acute asthma should participate in future trials, how we should measure response to treatments and what research areas should be prioritised. This study also highlights the importance of tailoring the use of research outcomes to local clinical and socioeconomic circumstances and geographic context of the patient.

The current findings will be used in parallel with a further PERN study focusing on the child and family perspectives. These will contribute to develop a core outcome set for future research.

Author affiliations
1Adelaide Medical School, Discipline of Paediatrics, The University of Adelaide, Adelaide, South Australia, Australia
2Paediatric Emergency Department, Flinders Medical Centre, Bedford Park, South Australia, Australia
3Zhuhai City People’s Hospital, Zhuhai, Guangdong, China
4Department of Paediatrics, School of Clinical Sciences, Monash University, Clayton, Victoria, Australia
5Murdoch Children’s Research Institute; Departments of Paediatrics and Critical Care, University of Melbourne, Parkville, Victoria, Australia
6Emergency Department, Royal Children’s Hospital, Parkville, Victoria, Australia
7Children’s Emergency Department, Starship Children’s Health, Auckland, New Zealand
8Surgery and Paediatrics, The University of Auckland Faculty of Health and Medical Sciences, Auckland, New Zealand
9Division of Population Medicine, School of Medicine, Cardiff University, Cardiff, UK
10Department of Emergency Medicine, Sidra Medicine, Doha, Ad-Dawhah, Qatar
11Department of Emergency Medicine, KK Women’s and Children’s Hospital, SingHealth Paediatrics Academic Clinical Programme, Singapore
12SAPPHIRE Group, Health Sciences, University of Leicester, Leicester, UK
13Paediatric Emergency Medicine Leicester Academic (PEMLA) Group, Children’s Emergency Department, Leicester Royal Infirmary, Leicester, UK
14Paediatric Emergency Department, Bristol Royal Hospital for Children, Bristol, UK
15Research in Emergency Care Avon Collaborative Hub (REACH), University of the West of England, Bristol, UK
16Department of Pediatrics, Hospital de Santa Maria, Lisboa, Portugal
17Clinical Pharmacology Unit, University of Lisbon, Lisboa, Portugal
18Pediatric Emergency Department, Cruces University Hospital. Biocruces Bizkaia Health Research Institute, Bilbao, Spain
19Department of Pediatrics, University of Utah Health, Salt Lake City, Utah, USA
20Emergency Department, Hospital Nacional de Ninos “Dr Carlos Saenz Herrera”, CCSS, San Jose, Costa Rica
21Regional Collaborative Center, Institute of Child Health, Madras Medical College, Egmore, Chennai, India
22Hospital for Sick Children Research Institute, University of Toronto, Toronto, Ontario, Canada
23Division of Pediatric Emergency Medicine, The Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada
24Department of Paediatrics & Child Health, University of Cape Town, Rondebosch, Western Cape, South Africa
25Paediatric Emergency Department, Monash Medical Centre, Monash Health, Clayton, Victoria, Australia

Twitter Charmaine S Gray @DrCharmaineGray and Simon Craig @DrSimonCraig

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ORCID iDs
Damian Roland http://orcid.org/0000-0001-9334-5144
Ricardo M Fernandes http://orcid.org/0000-0002-7253-6475
Simon Craig http://orcid.org/0000-0003-2594-1643

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