The Paradox of Informed Consent Issues in Paediatric Status Epilepticus Research

Thesis submitted by

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Abstract

Introduction

Status epilepticus (SE) has confounded clinicians for hundreds of years and remains the most common neurological emergency affecting children in emergency departments. Remarkably, management has changed little over the last century, and very little data are available to guide treatment. Potential new therapies are often adopted into clinical care without robust evidence, however clinicians seeking to evaluate the same therapies in methodologically sound studies face high levels of scrutiny as well as regulatory and ethical obstacles. This is partly because of the difficulty of conducting research in this setting, with informed consent issues in time-critical research being a major barrier. This leads to the ethical paradox of using untested therapies in critically ill children without informed consent, but the regulatory and ethical barriers existing in researching these same therapies.

Objectives

The objectives of this thesis are to explore the paradox of informed consent issues in paediatric SE research. The specific objectives of the thesis are: to 1) Identify gaps and opportunities for research from a review of the existing literature on paediatric SE; 2) Inform the future research agenda in the management of paediatric SE by achieving consensus on research priorities among experts in managing this condition, consisting of paediatric neurologists and emergency physicians who treat children; 3) Determine if research priorities identified by experts align with priorities identified by consumers (parents of children with SE); 4) Determine what is known about the public's perceptions and attitudes towards research in a paediatric emergency setting without prospective informed consent; 5) Explore attitudes of the general public to research in emergency settings without prior consent; 6) Explore parental attitudes to a deferred consent process in the emergency department (ED) setting, including the management of SE.

Methods

In this thesis multiple methodologies are used to achieve the stated objectives. The thesis consists of two separate, but interconnected streams. Stream one explores the existing knowledge of paediatric SE, identifies research priorities and explores the feasibility of addressing these knowledge gaps. Stream two explores the barriers to research in paediatric SE, namely issues of consent in time-critical research. At the confluence of these two streams is the discussion highlighting a roadmap for addressing the various knowledge gaps in paediatric SE, for the improved care of this condition. Methodologies used in the thesis include literature reviews (narrative, systematic, perspective), Delphi consensus

technique, a cross-sectional population-based survey (with qualitative and quantitative components), and a qualitative study (semi-structured interviews resulting in thematic analysis).

Results

Chapters 2 and 3 of the thesis comprise reviews of the existing literature on the epidemiology, investigation, management of paediatric SE as well as specifically exploring pre-hospital aspects of paediatric SE care. A historical lack of consistency with definitions and classification has been a limitation of existing comparative studies. Consistency in definitions moving forward is essential to future research efforts. The review found an incomplete understanding of the epidemiology of paediatric SE, with a dearth of local data. The fundamental question of whether seizure duration is an independent predictor of poor outcome, when confounding factors such as age and aetiology are controlled for, remains unanswered. Optimal investigation and management of paediatric SE are based on low level evidence. Observational data suggest that treatment is often delayed, but beyond first line care, management guidelines are based on expert opinion only. Definitive evidence on the pre-hospital management of paediatric SE is lacking, and the review highlighted substantial variation in local protocols around Australia and New Zealand.

Chapter 4 reports the results of a Delphi study to achieve consensus on research priorities in paediatric SE among experts (neurologists and emergency physicians). Nine priority research questions are identified, consisting of second line management including levetiracetam (efficacy, dose and timing), use of third line agents, induction of anaesthesia (timing and best agent), management of focal SE, and indicators of "subtle SE". Some of these priorities are unlikely to be addressed in clinical trials with traditional concepts of informed consent, and other methods will be required such as alternative study designs and alternative approaches to consent.

Chapter 5 outlines a protocol for a clinical trial of second line management of paediatric SE. This trial directly addresses two of the nine priorities identified by the Delphi process. The trial epitomises the paradox of informed consent in paediatric SE research as the study intervention (levetiracetam) is being rapidly adopted into clinical care and protocols without any robust evidence of efficacy. The study would not be possible with traditional models of informed consent applied and uses a controversial deferred consent process.

Chapter 6 presents the historical context of informed consent in emergency research, highlighting important principles of the Declaration of Helsinki and the historically inconstant

approach taken in emergency medicine as exemplified in the cardiac mega trials. Chapter 7 presents the results of a systematic review of empirical evidence on informed consent issues specific to paediatric emergency medicine. Thirteen studies included in the review found that the public are generally supportive of alternatives to prospective informed consent, with important considerations being the level of risk involved, and informing the parents about the research involvement as soon as possible. Other major themes explored in the review are capacity of parents to provide informed consent, feasibility of informed consent and modified consent processes. There were no Australian studies identified in the review.

Chapter 8 presents results of a national, cross-sectional, population-based survey on attitudes about research without prospective informed consent. This is the first study of its kind in an Australian population, and the results indicate that the public are generally supportive of the concept. Level of risk and the time-critical nature of the intervention are again identified as important considerations.

Chapter 9 reports the results of a novel Australian study on the attitudes and experiences of parents attending the ED with their children on the concepts of deferred or retrospective consent. The qualitative study of 39 parents finds universal support for emergency research and an acknowledgment of the limitations of traditional consent under these circumstances. Participants are generally supportive of deferred consent. Health and research literacy is identified as an important issue, potentially leading to some confusion with difficult concepts.

Discussion

In the modern era of evidence-based medicine, it is not satisfactory for the management of potentially life-threatening conditions such as paediatric SE to be based on inadequate evidence. It should not be acceptable to use untested or experimental therapies for clinical care without consent, when research and evaluation of the same therapies is burdened by regulations and administrative and ethical requirements. The literature reviews and Delphi study presented in this thesis outline many knowledge gaps in the management of paediatric SE and opportunities for further research. Several of the research priorities identified are unlikely to be addressed in adequately powered, traditional randomised controlled trials. Alternative study designs and alternatives to traditional concepts of informed consent will be required. Recent innovations and advances in electronic health information systems and electronic medical records may represent an elegant solution, and present an opportunity to embed data collection on infrequent presentations and conditions into routine practice. The added possibility exists of embedding treatment allocation into such systems where true equipoise exists, resulting in the necessary robust evidence to drive practice change.

Importantly, this could be achieved without exposing patients to any additional risk which represents a recurrent theme of concern in this thesis surrounding research without explicit prospective consent. This research demonstrates that the public recognise the requirement for research without prospective informed consent, with the degree of risk being a key consideration. Policy makers and guidelines need to explicitly address this type of research in regulatory documents, to ensure such research can continue, and the trust of the public and community in maintained. In Australia, guideline documents do not explicitly define requirements for emergency and time-critical research and specific requirements vary by jurisdictions due to local legal requirements. This needs to be addressed as a priority, to ensure that important research into time-critical and life-threatening conditions such as paediatric SE can continue. The involvement of consumers in the process, such as the data presented in this thesis, is essential in maintain the trust of the community.

Conclusion

Paediatric SE is an important cause of morbidity and mortality in children. Care often involves unproven therapies that are introduced into standard care and guidelines. This generally occurs with community acceptance and legal protections for time-critical interventions. Paradoxically, quality research is often thwarted due in part to ethical complexities, including the inability to obtain prospective informed consent in time-critical situations. In situations where there is clinical equipoise, and clear evidence does not exist, a compelling ethical argument can be made that similar standards should be applied to research, especially when considering the additional protections offered under the oversight of a high-quality randomised controlled trial. The data presented in this thesis indicates that the general public do not make a distinction between clinical care and research, providing that there is no exposure to additional risk. This research represents an important first step in the design of a program of research on paediatric SE to address these important clinical issues, in an ethical manner that will be acceptable to the community. A combination of real time registry, learning health systems, and innovative clinical trial designs is required, with consent requirements that are appropriate for the level of risk to participants, and congruent with community expectations.

Contribution statement

Statement of contribution by student

I, Jeremy Furyk was the primary person responsible for the following thesis components:
-conception and design of the research project
-coordination of the project
-obtaining funding for the projects
-conception of the research questions
-study design and drafting of research protocols for the component studies
-training and supervision of research staff associated with the projects
-data management and data analysis of projects
-drafting thesis and component manuscripts
-submitting for publication
Contributions of co-authors of publications arising from this work are listed below.

Conflict of interest

The author has no conflict of interest relating to any of the research contained within this thesis.

Funding of research

Townsville Hospital Private Practice Trust Fund 2015 $20,000 **Furyk J**, Ray R. Mixed methods evaluation of a deferred consent process in paediatric emergency research. Private Practice Trust Fund. (Chapter 8, Paper 5)

Statement of contribution of others

Nature of Assistance	Contribution	Names, Titles & Affiliations
Intellectual support	Editorial assistance / manuscript preparation	Listed co-authors of publications included in the thesis provided intellectual input and relevant expertise to published manuscripts. Contributions are detailed in individual publications.
	Supervision	Dr Kerrianne Watt was the primary advisor at James Cook University, Dr Theophilus Emeto was a secondary advisor at James Cook University, Dr Robin Ray was a secondary advisor at James Cook University, Dr Stuart Dalziel was an external secondary advisor from the University of Auckland and A/Prof Franz Babl was an external secondary advisor at University of Melbourne.
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Data collection	Research assistance	Ms Haylee Fox assisted with ethics and governance submissions, distribution and collation of surveys for the Delphi study (Chapter 4, Paper 2). Dr Kris McBain-Rigg

	assisted as secondary author in the systematic review (Chapter 7, Paper 5) with verifying study selection, quality assessment and data extraction and with conducting interviews in the qualitative study on deferred consent (Chapter 9, Paper 7).

Contribution of other to publications

Chapter No.	Publication	Intellectual input of author
Ch. 3	Furyk J, Watt K, Emeto TI, Dalziel S, Bodnar D, Riney K, Babl F. Review article: Paediatric status epilepticus in the pre-hospital setting: An update. Emerg Med Australas: 2017 Aug; 29(4):383-390. PubMed PMID: 28627014. DOI: 10.1111/1742-6723.12824	JF conceived the project, designed the search strategy and performed the literature search. JF drafted the first version of the manuscript. KW, TE, SD, DB, KR and FB provided expert input into interpretation of the data, and editing of the manuscript. All authors approved the final version of the manuscript.
Ch. 4	Furyk J, Ray R, Watt K, Dalziel SR, Oakely E, Mackay M, Dabscheck G, Riney K, Babl FE. Consensus research priorities for paediatric status epilepticus: A Delphi study of health consumers, researchers and clinicians. Seizure. 2018 Feb 5;56:104-9. PubMed PMID: 29471256. DOI: 10.1016/j.seizure.2018.01.025	JF, SRD, FEB, EO and RR responsible for the conception and development of the study, project management, reporting and publication. FEB, SRD, KR, MM, GB expert advice on content and developed of questionnaires. JF conduct of the surveys and data management. JF, RR performed data analysis. JF prepared the first draft of the manuscript, and all authors contributed to revisions and had full access to data. JF takes responsibility for the paper as a whole.
Ch. 5	Dalziel SR, Furyk J, Bonissch M, Oakley E, Borland M, Neutze J, Donath S, Sharpe C, Harvey S, Davidson A, Craig S, Phillips N, George S, Rao A, Cheng N, Zhang M, Sinn K, Kochar A, Brabyn C Babl FE,	The PREDICT network was responsible for identifying the research question. SRD designed the study. SRD, FEB, EO, MB, JN, CS, SH, SD, AD, MB refined the study design and developed

	PREDICT research network. A multicentre randomised controlled trial of levetiracetam versus phenytoin for convulsive status epilepticus in children (protocol): Convulsive Status Epilepticus Paediatric Trial (ConSEPT) - a PREDICT study. BMC Pediatr 2017 Jun 22;17(1):152. PubMed PMID: 28641582. DOI: 10.1186/s12887-017-0887-8.	the research protocol. All authors contributed to the development of the protocol, the implementation of the study at participating sites and the enrolment of patients, SRD and JF were responsible for the drafting of this paper. All authors provided comments on the drafts and read and accepted the final version. SRD, FEB, EO, MB, JN and SD comprise the study steering committee with responsibility for all aspects of the study. SRD takes responsibility for the manuscript as a whole.
Ch. 6	Furyk J, Lawton LD, Ting JYS, McD Taylor, D. Informed consent in emergency care research: An oxymoron? Emerg Med Australas. 2017 Feb;29(1):110-112. PubMed PMID: 27469986. DOI: 10.1111/1742-6723.12642.	JF conceived the project, conducted the literature search and drafted the first version of the manuscript. LL, JT, DT assisted with conception of the article, assisted with drafting and editing of the manuscript.
Ch. 7	Furyk J, McBain-Rigg K, Renison B, Watt K, Franklin RC, Emeto T, Ray R, Babl F, Dalziel S. A comprehensive systematic review of stakeholder attitudes to alternatives to prospective informed consent in paediatric acute care research. BMC Medical Ethics (2018) 19:89 https://doi.org/10.1186/s12910-018-0327-9	JF, KM and RR conceived the study, all authors assisted with drafting the protocol, JF, KM and RR performed the literature search, applied inclusion criteria, data extraction and quality assessment. JF, KM, BR, KW, RF, TE, RR, FB and SD contributed to interpretation of the data and drafting of the manuscript. JF, KM, BR, KW, RF, TE, RR, FB and SD approved the final manuscript.

Ch. 8	Furyk J, Franklin RC, Watt K, Emeto TI, Dalziel SR, McBain-Rigg K, Nikola Stepanov N, Babl FE and PREDICT. Community attitudes to emergency research without prospective informed consent: A survey of the general population. Emerg Med Australas. (2018) 30, 547–555. PubMed PMID: 29718588. DOI: 10.1111/1742-6723.12958	JF conceived the project. JF and RF designed and piloted the draft survey instrument. JF, RF, KM performed the data analysis. JF, RF, KW, TE, SD, KM, NS, FB contributed to interpretation of results. JF drafted the first version of the manuscript, RF, KW, TE, SRD, KM, NS, FEB provided input to manuscript and approved the final version.
Ch. 9	Furyk J, McBain-Rigg K, Watt K, Emeto T, Franklin RC, Franklin D, Schibler A, Dalziel SR, Babl FE, Wilson C, Phillips N, Ray R, on behalf of PREDICT. Qualitative evaluation of a deferred consent process in paediatric emergency research: a PREDICT study. BMJ Open 2017;7(11): e018562. PubMed PMID 29146655. doi:10.1136/bmjopen-2017-018562	JF, KM and RR contributed to the conception and development of the study, project management, reporting and publication. JF obtained funding. JF, KM, DF, AS, CW, FEB and SRD developed the interview schedule. KM, CW, FEB, NP, DF and AS participated in participant recruitment and data collection. KM performed all interviews. JF, KM and RR developed and refined the coding framework, and performed the data analysis. JF prepared the first draft of the manuscript, and all authors contributed to revisions and had full access to data. JF takes responsibility for the paper as a whole.

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List of abbreviations used

AED anti epileptic drugs

AMI acute myocardial infarction

BC buccal

CNS central nervous system

CSF cerebral spinal fluid

CT computed tomography

ED emergency department

EEG electroencephalogram

FIRES fever induced refractory epileptic encephalopathy

GABA gama-aminobutyric acid

GAD glutamic acid decarboxylase

GISSI Groupo Italiano per lo Studio della Sopravivenza nell Infacto Miocardico

GUSTO Global Utilisation of Streptokinase an Tissue Plasminogen Activator of Oclusive Coronary Arteries

HHV human herpes virus

HREC human research ethics committee

ICU intensive care unit

IHHS idiopathic hemiconvulsive hemiplegic syndrome

ISIS International Study of Infarct Survival

ILAE International League Against Epilepsy

IM intramuscular

IN intranasal

IO intraosseous

IV intravenous

LP lumbar puncture

MRI magnetic resonance imaging

NMDA N-Methyl-D-Aspartate

NHMRC National Health and Medical Research Council

PICU paediatric intensive care unit

PR per rectum

PRISMA preferred reporting items for systematic reviews and meta-analyses

RCT randomised controlled trial

RRCT registry randomised controlled trial

RSI rapid sequence induction

SDM surrogate decision maker

SE status epilepticus

SL sublingual

URTI upper respiratory tract infection

US United States

UK United Kingdom

Ethics statement

The research presented and reported in this thesis has been conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research. Ethics approvals for projects included in the thesis are listed below.

- Townsville Hospital and Health Service, Human Research Ethics Committee: HREC/15/QTHS/119 and HREC/15/QTHS/206
- Royal Children's Hospital (Melbourne) Human Research Ethics Committee: Reference Number: 35279A
- James Cook University Human Research Ethics Committee: Approval number H6458 and H6468
- Central Queensland University Human Ethics Review Panel: Project: H14/09-203, National Social Survey 2016
- Public Health Act Application – Approval number RD006083

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Chapter 1. Introduction

> *"Once a new drug or a new preparation is on the market a paradoxical situation arises. If I decide to treat my patients with the new drug, whether because a colleague thinks it is good, or because the advertisements are persuasive, or because I like to be regarded as avant-guard, I am perfectly free to do so. But if I decide that it would be more satisfactory to do a controlled study, either to compare the new drug with the old or to compare the new drug with no drug at all, it becomes research and I should seek the approval of my colleagues on the research ethics sub-committee.* ***I need permission to give a new drug to half my patients but not to give it to them all****."*
>
> (R.W. Smithells, Dept of Paediatrics, University of Leeds, 1975)

1.1 Overview

The above quote from Smithells illustrates the paradox of informed consent in paediatric emergency research that was present in 1975.[1] This paradox is no different today, and paediatric status epilepticus (SE) exemplifies the current situation, which is the basis of this thesis. In this introduction, the history of research in and the understanding of SE will be briefly outlined, including contemporary definitions and classifications. I will detail the barriers to research in the field, including the requirement for informed consent in time-critical research. This introduction will set the stage for the body of work that follows. Finally, I will outline the aims and objectives of the research, which is ultimately to improve the management of paediatric SE in Australia and New Zealand.

1.2 Case study

The ambulance service notifies the Emergency Department (ED) of the imminent arrival of a previously well, three-year-old girl who is currently having a generalised seizure. The seizure started 25 minutes previously and has been resistant to first line management by paramedics. Prior to arrival in four minutes, the ED has time to make some preparations. Team roles are allocated to staff, medical dosage calculations are made based on the estimated weight, and equipment is prepared for emergency treatment. The paediatric intensive care unit (PICU) team is also in attendance, as they were in the department for another case.

On arrival, the ambulance hands over that the child was home from childcare today due to a mild upper respiratory tract infection (URTI). She has no past medical history and is not taking any regular medications. Throughout the day she was resting on the couch and slightly lethargic. Twenty-nine minutes prior her eyes were observed to roll back, she became stiff, unresponsive, with symmetrical tonic-clonic seizure activity in all limbs. This seizure activity was still present when the ambulance arrived 11 minutes after it had started and has persisted (total time 29 minutes) despite one dose of midazolam intramuscularly (IM) and one dose intravenously (IV) as per ambulance protocols. A brief focused examination found airway, breathing and circulation to be intact, but confirms ongoing seizure activity with head and eyes deviated to the left, and fine tonic-clonic movements of both arms and legs.

The girl's mother is in attendance with the ambulance crew. An oxygen mask covers the girls face. You instruct the nurses to prepare an infusion of phenytoin, as a second line agent, as benzodiazepines have been ineffective. The PICU consultant suggests perhaps levetiracetam to be more effective, and promptly explains to the mother that a new medication, "Keppra" can be given through a drip to help stop seizures such as this. He continues, that even though the drug is not licenced for this role, he believes it is the best course of action. The mother nods and agrees that whatever will make her daughter better is fine.

The levetiracetam is administered, and preparations are made to intubate and ventilate the child. Ketamine is used as an induction agent, and seizures appear to finish as this agent is given. The endotracheal tube is placed easily, and the child is transferred to the PICU. Further evaluation of the child does not determine a specific cause for the seizure. Her course in PICU is uneventful and she makes an excellent recovery.

1.3 Status epilepticus

SE has confounded clinicians for hundreds of years. Paediatric convulsive SE remains the most common neurological emergency causing children to present to hospital EDs today. Early descriptions of SE decry the lack of data, lack of consensus definitions, incomplete understanding of pathophysiology, and lack of available effective therapies.[2,3] These themes are arguably equally evident in the contemporary medical literature on SE.

1.4 An historical perspective on status epilepticus and its management

Descriptions of convulsive SE have appeared in the medical literature for over a century.[2-4] Consistency in definitions has proven problematic for researching SE. In 1904 Clarke and Prout wrote "*We must admit that it is with status as with many other phases of epilepsy; it has no exact definition*".[2(p295)] The evolutions of SE definitions will be described in more detail in section 1.5.

While early observational reports provide some insights to the natural history of the condition, outcomes, pathological observations of fatal cases, and therapeutics of the time, the "*great rarity of the condition*"[2] has always been and remains a barrier to quality data. The systemic complications of SE were aptly described based on the astute descriptions in early reports: "*the state is almost always sooner or later accompanied by a marked rise of temperature, pulse and respiratory frequency, which is indicative of exhaustion*".[2(p305)] Early authors also recognized the higher potential for "*grand mal*" epilepsy to result in more significant consequences, and interestingly a description of decreasing motor symptoms with ongoing seizure duration: "*at last the convulsions lessen in frequency and the stuporous stage is ushered in with the coma or collapse*" then "*until death or convalescence, slight convulsive tremors may occasionally occur*".[2(p304)] However, even with limited therapeutic options, the prognosis was not uniformly poor. Survival in these early reported series was 30-50%, and cases of survival were described after more than nine to 12 days of ongoing SE.[2] Contemporary incidence, aetiology and outcome will be detailed in Chapter 2.

While some aspects of management have changed significantly, others have remained remarkably constant. In 1914 Shanahan wrote of the management of SE: "*the most urgently indicated procedure has been, in my experience, a free irrigation of the lower bowel*".[3(p287)] The basis was seemingly to rid the entire gastrointestinal tract of "*poisonous substances*" thought to be causative. However, Shanahan went on to recommend sedation: *"choral hydrate or amylene hydrate should be given by enema in a dosage of sufficient size to quickly bring about sedation of the patient".*[3(p288)] While guidelines today emphasize management of airway, breathing and circulation in preference to urgent bowel irrigation, the

importance of sedation is identified as important and continues to be a mainstay of therapy to this time.

1.4.1 Early drug treatments

Pharmacological agents have been used for treating SE for over 150 years. Bromides were the first effective antiepileptic drugs described for convulsive SE, introduced in the 1860s.[4] Since the early 1900s the importance of sedation has also been recognized, when inhalation of chloroform or concoctions of chloral hydrate, morphine, bromide and opium were introduced as treatments.[2,5] Barbiturates appeared on the scene in the 1920's and 30's, followed by phenytoin and paraldehyde in the 1950's.[4] Widespread administration of benzodiazepines diazepam and clonazepam was introduced after reports of successful treatment of convulsive SE in France in the 1960s,[2,5-7] and their use remains first line in current recommendations. Use of anaesthetic agents propofol and high-dose midazolam were first reported in 1977 and 1978.[4] Many of these drug classes continue to be used today, although some, like paraldehyde, have lost favour.

Since the 1960s there has been a continuous increase in drugs available for chronic epilepsy, however the number of drugs for SE has remained relatively unchanged. This trend likely reflects the highly profitable nature of medications for chronic conditions to the pharmaceutical industry, compared with medications for acute conditions. Some newer drugs have been reported in case series as effective, but none yet satisfy the levels of evidence to be incorporated into standard care.[8-10] Other advances such as sophisticated critical care techniques have increased the available treatment options.[9] Despite the progress over the last century it is likely that in another 100 years our current management strategies may appear as primitive as bowel irrigation. Current management of SE in children will be described in chapter 2.

1.5 Definitions of status epilepticus

Since 1970 SE has been included in the International League Against Epilepsy (ILAE) classification of seizures, where it was defined as a "*seizure that persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring condition*".[11] Since that time slight modifications to the definition have occurred, with the intent as with all medical classification systems, to facilitate communication among physicians, improve treatment, and facilitate the conduct of epidemiological and interventional research. In 1981 the definition was modified to describe a seizure that "*persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur*".[12]

While early ILAE definitions did not specify a precise definition for the duration of a seizure to qualify as SE,[11,12] definitions in standard texts, guidelines, major research papers and clinical trials have usually included such time frames.[13-19] From a pragmatic perspective, SE has traditionally been defined as more than 30 minutes of continuous seizure activity, or two or more sequential seizures without full recovery of consciousness between seizures.[20]

Seizures typically resolve spontaneously by 3-5 minutes. Spontaneous cessation becomes less likely once a seizure has been in progress for more than 5 minutes, and response to anticonvulsants decreases with increasing seizure duration. It is unusual for seizures to last 30 minutes. This led to a revised operational definition of convulsive SE in the late 1990s, based on when one would be expected to commence treatment, proposed as seizures of five minutes or more.[20] This definition has been implemented in recent and contemporary prospective trials of convulsive SE.[15,18,21]

Seizure duration has been a focus of SE research, since other factors that have been associated with poor outcome such as age and seizure aetiology are not modifiable. Animal data support the contention that longer seizures are harmful and result in irreversible brain damage and poorer outcomes,[22] although quality evidence in humans is lacking.

Recently the ILAE task force on the classification of SE released a report outlining a proposed new definition and classification of SE.[23] The new definition incorporates concepts outlined above, such as the importance of time points of clinical relevance to decision-making, and consistency with previous epidemiological and clinical work. The proposed definition is:

> *"SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t1). It is a condition that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures".*[23(p3)]

The proponents of this new definition concede that the definition is based on imperfect knowledge and should continue to evolve. Time points of *t1* and *t2* were based on animal data and correspond with traditional and operational definitions outlined above of 5 and 30 minutes for tonic-clonic SE (and 10 and > 60 minutes for focal SE with impaired consciousness). These terms are explained further below.

1.6 Classification

1.6.1 Overview

Classification systems for SE have evolved with definitions of SE.[11,24] In their report on the classification of SE in 2015, the ILAE task force proposed a system incorporating 4 axes:[23]

1. *Semiology*
2. *Aetiology*
3. *Electroencephalographic correlates*
4. *Age*

This classification acknowledges that at least half of patients presenting in SE will not have epilepsy, and therefore previously used seizure classifications are probably not appropriate. The framework is intended to promote "*clinical diagnosis, investigation, and therapeutic approaches for each patient*".[23(p3)]

Although it is preferable to classify the patient according to each of the four axes, they are of variable importance in the acute care and emergency setting. Where information about age and semiology would be immediately available, electroencephalographs (EEG) are sporadically available acutely outside of research settings in Australia and New Zealand, and aetiology may only become apparent with time and may not be available to assist with acute management decisions.

1.6.2 Axis 1 – Semiology

The semiology axis characterises the clinical presentation of SE and can be simplified as being composed of two main components; firstly, the presence or absence of prominent motor symptoms, and secondly the degree of impairment of consciousness. While conceptually this is relatively straight forward, the classification system entails more than 20 discrete categories (Table 1.1).[23] Components of SE presentation considered of vital importance by neurologists and epileptologists may not be considered part of a standard focused history and examination performed by acute care physicians or routinely documented in medical records, even if elicited in the ED. Further, recognition of subtle convulsive SE and non-convulsive SE is problematic in the ED.

Table 1. 1 Axis 1 Classification of status epilepticus

(A) With prominent motor symptoms
A.1 Convulsive SE (synonym: tonic–clonic SE)
- A.1.a. Generalized convulsive
- A.1.b. Focal onset evolving into bilateral convulsive SE
- A.1.c. Unknown whether focal or generalized

A.2 Myoclonic SE (prominent epileptic myoclonic jerks)
- A.2.a. With coma
- A.2.b. Without coma

A.3 Focal motor
- A.3.a. Repeated focal motor seizures (Jacksonian)
- A.3.b. Epilepsia partialis continua
- A.3.c. Adversive status
- A.3.d. Oculoclonic status
- A.3.e. Ictal paresis (i.e., focal inhibitory SE)

A.4 Tonic status
A.5 Hyperkinetic SE
(B) Without prominent motor symptoms (i.e., non-convulsive SE)
B.1 Non-convulsive SE with coma (including so-called “subtle” SE)
B.2 Non-convulsive SE without coma
- B.2.a. Generalized
  - B.2.a.a Typical absence status
  - B.2.a.b Atypical absence status
  - B.2.a.c Myoclonic absence status
- B.2.b. Focal
  - B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/ psychic/experiential, or auditory symptoms)
  - B.2.b.b Aphasic status
  - B.2.b.c With impaired consciousness
- B.2.c Unknown whether focal or generalized
  - B.2.c.a Autonomic SE

1.6.3 Axis 2 – Aetiology

The second axis, the classification of aetiology of SE, remains largely consistent with previous ILAE organisation of seizures and epilepsies.[25] The term epilepsy encompasses numerous different conditions with variable manifestations and many patients with SE will not have epilepsy. The aetiology of SE is divided into known (i.e. symptomatic) and unknown (i.e. cryptogenic) groups. The known group is further subdivided into acute, remote and progressive SE in defined electroclinical syndromes (Table 2).[23] A more extensive but not definitive list of potential causes is found in Appendix 1.1.[23] The aetiology of SE is different in adults and children, for example most published series report prolonged febrile seizures as a major cause in children, which would be an example of an electroclinical syndrome.[25] Other practical criteria for the classification of aetiology in epidemiological studies have been suggested by the ILAE.[26]

Table 1.2 Aetiology of status epilepticus

Known (i.e., symptomatic)
Acute (e.g., stroke, intoxication, malaria, encephalitis, etc.)
Remote (e.g., posttraumatic, postencephalitic, poststroke, etc.)
Progressive (e.g., brain tumor, Lafora's disease and other PMEs, dementias)
SE in defined electroclinical syndromes
Unknown (i.e., cryptogenic)

1.6.4 Axis 3 – Electroencephalograph correlates

EEG in the emergency setting is recommended where possible, particularly where non-convulsive SE is a possibility.[27,28] However, there are no evidence based EEG criteria for SE, with proposed terminology to describe EEG findings in SE including location, name of pattern, morphology, time related features, modulation, and effect of interventions on EEG. Currently this resource intensive investigation is not available in many EDs or acute care settings in Australia and New Zealand, and its utility remains unknown.

1.6.5 Axis 4 – Age

Electroclinical syndromes of SE differ according to age, therefore the taskforce has clarified this with axis 4. The discrete groups are:

Neonatal (0-30 days)

Infancy (1 month to 2 years)

Childhood (>2 to 12 years)

Adolescence and adulthood (>12 to 59 years)

Elderly (>=60 years)

1.7 Barriers to researching paediatric status epilepticus

The paucity of high-level evidence regarding paediatric SE management is typical of many areas of emergency medicine. Management strategies employed in EDs are frequently not evidence based or supported by high quality randomised controlled trials (RCT). The lack of high-quality evidence would perhaps surprise consumers of emergency services. Barriers to performing research in EDs include the chaotic environment and highly variable workload that is unpredictable and fluctuates, making the study of all but the most frequent conditions problematic. In addition, outcomes in modern EDs are generally excellent, therefore meaningful outcome differences are hard to prove, and regulatory requirements for research have become increasingly complex. The lack of high-quality evidence to guide management is perhaps even more evident in the pre-hospital setting. Chapter 3 will explore this knowledge gap by reviewing the existing literature on pre-hospital care of paediatric SE.

The majority of available literature concerning SE has been produced by neurologists, paediatric neurologists and critical care physicians, and published almost exclusively in neurology journals rather than directed to the emergency medicine community. This is despite the fact that the overwhelming majority of cases are managed by emergency physicians. The research culture within emergency medicine is perhaps not as established as within other specialties, but this situation is slowly changing, including in paediatric emergency medicine, with the creation of several successful research networks.[29,30] With many unanswered questions in paediatric SE, a widely consultative process to determine research priorities is required, involving ED physicians, neurologists and consumers.

One further barrier to research in SE, and emergency and critical care research in general, is the difficulty obtaining prospective informed consent for research. People seeking emergency care are considered a vulnerable population and involved in a dependent relationship with clinicians (who may also be researchers) leading to ethical dilemmas. These are exacerbated in paediatric emergency care research, where children themselves are often also considered vulnerable. For periods in recent history, ED research in developed countries such as the United States (US) and United Kingdom (UK) all but ceased because regulatory requirements were not conducive to research in critically unwell people.[31,32] Recently, strategies using alternatives to prospective informed consent have improved this situation, however little is known about the public's perception of research in these circumstances. It is imperative that researchers incorporate the attitudes and beliefs of the public into future research designs to ensure the maintenance of public trust, and that the research agenda can be continued to the benefit of society.

In Australia, while provisions exist in the National Health and Medical Research Council (NHMRC) statement[33] and the Declaration of Helsinki[34] for research to occur without prospective informed consent, the practice remains controversial and has seldom been utilised in paediatric research. In Queensland, the validity and legality of research under these circumstances has been questioned in draft documents circulated by Queensland Health (supplementary appendix 1.2) threatening current and future research efforts.

Research into paediatric SE is typical of the difficulty of conducting quality research in acute and emergency situations. Presentations are infrequent, but the consequences of inadequate management can be severe. Management beyond initial care is not evidence based, and issues of consent are applicable as management is time-critical, therapies have a narrow therapeutic window and the traditional valid prospective informed consent is

impossible to obtain prior to enrolling a particular patient in a study on SE in the emergency setting. Therefore, research efforts to improve outcomes of children with SE are inextricably linked to the concepts of informed consent in emergency research requiring both of these aspects to be addressed to improve the care of children with SE.

1.8 Aims and objectives

The aim of this body of work is to explore the paradox of informed consent issues in paediatric SE research, ultimately to improve the management of paediatric SE in Australia and New Zealand.

The specific objectives of the thesis are to:

1. Identify gaps and opportunities for research from a review of the existing literature on paediatric SE.

2. Inform the future research agenda in the management of paediatric SE by achieving consensus on research priorities among experts in managing this condition, consisting of paediatric neurologists and emergency physicians who treat children.

3. Determine if research priorities identified by experts align with priorities identified by consumers (parents of children with SE).

4. Determine what is known about the public's perceptions and attitudes towards research in a paediatric emergency setting without prospective informed consent.

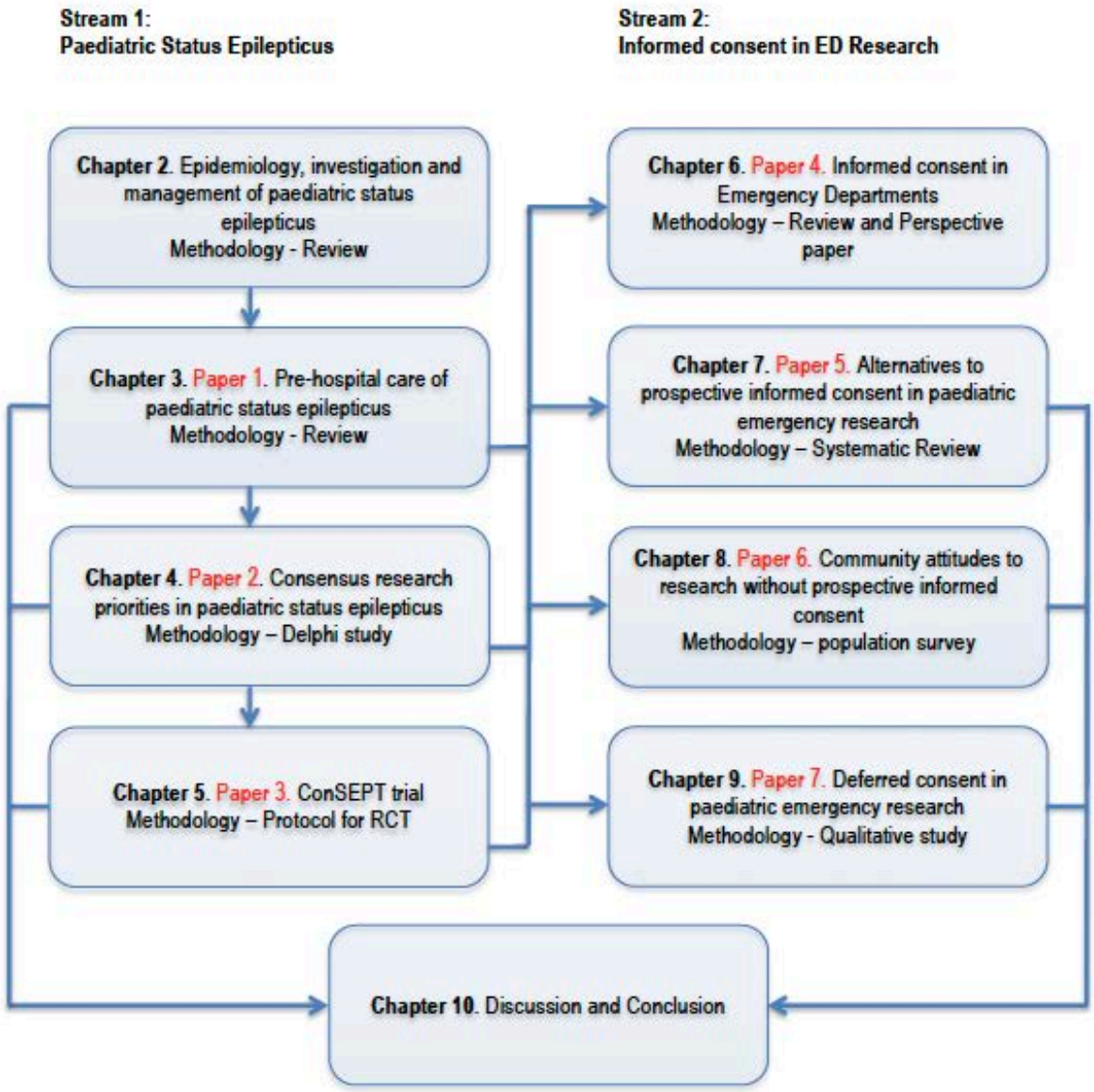
5. Explore attitudes of the general public to research in emergency settings without prior consent.

6. Explore parental attitudes to a deferred consent process in the ED setting, including the management of SE.

1.9 Conceptual model of thesis

This thesis consists of two separate, but interconnected streams. These streams are displayed graphically in Figure 1.1. Stream one explores the existing knowledge of paediatric SE, identifies research priorities for SE including those of the community, and explores the feasibility of addressing these knowledge gaps. Stream two explores barriers to research in paediatric SE, namely issues of consent for time-critical ED research. At the confluence of these two streams is the discussion, highlighting a roadmap for addressing the various knowledge gaps in paediatric SE, for the improved care of this condition.

Figure 1. 1 Conceptual model of thesis



1.10 Overview of the methods

In this thesis, multiple methodologies are used to achieve the stated objectives. The thesis structure and relevant methodology are summarised below. The thesis comprises two streams. Stream 1: four chapters, three of which are published manuscripts; Stream 2: Four chapters, each of which is a published manuscript.

Chapter 2 (objective 1) comprises a narrative review of existing literature on the epidemiology of paediatric SE, specifically the incidence, aetiology and outcome. The chapter goes on to explore investigation and management of paediatric SE. This will provide the context and background for the thesis.

Chapter 3 (objective 1) is a review of the prehospital care of paediatric SE, and focuses on the unique aspects of pre-hospital care as an opportunity to improve the management and outcomes of children with SE. This chapter is inserted as published [Furyk J, Watt K, Emeto TI, Dalziel S, Bodnar D, Riney K, Babl F. Review article: Paediatric status epilepticus in the pre-hospital setting: An update. Emerg Med Australas: 2017 Aug; 29(4):383-390. PubMed PMID: 28627014. DOI: 10.1111/1742-6723.12824].

Chapter 4 (objectives 2 and 3) reports on the findings of a Delphi study conducted to determine consensus priorities for research in paediatric SE with experts (emergency physicians and paediatric neurologists) and consumers. This chapter is inserted as published [Furyk J, Ray R, Watt K, Dalziel SR, Oakely E, Mackay M, Dabscheck G, Riney K, Babl FE. Consensus research priorities for paediatric status epilepticus: A Delphi study of health consumers, researchers and clinicians. Seizure. 2018 Feb 5;56:104-9. PubMed PMID: 29471256. DOI: 10.1016/j.seizure.2018.01.025].

Chapter 5 (objective 2) is the final chapter of the first stream of the thesis. It addresses a well-recognised knowledge gap in the second line management of paediatric SE. This chapter details the protocol of an RCT evaluating the second line management of paediatric SE, and incorporates the controversial deferred consent process. This chapter is inserted as published [Dalziel SR, Furyk J, Bonissch M, Oakley E, Borland M, Neutze J, Donath S, Sharpe C, Harvey S, Davidson A, Craig S, Phillips N, George S, Rao A, Cheng N, Zhang M, Sinn K, Kochar A, Brabyn C Babl FE, PREDICT research network. A multicentre randomised controlled trial of levetiracetam versus phenytoin for convulsive status epilepticus in children (protocol): Convulsive Status Epilepticus Paediatric Trial (ConSEPT) - a PREDICT study. BMC Pediatr 2017 Jun 22;17(1):152. PubMed PMID: 28641582. DOI: 10.1186/s12887-017-0887-8].

Chapter 6 (objective 4) is the first chapter in the second stream of this thesis. The issues of informed consent in emergency research such as SE clinical interventional trials are explored. This is a review and perspectives paper, and is inserted as published [**Furyk JS**, Lawton L, Ting JY, Taylor DM. Perspective: Informed Consent in emergency care research: An oxymoron. Emergency medicine Australasia: EMA. 2017;29(1):110-2. Epub 28 July 2016]. This chapter sets the scene for the remainder of the thesis.

Chapter 7 (objective 4) is a systematic review of alternatives to informed consent in paediatric emergency and acute care research. It is inserted as published [Furyk J, McBain-Rigg K, Renison B, Watt K, Franklin RC, Emeto T, Ray R, Babl F, Dalziel S. A comprehensive systematic review of stakeholder attitudes to alternatives to prospective informed consent in paediatric acute care research. BMC Medical Ethics (2018) 19:89 https://doi.org/10.1186/s12910-018-0327-9].

Chapter 8 (objective 5) reports on the findings of a national, population-based phone survey on community attitudes to research in emergency settings without prospective consent. This chapter is inserted as published [Furyk J, Franklin RC, Watt K, Emeto TI, Dalziel SR, McBain-Rigg K, Nikola Stepanov N, Babl FE and PREDICT. Community attitudes to emergency research without prospective informed consent: A survey of the general population. Emerg Med Australas. (2018) 30, 547–555. PubMed PMID: 29718588. DOI: 10.1111/1742-6723.12958].

Chapter 9 (objective 6) reports on the findings of a qualitative study of the attitudes of parents to research without prospective consent in the ED setting, including in the case of SE. This chapter is the final chapter in the second stream of the thesis. It is inserted as published [Furyk J, McBain-Rigg K, Watt K, Emeto T, Franklin RC, Franklin D, Schibler A, Dalziel SR, Babl FE, Wilson C, Phillips N, Ray R, on behalf of PREDICT. Qualitative evaluation of a deferred consent process in paediatric emergency research: a PREDICT study. BMJ Open 2017;7(11): e018562. PubMed PMID 29146655. doi:10.1136/bmjopen-2017-018562].

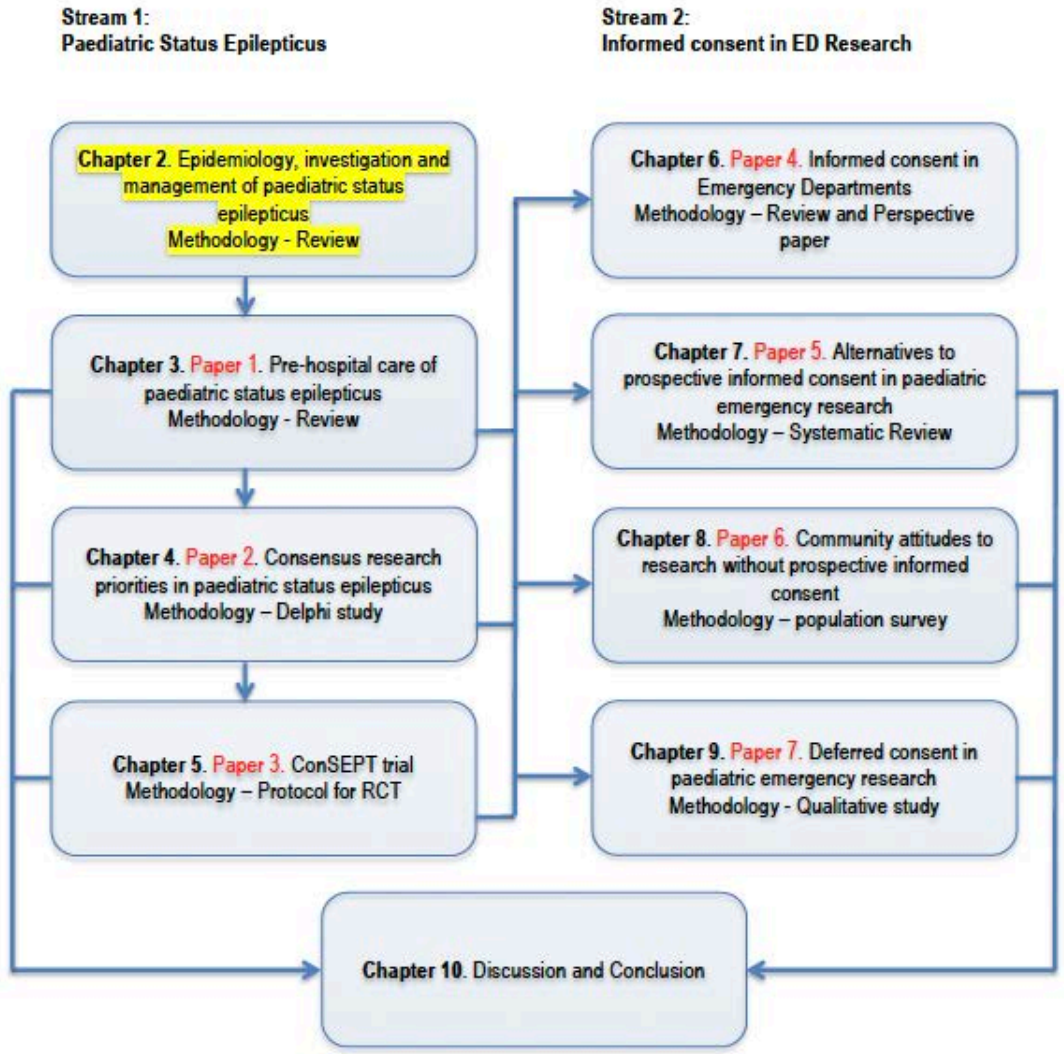
Chapter 10 is the final chapter of the thesis. It comprises a synthesis of the overall findings in the context of the relevant literature, strengths and limitations and concludes with implications for practice, research and policy, with a roadmap for further research in paediatric SE.

Chapter 2. Background – Epidemiology, investigation and management of paediatric status epilepticus

2.1 Overview

Paediatric SE represents a distinct clinical syndrome from adult SE. This chapter outlines the unique epidemiology of paediatric SE, focussing on incidence, aetiology and outcomes in a developed world setting. The chapter goes on and explores the investigation and management of SE in children, and highlights differences from adults. The objectives of this review and this chapter are to provide the context for the thesis, outline the magnitude and effect of paediatric SE on the community, outline current standard emergency management, and hence the potential impact of successful interventions for this condition *(thesis objective 1).* The Medline search strategy used in this literature review was developed with assistance of a medical librarian (supplementary appendix 2.1). Figure 2.1 places this chapter in the conceptual framework of the broader work relative to other elements of the thesis.

Figure 2. 1 Conceptual model of thesis



2.2 Incidence of paediatric status epilepticus

The epidemiology of SE has not been well studied in the paediatric population. There have been few population-based epidemiological studies of SE and convulsive SE on which to base estimates of incidence. Significant differences exist between resource rich and resource poor settings, and this review will focus on the former. The variation in published rates seen in the paediatric populations studied to date can be explained by methodological issues, particularly regarding case ascertainment.[16] Studies reporting incidence in mixed adult and paediatric populations generally report a bimodal age distribution, with peaks at < 1 year and greater than 60 years. These studies have demonstrated ethnic variation with higher rates in non-white populations possibly due to a combination of biologic, socioeconomic and cultural factors, although fewer data are available for paediatric populations.[35-38]

2.2.1 Population-based studies

Several population-based studies have attempted to estimate the incidence of paediatric convulsive SE.[35,38-43] The study with arguably the most robust methodology was a prospective population-based study of childhood convulsive SE in North London.[16] The North London Convulsive Status Epilepticus in Childhood Surveillance Study defined convulsive SE as tonic, clonic, or tonic-clonic (continuous convulsive SE), or two or more such seizures between which consciousness was not regained (intermittent convulsive SE), which lasted for at least 30 minutes.[16] They included children aged 28 days to 15 years, in a geographic area of approximately 500 square kilometres in north London, enrolled via a clinical network of 18 hospitals, with 24 hour ED care. The study enrolled 226 children, of which 176 had a first ever seizure (23% of which started in hospital), over 24 months. The authors estimated the crude incidence of convulsive SE (adjusted for ascertainment) to be 17 to 23 cases per 100,000 per year, a figure significantly higher than in adult studies. Incidence was highest in very young children, at 51 per 100,000 in children aged < 1 year and declined with increasing age to 2 per 100,000 in those aged 10 to 15 years. Extrapolation of these data to other regions is difficult, as key aetiological agents and triggers, such as congenital malformations and epidemiology of infectious diseases, may vary in different regions and countries.

2.2.2 Mixed adult and paediatric studies

Other studies reporting the incidence of SE have not been paediatric specific, have classified SE differently and have used varying methodology making comparisons difficult. These have included population studies in Finland, Switzerland, Reunion Island, Japan, Italy, and the US.[35,38-44] SE in La Réunion Island in children aged 1 to 10 years was reported

as 6.6 per 100,000 but specifically excluded the prolonged febrile seizure subgroup which constitutes a large proportion in other series, and the estimates were based on very small numbers.[40] In French-speaking Switzerland the incidence of convulsive SE decreased with increasing age from 38.7 per 100,000 in 0 to 4 year olds, to 10.9 per 100,000 in 5 to 14 year olds.[41] In Virginia, United States, DeLorenzo described incidence in the paediatric population (0 to 15 years) of almost 40 cases per 100,000, again highest in those < 1 year,[35] this was similar in other US studies.[44] In Italy and Finland results from two retrospective cohort studies were roughly concordant with other studies with incidence of 52 and 47.5 per 100,000 per year respectively.[39,42] In the only study of an Asian population, in Japan, the reported incidence was 38.8 per 100,000.[43] See Table 2.1.

Table 2. 1 Aetiology of paediatric status epilepticus

Author	Study description	Country / Setting	Definition of SE	Age range	Total number of children (n)	Aetiology (as described in report)	Incidence (as described in paper)
Bhalla 2014	Prospective, observational population study	French Reunion Island	> 30 minutes	0-19 years	13	excluded febrile seizures & not described for children separately	0-9 years: 6.6 per 100,000 population per year 10-19 years: 2.9 per 100,000 population per year
Ericksson 1997	Retrospective, Population based	Tampere, Finland	>30 minutes	1 month to 15 years	65	I 15 (23%) FSE 24 (37%) AS 13 (22%) RS 10 (16%) PN 3 (5%)	N/A
Nishiyama 2007	Retrospective, Population based, 12 months 2003	Okayama city, Japan	> 30 minutes	31 days to < 15 years	46 (37 first episodes)	AS 8 (22%) PFS 17 (46%) RS 5 (13%) C 7 (19%)	38.8 per 100,000 population, per year
Hussain 2007	Retrospective	PICU, UK	>30 minutes	1 month to 15 years	137	PFC 47 (34%) RS 38 (28%) AS 24 (18%) I 15 (11%) PE 6 (4%) U 7 (5%)	N/A
Singh 2010	Prospective "database"	Single centre US, tertiary paed	>20 minutes	< 18 years	144 (first episodes)	FSE 46 (32%) AS 24 (17%) RS 26 (18%) C 42 (29%) I 6 (4%)	N/A
Kravljanac 2015	Retrospective	Serbia, 1995-2011	>30 minutes	0.2 to 16 years	602 episodes SE (396 children)	I 113/602 (18.8%) RS 126 (20.9%) FSE 93 (15.4%) AS 101 (16.8%) PE 169 (28.1%)	N/A
Metsaranta 2004	Retrospective, population based	Tampere University Hospital, Finland	>5 minutes	1 month to 16 years	186	PFS 41.9% RS 28% AS 3.9% I 26.2%	47.5 per 100,000 per population per year
Chin 2006	Prospective, observational trial (Registry)	London, population based	>30 minutes		176	PFS 56 (31.8%) AS 30 (17.0%) RS 29 (16.5%) AR 28 (15.9%) I 18 (10.2%) C 3 (1.7%) U 12 (6.8%)	17-23 per 100,000 per population per year
Chamberlain 2014	Interventional, Randomized Controlled Trial (RCT)		1) ≥ 3 seizures in an hour 2) ≥ seizures without recovery 3) Current seizure > 5 min	3 months to < 18 years	273	Febrile 89 (32.6%) Low AED levels 25 (9.2%) Acute symptomatic 38 (13.9%) Remote symptomatic 27 (9.9%) Idiopathic 81 (29.7%) Other 12 (4.4%)	N/A
Lewena 2009	Retrospective cohort	Australia, 8 EDs	> 10 minutes	18 d to 20 years	542	Febrile 115 (21%) Epilepsy 188 (35%) Other neuro 130 (24%) Idiopathic 76 (14%) Enceph/mening 16 (3%) Metabolic 5 (1%)	N/A
DeLorenzo 1996	Prospective, population based	Richmond, Virginia (USA)	> 30 minutes	0 to < 16 (subgroup)	100	Febrile* 52 (52%) RS 39 (39%) LAED 21 (21%)	39 per 100,000 per population per year
Momen 2015	RCT	Iran	> 5 min	> 1 month	100	Febrile 49 (49%) RS 25 (25%) Idiopathic 26 (26%)	N/A

Coeytaux 2000	Prospective, population based	Switzerland	> 30 minutes	0-14 years	64	AS 42 (65.6%) RS 11 (17.2%) AR 5 (7.8%) Idiopathic 3 (4.7%) Cryptogenic (4.7%)	0–4 years: 38.7 per 100,000 population per year 5–14 years: 10.9 per 100,000 population per year
Bergamo 2015	Retrospective, population based	Italy	> 5 min (SE)	0-15 years	ϕAll seizures 214 SE 51	ϕFebrile 120 (56%) RS 41 (19%) I 19 (9%) ARS 11 (5%) CER 8 (4%) CwG 4 (2%) AS 5 (2%) U 7 (3%)	52 per 100,000 per population per year (SE > 5 minutes) 7 per 100,000 (SE > 30 minutes)
Wu 2002	Retrospective, population based	California, USA, 1991-98	> 30 minutes	0-19 years	2885	(Not reported for children separately)	0-4: 7.52 per 100,000 5-19: 2.57 per 100,000
Wlech 2015	RCT	Multi-centre USA, 33 EMS services, 79 hospitals	> 5 minutes	< 18 years (children eligible with estimate wt > 13 kg)	120	Known n=105 PFS 23/105 (21.9%) Idiopathic 47/105 (45%) Non compliance 12/105 (11.4%) non epileptic seizure 10/120 (8%)	N/A
Maytal 1989	Prospective and retrospective	New York, USA	> 30 minutes	1 month to 18 years	193	I 46 (24%) RS 45 (23%) PFS 46 (24%) AS 45 (23%) PE 11 (6%)	
Hesdorffer 1998	Population based, retrospective	Rochester Minesotta, USA	> 30 minutes	All ages (reported 0-19 reported separately)	76	PFS (21%) AS 36 (47%) I/C 11 (14%) RS 13 (17%)	< 1 year : 135 per 100,000 1-4 years: 35.3 per 100,000 5-9 years: 12.2 per 100,000 10-14 years: 3.7 per 100,000 5-19 years: 6.5 per 100,000

Notes: Notes: PFS prolonged febrile seizure, AS acute symptomatic, RS remote symptomatic, AR acute on remote, I idiopathic, C cryptogenic, U unclassified, RCT randomized controlled trial, FSE febrile status epilepticus, PE progressive encephalopathy, PFC prolonged febrile convulsion, PN progressive neurological, CER cryptogenic epilepsy related, CwG convulsions with gastroenteritis, *includes all infective causes, ϕAetiology includes seizures 0-5 minutes duration

Approximately 10% of children with childhood onset epilepsy will have at least one episode of SE in their lifetime.[45] Conversely, children who experience a first episode of SE only have a 30% chance of subsequent diagnosis of epilepsy.[46]

In summary, the incidence of convulsive SE in the paediatric population is highest in children < 1 year old and decreases with age. The reported incidence is probably in the order of 20 per 100,000 population at risk if using the traditional definition of SE being a seizure lasting > 30 minutes, the time point historically used in most studies. The incidence would certainly be higher if including children with seizures from 5 to 29 minutes. Incidence is much higher in developing world settings, where the underlying aetiology is different.

2.3 Aetiology of paediatric status epilepticus

Approximately 10% of first seizures in children with epilepsy present as SE.[16,43,47-49] It has been proposed that susceptibility to develop SE may result from a failure of endogenous anticonvulsant mechanisms in the brain.[50] The aetiology of SE seems to be different in adults and children. Even amongst the paediatric population, there are significant differences between children of varying ages in terms of incidence, aetiology, frequency and prior neurological abnormalities.[37] For example, in children less than two years, febrile SE and

acute symptomatic aetiologies predominate, whereas in older children the aetiology is more likely to be remote symptomatic or unknown.[37] Causes of SE in adults commonly include cerebrovascular accidents, non-compliance with medication in known epileptics, metabolic disturbances, drug toxicity, infection and inflammation.[51] Available data in children is limited by variability in methodology, the quality of studies to date and lack of uniformity regarding classification and reporting.

Aetiology represents the second of four axes within the proposed new SE classification system[23] and remains largely consistent with previous ILAE organisation of seizures and epilepsies.[25] The underlying cause or aetiology is first classified as either known (i.e. *symptomatic*) or unknown (i.e. *cryptogenic*). The terms "*idiopathic*" and "*genetic*" which have been previously used to classify SE are no longer preferred, as the underlying aetiology of the SE episode may be known, for example inappropriate AED levels. Known (*symptomatic*) causes are further subdivided to "*acute*", "*remote*", "*progressive*" and "*SE in defined electroclinical syndromes*".[23]

The "acute symptomatic" group is analogous to the previously used "provoked" term, and describes SE occurring during an acute illness or acute CNS insult e.g. stroke, intoxication, encephalopathy, meningitis, electrolyte disturbance, hypoxia, trauma or malaria.[16,23,52,53] The recommended definition of an acute symptomatic seizure encompasses the following: 1) seizures occurring within a week of cerebrovascular accident, traumatic brain injury, anoxic encephalopathy or intracranial surgery, 2) a subdural haematoma or CNS infection at the time of diagnosis, 3) during the active phase of multiple sclerosis or other autoimmune disease or 4) a specific biochemical or haematological abnormality within 24 hours, or drug intoxication or withdrawal including; serum glucose < 36 mg/dl (2.0 mM) or >450 mg/dl (25mM) associated with ketosis, sodium < 115 mg/dl (<5 mM), calcium < 5.0 mg/dl (<1.2 mM), magnesium < 0.8 mg/dl (<0.3 mM), urea nitrogen >100 mg/dl (>35.7 mM) and creatinine > 10.0 mg/dl (>884 lM).[23] Seizures associated with a fever greater than 38.5 degrees Celsius have at times been categorised as acute symptomatic,[52] however the outcome for prolonged febrile seizures is generally better than for other acute symptomatic causes.[54] Therefore, the usefulness of including prolonged febrile seizures within the acute symptomatic group is questionable, and some studies have reported prolonged febrile seizures as a separate category or as a subgroup of acute symptomatic (see Table 2.1).

The term "remote symptomatic" describes SE occurring without an acute provocation in a patient with a history of a CNS abnormality, more than a week previously e.g. following trauma, encephalitis, stroke or CNS malformation.[16,23,53] The "progressive" symptomatic

episodes of SE encompasses progressive CNS disorders such as tumours, other progressive epilepsies and dementias. The last group is SE in defined electro-clinical syndromes, and the recent proposed ILAE SE classification includes prolonged febrile seizures in this group.[23]

Numerous studies in various populations using various methodologies have described the aetiology of SE in the paediatric population in developed countries[15,16,35,41-44,46,49,55-58] (See Table 2.1). Prolonged febrile seizures account for 21-52% of cases (overall accounting for about 30% of cases).[15,16,35,41-44,46,49,55-58] Reported acute symptomatic SE cases ranged from 4 to 65% but were generally about 20% in most series, and remote symptomatic SE was ranged from 10 to 23 but were generally about 17%. Many studies used the term "idiopathic", which as stated earlier is no longer preferred, with the proportion of SE attributed as idiopathic ranging from 4 to 30% (with wide variation). Differences may be explained by variable methods of data collection, definitions, case ascertainment, and methodological rigour.

The most comprehensive data on the aetiology and natural history of convulsive SE comes from the North London convulsive SE in Childhood Surveillance Study.[16] In this study a third of episodes of convulsive SE were due to prolonged febrile seizures, 17% had acute symptomatic causes including electrolyte imbalance, hypoglycaemia, hypocalcaemia or hypomagnesaemia, or an acute CNS infection, and remote symptomatic and acute on remote symptomatic accounted for 16% each. Less than a quarter of the children had a past history of convulsive SE and over half were previously neurologically normal.[16]

The rate of meningitis in children presenting with febrile SE has shown wide variation in the literature to date, from close to 1%[49] up to 40%[59] of febrile SE presentations. This variation is again likely to be due to methodological differences in the studies. The authors of the North London SE in childhood surveillance study found that SE presentations with a fever of > 38°C had a rate of bacterial meningitis of 12%. A further 8% showed evidence of a viral CNS infection. The authors concluded that clinicians should have a high index of suspicion of an infective aetiology in such presentations.[16,60]

The only available Australasian data on paediatric SE comes from a retrospective study conducted by the PREDICT network.[61] The five-year study period (2000 to 2004) identified 542 episodes of SE in eight paediatric EDs in Australia and New Zealand. While the "practical" definition of SE was applied with duration of 10 minutes used, 94% had seizure duration of greater than 30 minutes. In this cohort a history of seizures was present in 67%

of cases, prolonged febrile convulsions accounted for 21% of cases (considerably less than in other studies), and encephalitis or meningitis was present in 3%.[61] The major methodological difference between the Australasian study and the North London study was that the Australasian study was retrospective and restricted to patients presenting to the ED, whereas the North London study was prospective and population-based.[61,62]

The following section will briefly review some of the important acute causes of SE, which may have implications for management e.g. prolonged febrile seizures, inflammatory, trauma etc.

2.3.1 Prolonged febrile seizure

All studies highlight the importance of prolonged febrile convulsions in causing SE in the paediatric population.[16,39,43] A prospective study specifically of febrile SE from five sites in the United States enrolled 199 patients, aged 4 months to 6 years from 2003 to 2010.[63,64] SE was again defined as lasting ≥ 30 minutes or a series of seizures without full recovery in between that lasted ≥ 30 minutes; the median seizure duration was 70 minutes.[64] The cohort specifically excluded children with meningitis and other acute symptomatic causes. Children underwent a standardised assessment, including imaging and testing for human herpesvirus (HHV) -6 and HHV-7, and interestingly found evidence of viraemia in a third of patients.[64]

2.3.2 Inflammatory status epilepticus

Inflammatory and immune mediated encephalopathies are being increasingly recognised as rare but important causes of seizures and SE. Infective causes of inflammation have long been considered an important subgroup of patients presenting with SE, including viral, bacterial and parasitic causes, but autoimmune causes are increasingly recognised. Autoantibodies to both neuronal surface and intracellular elements are important. Much of the current knowledge of this comes from adults, and although they are responsible for only a small proportion of cases of SE, outcomes may benefit from specific therapeutic approaches, therefore SE of unknown origin may benefit from screening for anti-neuronal antibodies.[65,66]

It is likely that further antibodies will be identified for encephalidities currently classified as unknown cause. These encephalidities can be divided into paraneoplastic and autoimmune.[65] The most commonly described include antibodies to glutamic acid decarboxylase (GAD) and N-methyl-d–aspartate (NMDA) receptors, thyroid and voltage gated potassium channel (VGKC) complex. With GAD and VGKC complex causing SE more frequently in paediatric populations, more commonly in older children.[67] Most patients

with an inflammatory cause will have a prodromal phase or preceding illness to suggest the diagnosis.

Two clinical syndromes have also been described, which although induced by fever, have not been found to be associated with microbiological or autoimmune causes. These are known as fever induced refractory epileptic encephalopathy in school age children (FIRES) and idiopathic hemiconvulsive hemiplegia syndrome (IHHS).[68] Both syndromes have a poor prognosis. FIRES can evolve into SE, refractory epilepsy, focal seizures and progressive cognitive decline. IHHS begins in infancy with unilateral clonic SE and is followed by hemiplegia and a treatment resistant epilepsy syndrome. Occurring in previously healthy children, the aetiology of FIRES and IHHS is unknown but is thought likely to have an inflammatory origin.[67,68]

2.3.3 Drug associated status epilepticus

Although drugs are well known to cause seizures and SE, they represent an infrequent cause of SE in children. Estimates in adults are that drugs, both in therapeutic doses and overdose, account for approximately 5% of SE,[69] but epidemiological studies are limited and of variable quality with causality difficult to establish. However, drug associated SE is an important aetiology for clinicians to consider, as ingested substances may have implications for management. Anti-epileptic drugs (AED) may themselves cause SE, although establishing this is itself very difficult. Most classes of AED have been implicated in causing SE in both toxic and therapeutic doses.[69]

Antidepressants, anxiolytics and illicit drugs are an important cause of SE in adults, but exposure to these agents in children is less common. Effects can involve multiple CNS neurotransmitters to lower the seizure threshold. Unintentional intoxication with these medications does occur in children, and can result in SE with tricyclic antidepressants an important class.[62] Intentional intoxication and suicidal intent becomes increasingly more prevalent in adolescents.[62]

A potentially important group is antibiotic associated seizures,[69,70] although again establishing causation is problematic. Biological plausibility exists, as neurotoxicity exists with certain antibiotics including cephalosporins, other beta-lactams and quinolones.[69-71] The mechanism is likely to be related to a decrease in gamma-aminobutyric acid (GABA) release, and subsequent increase in excitatory neurotransmitters. The relative importance in SE in children is unknown.

Another infrequent cause of SE is that of isoniazid toxicity, usually unintentional intoxication when children take medications of family members.[72,73] Such seizures are related to pyridoxine depletion, necessary for GABA production, and respond to pyridoxine replacement.[73] There are also several reports of theophylline causing SE, both at therapeutic and toxic levels.[69,74] Antihistamines, which may be available over the counter have also been associated with SE. Easy access to these medications may lead to toxicity in children.

In summary, drugs are rarely considered by front line practitioners, and potentially implicated drugs may be overlooked as a potential cause of SE if not specifically asked about. A medication history should always be sought in all SE presentations, and potential access to epileptogenic agents explored. Close contact with tuberculosis should lead to the consideration of possible isoniazid toxicity.

2.3.4 Genetic factors associated with status epilepticus

The genetics of SE are complex, and our knowledge and technology examining the genetic contribution to disease is constantly evolving. The importance of genetic factors in the development of SE has been verified by twin studies.[75] Many genetic mutations are known to be strongly associated with SE, relating to multiple different systems and pathways, however this knowledge has not yet led to any advances in management or improved outcomes.[76] Knowledge of genetic factors is currently not of practical utility for clinicians, and remains an area for further research.

2.3.5 Traumatic status epilepticus

Trauma with head injury is a well-documented cause of seizures and SE in children. Although the aetiology may be obvious from the history and examination, history may not be forthcoming in the case of non-accidental injury, thus the diagnosis should always be considered.[77,78] A further important cause of SE in children, is hypoxia or anoxia such as from drowning episodes. This is particularly relevant in Australia where rates of drowning remain high. As with infective, inflammatory and drug associated aetiologies identification of trauma or hypoxia as a cause of SE will lead to additional management focused on the causal mechanism.

2.3.6 Psychogenic status epilepticus

Although not included in most SE classifications of aetiology, psychogenic seizure presentations are an important differential diagnosis of paediatric SE. Under-recognised by emergency clinical staff in the paediatric population their incidence increases with age,

although they have been reported in children as young as eight.[79] Psychogenic seizures can present as non-epileptic SE, and result in unnecessary and potentially harmful interventions including medications, intubation, iatrogenic complications and can delay appropriate psychological therapies.[80] Commonly precipitated by acutely stressful events, most patients have a family or personal history of epilepsy and co-existent psychiatric diagnosis.[81] Pelvic thrusting is said to be a useful clinical clue, although such movements can occur in other epilepsy syndromes as well.[82] Repeated video EEG assessment provides the correct diagnosis. In a recent high-quality pre-hospital RCT of seizure management, 8% of paediatric patients (<17 years) with SE were adjudicated to have had non-epileptic seizures.[18,83]

2.4 Paediatric status epilepticus outcomes and consequences

SE is without doubt associated with significant morbidity and mortality. Outcomes are considerably better in the paediatric group compared with adults.[9] The prognosis of SE is highly dependent on the age of the patient, the aetiology and the duration of seizure activity.[9,84] Of these factors, only the duration of seizure activity is potentially modifiable, but it is not clear whether interventions to reduce the duration of seizure result in improved outcomes. From the available evidence, the confounding effect of aetiology is inextricably linked to seizure duration and prognosis.[84]

Apart from lack of data due to the relative infrequency of the condition, another difficulty in describing the outcome of paediatric SE is the lack of standardized definitions, including outcomes, over time.[54] Reviews of outcomes for SE have generally used a 30 minute cut-off, which may conflict with contemporary definitions and clinical practice.[23] In addition to mortality, studies of paediatric SE have reported morbidity including the subsequent development of epilepsy or recurrent seizures, neurological deficits, cognitive impairments, behavioural problems and hippocampal injury (particularly with febrile SE). The relative frequencies of outcomes have been associated with the quality of the primary studies, with higher quality studies generally reporting better outcomes, both in terms of morbidity and mortality.[54]

Although seeking treatable causes is a vital component of ED assessment as it may have implications for management, accurate prognostication in this acute phase is not possible. For example, while autoimmune SE may require a lengthy hospitalisation and prognosis may initially appear poor, many patients recover completely.[67]

2.4.1 Mortality

The reported mortality of SE in paediatric patients differs markedly from adult series[9,22] and has probably been decreasing over time; although this might be partly explained by variations in definitions, methodologies and variable quality of studies and limited follow up. A systematic review of 63 studies suggested that studies of higher quality tended to demonstrate lower morbidity and mortality than lesser quality studies.[54] In the highest quality studies, short-term mortality of convulsive SE was 2.7 to 5.2%, and this increased to 5-8% if admitted to PICU.[54] More recent studies report similar mortality. The North London convulsive SE childhood surveillance study reported that the case fatality rate for first ever episode of SE was 3%,[16] and a large study in Serbia reported a case fatality rate of 5.1%.[57] These rates are much lower than adult mortality from SE of up to 30%[9] or 38% in the elderly.[22] Refractory SE in children mortality is higher, at about 15-21% and neurological disability is also very high in survivors in this group.[57,85]

The main determinant of mortality is the causative factor, with most deaths occurring in acute or remote symptomatic patients.[22,54] For example, mortality of 0-2% was reported for "unprovoked" or febrile SE compare to 12-16% for acute symptomatic.[54] Children with meningitis and encephalitis appear to have a poor prognosis, as do children with brain injury or anoxia.[22,86] Young age of onset was also associated with high mortality, but this result was confounded by the same age group also having a high rate of acute symptomatic causes.[54] Studies have not consistently observed an association between longer duration of seizure activity and higher mortality.[22,35,44]

2.4.2 Recurrent status epilepticus and development of epilepsy

The association of SE with the development of epilepsy has also been addressed by a number of studies, although again hindered by similar problems with lack of consistent definitions. Where the aetiology is "unknown", previously called the idiopathic group, it is difficult to ascertain whether development of epilepsy resulted from the episode of SE or whether the SE was simply the first seizure in the presentation of epilepsy. Risk of seizure after first unprovoked episode of SE is similar to the rate of seizure after first non-SE seizures, although reported rates have varied remarkably from 13 to 74%.[54] Chin et al in North London reported 13% recurrence of SE during 12-month follow up,[16] whilst others have estimated rates of 25-40% up to 24 months.[46,55] Risk of development of epilepsy also seems to depend on the aetiology with rates highest for acute or remote symptomatic causes, or those with previous neurological abnormalities with rates up to 50%.[22]

Overall SE may recur in up to 20% of individuals within four years.[54] Similar to the development of epilepsy, there are low rates of recurrence in "idiopathic" and prolonged febrile seizures and higher rates in acute, remote and progressive symptomatic groups.

2.4.3 Duration of seizure

While it seems unusual to suggest that the effect of seizure duration on outcome is unknown, the often-quoted time frames of seizure duration *per se* resulting in harmful effects e.g. after 30 minutes of continuous seizure activity, are based on limited and inadequate evidence consisting mostly of extrapolation from animal models. These models of SE have found longer seizure duration to be associated with neuronal damage, poor outcome and the development of epilepsy.[23] In humans, studies have not been able to adequately control for the important effect of aetiology on outcomes of SE in clinical situations and clearly RCTs are impossible. An adult study found an association with epilepsy and duration only with acute symptomatic seizures.[87] It seems aetiology, resistance to treatment and poor outcome are all inextricably linked and it is difficult to separate the degree of neuronal damage secondary to prolonged convulsion and neuronal damage result from the underlying cause.[37]

2.4.4 Neurological, cognitive and behavioural impairments.

Long term sequelae such as focal neurological deficits, neurocognitive deficits and behavioural problems have been suspected to result from episodes of SE in children. The incidence appears to be less than 15%.[22] Again, the effect of aetiology is difficult to completely assess, and it is likely that this is the most important factor in determining the outcomes.[22,54] The effect of SE on intelligence quotient (IQ) has been studied, without any consistent findings, and further research is required.[22]

2.4.5 Outcome after febrile status epilepticus

Prolonged febrile seizures are an important cause of SE in children, and although mortality after febrile SE is low, other possible longer-term consequences of this condition have been explored.[63,88] There is concern about morbidity, including cognitive problems and development of epilepsy.[88] Data on epilepsy following a prolonged febrile seizure is controversial. Incidence of epilepsy after a febrile SE is about 5-10%, therefore significantly higher than the lifetime population risk of 1.6 to 3%, which is thought to double with brief febrile seizures.[22,54,89] Febrile SE has also been implicated in affecting memory and the development quotient.[90] It has been suggested that febrile SE may cause hippocampal injury and mesial temporal sclerosis leading to the development of temporal lobe epilepsy.[22,91] The alternative view is that such lesions merely indicate a predisposition to febrile seizures. Studies have not found an association between febrile SE characteristics (e.g. duration and

treatment) and outcomes. More widespread, subtle brain injury not confined to the hippocampal area has also been suggested but is not universally accepted.[88]

Understanding the pathogenesis of prolonged febrile seizures is the focus of ongoing research efforts with the intention of identifying novel treatments to reduce complications.[64] Whether the magnitude of the problem is sufficient to justify pursuing potentially expensive trials and therapies needs to be carefully considered and involve clinicians, researchers and the community to ensure that scarce research resources are allocated appropriately.

2.4.6 Non-convulsive status epilepticus

Whether non-convulsive SE causes neuronal injury is the subject of debate.[87] In animal models SE induces anatomical changes and reorganization of neural networks that may result in injury and epilepsy. It has been suggested that the "electronic seizure burden" may contribute to unfavourable outcomes in children,[92] however studies have not found this consistently. Mortality rate for non-convulsive SE seems to be higher than for SE per se in paediatric patients but again problems arise with various definitions, variety of settings and populations studied as well as variations in care.[92] It is likely that as with SE, the underlying aetiology remains the most important prognostic factor for outcome in non-convulsive SE.

2.4.7 Consequences of status epilepticus

Seizure activity can be considered detrimental both directly from neuronal damage to the brain, and secondary to systemic complications. Prolonged seizure activity can result in complications such as hypoxia and hypercarbia, hypotension, acidosis, rhabdomyolysis and hypoglycaemia.[93] Hypotension and respiratory compromise may be exacerbated by anticonvulsant administration. Rarely, cardiopulmonary complications can occur. Whether addressing these systemic complications has an effect on outcomes has not been adequately explored in the literature. They are usually not mentioned in existing guidelines but remain important considerations when managing an episode of SE.

2.5 Investigation of paediatric status epilepticus

A comprehensive diagnostic evaluation of children who present with SE is necessary to identify potential causes that may require specific therapy. A specific underlying cause is more likely to be detected in younger patients.[94] Investigations will be guided by patient history and examination findings with a detailed history most likely to be of highest yield. Investigations may include various combinations of laboratory testing, including AED levels if relevant, toxicology screening, neuroimaging with computed tomography (CT) or magnetic resonance imaging (MRI), video electroencephalogram (EEG), lumbar puncture (LP), and

genetic testing, depending on the circumstances. Patients with a first seizure presenting as SE warrant a more extensive evaluation than patients with known seizure disorder. Some of the workup may be performed after stabilisation, in the ED, ward or ICU.[94]

2.5.1 Laboratory Investigations

As with other life-threatening emergencies, evaluation and treatment of SE are performed simultaneously. Point of care blood glucose testing is important in the ED or pre-hospital setting, as although hypoglycaemia is a relatively uncommon cause of SE, it is a readily reversible cause.[53] Serum electrolytes are also routinely recommended in the ED, however abnormalities of electrolytes such as sodium, calcium or glucose are only found in about 6% of children with convulsive SE, and causality is not clear.[53] Low AED levels are infrequently thought to cause SE in children, but low AED levels have been reported in as many as a third of patients, hence checking of relevant serum levels is usually recommended in children known to have epilepsy without another predisposing cause.[53]

Blood cultures and full blood examinations should be obtained if there is any suspicion of sepsis on clinical grounds, although results are rarely useful in the acute setting. Central nervous system (CNS) infection is variably reported, however constitutes up to 10% in some series.[37,53,60] Prolonged febrile seizure (without CNS infection) is the most common cause of convulsive SE in children, but difficult to differentiate clinically from CNS infection. It is therefore prudent to evaluate any child with fever and SE for the possibility of CNS infection, with LP performed unless contraindicated especially in children less than two years old. Cerebrospinal fluid (CSF) interpretation can be problematic as it has been suggested that CSF pleocytosis can be present from seizures in the absence of CNS infection.[53] Recent retrospective and prospective studies found varying rates, however if detected it should be assumed to be due to infection.[95-97]

While conclusive data are lacking, CSF analysis is not routinely necessary in the absence of fever.[53] LP and CSF analysis can be considered if there is ongoing concern for infection or immune mediated encephalopathy, the latter being rare but increasingly recognised.[98] This diagnosis is especially important in adolescence and should be considered if there is a history of prolonged encephalopathy or suggestive findings on imaging.

2.5.2 Neuroimaging

Neuroimaging is indicated in all patients presenting with a first episode of SE and has a high diagnostic yield.[49,53,99] CT or MRI identify an aetiology in more than 30% of cases; mostly lesions associated with a remote cause, and often leading to a change in acute

management.[49,99] CT is routinely available in the ED setting, and is more sensitive at detecting acute intracranial blood, although with the disadvantage of exposure to potentially harmful ionizing radiation for the patient. MRI is generally less available in the acute setting, more commonly requires sedation, but has superior sensitivity for lesions other than acute intracranial blood.[49,99] In a prospective study of children with new onset seizures presenting as SE, MRI demonstrated abnormalities in 14/30 (47%) of children with a normal CT head.[49] These findings were supported by a more recent study where 27% of emergent findings were discovered on MRI in similar patients after a normal non-contrast CT scan.[99] While it may not be possible, or desirable, for the patient to undertake an MRI examination during the early phase of their hospital course, this examination should be undertaken once seizures are controlled and the patient stabilised.

In patients known to have epilepsy, clinical judgment permits omitting most of the above investigations, however these investigations should be considered if seizures are not typical for the patient, are prolonged or are refractory to treatment.

2.5.3 Special tests

Identification of genetic mutations related to syndromes associated with SE, such as SCN1A gene mutations of Dravet syndrome is possible,[100] however there is limited evidence for the utility of routine genetic testing in SE either acutely or as an outpatient.[53] Similarly, recommendations on immunological and metabolic testing are based on very little evidence, but may be warranted selectively in the ICU if no cause is apparent.[53] Circumstances that may suggest the requirement for genetic and metabolic testing include recurrent or periodic episodes of SE, which is not relevant on the first presentation or in the ED. Other clinical features may suggest the need for a more extensive work up, such as failure to thrive, developmental delay or ataxia. Toxicology testing may be indicated if a clinical suspicion exists based on history, examination or characteristic laboratory results, and may be performed on either urine or blood samples.[53]

2.5.4 Electroencephalogram in the emergency department

The EEG is an investigation that has been used for over 50 years to examine cortical electrical activity.[27] Guidelines and expert opinion recommend performing an EEG on all children presenting with SE as soon as possible, but these recommendations are based on low quality evidence.[28,101,102] The reported benefits of EEG include the identification of non-convulsive SE or subclinical seizures in comatose children, where non-convulsive SE maybe responsible for up to a third of cases and is associated with poor outcomes.[28,103-105] Conversely, EEG, and particularly video EEG, may also suggest non-epileptic seizures in

some circumstances, and avoid potentially harmful escalation of therapy. Other benefits of EEG include assisting with seizure characterisation and location and assessing the efficacy of interventions and guiding therapy.[28,106]

While EEG in the management of SE is referred to as "standard practice" in publications from the US and elsewhere,[27,107] the costly and resource intensive exercise is not routinely available in other settings, including Australia. A UK study of SE found it was infrequently available in adults,[108] with little reason to believe this would be different in children.

Future developments may include the use of a limited array of electrodes, or an electrode cap and the development of high-speed algorithms using quantitative analysis of EEG to assist with diagnosis.[102,107,109,110] An area of ongoing work is examining whether interpretation of EEG in ED by untrained individuals relying on "trend data" rather than the original trace recording might be possible[111] but this is not ready for clinical application currently.

In summary, while routine use of EEG in ED is difficult to justify without robust evidence of patient outcome benefit, or cost effectiveness data, it may be prudent instead to advocate for judicious use in circumstances where timely access to acute EEG is likely to have the most impact on SE management in children. These could include suspected psychogenic seizures, where escalation of therapy could be associated with harm without benefit, and when children fail to return to baseline after an episode of SE, as non-convulsive SE may be present and remain undiagnosed.[49,94]

2.6 Management of paediatric status epilepticus

2.6.1 General principles

SE is an infrequent presentation, consequently conducting high quality clinical trials has been difficult, and requires considerable resources and infrastructure. The duration of seizure activity is associated with poor outcomes and is potentially modifiable therefore this is often the focus of research efforts. Systematic reviews of management of SE in children include only trials of "first line" agents, with little data supporting management decisions beyond this stage.[112] Management beyond first line drugs is based on expert and consensus opinion only. As with any true emergency, assessment and management occur simultaneously. The immediate priorities include attending to basic resuscitation requirements (supporting airway, breathing and circulation), the administration of anti-convulsant medication to stop seizures, identifying and treating the likely cause, and the prevention of the secondary consequences of SE.[113]

Guidelines generally take a stepwise approach to treatment. Typically, two doses of benzodiazepines are given as first line anticonvulsants. If they fail, various second line anticonvulsants are administered followed by rapid sequence induction (RSI) of anaesthesia and intubation.[9,13] The use of benzodiazepines is supported by good quality evidence, and most patients achieve seizure control with these agents.[19,112] Recent guidelines have advocated replacing the terms "first line" and "second line", with a preference for "emergency", "urgent" and "refractory" management to stress the time-critical nature of the interventions[102] or "initial therapy phase" (5-20 min), "second therapy phase" (20-40 min), and "third therapy phase" (40-60 min).[9] Without disputing the time-critical element, there does not seem to be sufficient justification to change widely used nomenclature. Consequently, the new terms have not yet been widely adopted, therefore in the sections that follow, the traditional terms first and second line treatment will be used.

2.6.2 First line drugs

Multiple anticonvulsants have been studied as first line therapy and current evidence and expert opinion support the use of benzodiazepines in this situation.[102] The "Veteran Affairs" study of SE in adults was pivotal in establishing the efficacy of benzodiazepines as first line agents.[114] These agents are usually effective in terminating seizures, especially if used early and in an adequate dose.[115] The benzodiazepines most frequently studied and used for this purpose are lorazepam, diazepam and midazolam. Evidence based recommendations and guidelines have advocated either IV lorazepam (0.1mg/kg/dose) repeat if needed, IV diazepam (0.15-0.2mg/kg/dose) repeated if needed or IM midazolam 10mg for >40kg and 5mg for 13-40kg, single dose, all supported by high level evidence of efficacy.[9,116] The IM midazolam dosing above is based on a large RCT[18], although intuitively one would assume that a weight-based dosing regimen would be preferable, avoiding wide dose ranges. The recommended dosing of IM midazolam is 0.1-0.2 mg/kg/dose, repeated in 10 minutes.[13]

Attention to detail of benzodiazepine dosing is important in management of SE. Benzodiazepine dosing has been reported to be outside of recommended dose ranges nearly a quarter of the time,[117] with both under- and over-treatment potentially problematic. Under-dosing of benzodiazepine is potentially associated with reduced efficacy while excessive dosing of benzodiazepine can lead to respiratory depression and the need for ICU admission.[51,117]

In terms of choice of benzodiazepine, there is no strong evidence to favour any particular agent. Other considerations such as availability of agent, and availability of delivery route

influence decision-making. In the hospital setting, as in the home and pre-hospital setting, there has been much work on the preferred route of administration. While IV administration is likely to be preferable if available, administration of anticonvulsant medications should certainly not be delayed in cases where immediate IV access is not available or difficult. Other routes include sublingual (SL), per rectum (PR), buccal (BC), intranasal (IN), IM and intraosseous (IO).[118] Traditionally, rectal diazepam was administered, but recently other options are generally preferred. Although the rectal mucosa provides excellent absorption, there are a number of disadvantages to this route that limits its utility.[119] Potential barriers to use of the rectal route of administration include reluctance of parents or other caregivers (teachers, carers etc.) to use this route, the requirement to remove clothes which might lead to delays or may not be appropriate in public places, physical difficulties of administration while a patient is actively seizing, which may require multiple individuals in order to administer the medication, and the fact that this route may not be culturally acceptable in some societies.[119] Alternative routes of administration are gaining popularity due to efficacy and ease of use of which the best efficacy data supports IN or IM midazolam in situations where the IV route is not readily available.[118]

Internationally, a number of clinicians and guidelines recommend IV lorazepam as the preferred benzodiazepine for management of SE if IV access is available.[102] However, lorazepam is not available in some countries, including in Australia. Additionally, a recent high quality RCT in 2014 conducted in 273 children, demonstrated that 0.1 mg/kg of IV lorazepam was found to have similar seizure termination as 0.2mg/kg of IV diazepam, with the latter agent having less respiratory depression.[15] Further, lorazepam is relatively heat labile requiring refrigeration for storage, compared to diazepam and midazolam which have long shelf life at room temperature.[110] A high quality comparison of IV lorazepam with IV midazolam has not been conducted.

Midazolam is a highly water-soluble benzodiazepine, has a fast onset of action and excellent CNS penetration, a wide margin of safety and broad therapeutic index.[59] It is effective via multiple routes of administration, including IM and is a safe and effective alternative to IV lorazepam in the pre-hospital setting.[18] A further benefit is that midazolam can be used in higher doses as an infusion as a second or third line agent.[59] A meta-analysis comparing midazolam with diazepam found midazolam to be as effective as diazepam when the IV routes of administration of both drugs were compared, and superior to diazepam when routes other than IV were assessed, due to more rapid administration.[120] A recent network meta-analysis comparing the efficacy of midazolam, lorazepam and diazepam in treating

paediatric status epilepticus (including 16 RCTs from 1,821 patients) determined that midazolam had the highest probability of achieving seizure termination.[121]

The most recent Australian data regarding management of paediatric SE is over a decade old. At that time diazepam was the most frequently used first line agent.[61] It is not clear whether physicians have since adopted other agents, particularly midazolam.

2.6.3 Second line drugs

Studies have suggested that time to administration of second line agents may be slower than is desirable. A retrospective Australian study reported that in the EDs of seven children's hospitals the median time to administration of a second line drug was 24 minutes in SE.[61] In a prospective study in the US, this time point was a median of 69 minutes, suggesting delays in escalating care.[122]

Professional societies have stated that there is insufficient evidence to recommend any of the second line agents.[116] Although none of the second line therapies have been evaluated in children in high quality RCTs, surveys and observational data indicate that the preferred second line agent by emergency physicians and neurologists remains phenytoin or fosphenytoin.[123,124] Retrospective data suggest that phenytoin is only effective in about 60% of cases[61] and it has other potential problems that make the prospect of other agents desirable. Phenytoin has a well-documented adverse effect profile including hepatotoxicity, pancytopenia, phlebitis, Stevens-Johnson syndrome, hypotension, cardiotoxicity, extravasations causing tissue necrosis and purple glove syndrome.[125] The potential for cardiotoxicity necessitates slow infusion and cardiac monitoring.[125] The cardiac toxicity of phenytoin has resulted in a number of documented deaths from inappropriate dosing or infusion rates when phenytoin has been given as a loading dose, as is the case in SE management. Fosphenytoin is used internationally due to concerns about safety of phenytoin, mainly cardiac arrhythmias and tissue necrosis. Fosphenytoin can be administered more rapidly than phenytoin, but as a pro-drug, effective blood and tissue concentrations of the drug are probably not available any faster.[9,113] Further, idiosyncratic adverse events associated with phenytoin, such as Stevens-Johnson syndrome are still reported with fosphenytoin. Fosphenytoin is not available in Australia or New Zealand.

Newer agents such as levetiracetam, valproate and lacosamide have been proposed, and reported as effective second line SE agents, however evidence is limited to case reports and small case series.[9] Several observational studies have suggested levetiracetam may be safe and effective in SE, with doses ranging from 20-60mg/kg.[126,127] Advantages include that it

can be given rapidly, and has a favourable safety profile compared to phenytoin. In a retrospective study comparing two of these newer agents in adults with SE with phenytoin, efficacy of phenytoin did not differ from levetiracetam or valproate.[128] A recent RCT in India, also in adults, similarly did not demonstrate superiority of the "newer agents".[129] Lacosamide is another agent that has generated interest, but also without robust evidence.[127] In summary, despite the well-known problems with phenytoin, and no strong evidence to support its use, it would be premature to adopt these new agents at this point. Ongoing trials in Australia and New Zealand, United Kingdom and the U.S. will clarify the role of three of these agents in paediatric and adult SE.[21,130]

2.6.4 Management of refractory status epilepticus (third line therapy)

As with other aspects of SE, definitions of prolonged SE, refractory SE and super-refractory SE have changed over the years. Refractory SE usually now refers to when first and second line drugs fail to control the seizure, rather than indicating a specific time period for the length of seizure.[28,98,131] Super-refractory SE denotes seizures that persist or recur despite administration of continuous infusion anticonvulsants or general anaesthesia.[28,98,132]

Traditionally, if second line agents fail, guidelines – based on expert opinion - have advocated anaesthetic doses of thiopental, midazolam, pentobarbital or propofol.[127] Use of these medications is generally associated with the requirement for endotracheal intubation, because of the effect of the medications on respiratory drive and airway reflexes. There is no evidence that any of these agents is superior to another for refractory SE.

There is some evidence that high dose midazolam infusion is effective and is probably an appropriate initial choice for refractory SE.[131,133] A recent systematic review found 521 cases of midazolam infusion use in refractory SE, with seizure control achieved in 76% of cases.[132] The recommendation is to start therapy with a bolus of 0.1mg/kg and an infusion at 0.2mg/kg/hr, with a repeat bolus and doubling of the infusion at 10 minutes if seizure activity is ongoing.[133] The infusion can continue to be titrated up, ideally guided by continuous EEG monitoring but specialist advice sought, as complications can occur at high infusion rates, such as hyperchloraemic, non-anion gap metabolic acidosis. Rarely hemodynamic support is required.

Infusions of general anaesthetics are another option for refractory SE. Propofol infusions used in adults are considered to have an unacceptable risk of propofol infusion syndrome in children.[133] Barbiturates, in particular thiopentone, pentobarbital and phenobarbital are often recommended for this purpose. These agents have excellent CNS penetration, and have

actions on GABA receptors, NMDA receptors as well as effects on chloride, potassium and calcium channels.[133] These medications can reduce the cerebral metabolic rate, which is thought to be advantageous in management of refractory SE. High lipid solubility leads to prolonged drug effects, long elimination half-life, and consequently may lead to slow recovery.[133,134] The main problems with this class of drugs are respiratory depression and hypotension.[133,134]

An RCT in adults with refractory SE comparing propofol with barbiturates was terminated early for slow recruitment, with only 23 patients of a required 150 enrolled.[135] While no difference in outcome was shown, it was clearly underpowered to provide any useful information, except confirming the difficulty in conducting trials in this cohort of patients.[135] The best practices for airway management in SE are unclear.[136]

Another strategy that has been advocated is the use of third line agents without the requirement for intubation e.g. using agents without respiratory depressant effects (valproate, phenytoin, levetiracetam, lacosomide) when they have not been used as second line agents.[101,113,137,138] Put another way this could be considered repeating "second-line therapy". A recent adult trial in India demonstrated additional benefit when these agents were used third and fourth line, although this was not the primary objective of the study, but rather a pragmatic reflection of their practice environment and resources.[129] However, this may be instructive in patients for whom intubation is not desirable such as chronic patients with recurrent SE, and worthy of further study.

Ketamine has received recent attention as a method of terminating refractory SE,[8,10,139] and is an attractive option to emergency physicians, who are likely to be familiar with its use in other situations. It has favourable hemodynamic effects, and less effect on respiratory reflexes and ventilation than other agents. Ketamine is an NMDA-receptor antagonist that produces dissociative anaesthesia without cardiorespiratory depression. To date, reported series have used ketamine well down the treatment algorithm, after many other treatments have failed.[140] The effect of earlier use of ketamine, as a second or third line agent, is not known but is the subject of a current clinical trial in Italy.[139] If ketamine is found to be effective in seizure termination, it might be again most useful in circumstances when intubation is undesirable, e.g. in patients with frequent or recurrent SE with comorbidities.

Inhalational anaesthetics such as isoflurane have been used for refractory SE for many years. Although the precise mechanism of action is not known, it is likely to involve a number of receptors. These medications usually induce immediate cessation of seizure activity

regardless of duration, type or aetiology.[138,141] They are not generally available to ED providers, are usually tried only as a last resort, and there is very little supporting evidence in children. Titration is usually assisted with continuous EEG monitoring.[133]

2.6.5 Novel strategies

Therapeutic hypothermia for the management of refractory SE and super-refractory SE has also been described. A small case series describes cooling to 30-35 degrees Celsius, however treatment effect independent of other factors has not been established. There are adult trials underway.[142]

A ketogenic diet, consisting of high fat, low carbohydrate and adequate protein, has also been advocated for refractory epilepsy syndromes. The basis for this approach is the efficacy of a ketogenic diet in patients with poorly controlled drug resistant epilepsy with frequent seizures. In refractory SE and super-refractory SE the therapy is given through a feeding tube.[133] The use of this intervention is probably last line in patients with refractory SE and super-refractory SE and thus is likely to be of less relevance to emergency physicians, although there are trials underway in adults.

2.6.6 Management of non-convulsive status epilepticus

Historically, various definitions of non-convulsive SE have been used, making interpretation of the available literature problematic. Conventionally definitions have included both absence status epilepticus and complex partial status epilepticus, with known differences in outcomes.[92] These have been classified separately in a report on definition and classification from the ILAE task force, and are associated with differing time frames to tonic-clonic SE.[23] Studies have invariably been performed in the ICU setting rather than ED, and have incorporated EEG criteria for identification, making them of little relevance to ED physicians, who are unlikely to have this information available.[92] Whether treatment can improve outcome is unknown, and as with convulsive SE, the underlying cause is probably the most important prognostic factor.[92] Optimal management strategies are unknown, but until further data is available, if diagnosed or suspected in the ED, management should progress along similar lines as for convulsive SE.

2.6.7 Specific aetiology

Identification of a presumed cause of SE may necessitate specific directed treatment in addition to supportive and anticonvulsant treatment. For suspected infective aetiology, obviously antibiotics are indicated as per local and national guidelines for meningitis, as well as an antiviral such as acyclovir for possible *Herpes simplex* infection depending on the

clinical circumstances.[143] If suspected, treatment should not be delayed for confirmation by laboratory tests.

Other inflammatory conditions such as immunological or autoimmune encephalitis can cause refractory SE. If suspected clinically or by the presence of autoantibodies, oligoclonal bands in the CSF or typical MRI findings, immunomodulating treatments such as steroids or IV immunoglobulin can be used, but specialist advice from a neurologist or infectious disease specialist is warranted.[143] Other drugs with anti-inflammatory properties may also be useful, and some have advocated ketamine as having such properties.[67]

SE suspected to be due to a toxicological cause or overdose may result in changes to standard management algorithms. While phenytoin is most often recommended in SE protocols where benzodiazepines have failed, this agent may cause cardiac toxicity, and is not advised in this situation - barbiturates may be preferable.[144] The roles of valproate and levetiracetam are still unknown for this purpose.[69]

2.7 Summary

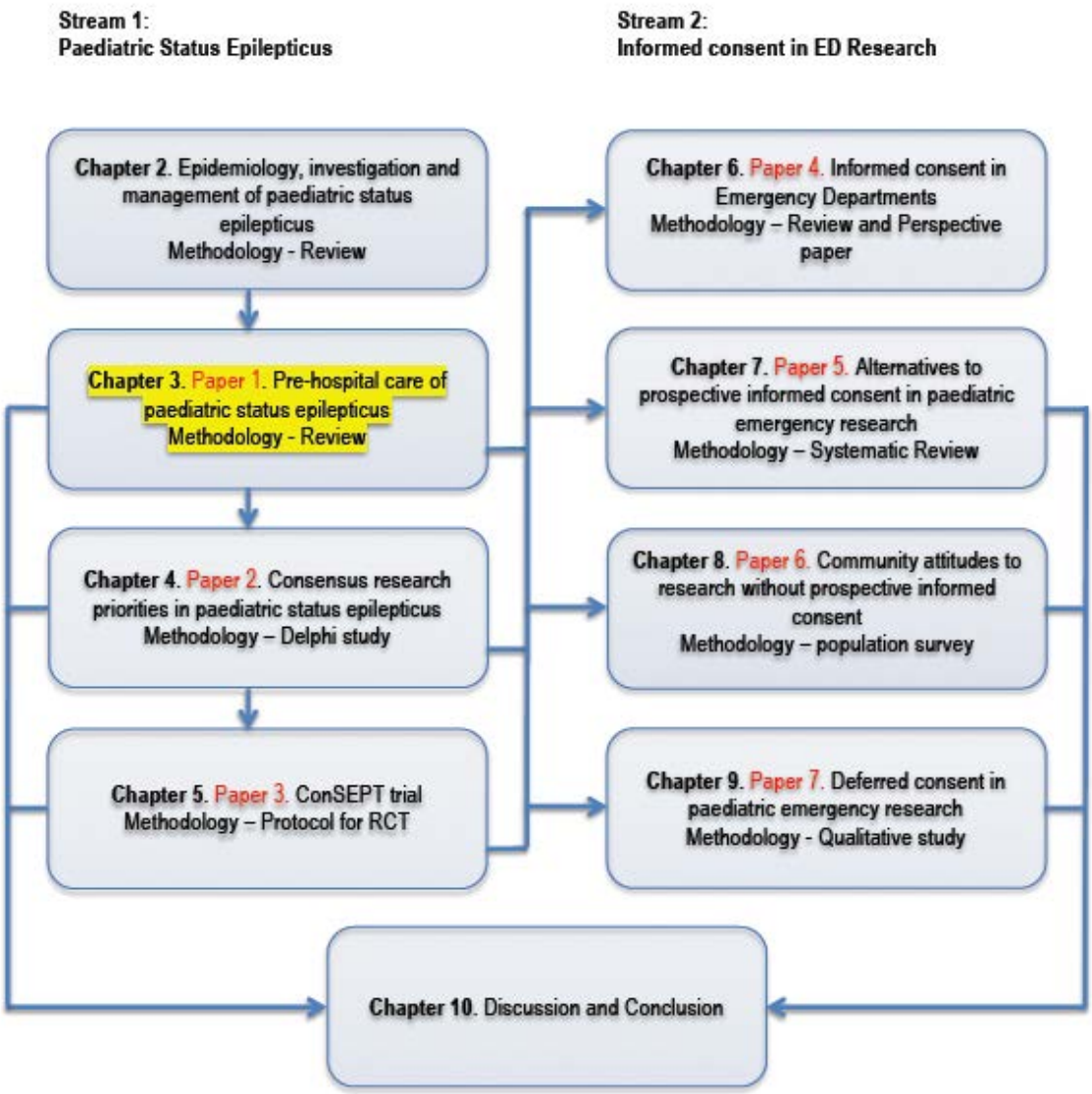
This chapter has outlined the epidemiology, investigation and management of paediatric SE, with a focus on the developed world. Within the limitations of the data and problems related to various definitions, the incidence appears to be in the order of 20 per 100,000 per year. Aetiology is varied and seems to be the most important contributor to outcomes. Prolonged febrile seizures are the most common cause of paediatric SE, and are generally associated with good outcomes, but can be difficult to differentiate from more sinister causes in the initial stages of evaluation. Investigation and management of paediatric SE usually occur simultaneously due to the urgency and time-critical nature of the condition. The quality of the evidence to inform decisions is generally poor, and management algorithms are based largely on theoretical considerations, tradition and expert opinion. Identification of likely aetiology may influence treatment decisions, therefore is of value, particularly for infective, inflammatory or toxicological causes. The duration of seizure activity is the only factor associated with outcome that is potentially modifiable, therefore research efforts have usually concentrated on this aspect of care. In advanced medical systems, emergency interventions are frequently delivered by highly trained paramedical staff in the field, before arriving at a hospital. As time to treatment is thought to be of key importance, this may prove to have a substantial impact on early intervention for paediatric SE. Chapter 3 presents a review of pre-hospital care of paediatric SE.

Chapter 3 – Paediatric status epilepticus in the pre-hospital setting: A review

3.1 Overview

Early intervention is important in achieving seizure control in SE, and a potentially modifiable factor affecting outcomes. Management in the pre-hospital environment represents an opportunity to affect outcomes but presents unique challenges. This chapter addresses objective 1 of this thesis, and specifically the topic of pre-hospital care of paediatric SE. As with the ED setting described in the preceding chapters, research in the pre-hospital setting is challenging, and most guidelines and protocols are not evidence based. Limited resources, time, and difficulties with informed consent are important barriers. Despite this, a number of important advances in the management of SE have occurred in the pre-hospital environment. The objectives of this review are to present an overview of the available evidence on pre-hospital aspects of paediatric SE, to describe current practice in Australia and New Zealand, assess for variation in care, make recommendations about care of these patients, and outline future research priorities. Figure 3.1 places this chapter in the conceptual framework of the broader thesis relative to other elements

Figure 3. 1 Conceptual model of thesis



This chapter comprises a published manuscript. It is inserted as published. The citation is:

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3.2 Publication in Emergency Medicine Australasia

EMA Emergency Medicine Australasia

Emergency Medicine Australasia (2017) doi: 10.1111/1742-6723.12824

REVIEW ARTICLE

Review article: Paediatric status epilepticus in the pre-hospital setting – an update

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Abstract

Paediatric status epilepticus (SE) is a medical emergency and a common critical condition confronting pre-hospital providers. Management in the pre-hospital environment is challenging but considered extremely important as a potentially modifiable factor on outcome. Recent data from multicentre clinical trials, quality observational studies and consensus documents have influenced management in this area, and is important to both pre-hospital providers and emergency physicians. The objective of this review was to: (i) present an overview of the available evidence relevant to pre-hospital care of paediatric SE; and (ii) assess the current pre-hospital practice guidelines in Australia and New Zealand. The review outlines current definitions and guidelines of SE management, regional variability in pre-hospital protocols within Australasia and aspects of pre-hospital care that could potentially be improved. Contemporary data is required to determine current practice in our setting. It is important that paediatric neurologists, emergency physicians and pre-hospital care providers are all engaged in future endeavours to improve clinical care and knowledge translation efforts for this patient group.

Key words: *ambulance, emergency, status epilepticus.*

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3.3 Supplementary file

See Appendix 3.1 – Medline search strategy

3.4 Summary

This chapter comprised a review article of paediatric SE. The objectives of the review were to present an overview of available evidence in pre-hospital care of paediatric SE and to assess current pre-hospital guidelines in Australia and New Zealand. A literature search was conducted on databases Embase, Medline and Web of Science. Title and abstracts were screened, and full articles retrieved for inclusion if relevant to the objectives. State and territory ambulance services were contacted for protocols, and additional searches were performed for grey literature and on Google scholar.

The main findings from this chapter are summarised below:

- Paediatric SE is a common critical condition encountered by pre-hospital providers, and management can be challenging in this environment.
- Epidemiology and the general principles of management of paediatric SE are described, including home treatment, choice of benzodiazepines, preferred routes of administration and blood glucose testing.
- Pre-hospital paediatric SE management protocols were evaluated, revealing significant variation in doses and routes of administration, which may influence treatment decisions in the ED.
- The optimal timing and dosing remain unknown.

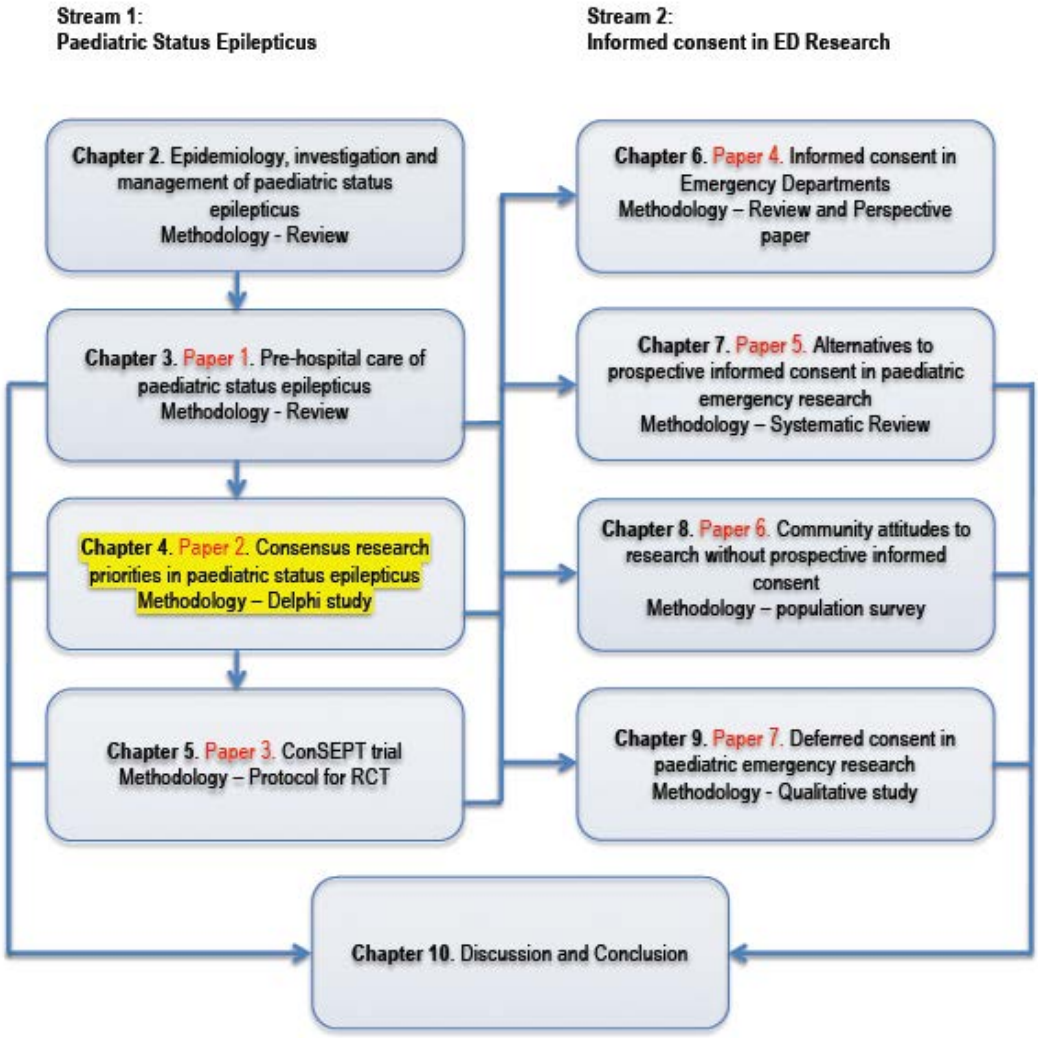
It is evident that variations exist in the pre-hospital management of paediatric SE, without robust evidence of the optimal pharmacological agent, timing and route of administration. While such variation in practice represents an opportunity to evaluate this “natural experiment” with quality, prospectively collected observational data, this alone is unlikely to change practice, and further high-quality clinical trials are required. In the emergency and pre-hospital setting, high-quality randomised controlled trials have traditionally been infrequent due to the many unique challenges of conducting research in this setting. One such challenge is the complex ethical issues surrounding obtaining prospective informed consent for research, in a time-critical situation. Given the difficulty involved in conducting such research, it is essential that valuable research resources are allocated appropriately, and that important stakeholders are engaged in the process of setting the research agenda. One strategy is to seek consensus on research priorities from experts. Chapter 4 outlines a Delphi consensus process of research priorities in paediatric SE.

Chapter 4 – Consensus research priorities for paediatric status epilepticus: A Delphi study of health consumers, researchers and clinicians.

4.1 Overview

Conducting high quality research in the pre-hospital and emergency settings is challenging. Presentations of individual conditions are infrequent and there are often competing priorities in an austere, stressful environment where the main focus is on managing time-critical and life-threatening conditions. The challenge is increased by the difficulty in obtaining informed consent. Given the substantial effort required to conduct research in this setting, it is crucial that a collaborative, widely consulted, systematic approach to identifying and clarifying the immediate research priorities in SE is utilised to ensure limited research resources are directed appropriately. One approach to identify research priorities among relevant stakeholders is a Delphi process. Chapter 4 addresses objectives 2 and 3 of the thesis. In this chapter a Delphi process for achieving consensus research priorities in paediatric SE among experts and consumers is presented. Figure 4.1 places this chapter in the context of the broader thesis.

Figure 4. 1 Conceptual model of thesis



The first part of the chapter comprises a brief overview of the Delphi process. The remainder of the chapter consists of a published article. It is inserted as published. The citation is:

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4.2 The Delphi technique

The Delphi technique was initially developed by the Research and Development Corporation in California in the 1950s for achieving consensus of opinion within a certain topic area from experts in the field.[145,146] It is named after the oracle on the island of Delphi in Greece, who

was believed to accurately predict the future. Originally designed for military planning purposes, the technique has been applied successfully in various fields and plays an important role in health sciences research, in the development of ideas and priorities. Briefly the technique involves the solicitation and collation of opinions and judgements from experts in a particular field through a set of carefully designed sequential questionnaires, with information from previous responses summarised and fed back to participants.[147]

The initial round is used to generate and verify issues and ideas. This first step usually consists of open-ended questions soliciting specific information about the content of subsequent questionnaires. Responses to the open-ended questions are then converted to a structured questionnaire to be used as the survey instrument in the second round. Subsequent rounds attempt to achieve consensus on the issues and ideas raised in round one, with researchers collating and returning responses to participants presenting the position of the whole group and the participants own position on the research issue. Every participant reassesses their initial judgement about the information provided. Generally, three to six iterations are employed, although three rounds is usually sufficient to reach consensus on a topic, as additional rounds produce minimal change in opinion.[147]

The major benefits of the technique are to avoid the limitations of using less formal techniques to achieve consensus such as through committees and panels, which can be prone to domination by powerful individuals and influenced by personalities. The benefits of anonymity and confidentiality contribute to the development of true expert consensus. The process also allows participants to generate additional insights and more thoroughly clarify information. As there is no requirement to meet face-to-face, clinicians from disparate geographical areas can be included. Modern technology such as electronic surveys have further simplified the execution of the process and facilitated the development and implementation.

In health sciences research the technique is most useful to address clinical issues that may not be amenable to evaluation in randomized clinical trials or quantitative data analysis where incomplete data exist. Delphi technique is useful to determine informed judgements on topics spanning a range of disciplines such as neurology and emergency medicine. Within paediatrics the technique has been successfully used to identify research priorities in the field of neurology with respect to cerebral palsy, and to identify general emergency medicine research priorities in the United Kingdom and Australia.[148-150]

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Consensus research priorities for paediatric status epilepticus: A Delphi study of health consumers, researchers and clinicians

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ABSTRACT

Purpose: Status epilepticus (SE) is a paediatric emergency with significant morbidity and mortality. Recommendations beyond first line care are not based on high quality evidence. Emergency physicians and neurologists are key stakeholders in managing this condition. A collaborative, widely consulted approach to identifying priorities can help direct limited research funds appropriately. The objectives of this study are to identify consensus research priorities in paediatric SE among experts and health consumers.

Methods: A three-stage Delphi process was conducted. Paediatric Neurologists and Emergency Physicians in Australia and New Zealand participated. Round one asked participants to generate three research questions important for further research in paediatric status epilepticus. Responses were refined into unique individual questions. Rounds two and three required participants to rate questions on a seven point ordinal scale. Health consumers were invited to participate by providing up to three problem areas that could be addressed by research.

Results: 54 experts and 76 health consumers participated in the process. Nine questions reached our definition of consensus "high priority", 21 questions achieved consensus "low priority" and seven questions did not achieve consensus. High priority areas included second line management including levetiracetam (efficacy, dose and timing), use of third line agents, induction of anaesthesia (timing and best agent), management of focal SE, and indicators of "subtle SE". Consumer priority areas included themes of treatment efficacy, aetiology, and community education.

Conclusion: We identified nine priority research questions in paediatric SE, congruent with the health consumer theme of treatment efficacy. Future research efforts should be directed towards these priority areas.

1. Introduction

Status epilepticus (SE) is the most common childhood neurological emergency and is, with its underlying aetiology, associated with an estimated mortality of 3% and significant morbidity [1,2] including development of focal neurological deficits, cognitive impairment, behavioural problems or epilepsy [3]. The incidence of paediatric SE is in the order of 20 per 100,000 population at risk [1,4]. Aetiology and outcomes of SE in children are different from adults [4]; therefore adult evidence is minimally applicable to paediatric settings. An operational definition of SE based on the indication to commence treatment has been proposed for seizures of five minutes or more [5], replacing the "traditional" definition requiring seizures of greater than 30 min

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1059-1311/

duration or two or more sequential seizures without full recovery of consciousness between seizures. These concepts have been incorporated into recent clinical trials [6] and conceptually into recent consensus documents [7].

Benzodiazepines are widely used in the first line pharmacological management of SE, supported by good evidence of efficacy, but recommended subsequent management is based on expert opinion, tradition and consensus [8]. Despite the considerable burden of SE, addressing important clinical questions is challenging with single centre studies, and generally requires a collaborative approach with considerable resources and infrastructure [9]. A collaborative, consultative and systematic approach to identify and clarify the immediate research priorities in SE is indicated to ensure limited research funds are directed appropriately. Incorporating stakeholders' perspectives into the development of research priorities might lead to highly engaged researchers and increased likelihood of translating research into clinical practice.

The Delphi technique is a common approach for the solicitation and collation of opinions from experts in a particular field in the development of ideas and priorities. The Delphi technique has been widely used in health sciences research and is appropriate to correlate informed judgements on topics spanning the disciplines of neurology and emergency medicine. Briefly, the technique involves a set of sequential questionnaires, with information from previous responses summarised and fed back to participants [10]. The first round usually consists of open ended questions soliciting specific information about the content of subsequent structured questionnaires. Three to six rounds are usually employed to reach consensus on a topic [10]. The technique has been successfully used to identify research priorities in the field of paediatric neurology [11], paediatrics [12] and paediatric emergency medicine [13,14].

The perspective of emergency physicians is perhaps historically underrepresented in SE literature and guideline development, despite being responsible for the majority of acute care decisions in SE in many health systems. It is also imperative that health consumers (i.e. patients and families of patients) are represented to ensure that community expectations about research priorities are met.

The primary objective of this study was to use the Delphi technique to achieve consensus on research priorities in the management of paediatric SE among paediatric neurologists and emergency physicians who treat children. A secondary objective was to determine if research priorities identified by experts aligned with priorities identified by health consumers. The results of this study will help determine where to allocate scarce research resources to achieve better outcomes for patients.

2. Methods

This was an assessment of expert clinician and health consumer opinion via a Delphi survey to identify research priorities for paediatric SE. The survey was conducted with the support of the Australia and New Zealand Child Neurology Society (ANZCNS) and Paediatric Research in Emergency Departments International Collaborative (PREDICT) network.

2.1. Participants

Expert participants were paediatric neurologists and emergency physicians in Australia and New Zealand. An invitation to participate was distributed to paediatric neurologists through the ANZCNS by email, explaining the purpose of the study, the expected time commitment, the proposed number of rounds and timelines. Emergency physicians were invited to participate through site representatives of the PREDICT network. Site representatives at PREDICT sites were asked to nominate interested clinicians, and provide email details, to approximate respondent numbers from neurologists to maintain balance and representation of both groups and inclusion of perspectives of non-researchers. Although controversy exists as to what constitutes the ideal number of subjects in a Delphi study [15–18], it has been recommended that one should have 30 experts from any one discipline, or at least 10 per category for different professional disciplines. It has been suggested that increasing a group size beyond 30 does not generally improve results [16]. A total sample of at least 30 respondents was sought, allowing for attrition.

Consumer participants included health consumers with a diagnosis of epilepsy and a prior SE event, as well as their families. Information regarding the study objectives was distributed through Epilepsy Queensland social media webpages, with an explanatory sheet, and a link to participation in the survey.

2.2. Study procedure and design

Surveys were constructed and distributed electronically via email, using SurveyMonkey [19]. In round one clinical participants were asked to identify research priorities in the field of paediatric SE that they believed was lacking by answering one single open question: *"Thinking about your experience with paediatric convulsive status epilepticus, what are the most important research questions that need addressing"*. The survey allowed for free text responses, and participants were encouraged to submit the research questions in the PICO format (referring to Population, Intervention, Comparison, Outcome). They were given three weeks in which to respond and could submit up to three questions. Non-responders were emailed a reminder at one and two weeks after initial contact. Consumers were asked to provide up to three problem areas associated with paediatric status epilepticus that could/should be addressed by research. Demographic details were collected from both experts and consumers.

Definitions of SE have been somewhat contentious and continue to evolve [7]. In the survey information we defined SE simply as an *"abnormally long seizure"* operationally defined as when emergency treatment should be started e.g. beyond 5 min for tonic-clonic SE. Questions concerning "children" referred to ages 1 month to 16 years, and "infants" as ages 1 month to 12 months.

Questions generated by round one were collated into themes, and developed into mutually exclusive research questions using NVivo 11 for Mac (NVivo qualitative data management Software; QSR International Pty Ltd. Version 10, 2014). Analysis of responses to round one used a grounded theory approach and a process of content analysis and open coding to categorize items into themes [17]. The compiled proposed questions were reviewed and refined by the investigator team and included in round two in a structured questionnaire. The investigator team included experienced paediatric emergency physicians, paediatric neurologists, clinician researchers and methodological expertise. Surveys were pilot tested for face validity on a group of ED physicians and paediatricians and amended as required. In round two participants were asked to rate the perceived priority of each research question using a seven point Likert-type, ordinal scale (Very low priority, low priority, fairly low priority, neutral, fairly high priority, high priority, very high priority). Participants were also encouraged to supply reasoning and further comments.

Round three consisted of the questions from round two that did not reach predetermined criteria for consensus "high" or "low" priority, together with a summary of feedback for each question including scores and text comments to allow responders to reflect on colleagues scores and thoughts. In round three participants were again asked to rate the perceived priority of each research question using the same seven point Likert-type/ordinal scale.

2.3. Analysis plan and statistical considerations

Data from round two and three were exported to an excel spread sheet and analysed on SPSS (Ver 20.0, IBM, Armonk, NY, USA). Overall support for group responses to questions were reported as means and standard deviation. Consensus priority was defined as more than 70% of total respondents rating a question as "fairly high priority" or higher [20]. Consensus "non priority" questions were defined as questions where more than half of the respondents rated the questions as "neutral" or lower priority. The pragmatic decision was made to stop the process at three rounds, considering the low likelihood of achieving consensus with further rounds and survey response fatigue, based on previous work suggesting that additional rounds produce minimal change in opinion [10,16].

Consumer participants completed a specifically developed questionnaire, and were asked to list three "questions or ideas for research" which they believe are important for children with convulsive status epilepticus. Responses were exported and qualitative thematic analysis was performed using NVivo 11 for Mac (NVivo qualitative data management Software; QSR International Pty Ltd. Version 10, 2014). These are reported separately and assessed for theme concordance with priorities identified by experts.

2.4. Ethics and consent

The study was approved by the Townsville Hospital Human Research Ethics Committee. Consent of experts was implied when participants responded to the survey via the survey portal. Consumers were given the opportunity to discuss participation with a member of the research team at a mutually convenient time if required, and asked to check a box on the survey instrument indicating consent to participate.

3. Results

3.1. Experts

The three round Delphi process was conducted from April to December 2016. The survey remained open for 4 weeks for each round, with ten weeks between rounds for analysis and development of subsequent surveys. Fifty-four experts agreed to participate in the Delphi process and provided questions and valid email address for subsequent rounds. The demographics of "expert" participants are shown in Table 1. Response rates for round two and three were 42/54 (78%) and 44/54 (81%) respectively.

Questions from round one were imported into NVivo, coded and developed into 37 unique questions in seven categories consisting of: first line agents, second line agents, timing of second line agents, induction of anaesthesia/intubation, home and pre-hospital care, investigation of SE, and general issues (Table 2).

The results of ranking the 37 questions constituting round 2 of the Delphi process are summarised in table S1 (Supplementary appendix) together with the proportion of responses that rated the question as greater or equal to "fairly high priority" or 4 on the scale. Six questions met our definition of high priority consensus (Table 3), while 15 questions met our definition for low priority consensus. The remaining 16 questions that did not reach consensus were refined, and with feedback included in the round 3 survey.

In round 3 a further 3 of 16 questions achieved high priority consensus (Table 3), and 6 questions reached low priority consensus, and seven questions failed to reach consensus (intermediate priority). Round 2 and 3 responses are summarised in Table 4 and S1. In addition to rating the perceived priority of each research question, participants were able to provide comments and additional insights in a free text response. Indicative quotes accompanying questions achieving high priority status are included in table S2.

Table 1
Demographic details of respondents to expert survey.

	n (%)
Gender	
Female	21 (39%)
Age Range	
25–34	1 (2%)
35–44	26 (48%)
45–54	20 (37%)
55+	7 (13%)
Years since medical graduation	
Median 21 (IQR 16 to 26)	
Speciality	
Emergency physician	22 (41%)
Paediatric Neurologist	32 (59%)
Hospital category	
Tertiary	43 (80%)
Secondary	5 (9%)
Both	6 (11%)
Full time/Part time	
Full time	39 (72%)
Part time	15 (28%)

IQR interquartile range, all.

Table 2
Demographic details of respondents to consumer survey.

	n (%)
Gender	
Female	68 (89%)
Age Range	
18–24	7 (9%)
25–34	13 (17%)
35–44	27 (35%)
45–54	16 (21%)
55+	13 (17%)
Highest level of education attained	
School certificate (Year 10)	12 (16%)
Higher school certificate (Year 12)	13 (17%)
Post school, non-university	23 (30%)
Undergraduate university degree	20 (26%)
Postgraduate university degree	8 (11%)
Religious preference	
Christianity	42 (55%)
No religion	33 (43%)
Islam	1 (1%)
Approximate annual household income	
Less than $25 K	14 (18%)
$25–49 K	15 (19%)
$50–74 K	14 (18%)
$75–100 K	15 (19%)
More than $100 K	18 (24%)
Diagnosis of epilepsy	
Self	34 (45%)
Child	37 (49%)
Sibling	2 (3%)
Previous episodes of status epilepticus	
Yes	58 (76%)

Table 3
Consensus high priority questions, rankings and scores.

Questions	Round 2		Round 3	
	% ≥ 4[a]	Mean (SD)	% ≥ 4[a]	Mean (SD)
1. In **infants** with convulsive SE, is levetiracetam superior to phenytoin (or phenobarbitone) for efficacy (seizure termination) and safety (adverse effects)?	85%	5.3 (1.1)		
2. In children with convulsive SE, is levetiracetam superior to phenytoin for efficacy (seizure termination) and safety (adverse effects)?	82%	5.5 (1.3)		
3. In children with convulsive SE is the early use of anaesthesia associated with more rapid seizure terminations, less complications and better long-term outcomes, compared to anticonvulsant treatment alone?	82%	5.2 (1.2)		
4. In children with convulsive SE, is earlier administration of a second line agent (e.g. levetiracetam) more effective than standard protocols?	74%	4.9 (1.1)		
5. If EEG is not available, what are the most reliable clinical indicators of ongoing subtle SE?	73%	4.9 (1.4)		
6. In children with focal SE should the medical management proceed according to similar treatment pathways as for convulsive SE, and within the same time frames?	72%	4.7 (1.1)		
7. In children with convulsive SE, what is the most appropriate dose of levetiracetam as a second line agent?	68%	5.0 (1.2)	77%	4.9 (1.2)
8. In children with convulsive SE who require intubation, what induction agent is most effective for seizure termination, long-term outcome and complications (e.g. ketamine, propofol, thiopentone, other)?	68%	4.8 (1.1)	81%	5.1 (1.2)
9. In children with convulsive SE, Is third line medical anticonvulsant drugs compared with induction of anaesthesia and intubation associated with improved long-term outcomes?	66%	4.9 (1.2)	81%	5.1 (1.0)

[a] Denotes percentage of respondents who ranked question fairly high priority (4 on scale) or higher. SD standard deviation.

Table 4
Consumer survey data. Common themes, counts and indicative quotes.

Drug Therapies and treatment efficacy (20 references)
"optimal agent/timing"
"Most effective treatment"
"maximal safe pre-hospital care"
"A simpler easy to use rescue medication as an alternative to what is available if available meds don't work."

Causes and Triggers (19 references)
"What causes it"
"Research the triggers and warning signals to help parents be proactive in preventing status episodes from occurring."
"What are the major triggers for CSE?"

Outcomes and prognosis (18 references)
"What are the long term cognitive effects of these episodes?"
"Neuropsych testing for school performance"
"What harm can occur"

Medicinal cannabis (6 references)
"Would medically approved marijuana help"
"get cannabis oil legalised not just for children"

Education (3 responses)
"More education for nursing and other medical staff on how to deal with status episodes"
"Community education around responding to status epilepticus for non-primary carers"

3.2. Health consumers

The consumer survey was made available from August to November 2016 and received 76 responses. Demographics of health consumer participants are shown in Table 2, and included people with epilepsy and family members of people with epilepsy; a high proportion had previous experience of status epilepticus. Over 100 questions or ideas were generated by the consumer survey. The most common themes included drug therapies and treatment efficacy, causes and "triggers", and outcomes and prognostication (Table 4). Less common themes (six responses) concerned medicinal cannabis and education of public and community in general.

4. Discussion

The Delphi consensus process involving expert emergency physicians and paediatric neurologists identified nine priority research questions for the management of paediatric status epilepticus. Three questions specifically concerned the use of levetiracetam, another concerned the timing of "second line agents" including levetiracetam, and two questions referred to induction of anaesthesia. These were broadly congruent with the "drug therapies" priority theme commonly identified by health consumers. Other questions concerned clinical indicators of subtle SE and management of focal SE.

Experts prioritised a comparative efficacy and safety study between levetiracetam and phenytoin in both infants and children (Table 3, questions 1 and 2). Many were aware that studies to address this issue were underway in Australia and New Zealand, the United States and the United Kingdom [21,22]. This finding confirms that these results are keenly anticipated, and are likely to affect management algorithms internationally. A separate research question that may not be adequately addressed by current trials was for the most appropriate dose of levetiracetam (Table 3, question 7). Current trials are investigating doses of 40 mg/kg to 60 mg/kg of levetiracetam [21,22]. Of interest, pre-hospital use of levetiracetam was not considered a research priority (intermediate priority) and second line usage of sodium valproate was of low consensus priority in round three. This may reflect unfamiliarity of the drug due to limited availability of the intravenous formulation in Australia and New Zealand, or concerns about safety in certain

subpopulations, particularly infants. Again, it is likely that ongoing trials will address this question in children older than two years. Other "newer" second line agents such as lacosamide were not proposed as priority research questions in our study.

Another research priority was the use of second line agents, such as levetiracetam earlier in the algorithm (Table 3, question 4). This has been advocated by some experts in the literature, including "combination" therapy, and may be facilitated if agents associated with less side effects (e.g. levetiracetam, sodium valproate, lacosamide) are found to be non-inferior to standard therapies. A trial in adults did not demonstrate benefit of the addition of levetiracetam to clonazepam in adult patients with SE in a pre-hospital trial in France [23].

Identifying clinical indicators of subtle SE when electroencephalogram (EEG) is not available was also identified as a high priority question (question 5, Table 3). Differentiating ongoing subtle SE from the postictal state can create difficulty in the acute setting, especially in children who may have baseline abnormal neurological function. EEG support in this setting is limited by access to urgent EEG, and the time taken to set up a recording. There are potential adverse consequences from under or over diagnosis of subtle SE (such as excessive SE treatment including intubation, and later long term medication and lifestyle restrictions advice that are based on the reported duration of seizure). Some respondents commented that there were perhaps no reliable clinical indicators of subtle SE. Other respondents, however, commented that increasing expert support at the point of clinical decision making regarding subtle SE, through review of the patient by experts in subtle SE (by acute video review or neurologist telemedicine consultation) could address this problem, at least in a proportion of SE cases.

Management of focal SE and whether algorithms should be similar to convulsive SE was also a high priority (Table 3, question 6). While recent consensus documents have indicated that different operational time frames are applied to focal SE to tonic-clonic SE, it was conceded that this was based on limited data [7]. Our results indicate that clinicians require further clarity in terms of management strategies in this area and may warrant further study.

Induction of anaesthesia was also a high priority area for clinicians (Table 3, questions 3 and 8). Whether early induction of anaesthesia improved outcomes achieved consensus with high levels of support, but divided opinion in comments with some suggesting it may be unethical (Table S2). Other experts commented that their clinical experience suggests practice in this regard is already highly variable, as indicated in observational data therefore it is valid to pursue this as a research priority. Conversely, the use of third line agents rather than induction of anaesthesia, a strategy that observational trials suggest is commonly used was also found to be a research priority (Table 3, question 9). Additionally, the preferred induction agent was identified as a high priority in round three of the process, with a lack of quality evidence cited. An attempt to investigate this question in adults, comparing Propofol to Barbiturates failed to demonstrate a difference, but this was predominantly due to poor recruitment and early closure of trial [24]. A similar study in children may prove equally difficult, and perhaps methodologies other than RCTs may be required initially. Use of Ketamine and Propofol in the non-intubated patient were both judged to be low priority questions, although proponents may argue they may have a role in specific circumstances e.g. when it is highly desirable to avoid intubation as with frequent recurrent SE.

In 2014 the U.S. Pediatric Status Epilepticus Research Group (pSERG) published a report summarizing the evidence of paediatric SE and refractory convulsive SE [9]. Based on their literature review, the group identified several knowledge gaps including risk factors for SE, biomarkers, second and third line treatment options and long-term outcome [9]. While the methods used by pSERG differed from our consensus Delphi approach, and knowledge gaps do not necessarily equate with research priorities, the congruence with priorities identified in our study reinforce the importance of our findings.

There were some differences between consumer and expert responses. Apart from the theme of treatment efficacy, consumer priority themes included "triggers" or causes, prognosis as well as medicinal cannabis and education. Differences may be partly explained by unique perspectives on SE. For example emergency physicians may be less likely to consider preventative strategies, however these are clearly no less valuable. The themes identified by consumers are illustrative of the issues important to people and their families affected by epilepsy, and future work can build on these ideas.

Our study had strengths and limitations. The Delphi process is widely used in health sciences [11–14]. The major benefits of the technique are to avoid the limitations of using less formal techniques to achieve consensus such as through committees and panels, which can be prone to domination by powerful individuals and influenced by personalities. The benefits of anonymity and confidentiality contribute to the development of true expert consensus [17,20]. Other advantages include that the process allows participants to generate additional insights and more thoroughly clarify information. Other methods of generating consensus opinions, and generating research priorities have been used, and include the Nominal Group Technique and the Hanlon Prioritisation Process [13,25–27]. The Delphi approach was considered the most appropriate in our circumstance, as experts were geographically dispersed and were not required to physically meet.

Limitations of our study included that our process of identifying and defining expert panellists for the sampling frame was somewhat subjective, and the Delphi technique works on the assumption that participants are equal in knowledge and experience, which may not be correct. However, involvement of emergency physicians and paediatric neurologists in this process was a strength of the design. A further concern is that minority opinion might be lost, and yet still have value. Participants had the opportunity to add comments that were handled in a qualitative analysis of responses. We do not contend that just because a research question did not achieve a consensus high priority by our process, that it is without value or incapable of contributing important knowledge or benefit to patients.

While a strength of the study was the inclusion of health consumers, our methods may have introduced some selection bias. Respondents identified through epilepsy support organisations likely represent patients with more severe or burdensome established epilepsy, only a subgroup of the children presenting with SE. This may have lead to some bias towards responses specific to chronic epilepsy and may account for differences in responses from experts. We did not seek the consensus of consumers through classic Delphi technique in this group, rather evaluated concordance with the consensus of experts.

There is no "gold standard" for defining consensus during a Delphi process, and various definitions have been proposed [17,20]. Methods used in our study had been advocated and used in similar studies [11,15,16,20]. Further limitations are inherent with any research involving surveys and rating scales include the central tendency bias, where participants tend to avoid rating at the extremes of the scales, acquiescence bias and social desirability bias.

Finally, in our instructions to participants we specifically excluded the neonatal period, for similar reasons that adult SE was excluded. In these age groupings SE was considered to have

different aetiologies and outcomes, therefore results of this study are not applicable to the neonatal population. This research only involved participants in Australia and New Zealand, a region with an advanced health system, with high standards of education and training, therefore results should be generalizable to other developed countries.

In summary, we sought to achieve consensus on research priorities in the management of paediatric SE. Our consensus process allowed experts to identify nine high priority research questions consisting of second line management including levetiracetam (efficacy, dose and timing), use of third line agents, induction of anaesthesia (timing and best agent), management of focal SE, and indicators of "subtle SE" concordant with consumer priorities. Results of this research should help inform where future research efforts in paediatric SE should be directed.

Meetings

Presented at the Salzburg colloquium on status epilepticus, April 2017.

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Conflicts of interest

No conflicts of interest.

Author contributions

JF, SD, FB, EO and RR responsible for the conception and development of the study, project management, reporting and publication. FB, SD, KR, MM, GB expert advice on content and developed of questionnaires. JF conduct of the surveys and data management. JF, RR performed data analysis. JF prepared the first draft of the manuscript, and all authors contributed to revisions and had full access to data. JF takes responsibility for the paper as a whole.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2018.01.025.

References

[1] Chin RF, Neville BG, Peckham C, Bedford H, Wade A, Scott RC. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet 2006;368(9531):222–9.
[2] Raspall-Chaure M, Chin RF, Neville BG, Scott RC. Outcome of paediatric convulsive status epilepticus: a systematic review. Lancet Neurol 2006;5(9):769–79.
[3] Novorol CL, Chin RF, Scott RC. Outcome of convulsive status epilepticus: a review. Arch Dis Child 2007;92(11):948–51.
[4] Chin RF, Neville BG, Scott RC. A systematic review of the epidemiology of status epilepticus. Eur J Neurol 2004;11:800–10.
[5] Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia 1999;40(1):120–2.
[6] Chamberlain JM, Okada P, Holsti M, Mahajan P, Brown KM, Vance C, et al. Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial. JAMA 2014;311(16):1652–60.
[7] Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015(September (4)) PubMed PMID: 26336950.
[8] Appleton R, Macleod S, Martland T. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database Syst. Rev. 2008;(3). doi:http://dx.doi.org/10.1002/14651858.CD001905.pub2 Art. No.: CD001905.
[9] Sanchez Fernandez I, Abend NS, Agadi S, An S, Arya R, Carpenter JL, et al. Gaps and opportunities in refractory status epilepticus research in children: a multi-center approach by the Pediatric Status Epilepticus Research Group (pSERG). Seizure 2014;23(February (2))87–97 PubMed PMID: 24183923.
[10] Okoli C, Pawlowski SD. The Delphi method as a research tool: an example, design considerations and applications. Inf Manage 2004;42(1):15–29.
[11] McIntyre S, Novak I, Cusick A. Consensus research priorities for cerebral palsy: a Delphi survey of consumers, researchers, and clinicians. Dev Med Child Neurol. 2010;52(3):270–5.
[12] Rudolph S, Hiscock H, Price A, Efron D, Sewell J, South M, et al. What research questions matter to australian paediatricians? National Delphi study. J Paediatr Child Health 2009;45(December (45))704–10 PubMed PMID: 19863713.
[13] Deane H, Krieser D, Cheek J, Babl F, Dalziel S, Craig S, et al. Establishing the research priorities of paediatric emergency medicine clinicians In Australia and New Zealand. In: Predict Delphi Study, editor. 32nd Annual Scientific Meeting of the Australasian College for Emergency Medicine (ACEM-ASM 2015) 22–26 November.
[14] Hartshorn S, O'Sullivan R, Maconochie IK, et al. Establishing the research priorities of paediatric emergency medicine clinicians in the UK and Ireland. Emerg Med J 2015;32:864–8.
[15] Crisp J, Pelletier D, Duffield C, Adams A, Nagy S. The delphi method? Nurs Res 199746(2).
[16] De Villiers MR, De Villiers PJ, Kent AP. The Delphi technique in health sciences education research. Med Teach 2005;27(7):639–43.
[17] Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs 2000;32(4):1008–15.
[18] Hsu C-C, Sandford BA. The Delphi technique: making sense of consensus. Pract Assess Res Eval 2007;12(10):1–8.
[19] SurveyMonkey Inc. San Mateo, California, USA. Available from: http://www.surveymonkey.com.
[20] Keeney S, Hasson F, McKenna H. Consulting the oracle: ten lessons from using the Delphi technique in nursing research. J Adv Nurs 2006;53(2):205–12.
[21] Emergency Treatment with Levetiracetam or Phenytoin in Status Epilepticus in Children (EcLiPSE) –an open label randomised controlled trial (Protocol) Clinical Trials Research Centre. National Institute for Health Research; 2018 (cited 2017 January 10). Available from: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0014/123350/PRO-12-127-134.pdf.
[22] Bleck T, Cock H, Chamberlain J, Cloyd J, Connor J, Elm J, et al. The established status epilepticus trial. Epilepsia 2013;54(September (6))89–92 PubMed PMID: 24001084. Pubmed Central PMCID: 4048822.
[23] Navarro V, Dagron C, Elie C, Lamhaut L, Demeret S, Urien S, et al. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. Lancet Neurol 2016;15(1):47–55.
[24] Rossetti A, Milligan T, Vulliémoz S, Michaelides C, Bertschi M, Lee J. A randomized trial for the treatment of refractory status epilepticus. Neurocrit Care 2011;14(1):4–10.
[25] Keijzers G, Thom O, Taylor D, Knott J, Taylor DM. Clinical trials group ACfEM. clinical research priorities in emergency medicine. Emerg Med Australas: EMA. 2014;26(Febraury (2))19–27 PubMed PMID: 24118984.
[26] Miller SZ, Rincon H, Kuppermann N. Pediatric Emergency Care Applied Research N. Revisiting the emergency medicine services for children research agenda: priorities for multicenter research in pediatric emergency care. Acad Emerg Med 2008;15(April (4))377–83 PubMed PMID: 18370994.
[27] Thom O, Keijzers G, Davies S, Mc DTD, Knott J, Middleton PM. Clinical research priorities in emergency medicine: results of a consensus meeting and development of a weighting method for assessment of clinical research priorities. Emerg Med Australas: EMA 2014;26(February (1))28–33 PubMed PMID: 24495058.

4.4 Supplementary file.

See appendix 4.1. Table S5.1.1 Complete Delphi question rankings and scores. Table S5.1.2 Expert text comments on consensus High Priority questions in round 2 and 3.

4.5 Summary

Chapter 4 address objectives 2 and 3 of this thesis and comprises a Delphi study designed to achieve consensus on research priorities in paediatric SE among experts and consumers. A three round Delphi process was conducted. Questions generated by round one were collated into themes, and developed into mutually exclusive research questions in structured questionnaires in rounds two and three. Participants rated the perceived priority of questions using a seven-point Likert-type, ordinal scale. Main findings from this chapter are summarised below:

- The perspective of emergency physicians is underrepresented in SE literature and guideline development.

- Consensus was achieved on research priorities in the management of paediatric SE among paediatric neurologists and emergency physicians and aligned with priorities identified by health consumers.

- The process identified nine priority research questions, consisting of second line management including levetiracetam (efficacy, dose and timing), use of third line agents, induction of anaesthesia (timing and best agent), management of focal SE, and indicators of “subtle SE”.

- Consumers identified important research themes including drug therapies and treatment efficacy, causes and “triggers”, and outcomes and prognostication

- Incorporating stakeholders’ perspectives into the development of research priorities may lead to highly engaged researchers and increased likelihood of translating research into clinical practice.

Important priority areas in the management of paediatric SE were identified in the research presented in this chapter. Many of the research questions may not be possible to address with traditional concepts of informed consent for research, and alternative approaches need further exploration. Some of the components raised in the process include therapies and interventions that have in some ways already been incorporated into clinical care and

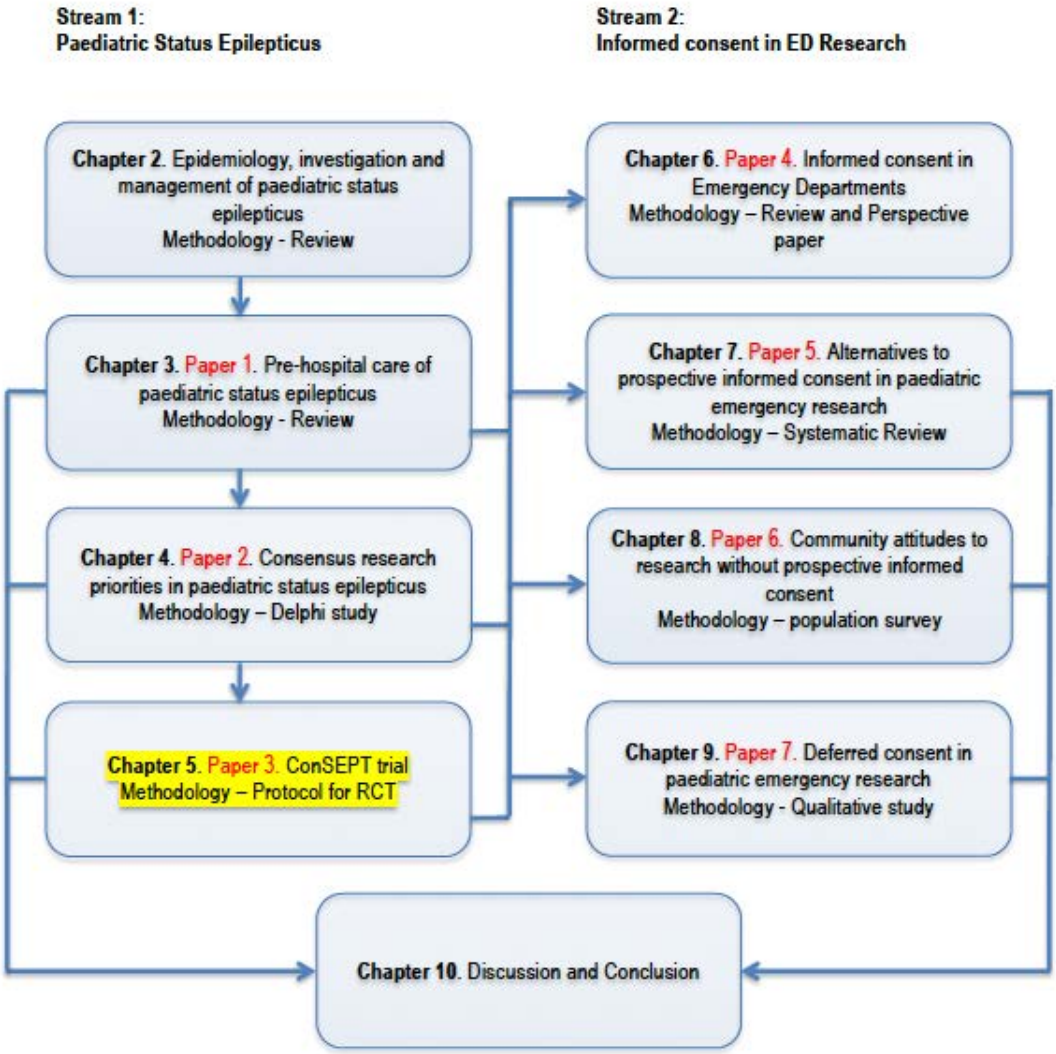
protocols for the management of paediatric SE, despite a striking lack of quality evidence. This highlights the paradox of informed consent in research and management of paediatric SE. Research has traditionally been difficult in these circumstances, however clinicians can opt to incorporate un-validated practices into clinical care without the need for informed consent. Comparative effectiveness research, where there is true equipoise (like comparing two “standard therapies”), and observational research in this context also requires informed consent in most circumstances in Australia and New Zealand. Involvement of stakeholders in determining research priorities justifies research in challenging circumstances, such as where prospective informed consent is not possible, and will ensure results are rapidly translated into practice. One of the main priority areas identified by the Delphi consensus process was that of second line management, and specifically levetiracetam. Chapter 5 outlines a protocol for a randomised controlled trial of levetiracetam and phenytoin in the second line management of paediatric SE. This trial represents one of the first paediatric trials conducted in Australia and New Zealand, using a “deferred” consent process.

Chapter 5 - A multicentre randomised controlled trial of levetiracetam versus phenytoin for convulsive status epilepticus in children (protocol): Convulsive Status Epilepticus Paediatric Trial (ConSEPT)

5.1 Overview

As outlined in Chapters 2 and 3 of this thesis, various benzodiazepines are most frequently used as first line in the management of paediatric SE, however there is a dearth of evidence to inform second line management. While no high-quality evidence supports the use of any of the interventions in common use, newer agents have found their way into clinical practice and guidelines. Second line agents, and in particular levetiracetam were identified in three of the nine research priority questions by the Delphi process of Chapter 4. This Chapter addresses objective 2 of this thesis and outlines the protocol for a randomized controlled trial of levetiracetam compared to phenytoin, in the second line management of paediatric SE. The trial protocol directly addresses the question identified by the Delphi process; "In children with convulsive SE, is levetiracetam superior to phenytoin for efficacy (seizure termination) and safety (adverse effects)?". Figure 5.1 places this chapter in the context of the broader thesis.

Figure 5. 1 Conceptual model of thesis



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5.2 Publication in BMC Paediatrics.

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BMC Pediatrics

STUDY PROTOCOL Open Access

A multicentre randomised controlled trial of levetiracetam versus phenytoin for convulsive status epilepticus in children (protocol): Convulsive Status Epilepticus Paediatric Trial (ConSEPT) - a PREDICT study

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Abstract

Background: Convulsive status epilepticus (CSE) is the most common life-threatening childhood neurological emergency. Despite this, there is a lack of high quality evidence supporting medication use after first line benzodiazepines, with current treatment protocols based solely on non-experimental evidence and expert opinion. The current standard of care, phenytoin, is only 60% effective, and associated with considerable adverse effects. A newer anti-convulsant, levetiracetam, can be given faster, is potentially more efficacious, with a more tolerable side effect profile. The primary aim of the study presented in this protocol is to determine whether intravenous (IV) levetiracetam or IV phenytoin is the better second line treatment for the emergency management of CSE in children.

Methods/Design: 200 children aged between 3 months and 16 years presenting to 13 emergency departments in Australia and New Zealand with CSE, that has failed to stop with first line benzodiazepines, will be enrolled into this multicentre open randomised controlled trial. Participants will be randomised to 40 mg/kg IV levetiracetam infusion over 5 min or 20 mg/kg IV phenytoin infusion over 20 min. The primary outcome for the study is clinical cessation of seizure activity five minutes following the completion of the infusion of the study medication. Blinded confirmation of the primary outcome will occur with the primary outcome assessment being video recorded and assessed by a primary outcome assessment team blinded to treatment allocation. Secondary outcomes include: Clinical cessation of seizure activity at two hours; Time to clinical seizure cessation; Need for rapid sequence induction; Intensive care unit (ICU) admission; Serious adverse events; Length of Hospital/ICU stay; Health care costs; Seizure status/death at one-month post discharge.

Discussion: This paper presents the background, rationale, and design for a randomised controlled trial comparing levetiracetam to phenytoin in children presenting with CSE in whom benzodiazepines have failed. This study will provide the first high quality evidence for management of paediatric CSE post first-line benzodiazepines.

(Continued on next page)

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(Continued from previous page)

Trial registration: Prospectively registered with the Australian and New Zealand Clinical Trial Registry (ANZCTR): ACTRN12615000129583 (11/2/2015). UTN U1111–1144-5272. ConSEPT protocol version 4 (12/12/2014).

Keywords: Convulsive status epilepticus, Paediatrics, Emergency medicine, Levetiracetam, Phenytoin, Intervention study, Randomised controlled trial

Background

Convulsive status epilepticus (CSE) is the most common life-threatening childhood neurological emergency [1]. It has an annual incidence of 17–23 cases per 100,000 children per year, with 22% of patients requiring Rapid Sequence Induction (RSI) and Intensive Care Unit (ICU) admission [2]. Mortality following paediatric CSE is reported at 3–5% and neurological sequelae occur in up to 34% of children [3].

Management guidelines for paediatric CSE recommend early and prompt use of anticonvulsant medication [4, 5]. Recommendations from the Advanced Life Support Group [4], the Scottish Intercollegiate Guidelines Network [5], the Status Epilepsy Working Party in the United Kingdom [6], and major textbooks [7, 8], are broadly similar and universally adopt a stepwise approach to treatment; 1.Two doses of benzodiazepine; 2.Second line anticonvulsant, with all recommending phenytoin or fosphenytoin; and 3.Final termination of CSE with RSI intubation with thiopentone and ICU admission. While there is reasonable evidence to support the use of benzodiazepines in CSE there is a paucity of evidence concerning the type and efficacy of second line anticonvulsant medication used with management guidelines based only on expert opinion [4, 5, 9].

The aetiology and outcomes of CSE in children is different to that of adults, thus adult evidence cannot be expected to be directly applicable to paediatric practice. A large population based study of CSE reported that less than a quarter of the children had a previous history of CSE. Of those with a first presentation of CSE over half were previously neurologically normal, a third of episodes were due to prolonged febrile convulsions, 17% of episodes were due to central nervous system (CNS) infection or acute metabolic derangement, with the remainder of episodes idiopathic or associated with a pre-existing CNS abnormality [2].

The term CSE was traditionally defined as 30 min of a continuous generalised tonic-clonic convulsion or recurrent tonic-clonic convulsions without recovery of consciousness between each convulsion [10]. Recently a revised operational definition based on the indication to commence treatment has defined CSE as seizures of a duration of five minutes or more [11]. This shortening of seizure duration for CSE definition is due to evidence that the natural history for typical generalised convulsive seizures is to resolve spontaneously by 3–5 min, with those not doing so requiring medication for termination [11, 12]. This revised definition has been adopted by recent trials on paediatric CSE [13]. Early medication use and cessation of seizures in CSE is important. There is a wealth of animal evidence suggesting that longer seizures are harmful and result in irreversible brain damage and poorer outcomes [1].

A survey of attending Paediatric Emergency Physicians in Australia and New Zealand confirmed that benzodiazepines are universally recommended for first line treatment in CSE and that 88% would use phenytoin as a second line agent, in keeping with guideline recommendations. However there was a large variation in third line agents, reflecting that the majority of consultants (68%) would try another agent prior to RSI [14]. A retrospective review of CSE management at eight large paediatric emergency departments (EDs) in New Zealand and Australia over five years identified 542 patients with CSE and found phenytoin resulted in cessation of seizures in only 60% of the 315 patients who received it as a second line anticonvulsant for CSE [15]. This success rate is comparable with other reported series [15–17].

In addition to its less than optimal effectiveness, phenytoin has a number of features that make it less than ideal to be used in CSE. Phenytoin is a potent inducer of hepatic enzymes resulting in reduced levels of a number of other anticonvulsants and non-anticonvulsant drugs. Its adverse events include hepatotoxicity, pancytopenia and Stevens-Johnson-Syndrome. Phenytoin can cause cardiac arrhythmias, hypotension, phlebitis, and severe soft tissue injury from extravasation and purple glove syndrome. Because of its cardiotoxicity it has to be given slowly (1 mg/kg/min) [16, 18]. Furthermore, phenytoin cannot be mixed with dextrose, a common component of paediatric intravenous (IV) fluids [16].

In North America fosphenytoin, the prodrug of phenytoin, is increasingly used instead of phenytoin [8, 16]. Although fosphenytoin can be administered more rapidly, the additional requirement to be metabolised into the active phenytoin means that it does not offer any true time advantages over phenytoin. However, fosphenytoin has a number of other advantages such as the ability to be administered intramuscularly and decreased infusion related adverse events, although deaths due to

fosphenytoin infusions have been reported. Furthermore, there are no data to show that fosphenytoin is more effective than phenytoin in stopping seizures. Importantly, for the purposes of this study, fosphenytoin is neither available nor approved for use in New Zealand and Australia.

Newer antiepileptic drugs such as levetiracetam, valproate and lacosamide have been proposed [9, 16, 17], and have been reported as effective in case reports and small case series in adults and in children [19–22]. The most promising, Levetiracetam, a broad spectrum, antiepileptic drug has been approved for use for over a decade and is widely used internationally for maintenance seizure prophylaxis for both focal and generalised seizure disorders in both children and adults. An IV formulation of levetiracetam is available for those unable to take oral preparations and appears to have an excellent safety profile including rapid IV use in children [16, 17, 20, 21, 23–26]. In adults, IV infusions of levetiracetam have been well tolerated [27], including at dosages and rates of infusion greater than recommended [28].

Levetiracetam has the following potential advantages when compared to phenytoin for use in CSE. Levetiracetam is easy to administer and can be given as a five-minute infusion into a peripheral IV cannula without the increased risk of serious adverse events (including hypotension, cardiac arrhythmias, extravasation or death). Furthermore, levetiracetam is compatible with both dextrose and normal saline infusion and has limited drug interactions.

On the basis of efficacy from the limited cohort data with levetiracetam, and concerns around low phenytoin efficacy and serious adverse events, IV levetiracetam is being increasingly used as a second line anticonvulsant in CSE in children. However, good quality evidence for IV levetiracetam use in CSE is lacking, and now is an ideal opportunity to compare it to phenytoin, the current recommended standard of care, in the robust environment of a randomised controlled trial (RCT).

Methods/Design

Aim

The primary aim of the study is to determine whether IV levetiracetam or IV phenytoin is the better second line treatment for the emergency management of CSE in children. Specifically, we hypothesise that children treated with IV levetiracetam for CSE will do better than children treated with IV phenytoin in terms of time to clinical cessation of seizure activity, need for RSI for ongoing seizure management, need for ICU admission, serious adverse events, length of hospital stay, health care costs, and long-term outcome.

Design

This is a RCT comparing IV levetiracetam with IV phenytoin in children presenting to EDs with CSE who are still seizing after two doses of benzodiazepines. The study will follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Participants

200 children aged between 3 months and 16 years presenting with CSE to EDs. The study is ongoing with 147 participants enrolled as of April 2017.

Setting

The study is taking place in 13 EDs in New Zealand and Australia that are members of the Paediatric Research in Emergency Departments International Collaborative (PREDICT), in New Zealand; Kids First Children's Hospital, Auckland, Waikato Hospital, Hamilton, and Starship Children's Hospital, Auckland; in Australia; Princess Margaret Hospital for Children, Perth, WA, Women's and Children's Hospital, Adelaide, SA, Royal Children's Hospital, Melbourne, VIC, Monash Medical Centre, Clayton, VIC, Children's Hospital at Westmead, Sydney, NSW, Sydney Children's Hospital, Sydney, NSW, John Hunter Hospital, Newcastle, NSW, Gold Coast University Hospital, Southport, QLD, Lady Cilento Children's Hospital, Brisbane, QLD, and Townsville Hospital, Townsville, QLD. The annual paediatric census of the participating 13 EDs is approximately 500,000. The central site for the study is Starship Children's Hospital, Auckland, New Zealand.

Time frame

Three years.

Interventions

Participants will be administered 40 mg/kg IV levetiracetam infusion over 5 min (100 mg/ml levetiracetam (Keppra®, UCB Pharma), maximum 3 g, diluted 1:1 with 0.9% sodium chloride to a minimum volume of 10 ml) or 20 mg/kg IV phenytoin infusion over 20 min (50 mg/ml phenytoin (DBL™ Phenytoin, Hameln Pharmaceuticals) maximum 1 g, diluted 1:4 with 0.9% sodium chloride to a minimum volume of 20 ml). The primary outcome is assessed 5 min following the end of the study intervention infusion. However, if seizures persist the alternative medication will be administered; IV phenytoin infusion if levetiracetam given first (LP regimen), IV levetiracetam if phenytoin given first (PL regimen). See Fig. 1 for study protocol.

Allocation concealment

A computer generated randomisation code using block randomisation was created by a statistician independent

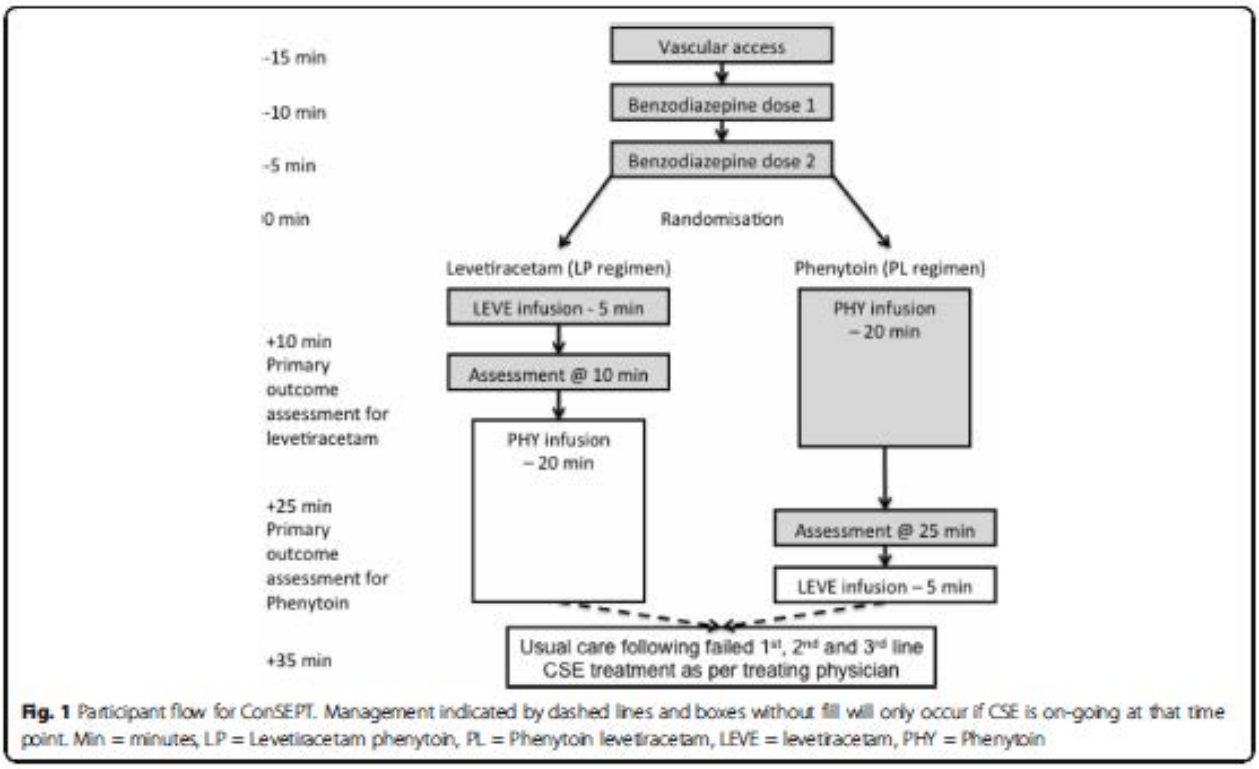

Fig. 1 Participant flow for ConSEPT. Management indicated by dashed lines and boxes without fill will only occur if CSE is on-going at that time point. Min = minutes, LP = Levetiracetam phenytoin, PL = Phenytoin levetiracetam, LEVE = levetiracetam, PHY = Phenytoin

to the study for each site and placed in sequentially numbered opaque, sealed and signed, envelopes for each site by central study pharmacists. Randomisation is stratified by site and age (≤5 years of age and >5 years of age). Stratification by age is utilised to account for the different aetiology of CSE within the paediatric age range.

Inclusion criteria

Children aged between 3 months and 16 years of age who are currently in CSE, following two doses of benzodiazepines (given by parents, paramedics, or hospital staff), who present to a study ED. CSE is defined as a child who is unresponsive with continuing abnormality of movement (increased tone or jerking) of greater than five minutes duration, or two or more recurrent convulsions without recovery of consciousness between convulsions, or three or more convulsions within the preceding hour, and currently experiencing a convulsion. This definition encompasses the International League Against Epilepsy (ILAE) seizure types of generalised tonic-clonic convulsions, secondarily generalised tonic-clonic convulsions, and complex partial status epilepticus, but not absence, myoclonic, tonic and simple partial status epilepticus.

Exclusion criteria

Exclusion criteria include previous randomisation, regular phenytoin or levetiracetam use, administration of second line anticonvulsants (phenytoin, levetiracetam, phenobarbitone or paraldehyde) in the last 24 h, a management plan stating refractory to phenytoin, known contraindication or allergy to levetiracetam or phenytoin, CSE due to an obvious major head injury or CSE due to eclampsia in late pregnancy.

Primary outcome

The primary outcome for the study is clinical cessation of seizure activity five minutes following the completion of the infusion of the study medication (primary efficacy outcome). As study medications have different optimal infusion rates this will be 10 min after starting study infusions in the case of levetiracetam and 25 min after starting study infusions in the case of phenytoin. Blinded confirmation of the primary outcome will occur with the primary outcome assessment being video recorded and assessed by a primary outcome assessment team blinded to treatment allocation.

Secondary outcomes

Secondary outcomes include: 1.Clinical cessation of seizure activity at two hours following the commencement of the study infusions without the need for further seizure management after the initial agent (levetiracetam or phenytoin); 2.Clinical cessation of seizure activity at two hours following the commencement of the study treatment regimen without the need for RSI or further

seizure management (comparison of LP versus PL regimens); 3.Time to clinical seizure cessation from commencement of study treatment regimen; 4.Need for RSI with thiopentone for on-going seizure management after administration of study treatment regimen; 5.ICU admission; 6.Serious adverse events (primary safety outcome) including death, airway complications, and cardiovascular instability (cardiac arrest, arrhythmia and hypotension requiring intervention); 7.Length of Hospital/ICU stay; 8.Health care costs (total costs associated with CSE admission); 9.Seizure status at one month post discharge, or two months post randomisation (whichever is the earliest); 10.Death at one month one post discharge, or two months post randomisation (whichever is the earliest).

Study process

At all sites patients arriving in clinically diagnosed CSE are assigned an Australasian Triage Category score of 1, as per current procedure, and are immediately taken to the resuscitation area for management. Standard seizure care is initiated in accordance with each site's clinical practice guidelines, including establishment of IV or intraosseous (IO) access. All clinical practice guidelines, Advanced Life Support Group guideline [4], and the Scottish Intercollegiate Guidelines Network guideline [5], recommend two doses of benzodiazepine prior to initiation of second line seizure medications. For the purposes of the study sites can give their usual benzodiazepine type (diazepam, lorazepam, or midazolam), route (rectal, buccal, oral, intranasal, IV, IO, or intramuscular) and dose. Doses given by parents and/or paramedic staff are regarded as an effective benzodiazepine dose for the purposes of the study. The minimum dose and route of each benzodiazepine is detailed in Table 1.

Within each study site's resuscitation area opaque study boxes for children ≤5 years of age and >5 years of age are stored. When potential patients are moved to the resuscitation areas clinical staff complete a study Clinical Research Form (CRF) addressing inclusion and exclusion criteria for the study. If all inclusion criteria, and no exclusion criteria are present, then clinical staff should open opaque study boxes. Boxes will be opened at the time the second dose of benzodiazepine is given, or on arrival if two doses have already been given, in order to allow nursing staff appropriate time to draw up the infusions of second line anticonvulsant agents. Opaque study boxes contain: An opaque, sealed and signed, envelope containing randomisation allocation and infusions instructions; A Timer; A video device and instructions; Seizure charts; Study information sheet and consent form.

According to the randomisation allocation clinical staff will draw up and administer a levetiracetam (5-min infusion) or phenytoin infusion (20-min infusion) (see Fig. 1, time 0 = start of study infusion). While the first study medication is being administered clinical staff will draw up the alternative study medication.

Five minutes following the completion of study medication infusion a formal assessment of seizure activity will be performed by the most senior treating physician. This assessment is video recorded to allow blinded confirmation of the primary outcome. The participant will be examined for the following: i)Increased tone; ii)Jerking movements (including nystagmoid jerking eye movements); iii)Level of consciousness according to the Alert, Voice, Pain, Unresponsive (AVPU) scale. Continued seizure activity is defined as presence of either increased tone or jerking movements. If seizure activity is present then the alternative study medication is to be infused (phenytoin if levetiracetam given or levetiracetam if

Table 1 Benzodiazepine dosing prior to enrolment in ConSEPT

Benzodiazepine	Route	Minimum dose prior to trial enrolment	Recommended dose*
Diazepam	IV/IO	≥0.1 mg/kg Total dose ≥5 mg	0.25 mg/kg Max 10 mg
	PR	≥0.1 mg/kg Total dose ≥5 mg	0.5 mg/kg Max 10 mg
Midazolam	IV/IO	≥0.1 mg/kg Total dose ≥2 mg	0.15 mg/kg Max 10 mg
	IM	≥0.1 mg/kg Total dose ≥2 mg	0.2 mg/kg Max 10 mg
	Buccal	≥0.1 mg/kg Total dose ≥2 mg	0.5 mg/kg Max 10 mg
	Intranasal	≥0.1 mg/kg Total dose ≥2 mg	0.5 mg/kg Max 10 mg
Lorazepam	IV/IO	≥0.05 mg/kg Total dose ≥2 mg	0.1 mg/kg Max 4 mg

*As per Advanced Paediatric Life Support guidelines (Australia/New Zealand) [4]
IV Intravenous, *IO* Intraosseous, *IM* Intramuscular, *PR* Per Rectum

phenytoin given). Five minutes following the completion of the second infusion (if required) a formal assessment of seizure activity will again be performed by the most senior treating physician.

If at any stage seizure activity has ceased (as per above definition) the time is recorded and participants will finish the infusion they are currently receiving. No further infusions will be commenced if participants remain seizure free. If seizure activity recommences and participants have only received one study infusion they can be treated with the other medication if this is felt to be appropriate by the treating team.

Clinical or research staff will collect the following data: Demographics; Date of presentation; Date and time of onset of seizure; Benzodiazepine type, dose, route and time given; Highest recorded temperature during resuscitation, at home or with ambulance service; Adverse events occurring prior to starting study medications requiring an intervention (airway repositioning, oral or nasal airway placement, application of positive pressure or ventilation with bag mask, tracheal intubation, fluid bolus, chest compressions, cardiac defibrillation); Adverse events occurring anytime in the first two hours after starting study infusions (in addition to above allergic reaction, IV/IO access tissued, extravasation of IV infusions, purple glove syndrome, any other clinical events deemed significant).

Trained research nurses will visit participants daily while they remain in-patients and contact families one month following discharge collecting the following data: Past medical history; Epilepsy/seizure history; Medication history; Background of presenting event; Family history; Length of stay in hospital/ICU; IV and nasogastric fluids use; Ventilator support; Medications; Seizures; Adverse events; Seizure classification during admission; Neurological investigations.

Blinded confirmation of primary outcome

In order to increase the robustness of the primary outcome assessment seizure continuation or cessation is video recorded and will be independently assessed by a blinded primary outcome assessment committee (comprising three study physicians, including at least one study ED physician and one study neurologist). At the time of primary outcome assessment the treating team will record the senior treating physician assessing the following: 1.Assessment of tone in lower limbs (i.e. flexion of bilateral ankles for clonus, or flexion of bilateral elbows) - approximately 10 s recording verbally confirming the presence or absence of increased tone; 2.Assessment of jerking movements by recording the hands of the patient (in cases of unilateral seizures the affected side, in cases of predominantly lower limb seizures the lower limbs) – approximately 20 s recording verbally confirming the presence or absence of jerking movements; 3.Assessment of jerking movements by recording the eyes of the patient – approximately 10 s recording verbally confirming the presence or absence of nystagmoid jerking eye movements; 4.Participant study ID.

Prior to the video's being reviewed by the blinded primary outcome assessment committee they will be reviewed by the study management team and edited so that any part of the video that confirms study medication is removed (i.e. syringe driver with study medication labelled accidentally included in video recording).

Adverse events

An independent three member Data Monitoring Committee (DMC), comprised of two clinicians each with both emergency medicine and ethics experience, and a biostatistician, has been established. The DMC will receive interim reports every 6 months of adverse events: Episodes of airway repositioning, oral or nasal airway placement, application of positive pressure or ventilation with bag mask, fluid boluses, and extravasation of IV/IO fluids in the first 2 h after starting study medication infusions; Episodes of tracheal intubation in the first 48 h; All episodes of chest compressions, cardiac defibrillation, allergic reactions, or purple glove syndrome.

The following are considered Serious Adverse Events (SAEs): Death; Serious airway complications in the first 24 h, defined as the "unexpected" use of an endotracheal tube, LMA; and cricothyrotomy. "Unexpected" is defined as the use of these interventions when it was not part of a planned RSI following failure of medical management, nor airway support required by a patient who develops a compromised airway secondary to seizure activity or first line CSE medications e.g. benzodiazepines; Cardiovascular instability (cardiac arrest or arrhythmia requiring electrical cardioversion); Any other event that is a life-threatening event. SAEs will be reported to the principal investigator within 24 h, and will be reported to the chair of the DMC within 48 h. The DMC will receive an interim analysis of trial data following the recruitment and follow-up of the first 100 participants. The study will be terminated early if: 1.The DMC, with regards to currently available evidence, following the death or cardiac arrest of a participant due to a study medication, thought that the risks for individual participants outweighed the benefits of continuing the study; 2.The independent DMC, with regards to currently available evidence, following the analysis from the first 100 participants, thought that the risks for individual participants outweighed the benefits of continuing the study.

Consent and ethical considerations

Due to the life threatening nature of CSE, and the need for urgent timely treatment, it is not possible to gain

informed consent prior to randomisation and treatment in this study. Delayed retrospective consent can be sought in New Zealand if consent prior to the intervention is impracticable and/or undesirable [29] and in Australia if prospective consent is not practicable, there is potential benefit to the patient, risk is low, the research has merit and there is no reason to suspect the parents would not give consent [30]. Ethics approval for the study and the accompanying consent process has been granted by the four ethics committees with governance for the 13 study sites. Thus written informed consent to remain in the study is sought from parents and guardians at the earliest possible time after emergency stabilisation of the CSE, i.e. after seizure cessation or seizure termination by RSI and intubation, by either trained research or clinical staff. Data for children whose parents and guardians do not wish for their child to remain in the study is destroyed, apart from demographic data, and will not be available for data analysis.

The use of videos during resuscitation has been standard of care in some of the PREDICT EDs, where they have been used for resuscitation research and found to be acceptable to families [31]. Consent to use the video recordings is a separate item on the consent form i.e. families can take part in the study but not have their child's video recordings used. If families do not consent to the video recordings these are deleted immediately at the time of consent.

Due to the study being undertaken exclusively in paediatric participants informed consent is not being sought from participants, but only from their parents and guardians.

Two members of the DMC, one in each country, are available to talk with the parent/guardian(s) on request if the parent/guardian(s) have concerns about the consent process.

Sample size, power and statistical methods

Using pilot data indicating a phenytoin seizure cessation rate of 60% [15] a total of 91 participants will be required to be randomised into each arm for the study to have at least 80% power to detect a total difference in seizure cessation rates between levetiracetam and phenytoin of 20% (alpha = 0.05). The 80% seizure cessation rate for levetiracetam that this study is powered for is at the conservative range of seizure cessation rates reported in retrospective series (75–100%) [19, 21, 22]. To allow for loss to follow-up a total of 100 participants will be randomised into each arm of the study.

Given that the five-year pilot study showed an average of eight possible participants per site per year the study will require three years to complete (8 participants × 13 sites × 3 years = 312). This allows for a third of possible participants to be lost due to exclusions, failure to enrol, or refusal of consent.

Analysis will be by intention to treat. Results from unadjusted comparisons between groups will be reported, together with analyses adjusted for possible imbalances between groups for results with appropriate data distributions. Categorical outcome variables (including the primary outcome) will be compared with chi-squared tests (unadjusted) and logistic regression (adjusted). Continuous outcome variables will be analysed using survival analysis and Cox regression. Continuous outcome variables with skewed distributions will be log-transformed. Continuous variables will be compared with unpaired *t* tests (unadjusted) and linear regression (adjusted). Continuous outcomes variables with skewed distributions after log-transformation will be compared with Mann-Whitney tests. Differences for categorical and unskewed continuous data will be reported as odds ratios (95% confidence interval (CI)) or difference between means (95% CI) respectively. Differences between log-transformed data will be reported as a ratio of geometric means (95% CI). Differences between skewed continuous data will be reported as difference between medians (95% CI). Planned subgroup analysis will be undertaken by focal or generalised onset of CSE, febrile or afebrile CSE, and type of benzodiazepine used. Sensitivity analyses will be undertaken using a modified intention-to-treat dataset (excluding those participants randomised but in whom seizure activity stopped prior to the start of the first study infusion) and a per-protocol dataset.

De-identified data will be collected by trained research nurses, managed using REDCap electronic data capture tools, including data range checks, securely hosted at The University of Auckland, Auckland, New Zealand [32], and analysed using Stata 12 (Statagroup, College Station, Texas, USA). Starship Children's Hospital, Auckland, New Zealand, is the co-ordinating centre for the study. Study sites will be audited for data collection and management by the co-ordinating centre. No independent audit of data is planned.

A per-protocol analysis of efficacy will be undertaken as a sensitivity analysis. A further sensitivity analysis will be undertaken using the blinded confirmation of the primary outcome data.

Discussion

Limitations

The primary outcome does not include electroencephalography (EEG) confirmation of seizure termination. While it is possible that a number of participants may have the "termination of seizure status" misclassified following the study infusion the primary end-point of the study is a pragmatic end-point and reflective of the real

clinical world practice and clinical decision points. EEG confirmation of seizure activity is not routinely available in any of the study sites' EDs, or indeed internationally in EDs.

In addition, the lack of EEG confirmation of seizure activity may possibly result in some pseudo seizures or seizure mimics enrolled in the study. In reality this is very unlikely and if such conditions were to be enrolled the presence of randomisation will make the effect minimal on the overall study results.

Those assessing the primary end-point are not blinded to the assigned intervention group and it is possible that this lack of blinding could introduce bias. As the two study interventions have different optimal infusion times, manufacturing presentations (vials and ampoules), and due to manufacturing technical difficulties related to phenytoin's high pH we could not instigate a blinded study. However, due to the life threatening nature of CSE it is unlikely that a physician would report that seizure activity had terminated when in fact it had not. Furthermore, the independent video confirmation of the primary outcome assessment will also reduce this possible bias.

Time line

The study commenced recruitment in March 2015, with the first patient enrolled on the 19th March 2015. Recruitment is expected to finish in 2018. This study is expected to provide robust evidence for second line management of CSE in children.

Abbreviations

CI: Confidence interval; CNS: Central nervous system; ConSEPT: Convulsive Status Epilepticus Paediatric Trial; CONSORT: Consolidated Standards of Reporting Trials; CRF: Clinical research form; CSE: Convulsive status epilepticus; DMC: Data Monitoring Committee; ED: Emergency department; EEG: Electroencephalography; ICU: Intensive Care Unit; ILAE: International League Against Epilepsy; IO: Intraosseous; IV: Intravenous; LP: Levetiracetam phenytoin; PL: Phenytoin levetiracetam; PREDICT: Paediatric Research in Emergency Departments International Collaborative; RCT: Randomised control trial; RSI: Rapid sequence induction; SAE: Serious adverse event

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Availability of data and material

Not applicable. This is a protocol manuscript, not a research findings report. All investigators will have access to the final dataset. Following the completion of the study results will be disseminated via medical conferences and publication in a peer reviewed medical journal with authorship determined according to International Committee of Medical Journal Editors (ICMJE) criteria. There are no current plans to use professional writers or to make the final participant-level dataset publically available. Participants, who wished to be informed of results, will be provided with a summary of the research findings at the time of publication.

Authors' contributions

The PREDICT network was responsible for identifying the research question. SRD designed the study. SRD, FEB, EO, MB, JN, CS, SH, SD, AD, MB refined the study design and developed the research protocol. All authors contributed to the development of the protocol, the implementation of the study at participating sites and the enrolment of patients. SRD and JF were responsible for the drafting of this paper. All authors provided comments on the drafts and have read and accepted the final version. SRD, FEB, EO, MB, JN and SD comprise the study steering committee with responsibility for all aspects of the study. SRD takes responsibility for the manuscript as a whole.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Ethical approval for this study has been obtained from the Northern B Health and Disability Ethics Committee, Auckland, New Zealand (13/NTB/83/AM01), Children's Health Services Queensland Human Research Ethics Committee (HREC), Brisbane, Queensland, Australia (HREC/13/QRCH/167), Princess Margaret Hospital for Children HREC, Perth, Western Australia, Australia (2013081EP), and Women's and Children's Hospital Network HREC, Adelaide, South Australia, Australia (HREC/13/WCHN/134), following peer review. All important protocol modifications will be reported to the four ethics committees with governance for the 13 study sites.

Publisher's Note

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References

1. Novorol CL, Chin RFM, Scott RC. Outcome of convulsive status epilepticus: a review. Arch Dis Child. 2007;92:948–51.
2. Chin RF, Neville BG, Peckham C, Bedford H, Wade A, Scott RC. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet. 2006;368(9531):222–9.
3. Raspall-Chaure M, Chin RFM, Neville BG, Scott RC. Outcome of paediatric convulsive status epilepticus: a systematic review. Lancet Neurol. 2006;5:769–79.
4. Advanced Life Support Group. Advanced Paediatric Life Support: The Practical Approach. 4th ed. London: BMJ Publishing Group; 2005.
5. Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsies in children and young people: a national guideline. 2005.
6. Appleton R, Choonara I, Martland T, Phillips B, Scott R, Whitehouse W. The treatment of convulsive status epilepticus in children. The status Epilepticus Working Party, members of the status Epilepticus Working Party. Arch Dis Child. 2000;83(5):415–9.
7. Cameron P, Jelinek G, Everitt I, Browne G, Raftos J. Textbook of paediatric emergency medicine. 1st ed. Philadelphia: Churchill Livingstone; 2006.
8. Kliegman RM, Behrman RE, Jenson HB, Stanton BF. Nelson textbook of pediatrics. 18th ed. Philadelphia: Saunders; 2007.
9. Appleton R, Macleod S, Martland T. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database Syst Rev. 2008;(3):CD001905. doi:10.1002/14651858.CD001905.pub2.
10. Epilepsy Foundation of America's Working Group on Status Epilepticus. Recommendations of the Epilepsy Foundation of America's Working group on status Epilepticus. JAMA. 1993;270:854–9.
11. Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia. 1999;40(1):120–2.
12. Lowenstein DH, Cloyd J. Out-of-hospital treatment of status epilepticus and prolonged seizures. Epilepsia. 2007;48(Suppl 8):96–8.
13. Chamberlain JM, Okada P, Holsti M, Mahajan P, Brown KM, Vance C, et al. PECARN. Lorazepam vs diazepam for pediatric status epilepticus: a randomized controlled trial. JAMA. 2014;311(16):1652–60.
14. Babl F, Sheriff N, Borland M, Acworth J, Neutze J, Krieser D, et al. Emergency management of paediatric status epilepticus in Australia and New Zealand: practice patterns in the context of clinical practice guidelines. J Paediatr Child Health. 2009;45(9):541–6.
15. Lewena S, Pennington V, Acworth J, Thornton S, Ngo P, McIntyre S, et al. Emergency management of pediatric convulsive status epilepticus. Pediatr Emerg Care. 2009;25(2):83–7.
16. Abend NS, Huh JW, Helfaer MA, Dlugos DJ. Anticonvulsant medications in the pediatric emergency room and intensive care unit. Pediatr Emerg Care. 2008;24(10):705–18.
17. Wheless JW, Treiman DM. The role of the newer antiepileptic drugs in the treatment of generalized convulsive status epilepticus. Epilepsia. 2008;49(s9):74–8.
18. National Patient Safety Agency. Rapid response report NPSA/2010/RRR018 Preventing fatalities from medication loading doses. London: National Patient Safety Agency; 2010.
19. Knake S, Gruener J, Hattemer K, Klein KM, Bauer S, Oertel WH, et al. Intravenous levetiracetam in the treatment of benzodiazepine refractory status epilepticus. J Neurol Neurosurg Psychiatry. 2008;79:588–9.
20. Michaelides C, Thibert RL, Shapiro MJ, Kinirons P, John T, Manchharam D, et al. Tolerability and dosing experience of intravenous levetiracetam in children and infants. Epilepsy Res. 2008;81:143–7.
21. Goraya JS, Khurana DS, Valencia I, Melvin JJ, Cruz M, Legido A, et al. Intravenous Levetiracetam in children with epilepsy. Pediatr Neurol. 2008;38:177–80.
22. Kirmani BF, Crisp ED, Kayani S, Rajab H. Role of intravenous levetiracetam in acute seizure management of children. Pediatr Neurol. 2009;41(1):37–9.
23. Wheless JW. Levetiracetam in the treatment of childhood epilepsy. Neuropsychiatr Dis Treat. 2007;3(4):409–21.
24. Gustafson M, Ritter FJ, Frost MD, Doescher J. Review of over 400 intravenous levetiracetam administrations in pediatric patients ages newborn through 11 years of age. Epilepsia. 2007;48(s6):248–380.
25. Grosso S, Cordelli DM, Franzoni E, Coppola G, Capovilla G, Zamponi N, et al. Efficacy and safety of levetiracetam in infants and young children with refractory epilepsy. Seizure. 2007;16:345–50.
26. Wheless JW, Clarke D, Hovinga CA, Ellis M, Durmeier M, McGregor A, et al. Rapid infusion of a loading dose of intravenous Levetiracetam with minimal dilution: a safety study. J Child Neurol. 2009;24(8):946–51.
27. Baulac M, Brodie MJ, Elger CE, Krakow K, Stockis A, Meyvisch P, et al. Levetiracetam intravenous infusion as an alternative to oral dosing in patients with partial-onset seizures. Epilepsia. 2007;48(3):589–92.
28. Ramael S, Daoust A, Otoul C, Toublanc N, Troenaru M, Lu Z, et al. Levetiracetam intravenous infusion: a randomized, placebo-controlled safety and pharmacokinetic study. Epilepsia. 2006;47(7):1128–35.
29. National Ethics Advisory Committee. Ethical guidelines for intervention studies. Wellington: Ministry of Health; 2009.
30. National Health and Medical Research Council, Australian Research Council, Australian vice-chancellors' committee. National Statement on ethical conduct in human research: National Health and Medical Research Council, 2007.
31. Oakley E, Stocker S, Staubli G, Young S. Using video recording to identify management errors in pediatric trauma resuscitation. Pediatrics. 2006;117(3):658–64.
32. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81.

5.3 Summary

Chapter 5 describes the protocol for a randomized controlled trial of second line management of paediatric SE, addressing a priority identified by the Delphi study, and utilizing a deferred consent process. The study aims to determine whether levetiracetam is a better second line agent than the current standard practice of phenytoin.

- 200 Children from three months to 16 years will be recruited in participating sites.
- The primary outcome will be cessation of seizure activity at five minutes following completion of infusion.
- As valid informed consent would be impossible to obtain in these circumstances the study uses a deferred consent process.

The results of this study will provide the first high quality evidence of second line management of paediatric SE. The results of this landmark study are likely to generate significant interest internationally and influence treatment guidelines globally. A controversial aspect of the trial design is the enrolment of participants without prior informed consent from parents. The trial protocol states that investigators will seek delayed retrospective consent for participation, with written informed consent to remain in the study sought as soon as possible after stabilization of the child. Four ethics committees in this multicenter trial approved this process, which has not been utilized in large multicenter paediatric trials in Australia or New Zealand previously. Recruitment prior to prospective informed consent was considered an important aspect of the study design, and integral to the validity of results and the success of the trial. While enrolment prior to informed consent is addressed in various ethical guidance documents, the unfamiliarity with the process provoked debate regarding the ethical acceptability of the trial by certain groups including clinicians, ethics committees and policy makers. In Australia, the NHMRC are currently reviewing their national statement guidance documents addressing precisely this issue and calling for input from stakeholders. In Chapter 6, issues regarding the conduct of emergency medicine research without prospective informed consent from a historical and international perspective are discussed, with a particular focus on those relevant to our local setting. How informed consent in time-critical research is addressed in future ethical guidance documents will have a profound influence on emergency medicine research in this country. This will in turn impact upon the quality of care in emergency departments in general and the availability of evidence-based therapies for the most vulnerable patients in particular.

Chapter 6. Informed Consent in Emergency Care Research

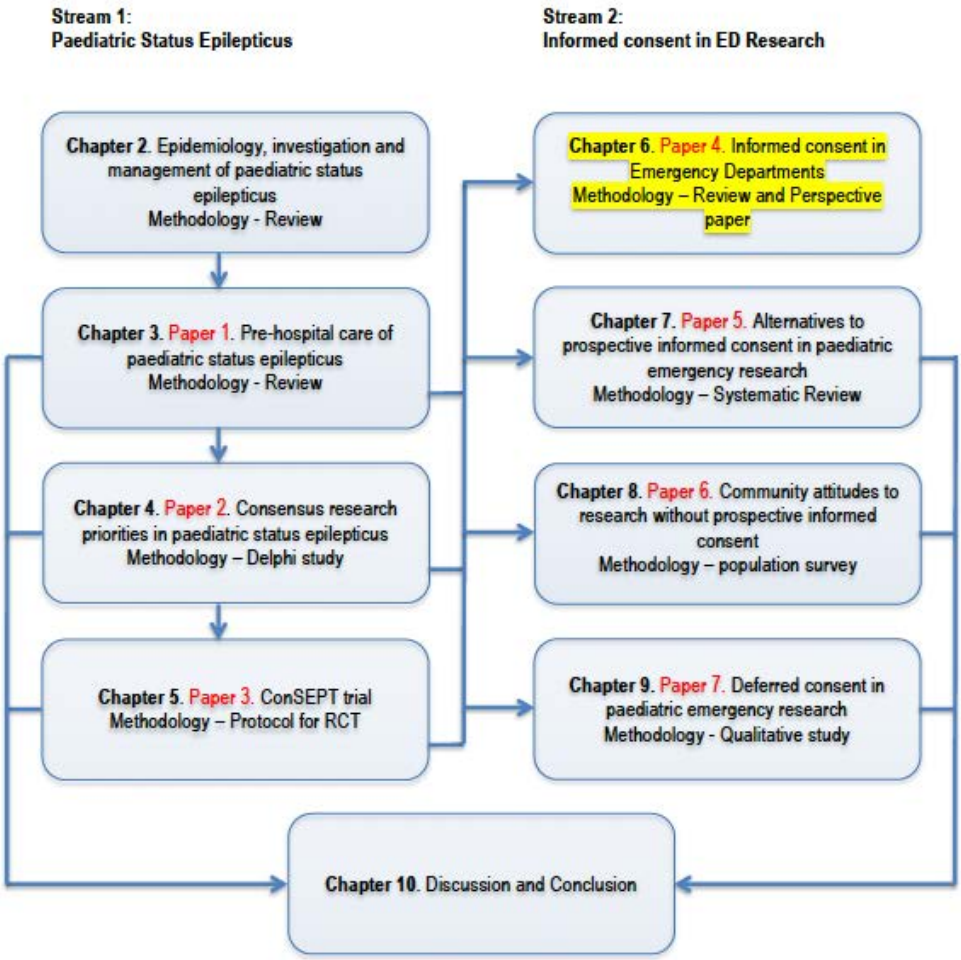
"The physician who is convinced a certain treatment works will almost never find an ethicist in his path whereas his colleague who wonders and doubts and wants to learn will stumble over piles of them"

Attributed to T.C. Chalmers (1917-1996, Physician, EBM pioneer, Harvard)

6.1 Overview

As previously stated much of the practice of emergency medicine, including paediatric SE is not based on high-level evidence. Performing randomised trials in paediatric SE such as the ConSEPT trial outlined in Chapter 6, and other types of research in the ED setting presents difficulties when prospective informed consent is not possible. This chapter provides a perspective on informed consent in emergency care research. Figure 6.1 places the chapter in the context of the broader thesis.

Figure 6. 1 Conceptual model of thesis



6.2 Introduction

Every day thousands of patients in Australia and New Zealand present to ED for emergent and critical care. Emergency physicians have an obligation to ensure their practice is underpinned by the highest quality evidence available, yet interventions that are utilized every day are often are not evidence based, remain controversial and are potentially harmful.[151] The role of adrenaline in out-of-hospital cardiac arrest is a prime example. Administration of adrenaline to patients in cardiac arrest is included in all international cardiac arrest algorithms and is frequently depicted as lifesaving in television and movies. However, this belies the reality that the utility of the adrenaline has been debated for decades, with no evidence of benefit, and some suggestion of harm.[152] Difficulties in conducting the necessary conclusive clinical trial means that adrenaline remains in management algorithms based on expert opinion and tradition, the lowest levels of medical evidence to inform practice.[153,154] The use of oxygen for patients suffering myocardial infarction is another example, which was routine for many years before researchers recently questioned the practice, with limited evidence suggesting potential harm.[155] Subsequently in a large RCT of over 6,000 patients the practice was not found to be beneficial.[156] In paediatric emergency medicine, the management of SE is another example, where practice beyond first line care is based solely on expert opinion and tradition.[9] Clinical trials are urgently needed in many areas of emergency medicine to clarify important clinical questions. Historically, many well-intentioned medical therapies, whose use was recommended based on expert opinion or tradition, have been found to be harmful after proper scientific study and subsequently discontinued, a phenomenon termed medical reversal.[151,157]

The requirement to obtain informed consent in emergency and critical care research has commonly been cited as a barrier to ED research.[32,158-161] While the role of informed consent is well established in conventional medical research and clearly delineated in the NHMRC guidelines,[33] aspects of the informed consent process in clinical research in the emergency setting deserve additional consideration. There are complex ethical, logistical and regulatory issues centred on informed consent that need careful deliberation in the unique context of research in critically ill patients. These issues are perhaps more problematic in paediatric emergency research as children are considered a vulnerable group, and generally do not consent to research themselves, with proxy consent from guardians usually sought.

A paradox exists where emergency medicine providers readily prescribe medications for clinical care that have not been rigorously evaluated, often without the explicit consent of the patient or ethical approval, yet barriers around issues of informed consent for research make evaluating such therapies problematic, even if they are in common use. Consequently,

many therapies in routine use remain unproven. This contravenes community expectations that the care patients receive from their treating clinician is evidence-based.

Confusion around the requirement for informed consent and the ethical and legal implications of research where informed consent is not possible are critical factors limiting research in emergent and life-threatening conditions.[158,160,162] Strategies to optimize the ethical and governance review process and ensure emergency research aligns with community expectations are necessary to ensure emergency interventions can be thoroughly evaluated.

6.2.1 Ethical conduct and ethical principles

Conducting research on humans is guided by the principles and values of respect for human beings, research merit, integrity, justice, and beneficence.[33] Respect for human beings includes acknowledging the importance of autonomy, and the importance of determining one's own life and making one's own decisions, and also providing protection for people with reduced autonomy. Research merit and integrity necessitates that the proposed research is appropriately designed to achieve its aims, based on rigorous science, and the researchers are capable of conducting such research, otherwise human participation cannot be ethically justified. Justice in the research context refers to the equitable distribution of the benefits and burdens of research. Finally, beneficence takes into account the relative risks, harms, and potential benefits of the research to participants and to the broader community. Ethics committees are given the responsibility of making judgments about research considering these elements and balancing the potential benefits and risks to the participant, and the requirement for informed consent from participants.[33]

6.3 Historical Perspective

6.3.1 Nuremberg Code

The public's trust in the credibility of medical research has had several setbacks during the evolution to what we now term as the era of evidence-based medicine. In the first half of the 20th century, in the name of "medical research", doctors in Nazi Germany performed heinous crimes on vulnerable populations including psychiatric patients, inmates of concentration camps, children with disabilities and others. Twenty-three individuals were subsequently tried for war crimes and crimes against humanity in Nuremberg in 1947; many received convictions and seven received the death penalty.[163] At the conclusion of the trials, the judges produced the "Nuremberg Code", a human rights document outlining the procedures necessary for acceptable medical research. The code included 10 points to protect the rights and welfare of research subjects. The code strongly emphasised informed consent,

starting with the statement *"the voluntary consent of the human subject is absolutely essential"*.[163] Critics considered this overly simplistic for clinician researchers, and questioned the relevance of consent to the atrocities committed in the name of research, which were experiments with little scientific merit, questionable importance or simply torture and mass murder.[163]

Although the Nuremberg code was a significant advance, it was not widely adopted. The emphasis on informed consent did not appear to recognise that situations may exist where informed consent may not be feasible, or indeed that the time taken to obtain informed consent may be detrimental. The document was written by lawyers and consequently criticized as "overly legal" and described by some as a "code for barbarians" and not required for civilised clinicians.[163] What cannot be disputed though was that the credibility of the medical research community was significantly shaken by revelations of the extent of atrocities committed.

6.3.2 Declaration of Helsinki

In 1964 the World Medical Association published a policy for research ethics referred to as the Declaration of Helsinki. A key element of the document was the clear distinction between therapeutic and non-therapeutic research, the former requiring consent *"if at all possible".*[34] The declaration was updated and expanded in 1975, again with some latitude for clinician researchers to consider the feasibility of consent in all circumstances. This was further refined in 1983 and 1996, with specific reference to minors included for the first time. The Declaration of Helsinki remains the ethical framework to guide investigators in clinical medical research.

The current version of the Declaration of Helsinki acknowledges that circumstances exist when prospective informed consent is not possible, proposing alternative strategies by stating;

> *"If the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative"* [34]

6.3.3 The Tuskegee syphilis experiment

Another episode that had a profound and possibly ongoing effect on the public's perception of medical research, particularly research involving minorities and other vulnerable groups, was the Tuskegee syphilis experiment in the US. Again, the actions of those involved are difficult to fathom, and the episode has been described as a "national tragedy".[163] From 1932 to as recently as 1972 the US Public Health Service conducted a "natural experiment" or non-therapeutic study of the effects of untreated advanced, tertiary syphilis in more than 400 mostly poorly educated and illiterate black males in Alabama. The study observed the clinical effects, and participants were actively denied treatment, despite penicillin becoming available in the 1940s as a known treatment for the condition. Consent was not obtained, and participants were deceived about the purpose of the study, with information withheld about their diagnosis. Many may have believed that they were receiving treatment.[164] The study was finally exposed in 1972 when a past employee of the Public Health Service provided information to the press about the experiment. The story generated widespread public outrage, leaving a legacy of resentment of government agencies, particularly in black American communities. The experiment has been described as *"a symbol of research malfeasance in which virtually every principle underlying the ethical treatment of human subjects of research was violated".*[163]

6.3.4 Belmont report

Prompted by the public outrage in the aftermath of the Tuskegee syphilis experiment the US government commissioned the Belmont report in 1978. The report offers a framework for analysing the ethical issues that arise from medical research, with the objective of improving research oversight systems to provide greater protection for research participants. The report outlined the three basic moral principles underlying the conduct of research as: respect for persons (informed consent), beneficence (risk versus benefit assessment), and justice (selection of research participants). Although not without critics, it has had a profound influence on medical ethics and government policy and even the practice of clinical medicine.[163]

6.4 What is informed consent?

6.4.1 Definitions

Informed consent for general medical care has not been a central tenant of the profession for as long as one might expect, with the term "informed consent" thought to have only first been used in a court ruling in the UK in 1981.[165] Prior generations of clinicians routinely sheltered patients from information that they considered might be harmful. Such paternalism is now generally discouraged, and informed consent for medical interventions is now

ethically and legally required, with the level of detail expected commensurate with level of risk. That is, the higher the risk, the more detailed explanation required. Key elements of informed consent include disclosure, comprehension, voluntariness, competence and consent.[166] In emergency situations doctors regularly provide clinical care without obtaining informed consent. The community has trust in the medical profession and individual doctors to behave in a responsible way, and provide care that is in the patient's best interests.[165]

Research standards for the Australian context are published by the NHMRC.[33] These standards specify that informed consent is an important component of conducting ethical research, and patients should be adequately apprised of the risks and benefits of participation.[33,167] Informed consent for research is an exercise of a voluntary choice to participate in research, based on the provision and subsequent comprehension of information about the purpose, methods, demands, risks, inconveniences, discomforts and possible outcomes of research.[33] However, a signature on a consent form does not equate with informed consent, and obtaining informed consent does not necessarily equate with ethical research.[168,169] Commonly accepted guiding principles are that a person's decision to participate in research needs to be voluntary. This includes having adequate time to consider the details of the research being proposed and the opportunity to ask questions about the requirements and risks of participation in the research.[33,167] In Australia valid consent requires three elements to be present: the capacity to make voluntary decisions; that the consent is free and voluntary; and that the consent covers the act performed. As noted by White et al, if any one of these elements is absent, consent is undermined and can "transform the treatment into a potential assault".[170] In the conventional model of medical research, often involving repeated visits to a clinician and an extended period of both consideration and prospective study, these requirements can be easily satisfied. Similarly, there are obviously situations where it is possible to obtain informed consent prior to enrolment in emergency medical research. In these circumstances, there is a requirement that ED staff are trained in the principles of Good Clinical Practice, provide comprehensive information, and allow sufficient time to consider participation without coercion.[33] Refusal should not prejudice clinical care.

6.4.2 Clinical care versus research

Consent for emergent clinical care is often not sought in life-threatening situations. The community generally accepts that medical staff in these circumstances are acting in patients' best interests. It remains controversial if such an approach is acceptable in research. In comparative effectiveness trials, where true equipoise exists between clinicians and allocation to treatment is determined by the trial process, it can be argued that from a

patient's perspective there is negligible additional risk in not seeking consent for participation in a trial in a life-threatening situation compared to treatment outside of a trial protocol in a similar situation.[171-173] However, there is insufficient data on what is acceptable to the community or general public in these situations. Further, some evidence from other research settings suggests that patients' understanding of research may be suboptimal, with concepts of clinical care and research often confused, while participation in research is often linked to personal gain for the participant.

6.4.3 Is informed consent possible in time-critical research?

For many important clinical questions in emergency medicine research, obtaining informed consent using the ideal or optimal principles described may not be feasible. The paradigm of informed consent is underpinned by the patient's competence. Unfortunately, in the context of emergency research, critically ill or injured patients will often lack capacity because of the illness or injury itself; patients with severe head injuries or unconscious cardiac arrest patients are obvious examples. Difficulty arises in other acute situations where patients may be alert or their proxies may be available, but it is unlikely they maintain sufficient decision-making capacity to consent to research. Examples include patients having an acute myocardial infarction (AMI) being approached for enrolment in an interventional trial, or parents of a child in SE being approached for consent in a clinical trial. The phrase *"situational incapacity"* has been used to described circumstances where decision-making abilities seem to be compromised because of highly emotional or stressful circumstances.[174,175] The possibility of coercion is also a factor even when patients are thought to retain capacity. All ED patients could be described as potentially vulnerable as they present at a time of crisis and may be anxious, sick, in pain, and/or disoriented as well as highly dependent on the acute care they are receiving.[174] Care must be taken to ensure that any consent process does not equate to exploitation.

Insufficient time is also a critical factor. If the participant retains capacity, there is often insufficient time available to adequately consider the pros and cons of participation. If the participant lacks capacity, there may be difficulties associated with locating an appropriate substitute or surrogate decision maker (SDM). Many interventions are time-critical and have a short therapeutic window. Contacting a SDM to consent for a cardiac arrest trial is logistically impossible. It has been postulated that delays involved in seeking consent in certain circumstances where the therapeutic window is short, may result in worse outcomes for patients, be less likely to show benefit in trials, and hence be unethical.[176,177] For example it has been estimated that in the second international study of infarct survival (ISIS-2) trial, a study of streptokinase and aspirin in over 17,000 adults with AMI, that a delay of 20 minutes

for consent procedures would have been associated with 10 more deaths in the active treatment arm.[178]

Other logistic issues also make the process of informed consent difficult in the emergency setting. Potential participants may present sporadically or after hours, and to achieve meaningful results enrolment may involve clinical staff rather than study investigators to screen, identify and consent eligible patients in busy environments. This delegates the duty of consent to non-investigator staff, with possible implications over the adequacy of the process and a conflict of responsibilities. In critical situations a recruiting clinician may feel that fully informed consent procedures interfere with adequate management of the patient and impede the ability to treat a patient expeditiously thus risking delays to lifesaving care. In multisite research, it is common for the same trial to be subject to differing consent requirements in different jurisdictions according to the requirements of local human research ethics committees (HREC).[179]

6.4.4 The Cardiac trials

An area of emergency medicine that has perhaps been the subject of more rigorous research than any other is the management of AMI. This is despite the significant ethical issues involved in conducting research in patients with AMI. Adequate informed consent is dubious given the extreme stress and anxiety of the situation and the potential effects of medications on cognition. Interventions for AMI are known to be time-critical, and obtaining informed consent, intended to protect participants from harm, conversely may cause harm if delays to treatment result. In clinical circumstances obtaining informed consent has been described as “uninformed trust” with patients often preferring to leave treatment decisions to the physician.[180] Various large cardiac trials have approached this issue from different perspectives.

The majority of trials have used a conventional approach to informed consent; the provision of oral and written information, followed by signing a consent form and allocation to a treatment arm.[178] Published reports of the trials provide very little information of how consent was approached, and little acknowledgement of the limitations of the procedure.[178,181] The first Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial in 1993, a study of thrombolytic agents in over 40,000 patients, from 1,000 hospitals in multiple countries including the US, Europe and Australia, reported only that “patients gave consent for participation”.[182] In contrast, the “Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico” (GISSI) thrombolytic trials between 1986 and 1994 enrolled patients without consent, but subsequently informed the

patients about participation.[178,181] This approach was apparently to *"protect the right of the patient not to be exposed to an emotionally burdensome request for informed consent",* and that ethics committees associated with the trials did not believe meaningful consent would be possible under the circumstances.[183] Contemporaneously, in the ISIS-2 trial in 16 countries, at 417 hospitals, informed consent requirements varied between sites from not being required to requiring formal prospective written consent.[184] US sites in ISIS-2 required a 4-page consent form, which was associated with lower recruitment rate than in other countries, and criticised as designed to protect physicians from litigation rather than be in the interests of participants.[178]

Research into the consent processes of these trials suggests that many participants considered themselves not to be competent at the time of consent. Many (11-43%) had no or almost no recollection of the consent process, and in one study almost a quarter were not aware that they had participated in a study.[178,185,186] Oral information was recalled better than written information.[178,185,186]

6.4.5 Issues specific to paediatrics

Historically children have been subject to exploitation by medical researchers, and as such are considered a potentially vulnerable group.[163] Clinical research in paediatric emergencies is necessary to ensure management of children is evidence-based and effective. The concept that participation in medical research involves accepting a certain level of personal risk for societal benefit may be too complex for children to grasp.[163]

The ability of children under the age of 16 to consent for medical treatment is often described in terms of "Gillick competence". This is based on a ruling in the UK House of Lords in 1985 and acknowledged under Australian law.[187] It is usually based on the individual doctor's assessment to determine if the minor in question can fully understand the treatment proposed.[187] The application of Gillick competence to medical research is controversial, as it has been argued that often the assessor stands to gain personally from the involvement in research, therefore similar standards are not appropriate.[187] Almost invariably, consent for participation in research is sought from parents. As children develop and mature, they can be more involved in discussions regarding participation in medical research, and many jurisdictions have a requirement for assent, which is said to be possible from as early as seven years of age.[188]

There are a number of limitations to seeking consent from parents in emergency situations, similar to seeking consent from other SDM of incapacitated adults. Briefly, these include that

parents may not be immediately available, which could be critical in interventions with a short therapeutic window. Parents are also affected by situational incapacity at a vulnerable moment, in a highly stressful setting and upsetting circumstances such as a sick child. Furthermore, there is evidence that decisions by proxies may not reflect those of the participants.[32] These issues are expanded on in the following sections.

Given that the child themselves usually does not get the opportunity to consent to or decline participation, the responsibility for protecting the participant, and the potentially complex risk benefit assessment lies with ethics committees, and generally requires the possibility of direct benefit to participants, and that the research is low risk.

6.4.6 What is informed consent in Australia

The principles of informed consent for research in Australia are outlined in the NHMRC National Statement on Ethical Conduct in Human Research.[33] The document outlines that consent needs to be a voluntary choice and based on sufficient information and adequate understanding of the research and the implications of participation. The document also outlines conditions under which the requirement can be qualified or waived. Importantly participants or proxies should not be subjected to any coercion and any inducements are ethically unacceptable. Involvement of children and young people in decisions should increase as maturity and capacity increases.[33]

6.5 Alternatives to informed consent

In Australia, over the last decade or so, administrative, ethical and legislative changes have had a significant impact on the implementation and conduct of emergency and critical care research. This is because the mechanisms of decision-making about persons who lack the capacity to make decisions for themselves, either temporarily or permanently, is facilitated by state and territory jurisdictional legislation about guardianship.[170] Each jurisdiction has enacted its own legislation with common law playing only a limited role.[170] Confusion among emergency physicians, ethicists, legal advisors and HRECs around differences between the guardianship requirements of each jurisdiction and terminology in documents suggests that the special circumstance of emergency, pre-hospital and critical care research was not adequately considered when legislation and other relevant documents were drafted. In Australia alternatives to prospective informed consent include proxy consent, a waiver from individual participant consent, and retrospective or deferred consent, although the implementation has been variably interpreted with repercussions for the research being conducted. Although the NHRMC specifies conditions for patients who cannot consent for themselves (table 6.1), these stipulations are subject to higher regulatory authority in all

jurisdictions of Australia.[33,179] Accordingly large multi-national clinical trials have frequently been conducted with varying consent procedures employed in differing jurisdictions. This may itself be unethical and has the potential to lead to bias.

6.5.1 Proxy consent

Seeking a surrogate decision maker, or proxy consent, is most commonly utilised when the individual participant is incapable of providing informed consent due to the effects of the medical condition of interest. This is the usual practice for invasive medical therapy or procedures when a patient otherwise lacks capacity. However evidence exists that relatives and friends often demonstrate poor agreement with the wishes of the participant.[32] Proxy consent also may not be available in an appropriate timely manner necessary for some interventions with a narrow therapeutic window, as is the case for many emergency conditions and treatments. In the Corticosteroid Randomisation After Significant Head Injury (CRASH) trial, seeking proxy consent was associated with a delay to treatment of 1.2 hours compared to when requirement for consent was waived.[177] Time spent seeking such consent may distract staff from appropriate clinical care in these circumstances, and treatment delays may harm patients. Even if available in a timely manner, close friends and relatives may also be too distressed to adequately comprehend information being provided to them to enable for them to provide truly informed consent.

6.5.2 Waiver of informed consent

A waiver of informed consent is allowable in Australia in certain circumstances unless prohibited by law (see Table 6.1).[33] While conducting research on individuals raises concerns about unethical practice and contravenes individual autonomy, conversely denying patients the opportunity of participating in such research, with associated potential benefit, contravenes the ethical principle of justice.[169] When emergency medicine research requires a waiver of informed consent, the responsibility to protect participants rests with a rigorous HREC approval process. The requirements that need to be satisfied to qualify for waived consent are open to interpretation by HRECs. Ethics committees are charged with weighing the balance of potentially waiving a patient's right to consent, the societal benefit and importance of undertaking the research, and the potential lost opportunity for the patient to participate in a study. For ethics committees used to considering the conventional model of medical research consent, the specific issues and needs of emergency researchers may not be apparent. Not infrequently, the same trial is conducted with differing consent requirements among study sites, even if operating under the same ethical guiding principles and legal framework in the same country.[189] This can affect patient recruitment, and potentially result in selection bias.

Table 6. 1 Requirements to qualify to waive consent

National Health and Medical Research Council – National Statement (section 2.3.6)
a) *involvement in the research carries no more than low risk to participants.* b) *the benefits from the research justify any risks of harm associated with not seeking consent.* *c) it is impracticable to obtain consent.* *d) there is no known or likely reason for thinking that participants would not have consented if they had been asked.* *e) there is sufficient protection of their privacy.* *f) there is an adequate plan to protect the confidentiality of data.* *g) in case the results have significance for the participants' welfare there is, where practicable, a plan for making information arising from the research available to them.* *h) the possibility of commercial exploitation of derivatives of the data or tissue will not deprive the participants of any financial benefits to which they would be entitled.* *i) the waiver is not prohibited by State, federal, or international law.*

To qualify to waive consent the NHMRC national statement in section 2.3.6 a, has a requirement that the research "carries no more than low risk" (See Table 6.1) which it goes on to define as where the "only foreseeable risk is one of discomfort".[33] The relevance to patients who are critically unwell is unclear. Such a statement is clearly unsuited to the unique nature of emergency research, which often by its nature is high risk. This terminology is confusing for researchers and is variably interpreted by committees. A related concept of "incremental risk" has been advocated by some authors.[31,190]

In the US the ability of the ethics committee to waive consent is supplemented by the requirement for consultation with community representatives and advocates. Experience from large international multicentre emergency trials suggests that conditions in Australia are more stringent and prohibitive than in other countries such as the UK and US,[191] which may have a negative impact on the attractiveness of Australia as a research destination, limiting opportunities to participate in large multicentre studies and stifling the development of research infrastructure in Australia.

6.5.3 Deferred consent

A further option is that of deferred, delayed or retrospective consent. Similar to a waiver of informed consent, deferred consent is used when it is not possible to obtain prospective informed consent from the participant before randomisation. Consent is obtained from participants (or proxy) as soon as practical, after the intervention has been given. Consent is obtained to remain in the trial, to use data and to allow follow up.[192-195] Critics argue that use of the term consent is a misnomer, as the intervention has already been given, and consent is being sought to continue in the trial and for the inclusion of data already collected.[196]

Waivers and deferred consent aim to avoid selection bias and maximise recruitment by including sicker patients who would otherwise not be offered the opportunity to take part in a trial. It allows study treatment to be delivered rapidly in an emergency, with potential benefits for the individual patient. Deferred consent reduces staff anxiety with regard to implementing a trial protocol and requires less deviation from routine clinical care.[197]

Barren et al suggest the informed consent process needs to be adapted to the emergency setting by *"eliminating some of the less essential elements"* where time pressures and certain amount of vulnerability existed but patients still may have capacity to consent and refuse.[174] Whether this is acceptable, and which elements can be excluded requires further research.

6.5.4 Alternative trial designs

The controversial Zelen trial design is another technique that has been suggested to overcome difficulties in obtaining informed consent for ED research.[198] Zelen originally described a design where randomisation occurs before consent is obtained, and consent is only sought in the intervention arm. The approach aims to reduce unnecessary anxiety and distress of those allocated to standard treatments, and Zelen argued that it may improve recruitment rates. However, ethical concerns that the design contravenes individual autonomy means that the approach has seldom been used, and it is not generally accepted in medical research culture.[199-201]

6.5.5 Clinical care versus research

The ease and acceptability of clinicians using unproven therapies clinically without the ethical and legislative obstacles involved in collecting data in the same patients remains a frustrating paradox to researchers. It is interesting to consider the patient's perspective in cases where there is no clear standard of care derived from evidence. In such cases the

person attending ED may or may not receive certain treatments depending on factors such as which clinician happens to be scheduled at work, individual clinician whims, experience or opinion, or local institutional protocol. Thus, for the patient with the condition under consideration, the treatment they receive is effectively "random". Therefore, from the patient's perspective, the distinction between therapy and research is somewhat artificial. Legislation designed to protect participants may be inadvertently leading to harm, by obstructing research efforts to identify which treatments are effective. A perplexing situation exists where patients often report a willingness to accept an unproven intervention, on the recommendation of their doctor for clinical care, but are more wary if told data will be collected as part of a study, and more concerned if they are to be randomised.[190,202] This does not seem to be related to trust, but it is difficult for medical researchers to understand given the rigorous protections in place as part of a clinical trial. This may be related to a poor understanding of the importance of rigorous scientific methods by patients. Participants' perceptions about the process of randomisation is a common theme of concern, with perhaps little understanding of the scientific importance of randomisation and perceptions of being a "guinea pig".[203] Regardless, the majority of patients are generally still willing to participate in an RCT.[202]

6.6 Publication in Emergency Medicine Australasia

A synopsis of this chapter was published in Emergency Medicine Australasia as a perspective piece, on behalf of the Australasian College of Emergency Medicine, Clinical Trials Group (ACEM-CTG). It is inserted as published.

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PERSPECTIVE

Informed consent in emergency care research: An oxymoron?

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Abstract

Emergency care needs to be underpinned by the highest quality evidence. However, research involving critically ill patients in the emergency setting has unique ethical, logistical and regulatory issues. Informed consent is a well-established principle in conventional research. In this article, we discuss informed consent as it pertains to the difficulties of research in the emergency setting. Alternatives to informed consent are discussed. Human research ethics committees require a greater understanding of consent issues in emergency care research for Australia to remain competitive internationally.

Key words: *emergency medicine, ethics, informed consent, research.*

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6.7 Summary

Chapter 6 outlines the historical background and current issues regarding informed consent in paediatric emergency medicine research, and emergency research in general. The paradox of using unproven treatments for clinical care, and obstacles involved in researching potentially lifesaving interventions were explored. The main findings of the chapter are:

- Many treatments commonly used in emergency medicine are not based on high quality evidence.
- In paediatric SE, and many other areas of emergency medicine, clinical questions remain unanswered because the research involves situations where informed consent would be problematic or impossible.
- Research studies and clinical trials are urgently needed in paediatric SE and other areas of emergency medicine to ensure that treatments being used are effective.
- International research ethical statements consider the requirement for research without informed consent, but Australian guidelines lack clarity, significant confusion exists and implementation is variable.
- Research about consent issues in emergency settings is inadequate; this is particularly true for children, rightly regarded as a particularly vulnerable group.

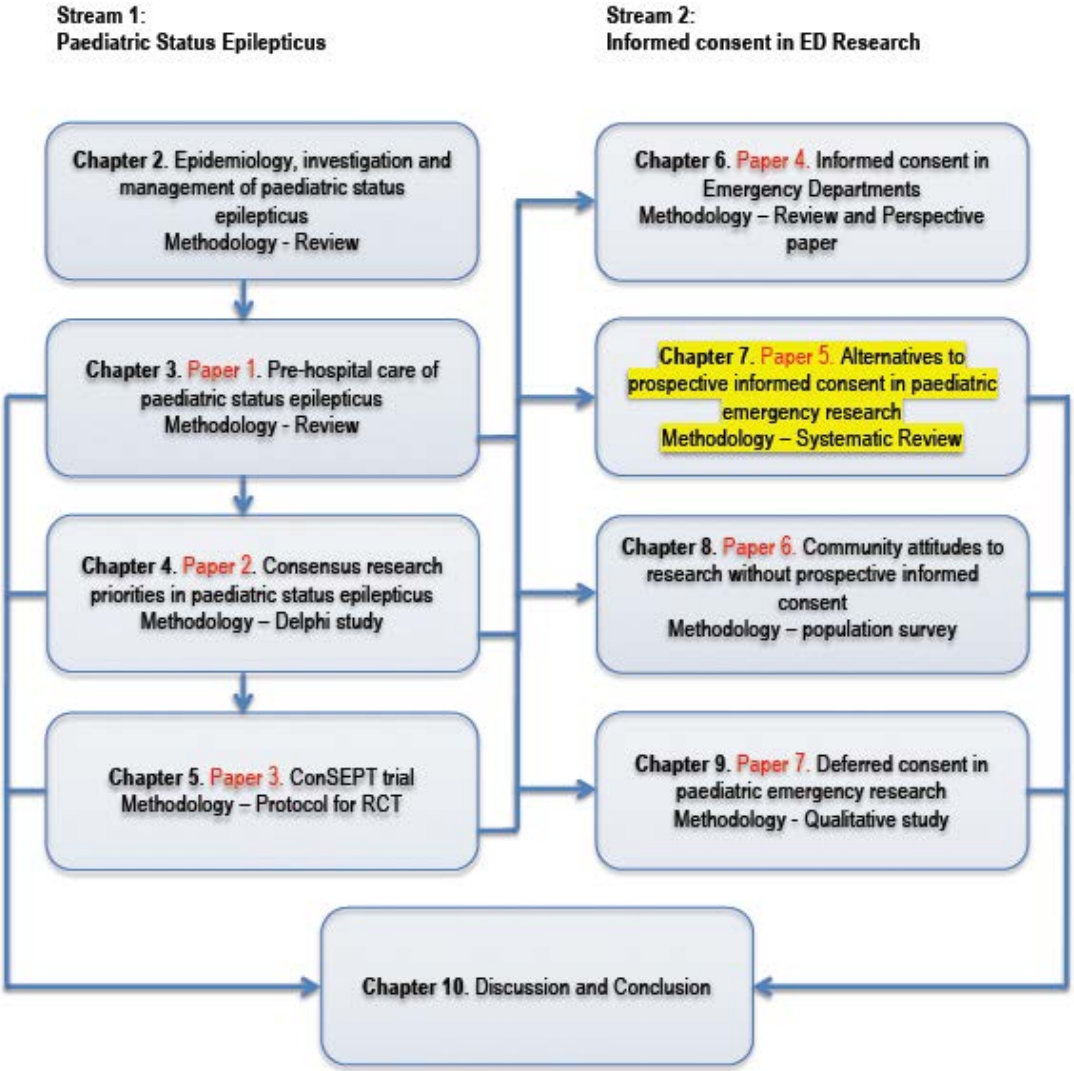
A synopsis of this chapter was published in Emergency Medicine Australasia, as a perspective piece, with input from members of the ACEM CTG. The intent of publishing the article was to stimulate debate and shine a light on the issues facing clinician researchers on a daily basis, that were impacting research in clinically important areas and affecting clinical care. An aspect of the debate that is under-represented in the Australian context is that of consumers. There are no available data on the views of the general public with regard to research in emergency situations when prospective informed consent is not possible. Chapter 7 begins to address this knowledge gap, using a comprehensive systematic review the chapter explores the available empirical evidence on research without informed consent specific to paediatric emergency medicine. This is particularly relevant to research in paediatric SE.

Chapter 7. A comprehensive systematic review of stakeholder attitudes to alternatives to prospective informed consent in paediatric acute care research.

7.1 Overview

Robust evidence is often lacking in paediatric SE and other areas of paediatric emergency and critical care. The approach taken to dealing with informed consent, one of the underlying principles of ethical research, is an important aspect of the design of research in this field. Due to the infrequency of utilising approaches other than prospective informed consent in these settings, researchers, clinicians and even ethics committees may be unfamiliar with the complex ethical issues involved. A comprehensive systematic review of the available empiric evidence on alternatives to prospective informed consent, including the attitudes and opinions of participants, parents, researchers and others is crucial to inform the planning and design of studies addressing important knowledge gaps in paediatric SE and other acute and life-threatening paediatric conditions. This chapter addresses objective 4 of the thesis and presents the results of a systematic review of the evidence relating to the process, experiences and acceptability of alternatives to prospective informed consent, in the paediatric emergency and acute care setting. Figure 7.1 places this chapter in the context of the broader thesis.

Figure 7. 1 Conceptual model of thesis



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RESEARCH ARTICLE Open Access

A comprehensive systematic review of stakeholder attitudes to alternatives to prospective informed consent in paediatric acute care research

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Abstract

Background: A challenge of performing research in the paediatric emergency and acute care setting is obtaining valid prospective informed consent from parents. The ethical issues are complex, and it is important to consider the perspective of participants, health care workers and researchers on research without prospective informed consent while planning this type of research.

Methods: We performed a systematic review according to PRISMA guidelines, of empirical evidence relating to the process, experiences and acceptability of alternatives to prospective informed consent, in the paediatric emergency or acute care setting. Major medical databases and grey sources were searched and results were screened and assessed against eligibility criteria by 2 authors, and full text articles of relevant studies obtained. Data were extracted onto data collection forms and imported into data management software for analysis.

Results: Thirteen studies were included in the review consisting of nine full text articles and four abstracts. Given the heterogeneity of the methods, results could not be quantitatively combined for meta-analysis, and qualitative results are presented in narrative form, according to themes identified from the data. Major themes include capacity of parents to provide informed consent, feasibility of informed consent, support for alternatives to informed consent, process issues, modified consent process, child death, and community consultation.

Conclusion: Our review demonstrated that children, their families, and health care staff recognise the requirement for research without prior consent, and are generally supportive of enrolling children in such research with the provisions of limiting risk, and informing parents as soon as possible. Australian data and perspectives of children are lacking and represent important knowledge gaps.

Keywords: Consent, Paediatrics, Emergency care

Background

There is a community expectation that children presenting to emergency departments (ED) and acute care settings receive the best possible care based on high-level evidence. The reality though is many treatment decisions are not evidence based, but rather based on theoretical considerations, simply reflecting "what we have always done" or extrapolated from adult data [1, 2]. This is inappropriate as children differ from adults both anatomically and physiologically and health conditions may be entirely unique to the paediatric population [3]. Clinical research in children is necessary for paediatric emergency medicine to advance.

The ethical issues involved in the conduct of paediatric clinical research are complex and are compounded in time critical and life threatening situations in emergency care. The guiding principles of conducting ethical research are:

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respect for autonomy, beneficence and justice [4]. Respect for autonomy is usually reflected in obtaining informed consent from participants, which remains a fundamental principle in the protection of human participants in medical research. When the participant is a child, consent must usually be obtained from a parent or proxy. While proposing to conduct research without informed consent may seem to contravene the ethical principle of respect for autonomy, denying participation in research to those unable to consent contravenes the ethical principle of justice, meaning fair distribution to the benefits of research participation and fair access to the benefits of research [4, 5].

Children are usually considered a "vulnerable" group in terms of participation in research due to their inability to consent and potential for exploitation [4]. While not without controversy, emergency research without consent has been performed in adults for some time; it is relatively less established in paediatric emergency and critical care. Emergency patients themselves are often considered a vulnerable group, given their reliance on the care being offered [6]. Thus research conducted on children in the emergency setting leaves participants vulnerable on multiple counts.

Performing clinical research in emergency settings is difficult. The environment is often chaotic and unpredictable, presentations of interest may be rare in individual institutions, staff are often stretched with clinical responsibilities, and interventions may have a narrow therapeutic window. One of the many challenges researchers face in conducting research in the ED and other acute care settings is the difficulty of obtaining prospective informed consent [7–9]. Valid prospective informed consent requires provision and comprehension of information about the purpose, methods, demands, risks, inconveniences, discomforts and possible outcomes of the research [4]. In Australia this assumes the capacity for decision-making, a free and voluntary process including adequate disclosure regarding the act performed. Several of these components may not be possible in time critical situations in the acute care setting and there may be an argument for a waiver of informed consent, retrospective or deferred consent. A waiver of informed consent refers to research that has ethical approval to proceed without the requirement for participant or proxy informed consent. Deferred or retrospective consent describes a process where participants are enrolled without informed consent, followed by requesting permission to continue in the study, or if the study intervention has ended, permission to use the data [1].

Guiding principles for use of alternatives to prospective informed consent in emergency research are outlined in the Declaration of Helsinki; "if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative" [10]. These principles are further reiterated in local documents such as the National Health and Medical Research Council (NHMRC) National Statement on ethical conduct in human research, which allows consent to occur after an intervention if consent is not practicable, there is potential benefit to the child, risk is low, the research has merit and there is no reason to suspect the parents would not give consent. Similar requirements exist in New Zealand [6], the United Kingdom (UK) [11], and the United States of America (USA) [12]. Although implementation is variable, and specific requirements differ internationally, most require the research to be "therapeutic" rather than "non-therapeutic", offering potential benefit to the participant and pose no more than "minimal risk" [7, 13].

The ethical issues of paediatric acute care research are complex. Even if the therapeutic window of the intervention allows an informed consent discussion and a proxy is immediately available, parents may not have capacity to undertake such decisions. There may be the perception of coercion to participate in research by parents who are dependent on receiving emergency care for their children. Locally, ethics guidance documents such as the NHMRC national statement lack clarity regarding specific requirements for research in these circumstances, and are variably interpreted by ethics committees. There is a paucity of evidence of the acceptability of research without prospective informed consent in paediatric acute care. It is important to explore and understand the perceptions and experiences of parents, health care workers and researchers to alternatives to prospective informed consent in paediatric acute care and emergency research to inform the design of future research and guidance documents.

Aim/objective

This paper aims to review and synthesize the available empiric evidence with regard to alternatives to prospective informed consent in the context of paediatric acute care research from the perspective of the children, their families, health care staff, institutions, and the community.

Methods

We performed a comprehensive systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline [14].

Search strategy

The literature search was designed in conjunction with a medical librarian (BR) and included major databases: Medline (Ovid), Embase (Ovid), Web of Science, CINAHL, and PsycINFO. No limits were set with regard to language or date restriction. See Additional file 1 for Medline (Ovid) search strategy. The electronic database search was run in April 2017 and updated in Jan 2018.

The database search was supplemented by a Google Scholar search using the "cited by" feature, and a grey literature search including conference proceedings, government reports, raw data, theses and dissertations using the key words identified for searching medical databases. Conference abstracts of key recent emergency medicine meetings were hand searched for additional studies. A manual search was conducted of reference lists from identified articles.

Registration

The review was prospectively registered on the PROSPERO registry for systematic reviews. (PROSPERO 2016 CRD42016053963).

Study selection

Studies identified by the search strategy were exported into an EndNote library and duplicates removed. Title and abstracts were reviewed independently by two authors (JF and KM), and assessed against eligibility criteria. Disputes were resolved with discussion, and adjudication by a third author (RR).

Inclusion/exclusion criteria

All study types (quantitative, qualitative and mixed methods) reporting original, empirical evidence relating to the process, experiences and acceptability of alternatives to prospective informed consent, in the paediatric, emergency or acute care setting were included. Perspectives of participants, parents or caregivers, clinicians, researchers and other staff were considered relevant. Studies reported in abstract only were considered. Studies conducted in the pre-hospital environment, emergency department and intensive care unit within all cultural and geographical contexts were included.

Studies that did not present original data e.g. reviews, commentaries, editorials, opinion pieces and letters to the editor were excluded. Studies conducted in the Neonatal Intensive Care Unit were excluded, as these units have their own unique clinical and ethical considerations, which were beyond the scope of this review. Studies only reporting adult patient data, or if paediatric subgroups were not reported separately, were excluded. Quality assessment was performed and reported; however study quality was not a selection criterion.

Data extraction

Data extraction was performed independently by two authors (JF and KM), and consisted of demographic details of the population studied, phenomenon of interest, methods used, main findings, and conclusions of the authors etc. Data extraction was an iterative process, and new emerging themes were crosschecked with primary articles.

Data analysis and synthesis

Identified full text studies and data extraction forms were imported into NVivo 11 for Mac for analysis (NVivo qualitative data analysis Software, QSR International Pty Ltd., version 11.1: 2016). We used an inclusive approach to data extraction, with all potentially relevant data included in the synthesis. Text from primary articles was coded into themes using the software. Primary themes identified from general background literature and reviews on alternatives to informed consent from adult literature formed the baseline analysis, and new themes iteratively added during analysis. The validity of the data extraction was reviewed by other authors (KW, RR, TIE).

We used thematic synthesis to synthesize results of our review, which involved free coding of textual data from primary studies, organization into descriptive themes, and generation of analytical themes producing a new interpretation. This technique is similar to meta-ethnography and grounded theory and is useful when drawing together common elements in heterogeneous studies [15, 16].

Critical appraisal of included studies

Quantitative observational studies were assessed using the "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies" from the National Heart, Lung and Blood Institute [17]. For qualitative studies we used the "Qualitative Assessment and Review Instrument" (QARI) developed by the Joanna Briggs Institute [18]. The assessment was made by two authors independently (JF and KM), by extracting the relevant text from the publication that addressed the quality assessment criteria, and assigning each question yes, no, unclear or not applicable as to whether quality criteria was met. Disagreements were resolved by consensus or by consulting with third author (RR).

Studies were not excluded on the basis of this assessment as there is no empirically tested method of exclusion of such studies on the basis of quality. Sensitivity analysis was performed excluding studies globally assessed as "poor quality" to determine to what extent exclusion of these studies affected the review e.g. if excluding themes generated from the original synthesis affects the "thickness" of detail in the synthesis.

Rigor

Methodological quality was ensured by a process coding by multiple authors and triangulation with disputes resolved by consensus.

Results

The search identified 443 studies (CINAHL 30, Embase (Ovid) 227, Medline (Ovid) 156, PsycINFO (Ovid) 9, Web of Science (21), leaving 295 after removal of duplicates. An additional 12 articles were identified from other sources including reference lists, cite feature and Google scholar. A review of titles and abstracts resulted in 37 articles for full text review. Of these 24 studies were excluded, five studies published as abstracts were duplications of subsequently published full text articles, five abstracts and 14 other studies were excluded as they did not meet inclusion criteria. This is summarised in Fig. 1. Thirteen studies were included in the review consisting of nine full text articles and four abstracts.

Characteristics of included studies are summarised in Tables 1. Critical appraisal of included articles is summarised in Tables 2 and 3. Critical appraisal of the four studies included in abstract form was not possible. Given the heterogeneity of the methods, results could not be quantitatively combined for meta-analysis. Qualitative results are presented in narrative form, according to themes identified from the data.

Capacity of parents or guardians to provide prospective informed consent

The capacity of the consenting individual is a critical requirement to providing valid prospective informed consent. Five quantitative, mixed methods and qualitative studies have provided data on capacity of parents to provide informed consent in the context of emergency and critical care research [19–23].

Practitioners' perspectives on parental capacity to provide prospective informed consent for a child in the context of emergency and critical care research indicated a divergence of views, largely regarding the ability of laypeople to process and comprehend information at a highly stressful time such as an emergency event [19, 21–23]. Practitioners across the included literature generally reported that parents had a diminished ability to process information and comprehend trial information, especially in the acute stages of a child's presentation [19, 21–23], and

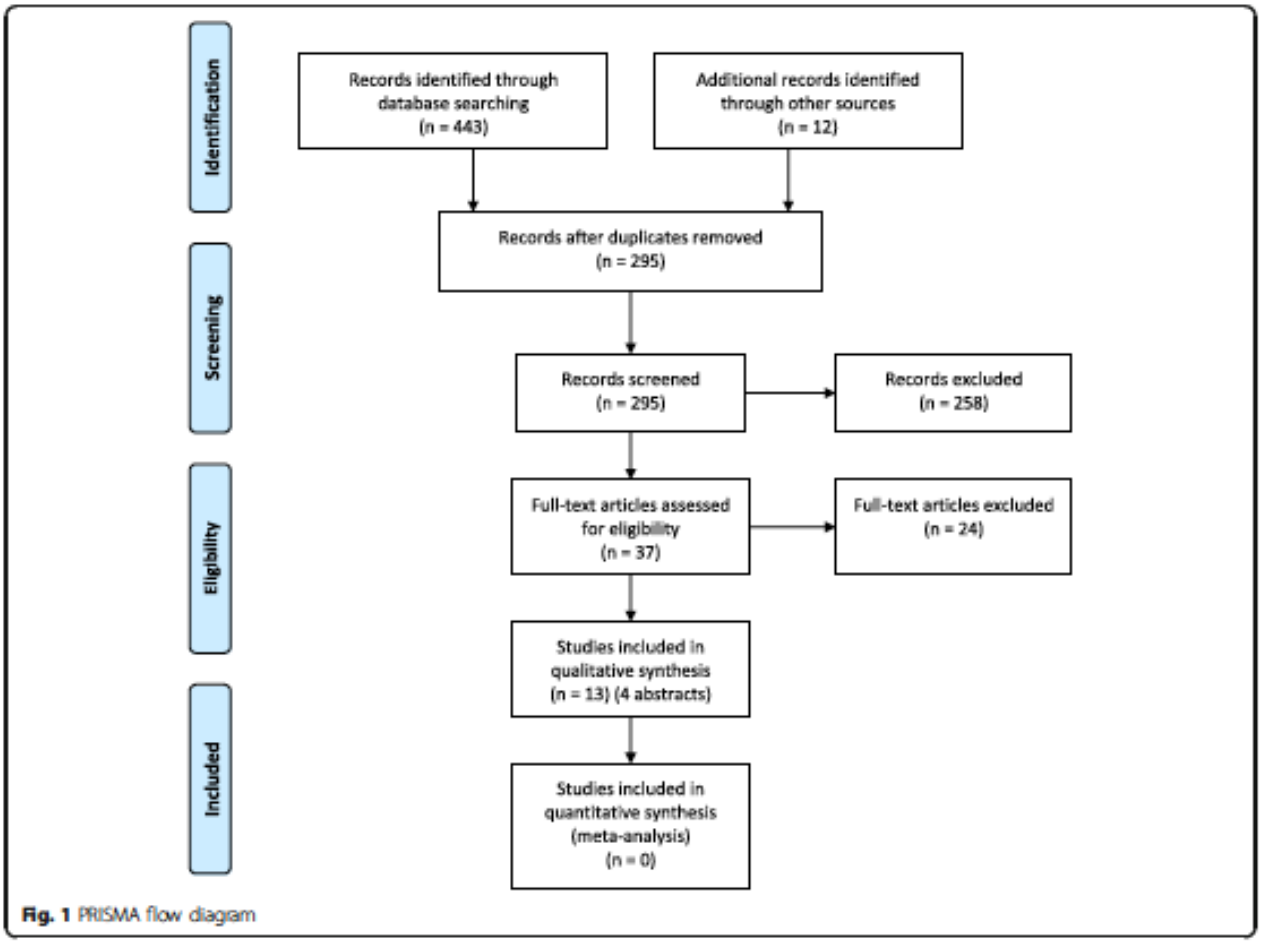

Fig. 1 PRISMA flow diagram

Table 1 Characteristics of included studies

Author/year	Setting	Phenomenon of interest	Study Design	Participants	Key findings	Comments
Bulger EM, 2009[26]	U.S. 5 urban centres (Dallas, Milwaukee, Portland, San Diego, Seattle)	Description of community consultation process for planned RCT	Random dialling survey	500 participants	A majority of subjects indicated a willingness to participate in the study should they become eligible. The average cost of surveys was US$15,000 per site.	Only a small portion data relevant to paeds. Proposed trial was adults, but included questions on children aged 15–17 years
Gamble C, 2012[27]	UK, proposed RCT with deferred consent	Parental perspectives on proposed use of deferred consent in double blind RCT	Postal survey	68 parents and families, 19 (28%) bereaved, members of the Meningitis Research Foundation (MRF).	Deferred consent was generally acceptable. Death of a child posed a uniquely difficult situation. Communication should be flexible and responsive to needs of parents	
Harron K, 2015[20]	U.K. 12 NHS trusts, RCT (CATCH trial)	Consent rates as a percentage of those approached, and those for whom consent was obtained.	Descriptive study of consent rates in RCT utilising varying methods of consent	1859 children included in CATCH trial	1859 children included in CATCH, 1358 (73%) admitted on an emergency basis. Families approached for DC 1178/1358 (87%) of emergency admissions (remaining 180 (13%) not included analysis). Inclusion rates differed according to whether the child died or survived	
Halsti, 2015[32]	15 sites in U.S and Canada. Academic paediatric emergency departments	Effectiveness of community consultation and public disclosure activities	Mixed methods. Survey of participants.	297 enrolled participants completed de-briefing form.	Activities varied widely among sites. Median time from protocol release to final IRB approval was 10 months. Focus groups not associated with another meeting were not well attended. Median cost of $6989.	
Molyneux 2013[21]	Kenya and Uganda, RCT	Staff and parental perceptions of the consent process	Qualitative study of parents and staff	34 interviews with parents of participants, 12 interviews with parents of admitted non-participants, 30 staff interviews. Two focus groups of health workers, 6 interviews with hospital managers.	The DC process with prior assent was supported. Prior assent was seen as protecting the interests of both patients and researchers, including through minimising delays in starting treatment	
Morris, 2004[19]	U.S. PICU setting	Attitudes to exception to informed consent in a clinical trial	Qualitative study	Focus groups. Parents of children resuscitated from cardiac arrest $n = 12$, parents of children in PICU $n = 11$, PICU nurses $n = 13$, physicians n = 10, administration $n = 10$	Concluded prospective informed consent was not feasible and endorsed exception of IC if have an explicit opportunity to decline participation	Proposed intervention was to be instituted within 30 min, therefore had more time that other scenarios
Scholefield, 2013[31]	28 UK EDs	"appropriateness" of DC	Web-based survey	77 Emergency Medicine consultants	74% approved the use of deferred consent in such a trial.	Limited data relevant to review question (single question)

Table 1 Characteristics of included studies *(Continued)*

Author/year	Setting	Phenomenon of interest	Study Design	Participants	Key findings	Comments
Stanley, 2017[24]	16 level I paediatric trauma centre EDs in USA	Describe the clinical characteristics, and timing of parent guardian arrival.	Prospective, observational study	295 children with blunt head trauma with Glasgow Coma Scale (GCS) scores of 3–12 (i.e., moderate-to-severe TBI).	The timing of patient and guardian arrival posed a challenge for timely enrolment. The Federal Exception from Informed Consent for Emergency Research is an important consideration for planning such research.	Limited data relevant to review question
Woolfall, 2013[22]	UK (clinical trial units)	experiences and attitudes of practitioners (doctors and nurses) involved in recruiting to clinical trials in the EC setting.	Semi-structured questionnaire	16 consultant grade doctors, 29 research nurses (purposeful sampling)	Views on DC differed with experience with the consent method. Practitioners with no experience reported negative perceptions, with concerns about the impact on the parent-practitioner relationship. Practitioners experienced in DC described how families were receptive to the consent method, if conducted sensitively at an appropriate time.	
Woolfall, 2014[28]	UK (in setting of planned RCT)	To explore the views of parents on proposed RCT i.e. approach to seeking DC and content of PIS.	Qualitative study	17 parents (11 telephone interviews) 6 in focus groups. Purposefully sampled from support groups with acute and chronic conditions.	Most supported DC to enable progress of emergency care research. The child's safety was a priority and parents were reassured interventions under investigation are both used in routine clinical practice. Parents made recommendations on the need to individualise approaches bereaved parents.	Limitation – low participation rate.
Woolfall, 2015 [23]	UK multicentre, (setting of RCT CATCH)	Parents' views and experiences of the CATCH trial recruitment, the consent seeking procedures and decision-making	Mixed method study (survey, interview and focus groups)	275 parents completed questionnaire, 20 families participated in interviews, 17 clinicians participated in focus groups.	Parents felt seeking DC at a time point after their child's stabilising was more appropriate than seeking consent at an earlier, more critical time point, assisted with considering trial information. Practitioners believed such timing assisted informed decision-making.	
Menzies, 2011 [25](Abstract only)	UK PICU	Acceptability of consent processes in emergency research	Qualitative study	Focus groups, 8 adults of 5 children	Parents want to make the decision about their child entering a trial. Deferred consent is only acceptable if there is some form of communication with them at trial entry	Quality not assessed
Rademacher, 2013[39](Abstract only)	USA	Parental attitudes about conducting research of therapies for severe TBI in children using EFIC	Cross sectional web based survey	1637 parents of children 0–17.	More than a third of parents agree with including children with TBI in research studies when parents are not present	Quality not assessed

Table 1 Characteristics of included studies *(Continued)*

Author/year	Setting	Phenomenon of interest	Study Design	Participants	Key findings	Comments
					for consent, less than half of parents disagree.	
Scholefield, 2011 [29](Abstract only)	UK	Children's views on the acceptability of DC	Qualitative study	Interviews, 14 childen (aged 9 to 18)	Trust of the medical profession, and emergency research is safe and therapeutic. Difficulty differentiating between research and clinical decision-making	Quality not assessed
Woolfall, 2016 [30](Abstract only)	UK	Children and young persons views on research without prior consent	Qualitative study	Interviews, 14 children and young people (aged 7 to 15 years)	Supported inclusion in research without prior consent if the trial intervention was thought to be safe and of potential benefit to participants and others. CYP felt that they have the right to be informed and have a say about their participation in a trial as soon as they had recovered	Quality not assessed

PIS participant information sheet, *USA* United States of America, *UK* United Kingdom, *TBI* traumatic brain injury, *DC* deferred consent, *IC* informed consent, *RCT* randomised controlled trial, *EFIC* exception from informed consent, *PICU* paediatric intensive care unit

Table 2 Critical appraisal of qualitative studies

	Gamble 2012	Molyneux 2013	Morris 2004	Woolfall 2013	Woolfall 2014
1. There is congruity between the stated philosophical perspective and the research methodology					
2. There is congruity between the research methodology and the research question or objectives.					
3. There is congruity between the research methodology and the methods used to collect data.					
4. There is congruity between the research methodology and the representation and analysis of data.					
5. There is congruity between the research methodology and interpretation of results.					
6.There is a statement locating the researcher culturally or theoretically.					
7. The influence of the researcher on the research, and vice-versa, is addressed					
8. Participants, and their voices, are adequately represented.					
9. The research is ethical according to current criteria or, for recent studies, there is evidence of ethical approval by an appropriate body.					
10. Conclusions drawn in the research report do appear to flow from the analysis, or interpretation, of the data.					

Criteria met, Criteria not met, unclear or not applicable

Table 3 Critical appraisal of quantitative studies

	Hamon 2015	Hoff 2015	Scholefield 2013	Stanley 2017
1. Was the research question or objective in this paper clearly stated?				
2. Was the study population clearly specified and defined?				
3. Was the participation rate of eligible persons at least 50%?				
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?				
5. Was a sample size justification, power description, or variance and effect estimates provided?				
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?				
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?				
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?				
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?				
10. Was the exposure(s) assessed more than once over time?				
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?				
12. Were the outcome assessors blinded to the exposure status of participants?				
13. Was loss to follow-up after baseline 20% or less?				
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?				
OVERALL QUALITY RATING BY AUTHORS (Good, fair, poor)	FAIR	FAIR	FAIR	FAIR

criteria met, criteria not met cannot determine, not applicable, or not reported

that meaningful consent in these circumstances was not possible [19]. Harron et al., found that some participants were not approached for deferred consent after randomization as research staff were concerned that they were *"not in the right state of mind"* [20]. However, this view was not universal, as in a study by Woolfall et al. 26/45 practitioners believed parents understood trial information provided in an emergency situation *"well"* or *"very well"*, with about one third of those surveyed remaining undecided [22].

Parental perspectives on capacity to provide informed consent were similar to those of practitioners, in terms of diminished ability to process and comprehend information in the face of high stress during the acute care stages of presentation [19, 21, 22]. Supporting this, in a study where deferred or retrospective consent was obtained, parents demonstrated relatively poor comprehension of important research elements and almost a quarter described their experience as clinical care [21].

Feasibility of prospective informed consent

Two studies specifically addressed whether prospective informed consent was feasible [19, 24]. A study conducted by the Pediatric Emergency Care Applied Research Network (PECARN), exploring the feasibility of various aspects of a study of moderate to severe traumatic brain injury, found that parents and guardians are often not available within the narrow therapeutic window of investigational therapies [24]. While children often arrived within an hour or two of injury, most parents and guardians did not arrive until 2 to 3 h or later. This was more apparent for children transferred from another site and more severely injured children. The authors concluded that an exception of informed consent would be necessary for timely enrolment of children into such a trial [24]. A qualitative study using focus groups of parents and staff of a paediatric intensive care setting to discuss a cardiac arrest research scenario, concluded that meaningful prospective informed consent was not feasible, and endorsed exception of informed consent, with the proviso that parents were offered an opportunity to decline participation prior to enrolment [19].

Support for alternatives to prospective informed consent

Estimates of support for research with alternatives to informed consent are broad and generally influenced by a number of factors. Five included studies were performed as part of a community consultation process, which is a federal requirement in the USA for research performed under a waiver of informed consent [12], and used in other settings as well [21, 25]. These studies have quantified the level of support; however combining these estimates is inappropriate because of the heterogeneity of methods used and the specific contexts of the individual studies. Community consultation has included perspectives of both the parents of prospective participants, as well as health professionals.

A random dialling phone survey of over 2000 participants, for an out of hospital resuscitation study conducted in 5 states in the USA explored support for the exception to written consent in both adult participants and the 15–17 year old subgroup of the trial [26]. The study found 42.7–71.0% supported the exception to written consent being justified for 15–17 year olds, and in the best interests of the patients and the community which was only slightly lower than support for adults in the same trial [26]. Similar support has been reported in a UK study of parents of children who had suffered bacterial meningitis or meningococcal septicaemia, including bereaved parents [27]. In a postal survey 45/66 (68%) indicated they would be willing for their child to be included in a trial without the trial being explained beforehand [27]. In a study of inpatient resuscitation research, more than 60% of parents were supportive of the study procedures including the exception to prospective informed consent [19].

In qualitative studies parents were generally supportive of research without prior consent [28], with reasons including altruism and general trust in the medical profession to make appropriate decisions [23, 27–30]. However, this sentiment was often accompanied by reservations about the level of risk or potential for harm of the intervention, or as dependent on the type of study being performed [23, 28]. A common theme was the importance to prioritise the management of the child prior to detailed explanations or excessive paperwork [23]. Some parents' support for research without prospective consent was contingent on the child's outcome [19, 28]. Such reservations led to an emphasis on the importance of appropriate explanations regarding the necessity for a deferred consent process in these research settings [28].

While the majority of studies have demonstrated that most parents understand and support the concept, some individuals hold strongly opposing views about research without prior consent, taking the perspective that a child should not be exposed to research without prior consent, and parents must be consulted before children are enrolled [23, 27]. Common reasons for opposing research without consent include the fear of adverse effects and feelings that the parents should *"not lose the right to consent"* [26].

The health professionals' perspective varied in terms of support for research without prior consent. USA researchers found only 50% of staff supported a trial with exception to informed consent. However a large proportion were neutral (38%) and only 12% opposed the planned trial procedures [19]. In the UK, a survey of emergency medicine consultants found that 34/46 (74%)

believed deferred consent would be acceptable for a planned trial evaluating therapeutic hypothermia following a paediatric cardiac arrest [31]. Qualitative studies have explored reasoning behind divergent views regarding research without prospective informed consent [19, 22, 23, 28]. Practitioners and researchers enrolling children in studies suggested familiarity with using a deferred consent process influenced acceptability and level of comfort of the procedure. Practitioners and researchers who had previous experience of the deferred consent method generally reported families as being receptive to the method if handled sensitively [22].

Only two identified studies reported the opinions of children on research without prior consent, and both were available in abstract form only [29, 30]. Children in these studies generally regarded the use of exception from informed consent as acceptable [29], especially in life threatening situations [30].

Community consultation

Two studies explored other issues around community consultation including cost, value and variability in implementation [26, 32]. Requirements of community consultation are at the discretion of local institutional review boards (IRBs) and variability in requirements was evident, particularly when involving multiple centres and different jurisdictions [26, 32]. Methods of community consultation included focus groups, interviews, surveys, town meetings, and public disclosure involving news releases, mailings and public service announcements. Another study with various modalities found focus groups were not well attended, with a quarter having no attendees. Only 5% of research participants had heard about the trial from community consultation and public disclosure activities [32]. The cost of community consultation was reported in two studies. The phone surveys conducted by one large multicentre study averaged US$15,000 per site [26]. Another study utilising various modalities calculated the median cost of activities was about US$7000 [32]. The median additional time of this process was 10 months.

Process issues

Parents commented on the amount of information provided on consent forms as an issue in decision making [23, 28]. When the child was ill, parents prioritised the treatment of the child over consent procedures, and preferred simple clear information on a single page [23].

A process of pre-consent was considered in two studies where potential participants are given the opportunity to consent or opt-out of participating in a trial, before they meet eligibility criteria, typically in an at risk population [19, 32]. In a study of paediatric status epilepticus, over 4000 patients considered at risk of prolonged seizures received information about the trial, but only 6 out of 208 patients who's parents were pre-consented were subsequently enrolled in the trial, constituting only 3% of the 310 patients enrolled in the trial [32]. A further 158 parents chose to place their child on the opt out list [32]. In a qualitative study of paediatric cardiac arrest in a paediatric intensive care unit (PICU) setting, pre-consent was perceived as an excessive burden to parents and the validity of consent in this situation was questioned by the authors, as parents may have presumed the study details were not applicable to them at the time of consent, and therefore did not consider the implications adequately [19].

In circumstances where consent is delayed, meaning that the intervention is commenced without consent, but consent sought later to continue with the trial and for the use of data, the timing of approaching parents with trial information is important. Such studies have been variably described as delayed, deferred or retrospective consent. Nine studies specifically used the term "deferred consent" [20–23, 25, 27–29, 31]. Four studies discussed implications concerning the timing of approach for consent when retrospective or deferred consent processes are used [22, 23, 27, 28]. Generally, across parents and practitioners there is agreement that approach for consent in these circumstances should occur once the child's condition is perceived to be stabilised [22, 23, 27, 28]. Both practitioners and parents expressed views that the timing of the approach, could affect the likelihood of agreeing [22, 23].

Modified or limited consent process

While acknowledging the difficulties of obtaining prospective informed consent in a number of studies, participants often preferred *"some consent"* rather than enrolment with no information at all [19, 21, 25]. The suggested modified consent usually took the form of brief verbal consent, or "assent" of parents at enrolment [19, 21, 25]. A study of the views parents of children admitted to a PICU about a deferred consent project, found they thought the process was only acceptable if there was some information provided at enrolment [25]. In a study that utilised both full prospective informed consent (when possible) and "assent" in other circumstances, consisting of a single paragraph briefly explaining the trial being read to participants. About half of participants were enrolled with each process overall, however the proportions varied between sites, suggesting physician preference and comfort with procedures, rather than only participant and parent factors influenced the type of consent used [21]. Only 0.4% who assented withdrew consent later. Staff generally supported the process in this setting, however some questioned the

validity of assent in these circumstances or thought it too might delay treatment [21].

Exploring issues of child death during the research

Six studies reported relevant data regarding the situation of child death during research and use of alternatives to prospective informed consent. Issues included whether seeking consent was appropriate, whether consent should be waived in this circumstance and the need to balance the additional burden of disclosure to parents against their right to be informed [27, 28].

Studies of parental opinion regarding the disclosure of participation in research and deferred consent being sought in the case of child death during a trial have found mixed results [27, 28]. Some data suggest the majority of parents favour disclosure, and altruism in that the data could contribute to the greater good, usually stated as a reason [23, 27, 28]. However, contrasting views were also apparent with some parents strongly favouring non-disclosure in this situation [28]. Gamble et al. explored and compared attitudes of bereaved and non-bereaved parents and suggests attitudes were different, with the majority (66%) of bereaved parents favouring disclosure contrasting with 57% of non-bereaved parents expressing a preference for non-disclosure. Preference for non-disclosure was usually to avoid causing additional distress to grieving parents [27].

Two studies reported data from the CATCH trial, where children were enrolled in both emergency and elective settings [20, 23]. Of children enrolled in an emergency setting consent was obtained for only 984/1358 (72%) because of lack of opportunity or because staff decided not to approach parents. Consent was refused for 26 children who died and 151 who survived, but the reasons for refusal differed between groups. The mortality rate of consented children was 9%, compared to 18% for non-consented children, whose data were excluded from analysis [20]. A qualitative evaluation of this trial including bereaved parents, found some were *"shocked"* that their children had been enrolled in research without prior consent [23]. Others described experiences where they thought the manner of approach had been insensitive. Doctors felt that approach after death was far more challenging [23], and clinicians frequently opted to not approach grieving families [20]. A contrasting method was adopted by investigators (and ethics committees) of the FEAST study, who deemed it *"unethical"* to approach parents when a child died, and included data for patients who provided assent and waived the requirement for informed, deferred consent [21]. Opinions varied in relation to the most appropriate time to approach parents for consent in the case of child death during a trial. Mostly, data suggest that approaching bereaved parents for consent should *"not be too soon"* and advocating clinician discretion [27, 28]. Children reportedly understood the potential for bias with refusal of parental consent in a deferred consent study [29].

Discussion

Our systematic review of stakeholder attitudes to alternatives to prospective informed consent in paediatric emergency medicine found the limited available evidence suggested that children, families and practitioners were aware of the limitations of prospective informed consent for emergency and time critical research, were generally supportive and seemed to acknowledge the requirement for alternative strategies. Identified barriers to informed consent included the capacity of parents, insufficient time (compared to therapeutic windows of interventions), and some process issues like paperwork. Modifications to some processes were proposed.

The diminished capacity of parents to consent under stressful circumstances should not be surprising. Even under ideal circumstances research participants are often demonstrated to have suboptimal understanding [33, 34]. Similarly, in emergency surgery situations the validity of consent for clinical care has been questioned due to poor retention of information [35]. In the research context a concept of the "therapeutic misconception" is a common theme, where it is not clear whether parents can accurately differentiate consent for clinical care and research participation.

The terminology used in studies with research without prospective informed consent differed between studies and international variation was apparent. Some authors have criticised terms such as "deferred", "delayed" or "retrospective" consent, and contend that consent is not possible after the fact, and contravenes the principle of respect for autonomy [1, 36]. However international guidance documents highlight the requirement for research when consent is not possible, and the importance of discussing the research with the patient or surrogate decision maker as soon as possible in such circumstances [4, 10]. The term deferred consent has been used in the medical literature since the 1990s, and tends to refer to permission to continue in the study, or if the study intervention has ended, permission to use the data [1]. Legislation was specifically introduced in Europe and the UK to allow much needed research to occur in situations where obtaining prior informed consent was not possible, which was identified as a problem under the previous legislative arrangements. The USA has similar legislation, where research needs to meet requirements for the federal "exception from informed consent" [12]. In our review, nine of the included studies specifically addressed, and used the term "deferred consent", meaning it was the most commonly evaluated strategy when prospective informed consent was not

possible [20–23, 25, 27–29, 31]. In the Australian context, while the NHMRC National Statement does not specifically use the term deferred consent, section 4.4.14 reinforces the process of informing participants, with the statement *"As soon as reasonably possible, the participant and/or the participant's relatives and authorised representatives should be informed of the participants inclusion in the research and the option to withdraw from it without any reduction in quality of care"* [4]. This seems to refer to and seek to achieve similar objectives as a deferred consent process.

While research evaluating alternatives to prospective informed consent has been performed in adults, there is relatively few studies in the paediatric setting. We hypothesized that parents and the general community may be less inclined to support research of this type in children, however the majority of people recognised the need for this research to occur, and supported the requirement for research without prospective informed consent, which was similar to previous adult studies [5]. A major limiting factor was the "situational incapacity" of parents precluding valid consent even if immediately available, and limited time for valid prospective informed consent in many situations.

Alternative strategies were proposed that included the opportunity to consent prior to meeting inclusion criteria, the option to "opt out" at the time of enrolment and versions of a modified consent process [19, 21, 25]. Prior consent is seldom a viable option for emergency research, as prior identification of potentially eligible patients is often not feasible, and efforts for prior consent are usually prohibitively inefficient, and may result in selection bias. In emergency trials, particularly in paediatrics the target population is not easily identified in advance. Community consultation efforts in the USA have often included an "opt out" option for clinical trials conducted under the exception to informed consent legislation, but again the process is inefficient, and difficult to implement, with few patients excluded on this basis [26, 32]. An alternative that may not be applicable in all circumstances is the middle ground, of including a brief verbal consent or "assent" process, prior to enrolment in a trial [21]. In extremely time critical interventions, such as cardiac arrest, delays of just minutes may cause harm, therefore this approach would not be useful, but in other circumstances it may be a viable option and fulfil the parents desire to be involved in decision making, reduce some processes of informed consent like paperwork, focus more on managing the child and importantly given the opportunity to decline participation prior to enrolment.

Limitations

Our review had a number of limitations. Firstly there is no consensus on how to assess quality in qualitative research, or the utility of such an assessment [37]. Over 100-quality assessment tools have been proposed and used for the purposes of critical appraisal of qualitative studies and several are in relatively common use [38]. We used the Qualitative Assessment and Review Instrument (QARI) from the Joanna Briggs Institute [18], which has been widely used for this purpose, and no studies were excluded on the basis of quality assessment, and no studies were deemed to be of low quality. Abstracts were included in the review, which did not contain sufficient information to allow formal quality assessment. It should be recognised that this review identified only 13 studies, which limits the conclusions that can be made. In particular, data on the perspectives of children were lacking. Implications and conclusions for our setting are also hampered by the absence of any Australian studies. Most included studies were from the USA or UK, which may be somewhat applicable in the Australian context due to a degree of similarity with health systems, societal norms and shared values.

Conclusion

In conclusion, our systematic review of attitudes of stakeholders on alternatives to prospective informed consent in paediatric emergency research demonstrated that children, their families, health care staff, institutions, and the community seem to recognise the requirement for research performed without prior consent, and are generally supportive of enrolling children in such research with the provisions of limiting the degree of risk, and informing parents and/or children as soon as possible. There is a noted lack of Australian data as well as an insufficient understanding of the perspectives of children; both areas represent important knowledge gaps that need to be addressed through high quality research. Giving patients and their families a voice in discussions of alternatives to informed consent in emergency and critical care research in children, and greater engagement in the design of studies is necessary to maintain the trust of the community, and allow vital research to continue.

Additional file

Additional file 1: Medline (Ovid) search. (DOCX 109 kb)

Abbreviations

ED: Emergency departments; IRB: Institutional review boards; NHMRC: National Health and Medical Research Council; PECARN: Pediatric Emergency Care Applied Research Network; PICU: Paediatric intensive care unit; UK: United Kingdom; USA: United States of America

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Authors' contributions
JF, KM and RR conceived the study, all authors assisted with drafting the protocol, JF, KM and RR performed the literature search, applied inclusion criteria, data extraction and quality assessment. JF, KM, BR, KW, RF, TE, RR, FB and SD contributed to interpretation of the data and drafting of the manuscript. JF, KM, BR, KW, RF, TE, RR, FB and SD approved of the final manuscript.

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Ethics approval and individual participant consent was not sought for this systematic review.

Consent for publication
None

Competing interests
The authors declare that they have no competing interests.

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References

1. Briefey J, Larcher V. Emergency research in children: options for ethical recruitment. J Med Ethics. 2011;37(7):429–32 PubMed PMID: 21345861. Epub 2011/02/25. eng.
2. Furyk JS, Lawton LD, Ting JY, McD Taylor D. Informed consent in emergency care research: an oxymoron? Emerg Med Australas. 2017;29(1):110–2.
3. Advanced Paediatric Life Support. In: Samuels M, Wieteska S, editors. A practical approach to emergencies. Chichester, West Sussex: Wiley; 2016.
4. NHMRC. National Statement on ethical conduct in human research (2007) - updated May 2015. Canberra: National Health and Medical Research Council; 2007.
5. Lecouturier J, Rodgers H, Ford GA, Rapley T, Stobbart L, Louw SJ, et al. Clinical research without consent in adults in the emergency setting: a review of patient and public views. BMC Med Ethics. 2008;9:9 PubMed PMID: 18445261. Pubmed Central PMCID: PMC2390563. Epub 2008/05/01. eng.
6. National Ethics Advisory Committee. Ethical guidelines for intervention studies. Wellington, New Zealand: Ministry of Health; 2009.
7. Biros M, Lewis RJ, Olson C, Runge JW, Cummins R, Fost N. Informed consent in emergency research. JAMA. 1995;273(16):1283–7.
8. Chamberlain JM, Lillis K, Vance C, Brown KM, Fawumi O, Nichols S, et al. Perceived challenges to obtaining informed consent for a time-sensitive emergency department study of pediatric status epilepticus: results of two focus groups. Acad Emerg Med Off J Soc Acad Emerg Med. 2009;16(8):763–70 PubMed PMID: 19673713. Epub 2009/08/14. eng.
9. CRASH. Research in emergency situations: with or without relatives consent. Emerg Med J. 2004; Nov;21(6):703. PubMed PMID: 15496698. Pubmed Central PMCID: PMC1726499. Epub 2004/10/22. eng.
10. Association WM. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191–4.
11. United Kingdom Government. Medications for Human use (Clinical Trials) Amendments (No. 2). 2006.
12. 21 CFR 50.24 and 45 CFR 46.101(i) (1996). Protection of human subjects; informed consent, and waiver of informed consent requirements in certain emergency research; final rules. Fed Reg. 1996;61(192, Oct 2):51498–533.
13. Gray JD. The problem of consent in emergency medicine research. CJEM. 2001;3(3):213–8 PubMed PMID: 17610787. Epub 2007/07/06. eng.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Plos Med. 2009;6(7):e1000097.
15. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol. 2008;8:45.
16. Ring N RK, Mandava L, Jepson R.. A guide to synthesising qualitative research for researchers undertaking health technology assessments and systematic reviews. 2010 [cited 2016 August 20]. Available from: http://www.healthcareimprovementscotland.org/previous_resources/hta_report/synthesising_researchaspx.
17. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. United States; Department of Health and Human Services, National Heart, Lung, and Blood Institute; [cited 2016 21 Dec]. Available from: www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort.
18. The-Joanna-Brigs-Institute. Joanna Briggs Institute Reviewers Manual. 2014th ed; 2014.
19. Morris MC, Nadkarni VM, Ward FR, Nelson RM. Exception from informed consent for pediatric resuscitation research: community consultation for a trial of brain cooling after in-hospital cardiac arrest. Pediatrics. 2004;114(3):776–81.
20. Harron K, Woolfall K, Dwan K, Gamble C, Mok Q, Ramnarayan P, et al. Deferred Consent for Randomized Controlled Trials in Emergency Care Settings. Pediatrics. 2015;136(5):e1316–22.
21. Molyneux S, Njue M, Mwanamvua Boga, Akello L, Olupot-Olupot P, Engoru C, et al. 'The Words Will Pass with the Blowing Wind': Staff and Parent Views of the Deferred Consent Process, with Prior Assent, Used in an Emergency Fluids Trial in Two African Hospitals. PLoS One. 2013;8(2).
22. Woolfall K, Frith L, Gamble C, Young B. How experience makes a difference: practitioners' views on the use of deferred consent in paediatric and neonatal emergency care trials. BMC Med Ethics. 2013;14(45).
23. Woolfall K, Frith L, Young B. P07 Evidence-based guidance to inform consent seeking in children's critical care trials. Arch Dis Child. 2015;100:A3–4.
24. Stanley RM, Johnson MD, Vance C, Bajaj L, Babcock L, Atabaki S, et al. Challenges Enrolling Children Into Traumatic Brain Injury Trials: An Observational Study. Acad Emerg Med. 2017 01 Jan;24(1):31–39. PubMed PMID: 61406790S. English.
25. Menzies J, Callens C, Agrawal S, Whitehouse W. Consumer involvement in the design of a refractory status epilepticus trial in children. Pediatr Crit Care Med. 2011 May;1):A120. PubMed PMID: 70418967. English.
26. Bulger EM, Schmidt TA, Cook AJ, Brasel KJ, Griffiths DE, Kudenchuk PJ, et al. The random dialing survey as a tool for community consultation for research involving the emergency medicine exception from informed consent. Ann Emerg Med. 2009;53(3):341–50.
27. Gamble C, Nadel S, Snape D, McKay A, Hickey H, Williamson P, et al. What parents of children who have received emergency care think about deferring consent in randomised trials of emergency treatments: postal survey. PLoS One. 2012;7(5):e35982 PubMed PMID: 22586456. Pubmed Central PMCID: 3346812.
28. Woolfall K, Young B, Frith L, Appleton R, Iyer A, Messahel S, et al. Doing challenging research studies in a patient-centred way: a qualitative study to inform a randomised controlled trial in the paediatric emergency care setting. BMJ Open. 2014;4(5):e005045 PubMed PMID: 24833694. Pubmed Central PMCID: 4025463.
29. Scholefield B, Gosney J, Callens C, Duncan H, Morris K, Draper H. Consultation with children regarding deferred consent in emergency care research. Pediatr Crit Care Med. 2011 May;1):A44. PubMed PMID: 70418568. English.

30. Woolfall K, Roper L, Sherratt F, McNamara P, Appleton R, Crawley E, et al. Children and young people support research without prior consent in life threatening situations: a qualitative study. Eur J Pediatr. 2016;175(11):1525–6
31. Scholefield BR, Lyttle MD, Berry K, Duncan HP, Morris KP. Survey of the use of therapeutic hypothermia after cardiac arrest in UK paediatric emergency departments. Emerg Med J. 2013;30(1):24–7 PubMed PMID: 22389354. English.
32. Holsti M, Zemek R, Baren J, Stanley RM, Mahajan P, Vance C, et al. Variation of community consultation and public disclosure for a pediatric multi-centered "Exception from Informed Consent". Clin Trials. 2015;12(1):67 PubMed PMID: 25369796. Pubmed Central PMCID: NIHMS631494. English.
33. Yuval R, Halon DA, Merdler A, Khader N, Karkabi B, Uziel K, et al. Double comprehension and reaction to participating in a double blind randomized clinical trial (ISIS-4) in acute myocardial infarction. Arch Intern Med. 2000; 160:1142–6.
34. Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research. A Systematic Review. JAMA. 2004;292(13):1593–601.
35. Li FX, Nah SA, Low Y. Informed consent for emergency surgery–how much do parents truly remember? J Pediatr Surg. 2014;49(5):795–7 PubMed PMID: 24851773. English.
36. Johnson LR, Siddaiah R. Use of deferred consent for enrolment in trials is fraught with problems. BMJ. 2015;351:h4609 PubMed PMID: 26330402.
37. Carroll C, Booth A. Quality assessment of qualitative evidence for systematic review and synthesis: is it meaningful, and if so, how should it be performed? Res Synth Methods. 2015;6(2):149–54 PubMed PMID: 26099483.
38. Higgins J GS. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. Available from http://www.cochrane-handbook.org.: 2011 [[cited 2016 August 25]].
39. Rademacher NJ, Clark SJ, Davis, MM, Al-Lawati, Z, Stanley, R. Parental attitudes towards the use of the federal exception from informed consent (EFIC) for emergency studies of severe traumatic brain injuries. Acad Emerg Med. Vol1. S192-S193 (Abstract).

7.3 Supplementary file

See supplementary appendix 7.1 – Medline (Ovid) Search.

7.4 Summary

Chapter 7 addresses objective 4 of the thesis and describes a comprehensive systematic review conducted according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines on alternatives to prospective informed consent in paediatric acute care research. Thirteen studies (none of which were Australian) were included in the review. The main findings were:

- Researchers, health practitioners and the community are generally supportive of enrolling children in studies where prospective informed consent is not possible with the provisions of limiting risk and informing parents as soon as possible.
- Other major themes explored in published literature were the capacity of parents to provide informed consent, feasibility of informed consent, process issues, modified consent processes, child death, and community consultation.

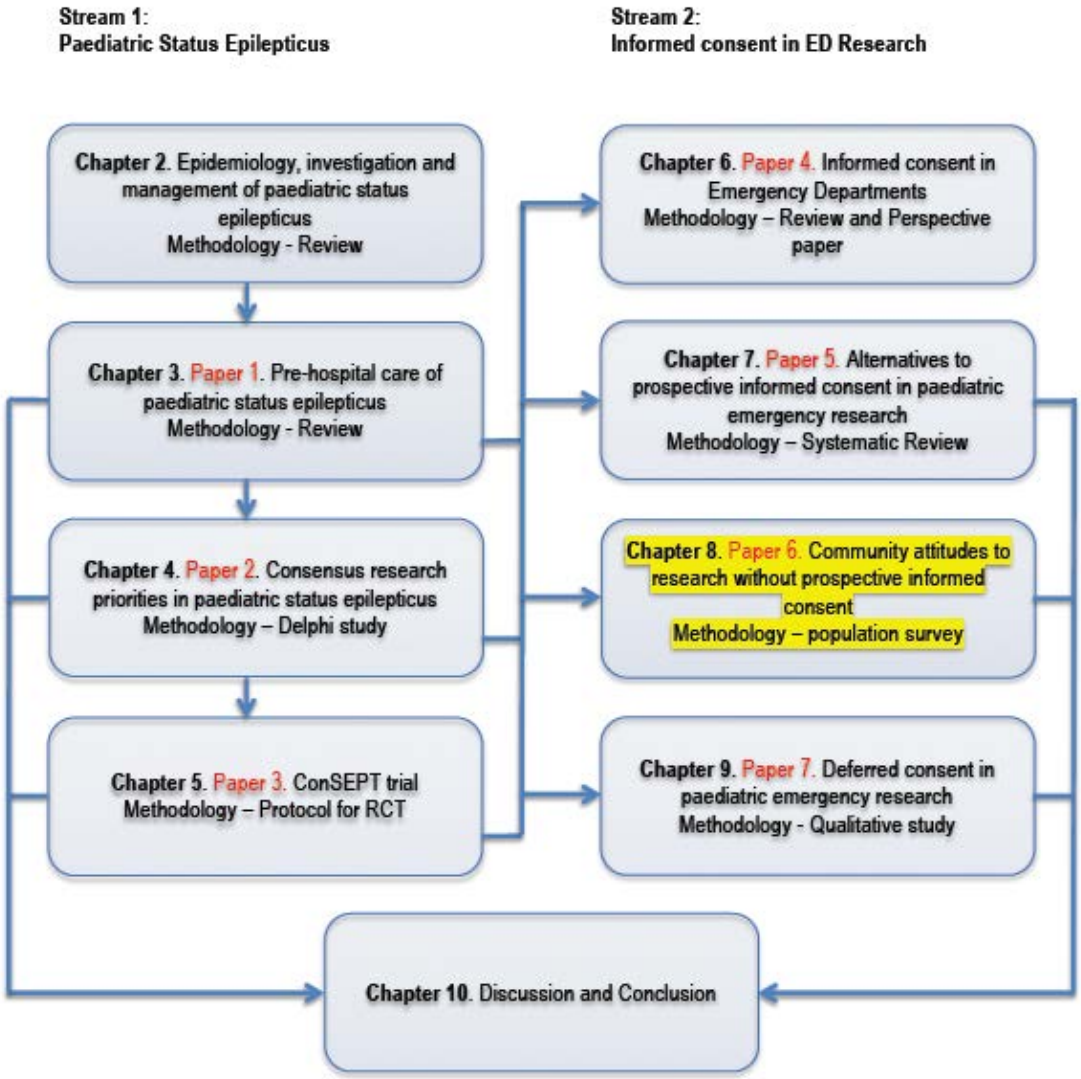
The review outlined the limited experience from international settings on alternatives to prospective informed consent in paediatric emergency medicine and critical care research. The results are highly relevant to the design of paediatric SE research locally, although data from the Australian and New Zealand setting are urgently needed. Chapter 8 describes a survey of the Australian public on attitudes to research without informed consent in both adults and children. To ensure that research in emergency situations such as paediatric status epilepticus can continue, researchers and policy makers need to ensure strategies for enrolling participants into research studies and clinical trials align with community expectations, and that the voices of consumers are involved in the development of guiding frameworks for undertaking such research.

Chapter 8: Community attitudes to emergency research without prospective informed consent: A survey of the general population

8.1 Overview

Medical research in Australia is performed under guidelines issued by the NHMRC, local governance requirements, and legal requirements. As outlined in Chapter 6, requirements can vary for the same research in different jurisdictions. Prospective, voluntary informed consent is a key aspect considered when approving conventional medical research. However, in certain emergency conditions, such as paediatric SE, when every minute counts, research must occur prior to obtaining informed consent, in order to evaluate new and existing therapies, and ensure patients are receiving the best possible care. While provisions for this exist in research guidelines, the ethical basis for this is complex, and it is not known what the general public thinks about this type of research. This chapter addresses objective 5 of the thesis. Results are presented from a survey of the general public on the views and perspectives of clinical research in time-critical situations, when prospective informed consent is not possible. Involving consumers in planning research and developing research guidelines is fundamental to maintaining the trust of the community. Figure 8.1 places this chapter in the context of the broader thesis.

Figure 8. 1 Conceptual model of thesis



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ORIGINAL RESEARCH

Community attitudes to emergency research without prospective informed consent: A survey of the general population

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Abstract

Objective: To give voice to the general public's views of prospective and retrospective (deferred) consent in the emergency research setting.

Methods: A cross-sectional, stratified population-based, telephone survey was conducted in April to July 2016. A questionnaire consisting of standardised health and demographic details, and seven specifically designed, and pilot-tested questions, five closed and two open text, based on literature review and previous surveys in the field was used. Quantitative and qualitative techniques were used in the data analysis. This was a centrally coordinated national telephone survey in Australia, the 2016 National Social Survey, coordinated by Central Queensland University. Data for 1217 adult (18+ years) participants were included in the analysis, with a response rate of 26%. The sample demographics were broadly representative of the Australian population.

Results: The majority of respondents were supportive of research in emergency circumstances without prospective informed consent. However, the type of research and level of risk influence its acceptability. Common themes in qualitative analysis included the critical or life-threatening nature of the illness being researched, and the potential harms and benefits of participation.

Conclusions: This research provided the first opportunity for the community to contribute to discourse about prospective and retrospective (deferred) consent in the emergency research setting in Australia. Further work is needed to determine community expectations of how this process can be optimised and implemented, and to identify potential situations where this may not be acceptable.

Key words: *consent, ethics, survey.*

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8.3 Supplementary file

See supplementary appendix 8.1. Manuscript appendices. Complete survey transcript. Table S1. Description of themes in qualitative analysis.

8.4 Summary

Chapter 8 addressed the significant knowledge gap around the Australian public's perspectives on research in time-critical situations, without prospective informed consent. This study makes an important contribution to knowledge, as it is the first published study in Australia on this topic. The main findings of the population-based survey of 1200 participants were:

- The public was generally supportive of the concept of research without prospective informed consent.
- This was true for both adult and paediatric research.
- The degree of risk, and the time-critical nature of the intervention were important considerations

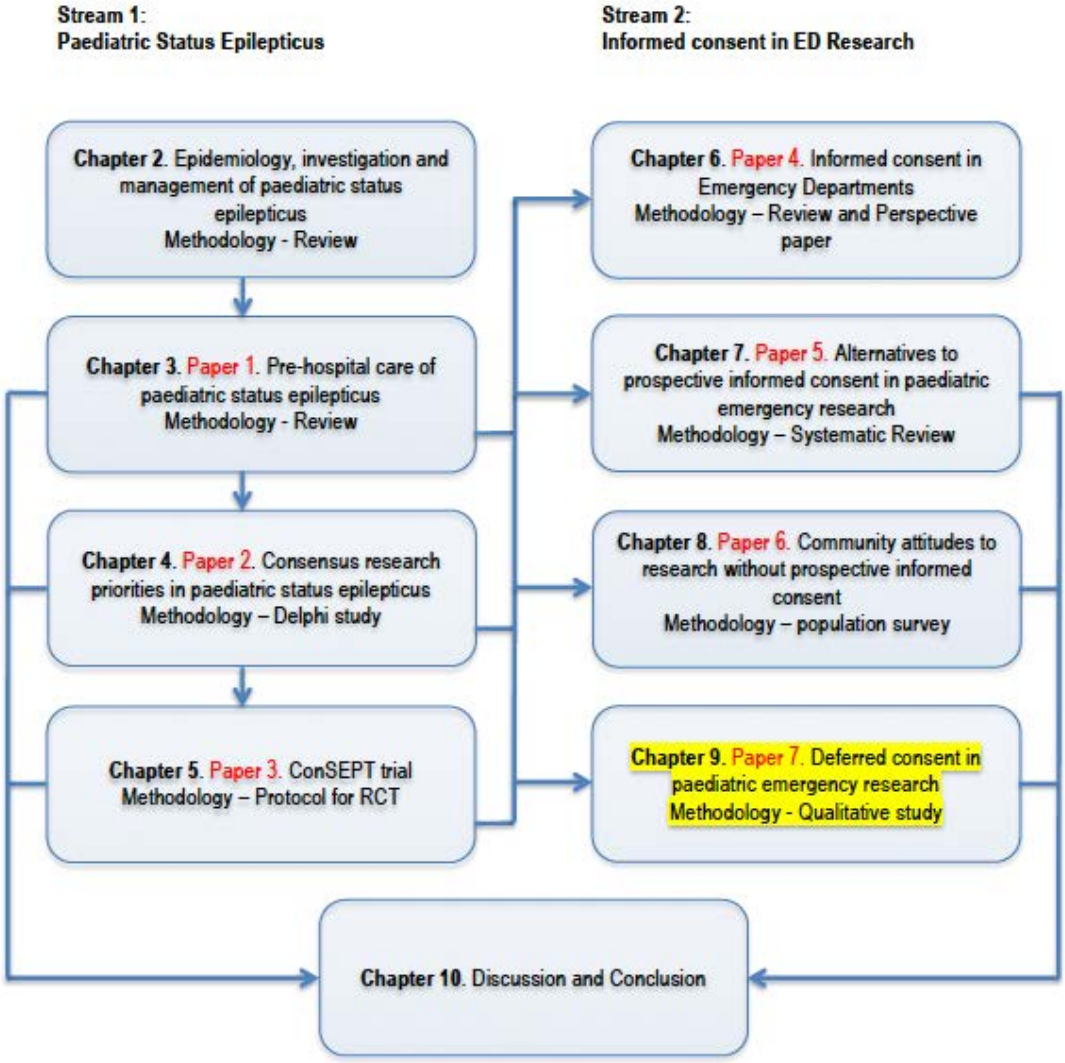
This was the first survey of this type in an Australian setting. The methodology used was limited in its ability to probe the reasoning behind individual responses. However, this research implied that research guidelines are consistent with community expectations, and that the public is supportive of emergency research. The next chapter (Chapter 9) will explore the attitudes and opinions of parents presenting to Australian EDs on research without prospective informed consent in the context of two clinical trials in children, including an interventional trial in paediatric SE.

Chapter 9: Qualitative evaluation of a deferred consent process in paediatric emergency research.

9.1 Overview

Alternative strategies to prospective informed consent have rarely been used in Australia and New Zealand to enrol participants into randomised controlled trials in paediatric emergency medicine. Emergency treatments are often instituted without informed consent for clinical care, even if treatments are unproven. When a child is enrolled in a clinical trial and receives an intervention, and consent is sought from parents at a later stage to use the data and continue in the trial, the process is termed deferred, delayed or retrospective consent. The acceptability of the process in paediatric emergency and critical care research is not known, as demonstrated by a systematic review (Chapter 7) during which no published Australian data were identified. Chapter 8 provided the first Australian population data on attitudes to alternatives to prospective informed consent in emergency research, but the methodology had limited ability to explore reasoning behind attitudes. This chapter addresses objective 6 of this thesis and explores the experiences and attitudes of parents of children attending ED for acute conditions in relation to participation in research, when prospective informed consent is not possible. Scenarios discussed in the interviews were based on authentic descriptions of cases of paediatric SE and bronchiolitis, and related to the parents' recent experience in the ED. The qualitative methodology was well suited to address the aims of the study, enabling parents to provide greater insights into the reasoning behind opinions, and explore key issues in further detail. Parents of children attending the emergency department were recruited and interviewed for the study. The recent experience in attending the ED with a sick child enabled parents to contextualize the feelings of anxiety and vulnerability associated with such visits. Figure 9.1 places this chapter in the context of the broader thesis.

Figure 9. 1 Conceptual model of thesis



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Qualitative evaluation of a deferred consent process in paediatric emergency research: a PREDICT study

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ABSTRACT

Background A challenge of conducting research in critically ill children is that the therapeutic window for the intervention may be too short to seek informed consent prior to enrolment. In specific circumstances, most international ethical guidelines allow for children to be enrolled in research with informed consent obtained later, termed deferred consent (DC) or retrospective consent. There is a paucity of data on the attitudes of parents to this method of enrolment in paediatric emergency research.

Objectives To explore the attitudes of parents to the concept of DC and to expand the knowledge of the limitations to informed consent and DC in these situations.

Method Children presenting with uncomplicated febrile seizures or bronchiolitis were identified from three separate hospital emergency department databases. Parents were invited to participate in a semistructured telephone interview exploring themes of limitations of prospective informed consent, acceptability of the DC process and the most appropriate time to seek DC. Transcripts underwent inductive thematic analysis with intercoder agreement, using Nvivo 11 software.

Results A total of 39 interviews were conducted. Participants comprehended the limitations of informed consent under emergency circumstances and were generally supportive of DC. However, they frequently confused concepts of clinical care and research, and support for participation was commonly linked to their belief of personal benefit.

Conclusion Participants acknowledged the requirement for alternatives to prospective informed consent in emergency research, and were supportive of the concept of DC. Our results suggest that current research practice seems to align with community expectations.

Strengths and limitations of this study

- The study addresses the important question of parental attitudes, perceptions and acceptability of deferred consent in paediatric emergency research.
- Qualitative methodology used is well suited to address this question.
- Participants had recent experience in emergency departments, and could contextualise the feelings of anxiety and vulnerability frequently associated with such visits.
- Participants were not involved in any clinical research; therefore, responses are hypothetical.

BACKGROUND

Conducting clinical trials with critically ill children is frequently associated with ethical dilemma. The therapeutic window for many interventions is too short to seek informed consent, and parents may be unavailable or lack capacity to provide adequately informed consent when their child is critically ill.[1] Yet critically ill children deserve high-quality care based on robust evidence of benefit, requiring clinical trials. It is generally not possible to predict in advance which children may be eligible for research in emergency settings, a limitation that makes prior consent unhelpful in most circumstances. To allow robust evidence to be generated, provisions for waiver, or exception to prospective informed consent, in certain narrow circumstances is incorporated into most international ethical guidelines for medical research.[2–6]

The process of seeking consent from a participant, or their proxy, at a time point after an experimental intervention is often termed deferred consent (DC), delayed or retrospective consent. When DC is provided, the participant continues in the trial, and their data are retained for analysis. When DC is not provided, the participant and their prior data are withdrawn from the trial and the analysis. The process of DC, while increasingly common, has a number of ethical dilemmas.[7–9] Parents do not get the opportunity to refuse the intervention as it has already been instituted by the time consent is sought; consequently, the term 'deferred consent' may be considered misleading, and consent for continued participation and for consent

to use data might be preferable. Opponents argue that such a process violates the autonomy of patients or parents; however, equally important is the argument that vulnerable populations should not be denied justice and the opportunity to participate in research.

While there is some limited data describing the attitudes, perceptions and the acceptability of DC and other alternatives to prospective informed consent in parents of critically unwell children internationally,[6 7 10] there are no data available in the Australian context. The objective of this study was to explore and describe the experiences and attitudes of parents of children attending emergency departments (EDs) for acute conditions in relation to participation in research, when prospective informed consent is not possible. This knowledge is vital to help inform the design of future trials that maintain the trust of the community and ensure research adheres to community expectations.

METHODS

We used a modified grounded theory methodology to describe and explore the phenomenon of parental attitudes to DC in parents of children presenting to EDs for emergency care.[11–13] The study was reported according to the consolidated criteria for reporting qualitative research statement on qualitative research.[14]

Conceptual perspective

This study was conceived and developed from the experiences of paediatric emergency physicians. Time-critical and stressful situations impede obtaining meaningful prospective informed consent in both clinical and research contexts. Within medicine, there exists a paradoxical acceptance of using unproven interventions outside of a research protocol without recriminations and prohibitive scrutiny, and of using either proven or unproven interventions without prospective informed consent in true emergency life-threatening situations. If the same interventions are provided as part of research, there is increased regulatory oversight whether collecting deidentified data within negligible risk, observational research or collecting data as part of a randomised controlled trial, the gold standard of robust evidence. Underlying this paradox is the strong belief that emergency research is vital, that interventions used in EDs should be evidence based and that researchers need to engage the general public to ensure that research practices are within acceptable community standards.

Setting

Data were collected in three Australian EDs: two tertiary urban paediatric facilities and one regional referral, mixed adult and paediatric centre. All are members of the Paediatric Research in Emergency Departments International Collaborative (PREDICT). At the time of the study, there were two PREDICT clinical trials in progress: The Convulsive Status Epilepticus Paediatric Trial (ConSEPT), an evaluation of levetiracetam versus phenytoin for the second-line management of convulsive status epilepticus[15]; and the high-flow nasal cannula treatment for viral bronchiolitis, a Randomised Controlled Trial—Paediatric Acute Respiratory Intervention Studies (PARIS) trial, which compared nasal high-flow therapy versus standard oxygen therapy in the management of bronchiolitis in infants and the need for escalation including higher level of care or intensive care.[16] The majority of participants in these studies are previously healthy children, with little or no contact with emergency medical services. In both circumstances, researchers and ethics committees determined that obtaining prospective informed consent would not be possible and a DC process was approved.

Participants

Using purposive sampling parents of children presenting with simple febrile seizures (non-status epilepticus) and uncomplicated bronchiolitis (not requiring admission) was identified from participating ED databases. Children in this study were not eligible for the two clinical trials described, although presented with milder forms of the same acute presentations. This was to replicate the contexts of the two studies, so that parents could contextualise the proposed research in light of their experiences.

Consent

Participants were contacted via mail up to 3 months following presentation to hospital to explain the study, with participant information and consent forms, allowing them to 'opt out' of the study (via return mail or email). Participants who opted out were not contacted further. Those who did not opt-out were contacted via telephone and again given the opportunity to decline participation. Those who consented nominated a suitable time for telephone interviewing. At interview, verbal consent was obtained and digitally recorded.

Data collection methods

Semistructured interviews were guided by a schedule of topics generated from literature and input from ConSEPT and PARIS Bronchiolitis High Flow investigators (online supplementary appendix 1). Open-ended questions encouraged participants to explore other topics and concepts. General topics included various approaches to consent in emergency medicine research, parental understanding of these research processes and decision-making, trial design and acceptability of DC as well as issues of DC in the event of poor outcome or child death. We used an iterative process, where the schedule was refined during the process of data collection and analysis.

Digitally recorded telephone interviews were conducted from March to December 2016 by a trained researcher (KM). Data collection and recruitment continued until no new themes or information was forthcoming from the data indicating that saturation had been achieved.

Data analysis

Inductive thematic data analysis followed a modified grounded theory approach, conducted iteratively throughout the study in conjunction with ongoing data collection. Interview recordings were deidentified and transcribed verbatim, and transcripts and audio imported into data management software. All analysis was supported using the qualitative software programme NVivo for Mac (QSR International Pty Ltd V.11, 2016). An initial open-coding structure was developed and was continually refined and clarified as data collection and analysis continued alongside refinements of the interview schedule. Through axial coding, emerging themes were produced through repeated reading and constant comparison between transcripts. Memo writing clarified ideas about the data and concepts regarding parental attitudes as patterns were identified.[17] This was done contemporaneously with interviews to allow refinement and test any new topics raised by participants that were of relevance to the study. At the completion of all interviews, the text was re-examined using the identified themes and coded accordingly. Audio data were examined with attention to intonation and to gain clarity of issues. A process of intercoder agreement was used to ensure the trustworthiness of the thematic analysis process, and the data further triangulated through discussion of themes in reference to literature on the topic.

RESULTS

Thirty-nine interviews were conducted over 9 months. Demographic details are presented in table 1. Participants were predominantly female (85%), identified only as 'Australian' with no religion or Christianity, were well educated and with half (54%) having a household income in excess of $A100 000.

Without exception, participants were supportive of medical research and research in emergency medicine. Themes arising from the data with regards to DC were positive and negative attitudes to DC; with reasoning behind attitudes categorised as patient/parental factors, trial design and research factors, process factors and specific issues.

Attitude to DC process

There was general, but not universal, support for research in emergency settings with DC. Demographic details did not seem to influence positive or negative attitude towards DC, neither did the condition at presentation (bronchiolitis or febrile seizure). Participants discussed several barriers to obtaining meaningful prospective informed consent such as the time-critical element of emergency research, the highly emotive environment contributing to impaired decision-making capacity:

> *I think in an emergency situation, you know, whatever has to happen has to happen*

Table 1 Participant demographics details

	n (%)
Hospital	
TTH	20 (51)
RCH	10 (26)
LCCH	9 (23)
	Total 39 (100)
Presentation	
Bronchiolitis	22 (66)
Febrile seizure	17 (44)
Age (years)	
18–34	18 (46)
35–44	17 (44)
45+	4 (10)
Sex	
Female	33 (85)
Ethnicity	
Australian	24 (61)
ATSI	1 (3)
Asian	4 (10)
Other	8 (21)
Not specified	2 (5)
Religion	
None	18 (46)
Christian	13 (33)
Buddhism	1 (3)
Islam	1 (3)
Jehovah's witness	1 (3)
Other/not identified	5 (13)
Education	
Did not complete year 12	4 (10)
Completed year 12 only	5 (13)
Postschool/non-university	11 (28)
Undergraduate university	15 (38)
Postgraduate university	4 (10)
Annual household income	
Less than $A50K	6 (15)
$A50–$A100K	8 (21)
More than $A100K	21 (54)
Unsure	4 (10)

ATSI aboriginal and/or Torres Straight Islander, $ are Australian Dollars (AUD).TTH, The Townsville Hospital; GCUH, Gold Coast University Hospital; LCCH, Lady Cilento Children's Hospital; RCH, Royal Children's Hospital.

> *I wouldn't want doctors to delay what they needed to do, if it would possibly affect my kid even more by coming out and making sure what I had to know, you know read all this and read all that, sign all this and sign all that, I just want them to do what they need to do*

Very few participants demonstrated clear negative attitude towards the concept of DC, stating 'control had been taken away'.

I don't think asking for consent later would be appropriate

Consent should always be asked before anything, not after anything

Some participants qualified comments suggesting that being 'updated' or 'kept in the loop' was important and influenced support for the concept of DC. Some could see both sides without making a definitive response either way, and indicated a preference for prior consent if at all possible.

So I can understand that sometimes it would be better in emergency just to do what needs to be done even if, especially if it was better for the child, but at the same time I… if time permits I would rather be asked or be informed in advance

Patient/parental factors

Emotional state

The majority of parents did not feel that meaningful informed consent was possible in circumstances such as attending the ED with their unwell child. The major barrier identified was their emotional state at this time, variously described as 'anxious', 'freaking out' or 'a state of shock'. Parents indicated they would not have been in the 'right frame of mind' to consider research decisions, with their focus on ensuring the child was being looked after.

when you are in an emergency situation… you're not really taking in everything they're saying anyway

I think when you are in that situation where you are so stressed, it would be extremely difficult for you to read any document or to have someone explain anything to you and for you to actually be able to go through it the way you would when you are not stressed

Those parents who felt able to make meaningful decisions at the time of ED presentation had children who tended to be improving or stable in ED. The emotional burden and ability to process information was perceived as a very personal experience; some participants suggested that their partners would have different opinions and responded differently in the same situation. One participant suggested previous work experiences were a factor contributing to decision-making ability under stressful circumstances.

my partner may not [be capable of decision making], she might be so emotionally affected that, she'd waste time trying to understand

mothers they just stress a little bit more. I think I would have been fine in that situation

in that scenario, I probably would have [been able to make an informed decision about research participation]… only cause I, like I said I am probably used to handling stressful situations [at work experiences]

Preconceptions

Regardless of the difficulty in interpreting information at certain times, if approached to participate in research under those circumstances, some implied they would be likely to respond in a predetermined way, irrespective of specific details.

I think I am always willing to help with research and I probably would have said yes straight away

I was pretty upset at the time already, and then if you think about a study you would be like, no, no, no just try the normal thing

Trust in medical teams

Generally positive attitudes to research with DC were accompanied by the theme of trust in medical teams. Parents generally expressed confidence that treating clinicians had the required expertise to make the best decisions for their child and had the best interest of the child in mind.

you guys are the professionals and if it is endorsed by the Hospital then I would be happy, honestly, like I'm not a doctor and I will never try to override what a doctor is saying and wants to do in doing their job

I wouldn't bat an eyelid if we had gone in there and you [the doctor] said look this is what we are doing

Research understanding and perceived personal benefit

Some comments suggested participants' demonstrated only a limited understanding of the research process, and often had the perception of personal benefit from research participation. Support for research with DC was occasionally conditional on such benefit.

It would have been [acceptability of research with DC] as long as it was in the best interest of my child and was going to get him better

If it was going to save his life, then yes [would be acceptable]

Trial design and research factors

Clinical severity and emergency situations

The 'critical' or 'life-threatening' nature of the condition, as well as the time-critical nature of the proposed intervention influenced attitude to research with DC. Most often, participants indicated a greater acceptability of a DC process in these circumstances.

I think if their child was critically ill and there was… no time for a parent to process all that information, then I think that a parent will understand

if it was life threatening I would say please do whatever you have to do, but if it is not necessarily life threatening and then there's going to be unknown consequences…I would like to be able to make that choice myself

Potential harm

The potential 'risk' or 'unknown consequences' associated with research was another factor that concerned parents. Whether the intervention was commonly used or equivalent to 'standard care' was important to some.

I would suppose in that case it would be [acceptable], as long as the proposed method is going to be just as safe as the regular way

you don't want to ever feel like you're putting your child at risk.

Complexity

The complexity of the proposed intervention also influenced the acceptability of the DC process. For example, when the intervention was considered to be uncomplicated, informed consent might be possible in some form.

if the research was reasonably straightforward, I think it's okay, I think you could still be stressed and you know sort of consent

Process factors

Ethics committee approval

Participants were mostly comfortable with the hospital ethics/institutional review board review procedure, and considered that these processes protected individuals' rights and well-being when participating in research. A minority acknowledged the limitations of the process.

you guys are the professionals and if it is endorsed by the Hospital then I would be happy

an ethics committee is neutral and they know the guidelines to go by and what lines not to cross and all that sort of thing, so yeah, and that to me is fine

I mean committees aren't perfectly made up of people and everybody, people have their faults, their flaws and agendas

Community consultation

The concept of community consultation was less well supported. Some responses indicated that the process may not add value, and that the 'community' chosen may not necessarily represent their personal opinions, beliefs and values.

as long as they are asking the right focus groups…,'cause different people have an opinion who shouldn't have an opinion'

but everyone doesn't have the same opinion as me

Legal issues and paperwork

Informed consent was often considered synonymous with the act of completing paperwork rather than the exchange of information. Experiences of consent processes in other circumstances, such as for routine or emergency clinical care, contributed to this notion. Some viewed the process solely as a legal issue required to 'protect both parties'.

on the night you might have signed the consent which may not mean anything because you know you are all over the place already and you just sign any paperwork that they put in front of you

just scribble a signature on a piece of paper if you really need to

The DC procedure

The most appropriate time to approach parents for consent was considered to be 'as soon as possible' but to wait until the situation had 'calmed down' or 'stabilised', for both child and parent. Parents valued being kept informed or 'in the loop' about decisions being made both in research and in clinical care. The benefit of having a dedicated support person available during the process was also mentioned.

In the situation where I was in, probably no, [I wouldn't have consented to participate in research] [be]cause I was there by myself, if there was somebody else, probably yes.

the ideal situation [is] usually [to] have several doctors that are able to, one is able to start on what's going on… another doctor is able to come and explain what is happening

I think that [being enrolled in research without prior consent] would make me feel pretty uncomfortable if I wasn't being told what was going on

Specific issues

Child death

There was considerable variation in responses regarding whether consent should be sought, or data included without consent (waiver of consent), when children died during a research study prior to obtaining consent from families. Some participants felt strongly that consent should be sought, citing respect for the family's right to know details of the circumstances. However, other participants expressed concern that informing the family would not benefit them, and may potentially cause stress and anxiety.

Definitely have to ask

there might be unfortunate outcomes but you have still got to go and seek consent

The complexity of the issue was highlighted by contrasting views advocating inclusion of data without seeking consent.

I mean if you are just looking at pure statistic numbers, and nothing more… I think just use the data

you're not putting through parents anything on top of what they have already been through

I would say I wouldn't even bother telling them, honestly

Some parents brought up the issue of potential bias in such cases. The issue of confidentiality was more important when discussing child death than in other circumstances.

But if the parents said no it wasn't included well then that stuffs up things doesn't it?

if you didn't count the children that passed, the treatment, it wouldn't be too statistical

If, if someone dies, and that's not used in the study, that's precious information lost.

One reason given for seeking consent was demonstration of the concept of beneficence. Participants felt that knowledge and skill gained when participating in research may result in contribution to the 'greater good' or something positive coming from the tragic situation, might be of comfort to grieving families.

I would want to know that the data from what would have happened with my child might help another child

Variability in responses extended to the best time to seek DC in such situations. While most agreed that this should be performed after a suitable period of grief was allowed, this varied from 'a few hours', to 'weeks', 'months' or 'case by case'. Most felt that contact should occur within weeks of the child's passing, and that it should be in a face-to-face context.

Don't send a letter, it's got to be face to face, It's got to be personal'

DISCUSSION

Our study of parents of infants and children attending EDs with bronchiolitis or febrile seizures found a generally positive attitude to DC in emergency research involving time-critical and life-threatening situations. Our results are broadly consistent with the international qualitative and quantitative research in the field.[6 7 10 18–25] Surveys in various populations including scenarios of adult trials found the majority of respondents would be willing to participate in research without informed consent,[18–20 22 23 25] which seems to be consistent in paediatric studies.[6 7 10 21 24]

Participants in our study acknowledged barriers to obtaining valid or meaningful informed consent in emergent circumstances due to their emotional state and limited time available. This is situational incapacity and is congruent with previous studies.[6 9 10 24] A United Kingdom group examined DC in a hypothetical trial similar to one of the scenarios presented in our study.[10] Parents described that capacity to provide informed consent in such circumstances was likely to be impaired, and they trusted practitioners to make research-related decisions.[10] Parents reported DC to be more acceptable if both treatment options represented 'standard care' or were 'low risk', and less acceptable if higher risk interventions were involved. Also influencing the acceptability of DC was the 'critical nature of the illness' and the therapeutic window, or how urgently the intervention needed to be administered. It is reassuring that these comments reflect existing guidance[4 26] on research without consent, which implies that guidance is in line with community expectations.

Ideas of keeping parents informed or *'in the loop'* or of limited consent expressed as *'sort of consent'* were raised during interviews. Many participants expressed that informed consent was preferred if possible or *'if time permits'*. A staged consent process was used in a large paediatric critical care trial with mixed results.[8 27] The Fluid Expansion as Supportive Therapy (FEAST) trial which explored the effect of intravenous fluids boluses in critically unwell children in Africa sought the 'assent' of parents prior to enrolment of children into the trial according to a predetermined script.[8 27] This was followed by formal written informed consent to continue in the trial and use of data. Advantages are that participants are aware of the research and have the opportunity to 'opt out' or decline participation, although this decision may not be based on a balanced assessment of the risks and benefits of participation. An opportunity to decline participation may have appealed to respondents in our study who had preconceptions about clinical trial participation, and may be perceived as respecting individuals' beliefs and values. In the FEAST trial, preconceptions were thought to contribute to automatic refusing or agreeing based on previous negative or positive experiences.[9] The opportunity to decline participation has also been identified as important in other studies.[24] While a qualitative evaluation of the FEAST trial consent process highlighted some limitations,[9] it may be worth exploring further in other settings.

Some participant responses in our study suggested that research understanding might be suboptimal, particularly with regard to the perception of personal benefit. The lack of distinction between clinical care and research has been labelled 'therapeutic misconception',[28 29] and is not unique to research in emergency settings. Estimates indicate that this is an issue up to 70% of the time in a variety of research settings.[28] The validity of consent under these circumstances is questionable. This concept was at times enmeshed with the theme of trust in medical teams to make research decisions, which seemed to contribute significantly to respondents' positive attitudes to participation in research with DC which has been previously reported.[10] While it is pleasing to think that the general public has confidence in the medical profession, and many respondents clearly understood the experimental nature of a clinical trial, in the setting of a research project the preposition that medical teams 'know what is best', or act in the patients 'best interests', is perhaps contrary to the concept of equipoise that justifies any ethical research. It may be that participants were expressing the related concept that they were confident that doctors would not be exposing patients to additional risk, but this is speculation and should be explored further in future studies. Parents were most comfortable with comparisons of two equally acceptable alternative interventions, without evidence of superiority and the concept of low or negligible 'incremental' risk.

In our cohort, the least consistent responses were found in discussions about DC in the event of child death

during a trial. Opinions were divergent on whether data should be used automatically, or consent always sought. In a postal survey in the UK, two-thirds of bereaved families anticipated wanting to be informed of trial participation at some time.[7] The deeply personal and difficult nature of this scenario may mean that generalisations are not possible. Researchers may need to consider that a 'one size fits all' approach is not appropriate, and a tailored approach taking into account patients preferences, values and beliefs is required. Implementing such an approach may require special skills.[10] Astute participants raised the potential for bias when data on bad outcomes was not collected. This has been shown to be a significant problem in the recent UK CATheter infections in CHildren (CATCH) trial, evaluating three different central line devices in elective surgery with prospective consent, and critically unwell acute presentations without prospective informed consent later approached for DC to use data collected.[30] The trial had a high mortality overall; however, the likelihood of being approached for consent was different according to outcome, disproportionately excluding children who died, and only 72% of patients randomised on emergency basis had DC obtained. The authors conclude that researchers and ethics committees need to balance the additional burden of seeking consent with the potential for bias by excluding such cases.[30] With our data suggesting divided opinion, this is an important issue for ethics committees, with the consideration of using a waiver of informed consent for primary outcome data.

Community consultation and public disclosure is a requirement in the United States for research without consent. The process has been criticised as vague and poorly defined, with identification of an appropriate 'community' to seek views for research in emergency settings being problematic.[18 51] This process was not viewed favourably by participants in our study, with parents aware that individuals participating in community consultation might not reflect their views.

Our study had a number of limitations. The population sampled was parents of infants and children attending the ED with bronchiolitis and febrile convulsions. This population was chosen to contextualise two concurrent randomised trials using DC in critically ill children. Due to resource and logistical issues, interviews were conducted up to 3 months after the presentation, which may have lead to some recall bias. Some of the included parents reported not being distressed or anxious when their children presented to the ED, and consequently they may not have been able to provide insights reflecting a true emergency situation when children present with more severe disease. However, the vast majority of participants reported distress when presenting to the ED and were mindful of the emotional impact of this situation. Second, our study was conducted in an Australian population, and may not be representative of other settings. The study population was relatively wealthy and well educated; therefore, caution is advised in transferring results to other settings. However, we purposively sought to include parents from two state capital cities and a metropolitan centre, testing the relevance of findings in different settings. Third, fewer fathers (than mothers) participated limiting this important perspective. However, this is reflective of ED presentations of children in general and the population from whom consent is likely to be obtained. Finally, parents in our study did not have direct experience of this consent process or clinical trials; therefore, their responses, although informed by recent experiences, may not reflect actual responses if exposed to this process.

In conclusion, we found parents attending EDs with their children to be broadly supportive of DC in paediatric emergency research, and aware of the limitations of prospective informed consent in emergency situations. Concerns of parents are broadly reflective of existing guidance on research in these circumstances, suggesting that current research practice seems to align with community expectations. DC in cases of child death was a difficult and contentious issue, which needs careful consideration by researchers and ethics committees when planning future clinical trials.

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REFERENCES

1. Brierley J, Larcher V. Emergency research in children: options for ethical recruitment. *J Med Ethics* 2011;37:429–32.
2. U.S. Department of Health and Human Services: Food and Drug Administration. Exception from informed consent requirements for Emergency Research; guidance for Institutional Review Boards, Clinical Investigators, and Sponsors, 2013. cited May 2017. https://http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm249673.pdf.
3. Biros MH. Research without consent: exception from and waiver of informed consent in resuscitation research. *Sci Eng Ethics* 2007;13:361–9.
4. NHMRC. National Statement on Ethical Conduct in Human Research. NHaMR C, ed: Australian Government, 2007.
5. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191–4.
6. Woolfall K, Frith L, Gamble C, *et al*. How parents and practitioners experience research without prior consent (deferred consent) for emergency research involving children with life threatening conditions: a mixed method study. *BMJ Open* 2015;5:e008522.
7. Gamble C, Nadel S, Snape D, *et al*. What parents of children who have received emergency care think about deferring consent in randomised trials of emergency treatments: postal survey. *PLoS One* 2012;7:e35982.
8. Maitland K, Molyneux S, Boga M, *et al*. Use of deferred consent for severely ill children in a multi-centre phase III trial. *Trials* 2011;12:90.
9. Molyneux S, Njue M, Boga M, *et al*. 'The words will pass with the blowing wind': staff and parent views of the deferred consent process, with prior assent, used in an emergency fluids trial in two African hospitals. *PLoS One* 2013;8:e54894.
10. Woolfall K, Young B, Frith L, *et al*. Doing challenging research studies in a patient-centred way: a qualitative study to inform a randomised controlled trial in the paediatric emergency care setting. *BMJ Open* 2014;4:e005045.
11. Bahora M, Sterk CE, Elifson KW. Understanding recreational ecstasy use in the United States: a qualitative inquiry. *Int J Drug Policy* 2009;20:62–9.
12. Vågan A. Medical students' perceptions of identity in communication skills training: a qualitative study. *Med Educ* 2009;43:254–9.
13. Birks M, Mills J. *Grounded theory - a practical guide*. Second Edition. London EC1Y 1SP: Sage Publications Inc, 2015.
14. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care* 2007;19:349–57.
15. Dalziel SR, Furyk J, Bonisch M, *et al*. A multicentre randomised controlled trial of levetiracetam versus phenytoin for convulsive status epilepticus in children (protocol): Convulsive Status Epilepticus Paediatric Trial (ConSEPT) - a PREDICT study. *BMC Pediatr* 2017;17:152. Accepted for publication.
16. Franklin D, Dalziel S, Schlapbach LJ, *et al*. Early high flow nasal cannula therapy in bronchiolitis, a prospective randomised control trial (protocol): A Paediatric Acute Respiratory Intervention Study (PARIS). *BMC Pediatr* 2015;15:183.
17. Patton MQ. *Qualitative research & evaluation methods*. Third Edition ed. London: SAGE Publishing Ltd, 2015.
18. Biros MH, Sargent C, Miller K. Community attitudes towards emergency research and exception from informed consent. *Resuscitation* 2009;80:1382–.
19. Booth MG, Lind A, Read E, *et al*. Public perception of emergency research: a questionnaire. *Eur J Anaesthesiol* 2005;22:933–7.
20. Bulger EM, Schmidt TA, Cook AJ, *et al*. The random dialing survey as a tool for community consultation for research involving the emergency medicine exception from informed consent. *Ann Emerg Med* 2009;53:341–50.
21. Dickert NW, Mah VA, Baren JM, *et al*. Enrollment in research under exception from informed consent: the Patients' Experiences in Emergency Research (PEER) study. *Resuscitation* 2013;84:1416–21.
22. Goldstein JN, Espinola JA, Fisher J, *et al*. Public opinion of a stroke clinical trial using exception from informed consent. *Int J Emerg Med* 2010;3:385–9.
23. Kämäräinen A, Silfvast T, Saarinen S, *et al*. Conduct of emergency research in patients unable to give consent-experiences and perceptions of patients, their consent providing next of kin, and treating physicians following a prehospital resuscitation trial. *Resuscitation* 2012;83:81–5.
24. Morris MC, Nadkarni VM, Ward FR, *et al*. Exception from informed consent for pediatric resuscitation research: community consultation for a trial of brain cooling after in-hospital cardiac arrest. *Pediatrics* 2004;114:776–81.
25. Sims CA, Isserman JA, Holena D, *et al*. Exception from informed consent for emergency research: consulting the trauma community. *J Trauma Acute Care Surg* 2013;74:157–65. discussion 65-6.
26. Declaration of Helsinki: World Medical Association. 2013 [cited Jan 12 2017]. Available from: http://www.wma.net/en/20activities/10ethics/10helsinki/.
27. Maitland K, Kiguli S, Opoka RO, *et al*. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011;364:2483–95.
28. Appelbaum PS. Clarifying the ethics of clinical research: a path toward avoiding the therapeutic misconception. *Am J Bioeth* 2002;2:22–3.
29. Morrow BM, Argent AC, Kling S. Informed consent in paediatric critical care research-a South African perspective. *BMC Med Ethics* 2015;16:62.
30. Harron K, Woolfall K, Dwan K, *et al*. Deferred consent for randomized controlled trials in emergency care settings. *Pediatrics* 2015;136:e1316–e1322.
31. Salzman JG, Frascone RJ, Godding BK, *et al*. Implementing emergency research requiring exception from informed consent, community consultation, and public disclosure. *Ann Emerg Med* 2007;50:448–55.

9.3 Summary

Chapter 9 addressed objective 6 and described a qualitative study of deferred consent in an interventional trial of paediatric SE in the ED setting. Interviews were conducted with 39 parents of children who presented to the ED with uncomplicated febrile seizures or bronchiolitis. The main findings of the study were as follows:

- Parents were cognisant of the limitations of prospective informed consent in time limited situations.
- Parents were generally, but not universally supportive of alternatives to prospective informed consent.
- There was a strong theme of trust in the medical profession.
- Research literacy was suboptimal, with confusion of some important concepts.

This study gives voice to consumers in the design of paediatric emergency medicine clinical trials. This research, performed in the context of two current clinical trials (1: second line management of paediatric SE; 2: high flow nasal cannula therapy in bronchiolitis), included participants from various geographic locations and varying ED types, making the results highly transferable. The qualitative methodology allowed a greater exploration of important questions and to clarify understanding of certain concepts. The results build on and are broadly consistent with international literature identified in the systematic review (chapter 7) and our population survey (chapter 8) and support current research guidelines as aligning with community expectations. Chapter 10 is the discussion and conclusions based on the work included in the thesis. The paradox of informed consent in the management and research of paediatric SE is discussed, with implications for future research and policy examined.

Chapter 10: Discussion and Conclusion

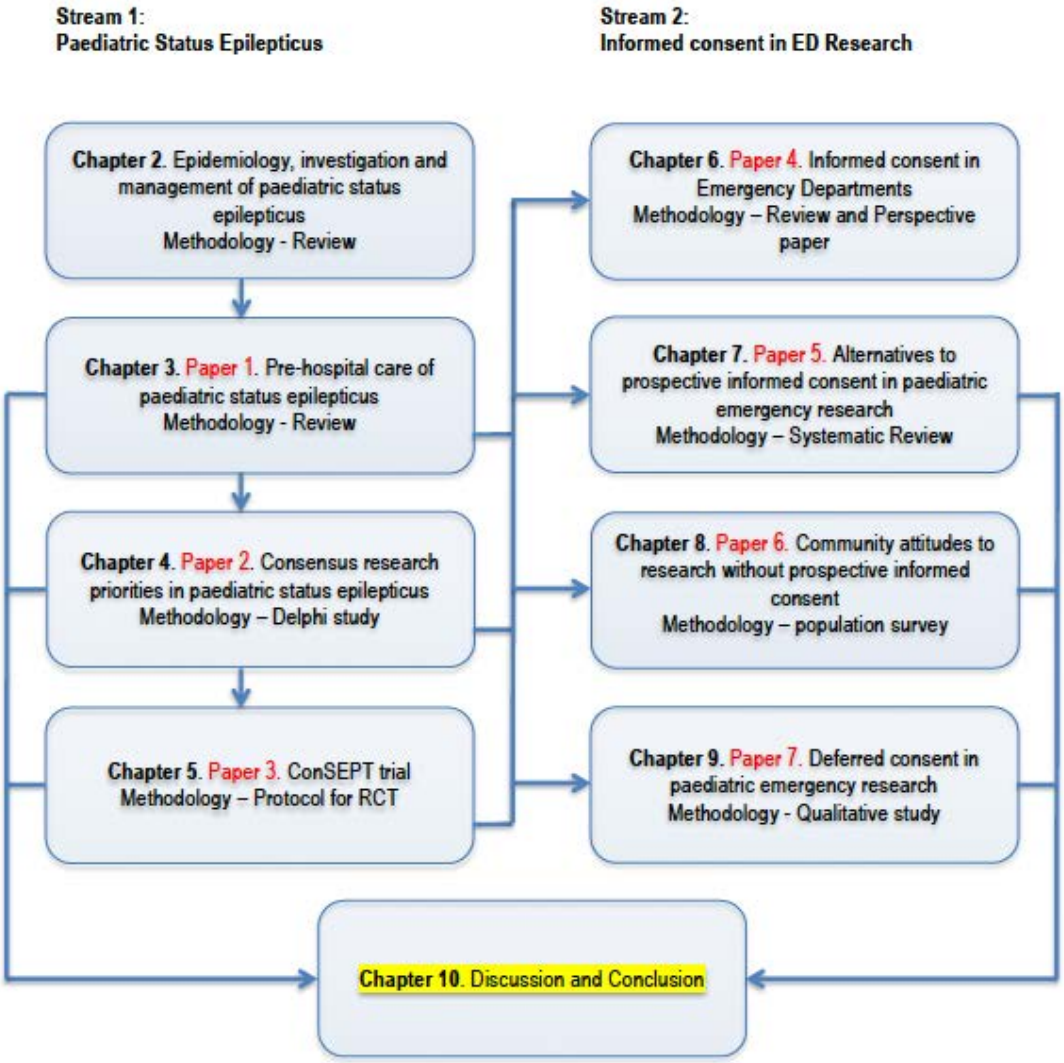
10.1 Overview

This thesis has explored the paradox of informed consent in paediatric status epilepticus (SE) research, with the aim of improving management of the condition in Australia and New Zealand. As in many areas of emergency medicine, new therapies have been adopted without high quality evidence, partly because of the difficulty of research in emergency and time-critical situations. Astute clinicians have for decades observed the paradox that it seems acceptable for clinicians to adopt new therapies for the clinical care of patients without robust evidence, whereas physicians who would rather evaluate these same therapies with methodologically sound studies, face high levels of scrutiny as well as regulatory and ethical obstacles. Inadequate medical and research literacy may be at the core of this apparent contradiction. Clinicians and the public often overestimate the effectiveness of the therapies used and fail to appreciate the additional protections that are afforded to research participants as part of a research protocol, compared to treatment decisions at the discretion of individual medical practitioners. The exposure to risk of harm is a key concern of patients. Ethical considerations should include any degree of additional risk to patients if exposed to an intervention as part of a research protocol, and the potential benefit to patients and the community of valuable medical knowledge about the efficacy of treatments. These considerations must include informed consent requirements.

A fundamental issue in a research programme to improve outcomes in paediatric SE is informed consent. The requirement for prospective informed consent remains a significant barrier to the conduct of research in paediatric SE and time-critical situations, impairing the progress of medical knowledge. Instead interventions of unknown or dubious benefit are used routinely. This is contrary to patients' expectations and is not acceptable in the era of evidence-based medicine. In my thesis I have used multiple methodologies to explore these issues, including literature reviews (narrative, systematic, perspective), Delphi consensus technique, cross-sectional population-based survey (with qualitative and quantitative components), and qualitative study (semi-structured interviews resulting in thematic analyses). The body of work has resulted in seven peer-reviewed publications. Journals were actively chosen to disseminate the research findings to the most appropriate audience, to stimulate discussion and debate among stakeholders, with the primary objective of facilitating research in paediatric SE. Despite the research being situated primarily in paediatric SE, results are also more broadly applicable to other areas of emergency medicine.

This thesis comprised two parallel, yet complimentary streams. The first stream (chapters 2 to 5) explored existing knowledge of paediatric SE, and identified stakeholder research priorities for SE, as well as the feasibility of addressing these knowledge gaps. In stream two, barriers to research in paediatric SE, namely issues of consent for time-critical ED research, were explored (chapters 6 to 9). This final chapter of the thesis is at the confluence of these two streams. In this discussion the six objectives of the thesis are reviewed, chapters and results are summarised, integrated and discussed in the context of previous research. Figure 10.1 provides an outline for the thesis as a whole and places this chapter in the context of the broader thesis. This chapter concludes with the implications for policy, practice and further research.

Figure 10. 1 Conceptual model of thesis



Initial chapters of the thesis set the scene by outlining the background of paediatric SE. In chapters 1 and 2, the background of paediatric SE was discussed, specifically in the Australasian emergency setting, and chapter 3 highlighted issues pertinent to the pre-

hospital setting. Collectively, these chapters addressed objectives 1 of the thesis. Chapter 4 was a study designed to achieve consensus on research priorities in paediatric SE using a Delphi technique, in clinical experts (emergency physicians and paediatric neurologists), as well as consumers. This chapter addressed objectives 2 and 3 of the thesis. Chapter 5 outlined the protocol for a randomised controlled trial addressing a key question in the management of SE in children. As valid, prospective informed consent is not possible in this trial, the protocol includes a controversial deferred or retrospective consent process. This chapter addresses objective 2 of the thesis. Chapters 6 to 9 comprised stream 2 of this programme of research and explored various aspects of alternatives to informed consent in emergency and paediatric emergency research. This consisted of a literature review in the broader emergency medicine context, as well as the historical background (chapter 6), a systematic review of paediatric specific issues with alternatives to informed consent (chapter 7 – objective 4); a national cross-sectional population-based survey of community attitudes to research in emergency settings without prospective informed consent (chapter 8 – objective 5) and a qualitative study of parents' views in the context of paediatric SE research without prior consent (chapter 9 – objective 6).

10.2 Knowledge gaps and research priorities in paediatric status epilepticus

Treatment of SE has confounded physicians for over a century. "Sedation" proposed as an effective modality by Shanahan in 1914, remains the mainstay of therapy and the only evidence-based approach to this day.[3] Chapters 1 and 2 provide a synopsis of the existing evidence and highlight important knowledge gaps in terms of epidemiology and aspects of diagnosis and management.

Chapter 1 reviewed the definitions, history and classifications of paediatric SE. A lack of consistency in definitions of SE over time has been problematic in SE research. Accurate and consistent medical definitions are vital for communication among physicians, to improve treatment and facilitate research. The traditional SE definition of a seizure of at least 30 minutes has recently been replaced by an "operational" definition that has been utilised in clinical trials and addressed by the ILAE in a proposed consensus statement.[15,20,23] This clinically relevant time frame of 5 minutes of continuous seizure activity emphasizing the time-critical nature of the condition, which would however prohibit obtaining prospective informed consent for research, and alternative strategies are required.

A re-worked classification system has also been developed, and accompanied the new definition.[23] This change was designed to facilitate future research efforts, and addressing issues with the previous classification used which was designed for epilepsy syndromes,

and not designed for a large proportion of patients with SE that do not have epilepsy. While significant steps forward, the reworked definitions and classification systems make interpretation of previous comparative studies difficult due to inconsistencies, and new data are urgently required.

Chapter 2 highlighted the incomplete understanding of the incidence and epidemiology of paediatric SE, signifying opportunities for further research. What many consider to be the highest quality estimate for the incidence of paediatric convulsive SE comes from London, where the crude incidence was estimated at 17-23 per 100,000 per year.[16] However, the definition used in this study included only seizures of greater than 30 minutes duration, therefore this likely represents a significant underestimate of incidence based on contemporary definitions. No quality observational studies to date have used such definitions; consequently, the true burden of disease remains unknown. A further limitation of the existing epidemiological research is that these estimates are based solely on episodes of convulsive SE. The impact of other types of SE is unknown.

As identified in chapter 2, aetiology of SE is different in children compared to adults, and changes with different ages among children. Again, childhood data is limited by varying quality and methodologies of existing data. Along with changing definitions, classification systems have also undergone revisions.[23] While the usefulness of the new system is evident, the changes again preclude comparisons with historical data. Febrile SE remains an important cause in known SE, but estimates vary greatly in available studies. The clinical utility of febrile SE as a diagnosis is also questionable, as differentiation from potentially important infective syndromes including meningitis and encephalitis is difficult. Estimates of the incidence of meningitis vary greatly, from one in five to one in ten[60,61] and robust local data is urgently needed. Other associations with potential causative factors such as antibiotics or other drugs, or inflammatory SE need to be explored. Even fundamental questions remain unanswered, such as whether seizure duration is an independent risk factor for poor prognosis, when controlled for the confounding effect of age and aetiology. Existing research does not provide conclusive evidence. With improvements in technology and infrastructure (e.g. electronic health records, learning health systems and embedded clinical registries), that can improve routinely collected data, has the potential to improve the evidence base.

Chapter 2 goes on to review the literature on the emergency investigation and management of paediatric SE. In emergency settings, assessment and management occur simultaneously. The adequacy of the patient's airway, breathing and circulation are

evaluated as a priority, and time-critical interventions are not delayed. Identification and accurate diagnosis of potential aetiology that may influence management decisions take precedence in this early phase of care. Workup may vary according to the specifics of the clinical situation. LP and CSF analysis are required if infection or immune mediated encephalopathy is suspected.[53] Neuroimaging is indicated in first episodes of paediatric SE, but may be avoided in patients with known seizure disorders.[53] Other investigations such as genetic testing are unlikely to affect management, but are an increasing area of research. Acute EEG although recommended, is infrequently available in the ED setting, even in well-resourced paediatric specialist facilities in Australia and New Zealand. Use of simplified EEG tests and algorithms that may be more broadly applicable is a current area of research interest not yet proven to modify outcomes, but perhaps could be used judiciously in cases likely to affect outcome or management decisions such as suspected psychogenic or non-convulsive SE.

As mentioned, age, aetiology and duration of seizure activity are all associated with poor outcomes, but only seizure duration is potentially modifiable. Therefore, this is often the focus of attempts to improve outcomes. With regard to treatment, high-level evidence is available only for first line agents (benzodiazepines). Observational research suggests that treatment is often delayed or inappropriate doses are administered, and that timeliness is probably more important than routes of administration.[63,122] Beyond first line treatment, data are inadequate and newer agents are increasingly used without evidence or based on low quality evidence. Levetiracetam, valproate, and lacosamide have all been variously proposed as second line agents in favour of the traditional phenytoin, which itself lacks high-level evidence.[127] None of these have been evaluated in high-quality trials. Once suspected, treatment should be directed at specific causes, including antibiotics and/or antivirals if an infective cause is suspected. Similarly, toxicological causes or inflammatory conditions may benefit from directed treatments. This represents an important knowledge gap, and a potential area to improve outcomes.

If timeliness of achieving seizure control is the most important modifiable factor, then addressing care in the pre-hospital setting represents an opportunity to improve outcomes. Pre-hospital care has evolved from merely patient transportation, to the early delivery of quality care by highly trained healthcare providers. Chapter 3 summarises the available evidence on pre-hospital management of paediatric SE. This literature review identified that definitive evidence is lacking, and that there is substantial variation in guidelines and protocols around Australia and New Zealand. Like in the ED, one of the barriers to pre-hospital research is consent. Overseas adult studies in this setting have made significant

contributions to new knowledge over the last few decades in spite of the difficulty of performing clinical trials in this setting.[18] Clear and consistent guidance on the requirements for emergency research utilising a waiver of informed consent in the US may have enabled this. Clarification of the requirements in the Australian setting is urgently required, to encourage clinical trials in this space in Australia. Guideline and policy makers need to consider this unique environment when developing standards. The population distribution in Australia requires the coordination of various states and territories, and alignment of requirements to allow adequate power to answer important clinical questions. The present situation in Australia with variation in care among disparate agencies represents a unique opportunity for quality observational research, and a natural experiment to examine effectiveness of protocols in routinely collected data or clinical registries, as well as opportunities to standardise care.

10.3 Engaging relevant stakeholders in planning paediatric status epilepticus research

Conducting research in the emergency setting is difficult and requires considerable infrastructure and costs. To ensure limited research funds are directed appropriately, it is vital that a collaborative, widely consultative, systematic approach is used to identify and clarify the immediate research priorities in paediatric SE. The engagement of key stakeholders such as experts in acute management, consumers and the general public is vital to provide input on both research priorities, and consent methods that are within acceptable community standards.

The Delphi process outlined in Chapter 4 to develop consensus represents an important first step in developing research priorities for paediatric SE. Involvement of consumers ensured that their voice was represented in the process, which is increasingly required by funding agencies, and research ethics committees as a requirement for approval. The chapter described the multistage process of solicitation and refinement of research priorities in the management of paediatric SE among paediatric neurologists and emergency physicians using an electronic online survey. The study also involved determining if these priorities aligned with priorities identified by health consumers. Nine priority research questions were identified, consisting of second line management including levetiracetam (efficacy, dose and timing), use of third line agents, induction of anaesthesia (timing and best agent), management of focal SE, and indicators of “subtle SE”. Consumers priorities included themes of drug therapies and treatment efficacy, causes and “triggers”, and outcomes and prognostication. Some of these priority areas are unlikely to be addressed in clinical trials with traditional concepts of informed consent, and other methods may be more appropriate including alternative study designs and alternative approaches to consent.

Highlighting the paradox of informed consent in emergency management of paediatric SE, some of the priorities identified have already been incorporated into clinical care. For example, intravenous levetiracetam has been increasingly recommended and used "off label" in EDs or incorporated into guidelines despite no high-level evidence in adults or children.[204] Similarly, no studies are available to guide clinicians on anaesthetic induction agents, and well-meaning clinicians facing this clinical situation choose agents on nothing more than speculation, and loose theoretical considerations. Given the infrequency of this scenario, study designs other than traditional RCTs may be more appropriate. These may include cluster RCTs, quality observational studies or studies that access data from registries or electronic medical records, so called "learning health systems" or potentially registry randomised controlled trials (RRCT).

It could be argued that the ethical and consent requirements for comparative effectiveness research, where two "standard therapies" exist should not be as stringent as for truly experimental research. Recently, in adult emergency medicine, elegant research designs incorporated into clinical care where genuine equipoise has existed for decades, and large adequately powered clinical trials, have addressed important clinical questions without individual patient consent. These include investigating the most appropriate crystalloids in sepsis,[205] and oxygen administration in high-risk acute coronary syndromes.[156] For example a recent large single centre trial in the US was conducted without individual patient consent, instead allocating patients intravenous fluid (balanced solutions versus normal saline) alternating between interventions according to the calendar month.[205] This important trial demonstrated significant differences between the two commonly used and previously interchangeable fluids in terms of serious morbidity and mortality.[205] Such a definitive trial has not previously been possible with conventional trial design and consent approaches. These designs have incorporated a randomisation process into a registry, so called RRCT. Although this design has methodological drawbacks compared to individual patient allocation, the benefits probably outweigh the downsides in acute care and emergency medicine where there are considerable competing priorities. These designs enrol patients to a specific intervention, without prospective informed consent. Ethically and from the patient's perspective, there is little difference to enrolling participants into an individually allocated RCT without prospective informed consent if this is logistically feasible in a given circumstance. In developing a programme of research to improve outcomes in paediatric SE, including research without prospective informed consent, it is imperative to assess the acceptability of these designs to the public to maintain the trust of the community.

A protocol for a clinical trial of second line management of paediatric SE was outlined in Chapter 5, the ConSEPT trial. The study directly addressed two of the nine priorities identified in the Delphi process, being efficacy and dose of levetiracetam. The trial seeks to determine if levetiracetam is a better second line agent than the current standard care of phenytoin. The trial is urgently needed. The situation with levetiracetam epitomises the paradox of informed consent in paediatric SE research. The drug is being rapidly adopted into practice by well-meaning clinicians without evidence (or informed consent), because of presumed advantages over the current standard care.[204] For many clinicians, the compulsion to use the new drug levetiracetam has proved too strong to resist. Although not the intention of the study design, the trial may also inform whether administration of a drug as a "third line" agent is a safe and effective strategy, rather than escalating to anaesthetic agents and intubation, as the protocol allows for cross over between agents as a treatment option at the clinician's discretion. Use of third line agents was also a priority identified by the Delphi process and as with anaesthetic or induction agents is unlikely to be addressed in clinical trials due to the infrequency of reaching this stage in the algorithm. Results of this pivotal trial are keenly anticipated worldwide and are likely to have a profound and immediate influence on protocols for the management of this condition.

A controversial aspect of the design of the ConSEPT trial was the "deferred consent" process. Such a consent procedure has not previously been used in a major multicentre clinical paediatric trial in Australia and New Zealand. Evaluation of this strategy and ensuring this was acceptable and within community standards was an important consideration when planning the trial. Chapters 6 to 9 of this thesis present the results of work conducted to determine acceptability of this approach. The protocol outlines the ethical justification for this consent process, which while allowable under current guidelines, and approved by several ethics committees, is being variably implemented at different sites. The NHMRC are aware of the limitations of the current guidance provided in the national statement, and the resultant confusion and inconsistency with implementation, and are currently reviewing the document with a stakeholder consultation process. Empirical research into alternatives to informed consent is lacking in the Australian setting. Chapters 7 to 9 address this knowledge gap and contribute valuable evidence to inform this issue. Ensuring a robust and consistent approach to consent requirements for clinical research is vital in ensuring that children with acute and life-threatening conditions receive evidence-based care.

Chapter 6 presents the background of the paradox of informed consent in emergency medicine research and presents some of the historical context including the Nuremburg

code and the Declaration of Helsinki.[34] The historically inconsistent approach to consent in emergency research is illustrated by the cardiac "mega-trials" in one of the most researched areas of emergency medicine.[178] A synopsis of this chapter was published as a perspective piece in Emergency Medicine Australasia, the journal of the Australasian College of Emergency Medicine. The article was designed to stimulate debate and discussion among clinicians and researchers on the unique challenges of emergency medicine research, and the specific need to address research where informed consent is not possible when developing guidelines for research ethics committees.

To gain a global perspective on issues of informed consent in paediatric emergency research, Chapter 7 detailed a systematic review of empirical evidence in this setting. The thirteen studies included in the review were generally supportive of the process with limiting risk and informing parents as soon as possible important considerations. The lack of Australian studies was notable and clearly local data are urgently required.

The requirement for informed consent in research was designed to protect participants from harm.[34] However, internationally, and particularly in the US, consent processes are instead focused on protecting researchers from litigation.[184] Seeking prospective informed consent in many circumstances may paradoxically lead to increased harm, associated with delays in treatment.[176,177] Waivers of consent, delayed or retrospective consent have been utilised infrequently in paediatric emergency care research in Australia. The ethical issues when children are involved are more complex than when contemplating similar research in adults, as children are generally not viewed as able to understand the altruistic importance and societal benefits associated with involvement in medical research. Consequently, chapter 8 presented the results of a national, cross sectional, population-based survey of community attitudes on views about research without prospective informed consent, with quantitative and qualitative components. This novel research demonstrated, for the first time in an Australian setting that the public are generally supportive of emergency research without prospective consent, although the degree of risk and time-critical nature of the intervention were identified as important considerations. Importantly, attitudes of participants were similar when considering both adult and paediatric research, implying similar standards should apply, and providing important empirical evidence relevant to policy makers and revision of guidance documents.

In chapter 9, the results of novel Australian research on attitudes and experiences of parents attending the ED with their children on the concepts of deferred or retrospective consent were presented. The qualitative study included interviews with 39 parents and found

universal support for research in this setting. As with consent for management in emergency situations, parents acknowledged the limitations of consent for research in time-critical conditions such as paediatric SE and recognised the requirement for strategies such as deferred or retrospective consent. Strong themes of trust in the medical profession emerged from the interviews. Health and research literacy was identified as an important issue, possibly leading to confusion with difficult concepts. The methodology allowed greater exploration of ideas and clarification of relevant issues. The data provided valuable insights for the design of future randomised controlled trials in this setting.

10.4 Implications for practice, policy and research

In the current era of evidence-based medicine, it is not satisfactory for the management of children with SE or other acute and time-critical conditions to be based on inadequate evidence, tradition or extrapolated from other settings. Alternatives to traditional concepts of informed consent and a consistent approach from ethics committees and guidance documents to encourage research in these important areas are required. In comparative effectiveness research, where two truly comparable and acceptable treatment strategies exist, signifying true equipoise, the paradox of informed consent for research and clinical care must be addressed. It should not be acceptable to use untested or experimental therapies for clinical care without consent, when research and evaluation of the same therapies is burdened by regulations and administrative and ethical requirements.

Advances in technology including integrated health information systems and electronic medical records may present an elegant solution to this paradox. These systems are now commonplace, and these innovations provide an excellent opportunity to embed data collection on infrequent presentations into routine data capture for clinical care, thereby enabling critical questions to be addressed more easily than has been possible previously. The level of evidence yielded would however fall short of what many consider to be the gold standard in evidence-based medicine, the RCT. Consequently, the evidence may not be sufficient to change the practice of some clinicians, although clearly representing a significant advance on the current situation.

An extension of such routine data capture or registries is the embedding of treatment allocation into registries, so called RRCT. The contention is that if true equipoise exists between two treatments for a given clinical situation, allocation can be embedded into these systems, producing the highest level of evidence, without exposing participants to any additional risk than what they would receive with “standard clinical care”, and in a very efficient manner. This is crucial. A recurrent theme in the research presented in this thesis is

that the “level of risk” is the main concern for potential participants regarding the acceptability of research without prior consent. This needs to be recognised as a priority, and ethical and legislative obstacles should be removed to facilitate this advance, and the potential to improve patient outcomes, whilst always protecting patient privacy and confidentiality.

A Delphi process involving experts including emergency physicians and paediatric neurologists identified research priorities in paediatric SE. The robust methodology will provide support for future research funding applications, and involvement of a representative group of stakeholders should not only facilitate the research conduct, but also ensure results are rapidly translated into practice. Funding bodies and human research ethics committees increasingly require methodologically sound community consultation about the acceptability of research to ensure it is consistent with societal standards and expectations. Involvement of consumers in the Delphi process strengthens the findings of the study. In this way, this research has paved the way for a comprehensive approach to improving the management and outcomes of children with SE utilising multiple methodologies.

Several of the research priorities identified are unlikely to be addressed in adequately powered, traditional RCTs. These include third line agents, and anaesthetic agents, which are used further down the algorithm when other treatments are ineffective. Observational designs using routine data capture and so called “learning health systems” provide an excellent opportunity to standardise care and affect outcomes in this group. Governments in advanced public health systems should fund such activities, which should become standard practice in health systems such as ours. The possibility of RRCT, integrating clinical trials into these platforms, exists in the future. The integration of research into clinical care may lead to increased awareness of the importance of acute and critical care research, with the flow on effects of increased research literacy in the community.

This research demonstrates that the public recognises the requirement for emergency research where prior informed consent is not possible, and generally support this type of research with the degree of risk and being informed as soon as is practical. In Australia, a national approach to conducting emergency research is challenging because informed consent requirements vary according to jurisdiction, and current guidelines are unclear and variably interpreted. Such a situation is itself unethical as it may affect the scientific validity of the research, with selection bias or delays to receiving interventions affecting efficacy, resulting in studies less likely to show benefit. This must be addressed as a priority in the form of clear and transparent guidance by the NHMRC, in explicitly outlining the

requirements for research without prospective informed consent, and by aligning various state guardianship laws, ensuring that legal barriers to such research are removed. The NHMRC has recognised the need for greater clarity in this domain, and requested feedback on a document on research without consent. This thesis can ensure that the views of the public will contribute to this discussion and result in greater participation of emergency patients in research, improving the quality of care in time-critical illness.

10.5 Strengths of the research

The research presented in this thesis has many strengths, which have been highlighted in individual chapters and publications throughout the thesis. Firstly, the research addresses an important clinical issue. Paediatric SE is the most common emergency neurological condition in children. Although presentations to individual emergency departments remain relatively infrequent, nationally it represents a considerable burden of disease, and is associated with morbidity and occasional mortality. It is a source of considerable anxiety and stress for clinicians and families, which has resource implications for health services. While the research focussed on paediatric SE, the themes and issues of informed consent are directly transferable to other paediatric emergencies and time-critical research. Multiple methodologies, including both qualitative and quantitative techniques, were actively chosen to explore greater depth and breadth of insights in relevant consumers (clinicians and parents) concerning research without prospective informed consent. This was novel research that has not been reported in an Australian population previously.

Prior research in paediatric SE has been dominated by neurologists and intensive care physicians. A further strength of this thesis, is that this work was designed and conducted by an emergency physician, facilitating a unique perspective of front-line clinicians involved in acute care decisions. This aspect and involvement of emergency physicians in identifying research priorities is a unique and compelling aspect of the research.

10.6 Limitations of the research

The limitations of the individual studies that comprised this programme of work have been discussed in detail in the individual chapters throughout the thesis. Salient limitations are briefly summarised here.

Chapter 2 (the literature review on the epidemiology, investigation and management of paediatric SE) was not a comprehensive systematic review. Although recognised and methodologically sound techniques were used to identify relevant literature, the additional requirements of a comprehensive systematic review were not undertaken. This was

intentional – the subject has previously been extensively reviewed, and there was a well-documented lack of original data on this topic. Hence a further systematic review was not expected to add anything meaningful to the evidence base but was important to include in this thesis to provide context. Hence, a traditional narrative approach was used. The additional (published) literature review on pre-hospital aspects was conducted to highlight the potential for advances in that space. For all published literature reviews, an acknowledged potential limitation, is publication bias, and inclusion of articles published in the English language.

In chapter 4, the Delphi study, without a recognised gold standard of consensus, and various definitions used previously in health research, pragmatic decisions were made. Further, only the single round was conducted for consumers. While the input of this group was considered highly important, this group were not considered "experts", with variable health literacy. Achieving consensus among this group was not thought to be achievable or of additional value.

In both chapter 8 (the national population-based survey) and chapter 9 (the qualitative study of deferred consent), hypothetical patients and scenarios were used, rather than parents of children who had actually been involved with interventional research. The inclusion of these hypothetical cases allowed the data to be available sooner, to assist with planning of future and subsequent trials. Participants in the qualitative study (chapter 9) were parents of sick children who had recently presented at an ED, to enable contextualisation of the feelings of anxiety and vulnerability associated with such visits. However, it is acknowledged that exploration of the perspectives of parents of children exposed to such research may provide additional useful insights.

Other biases already mentioned in the relevant section of the thesis include selection bias (chapter 4, chapter 8), and measurement bias (chapter 8, chapter 9). It is acknowledged that the findings presented here should be interpreted in the context of these limitations.

11.7 Conclusion

Paediatric SE remains an important clinical issue, resulting in significant morbidity and rarely mortality. Care is often not evidence based, and unproven therapies are introduced into standard care and guidelines. Paradoxically, quality research is often thwarted due in part to ethical complexities, including the inability to obtain prospective informed consent in time-critical situations. The solution to this issue is itself not straightforward but is achievable.

This thesis has utilised multiple methodologies to identify knowledge gaps and achieve consensus among key stakeholders on research priorities for paediatric SE and provided important novel insights into the community's expectations around the requirement for prospective informed consent in such situations. Future research in paediatric SE must utilise this information. It is crucial that clinical questions are addressed with quality study designs. A combination of strategies is necessary which could involve observational data based on routinely collected registry data or as part of learning health systems for infrequent situations such as third line agents and anaesthetic agents, and for preliminary data for planning of RCTs. The continued evolution and refinement of the concept of RRCTs has been an important recent innovation, and poses exciting prospects for addressing less frequent presentations, where clinical equipoise between two comparable treatment alternatives exists. Alternatives to prospective consent are required to perform high quality RCTs, to provide high level, definitive evidence for important clinical questions such as second line drugs for managing paediatric SE. Consent requirements for comparative effectiveness research, when true equipoise exists, should be reviewed, with data capture integrated into electronic health records and data collection systems. To enable this vision to move forward, policy and ethical and legal guidance must recognise the value of this data to society. Community debate about this issue would encourage higher research literacy among the general public. Maintaining the trust of the public is vital in ensuring the research is within community expectations and is the key to achieving this objective.

An important insight from the work presented was the trust in the medical profession. While this was both pleasing and reassuring, the premise underlying this trust seems to include that the physician "will do what is in the best interests of the patient". This however, belies the fact that often we simply do not have high quality evidence for many of the interventions that are commonly employed in acute care and emergency medicine, and the optimal therapeutic approach is often speculative and left to the whims and preferences of individual clinicians. The medical profession traditionally does not publicise uncertainty, presumably for fear of undermining the public's trust. Yet, greater transparency with the public about the paucity of high-quality evidence in emergency medicine may lead to increased support for emergency care research, with improvements in health and research literacy of the community. This may facilitate and encourage research in this important area.

The acceptance of emergency care without consent is well documented, and legal protections are in place for clinicians. In situations where there is clinical equipoise, and clear evidence does not exist, a compelling ethical argument can be made that similar standards should be applied to research. The paradox of the apparent community

acceptance of unproved interventions for clinical care, compared with the relative protections offered under the oversight of a quality randomised controlled trial are difficult to defend, and the data presented in this thesis does not seem to indicate that the general public make a distinction, providing that there is no exposure to additional risk.

Research in the field of paediatric status epilepticus is inextricably linked to issues of informed consent in emergency and time-critical research. This research represents an important first step in the design of a program of research on paediatric SE to address these important clinical issues, in an ethical manner that will be acceptable to the community. A combination of real time registry, learning health systems, and innovative clinical trial designs is required, with consent requirements that are appropriate for the level of risk to participants, and congruent with community expectations.

References

1. Smithells R. Iatrogenic hazards and their effects. . Postgrad Med J 1975;52 (suppl):39-52.
2. Clark P, Prout TP. Status Epilepticus: A clinical and pathological study in Epilepsy. The American Journal of Insanity 1903;LXI.
3. Shanahan WT, Colony C. Report of the meeting of the american association for the study and the care and treatment of epileptics. Epilepsia 1914;V.
4. Shorvon S. The historical evolution of, and the paradigms shifts in, the therapy of convulsive status epilepticus over the past 150 years. Epilepsia 2013;54 Suppl 6:64-7.
5. Turner W. Epilepsy, a study of the idiopathic disease. London: Macmillan; 1907.
6. Gastaut H, Courjon J, Poire R, Weber M. Treatment of status epilepticus with a new benzdoazepine more active than diazpam. Epilepsia 1971;12:197-214.
7. Gastaut H, Naquet R, Poire R, Tassinari CA. Treatment of status epilepticus with diazepam (Valium). Epilepsia 1965;6:167-82.
8. Gaspard N, Foreman B, Judd LM, et al. Intravenous ketamine for the treatment of refractory status epilepticus: a retrospective multicenter study. Epilepsia 2013;54:1498-503.
9. Glauser T, Shinnar S, Gloss D, et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Currents 2016;16:48-61.
10. Ilvento L, Rosati A, Marini C, L'Erario M, Mirabile L, Guerrini R. Ketamine in refractory convulsive status epilepticus in children avoids endotracheal intubation. Epilepsy & behavior : E&B 2015;49:343-6.
11. Gastaut H. Clinical and electroencephalographic classification of epi eptic seizures. Epilepsia 1970;11.
12. Angeles K. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. . Epilepsia 1981;22:489-501.
13. Advanced Paediatric Life Support. A Practical Approach to Emergencies. Chichester, West Sussex: John Wiley & Sons; 2016.
14. Cameron P, Jelinek G, Everitt I, Browne G, Raftos J. Tesxtbook of paediatric emergency medicine. 1st Ed ed. Philadephia, USA: Churchill Livingstone; 2006.
15. Chamberlain JM, Okada P, Holsti M, et al. Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial. JAMA 2014;311:1652-60.
16. Chin RF, Neville BG, Peckham C, et al. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet 2006;368:222-9.
17. Lowenstein D, Cloyd J. Out-of-hospital treatment of status epilepticus and prolonged seizures. Epilepsia 2007;48:96-8.
18. Silbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med 2012;366:591-600.
19. Prasad K, Al Roomi K, Krishnan P, Sequeira R. Anticonvulsant therapy for status epilepticus (Review). Cochrane Database Syst Rev 2014.
20. Lowenstein D, Bleck T, Macdonald R. It's time to revise the definition of status epilepticus. . Epilepsia 1999;40:120-2.
21. Lyttle MD, Gamble C, Messahel S, et al. Emergency treatment with levetiracetam or phenytoin in status epilepticus in children—the EcLiPSE study: study protocol for a randomised controlled trial. Trials 2017;18:283.
22. Novorol CL, Chin RFM, Scott RC. Outcome of convulsive status epilepticus: a review. Archives Of Disease In Childhood 2007;92:948-51.
23. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus - Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015;56:1515–23.
24. ILAE. Commission on Epidemiology and Prognosis of the ILAE. Guidelines for epidemiological studies on epilepsy. Epilepsia 1993;34:592-6.

25. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010;51:676-85.
26. Thurman DJ, Beghi E, Begley CE, et al. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia 2011;52 Suppl 7:2-26.
27. Falsaperla R, Striano P, Parisi P, et al. Usefulness of video-EEG in the paediatric emergency department. Expert review of neurotherapeutics 2014;14:769-85.
28. Fernandez IS, Loddenkemper T, Datta A, Kothare S, Riviello JJ, Jr., Rotenberg A. Electroencephalography in the pediatric emergency department: when is it most useful? Journal of child neurology 2014;29:475-82.
29. Babl F, Borland M, Ngo P, et al. Paediatric Research in Emergency Departments International Collaborative (PREDICT): First steps towards the development of an Australian and New Zealand research network. Emerg Med Australas 2006;18:143-7.
30. Network) PTPECAR. The Pediatric Emergency Care Applied Research Network (PECARN): Rationale, Development, and First Steps*. Acad Emerg Med 2003;10:661-8.
31. Biros M, Lewis RJ, Olson C, Runge JW, Cummins R, Fost N. Informed consent in emergency research. JAMA 1995;273:1283-87.
32. Booth MG. Informed consent in emergency research: a contradiction in terms. Science and engineering ethics 2007;13:351-9.
33. NHMRC. National Statement on Ethical Conduct in Human Research (2007) - Updated May 2015. Canberra: National Health and Medical Research Council; 2007.
34. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-4.
35. DeLorenzo R, Hauser W, Towne A, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. Neurology 1996;46:1029-35.
36. Dham BS, Hunter K, Rincon F. The epidemiology of status epilepticus in the United States. Neurocrit Care 2014;20:476-83.
37. Raspall-Chaure M, Chin RF, Neville BG, Bedford H, Scott RC. The epidemiology of convulsive status epilepticus in children: a critical review. Epilepsia 2007;48:1652-63.
38. Wu Y, Shek D, Garcia P, Zhao S, Johnston S. Incidence and mortality of generalized convulsive status epilepticus in California. Neurology 2002;58:1070-76.
39. Bergamo S, Parata F, Nosadini M, et al. Children with convulsive epileptic seizures presenting to padua pediatric emergency department: the first retrospective population-based descriptive study in an Italian Health District. Journal of child neurology 2015;30:289-95.
40. Bhalla D, Tchalla AE, Mignard C, et al. First-ever population-based study on status epilepticus in French Island of la Reunion (France) - Incidence and fatality. Seizure 2014;23:769-73.
41. Coeytaux A, Jallon P, Galobardes B, Morabia A. Incidence of status epilepticus in French-speaking Switzerland (EPISTAR). Neurology 2000;55:693-97.
42. Metsaranta P, Koivikko M, Peltola J, Eriksson K. Outcome after prolonged convulsive seizures in 186 children: low morbidity, no mortality. Developmental Medicine and Child Neurology 2004;46(1): 4-8.
43. Nishiyama I, Ohtsuka Y, Tsuda T, et al. An epidemiological study of children with status epilepticus in Okayama, Japan. Epilepsia 2007;48:1133-7.
44. Hesdorffer D, Logroscino G, Cascino G, Annegers J, Hauser W. Incidence of status epilepticus in Rochester, Minnesota, 1965-1984. Neurology 1998;50:735-41.
45. Berg AT, Shinnar S, Testa FM, et al. Status epilepticus after the initial diagnosis of epilepsy in children. Neurology 2004;63:1027-34.
46. Maytal J, Shinnar S, Moshe S, et al.. Low morbidity and mortality of status epilepticus in children. Pediatrics 1989;83(3): 323-31.
47. Berg AT, Shinnar S, Levy SR, Testa FM. Status Epilepticus in Children with Newly Diagnosed Epilepsy. Ann Neurol 1999;45:618-23.

48. Shinnar S, Berg AT, Moshe SL, et al. The Risk of Seizure Recurrence After a First Unprovoked Afebrile Seizure in Childhood: An Extended Follow-up. Pediatrics 1996;98(2): 216-25.
49. Singh RK, Stephens S, Berl MM, et al. Prospective study of new-onset seizures presenting as status epilepticus in childhood. Neurology 2010;74:636–42.
50. Henshall DC, Engel T. P2X purinoceptors as a link between hyperexcitability and neuroinflammation in status epilepticus. Epilepsy & Behavior : 2015;49:8-12.
51. Chin RF, Verhulst L, Neville BG, Peters MJ, Scott RC. Inappropriate emergency management of status epilepticus in children contributes to need for intensive care. Journal of neurology, neurosurgery, and psychiatry 2004;75:1584-8.
52. Beghi E, Carpio A, Forsgren L, et al. Recommendation for a definition of acute symptomatic seizure. Epilepsia 2010;51:671-5.
53. Riviello JJ, Ashwal S, Hirtz D, et al. Practice Parameter: Diagnostic assessment of the child with status epilepticus (an evidence-based review) Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2006;67:1542-50.
54. Raspall-Chaure M, Chin RF, Neville BGR, Scott RC. Outcome of paediatric convulsive status epilepticus: a systematic review. The Lancet Neurology 2006;5:769-79.
55. Eriksson K, Koivikko M. Status epilepticus in children: aetiology, treatment, and outcome. Developmental Medicine & Child Neurology 1997;39:652-8.
56. Hussain N, Appleton R, Thorburn K. Aetiology, course and outcome of children admitted to paediatric intensive care with convulsive status epilepticus: a retrospective 5-year review. Seizure 2007;16:305-12.
57. Kravljanac R, Djuric M, Jankovic B, Pekmezovic T. Etiology, clinical course and response to the treatment of status epilepticus in children: A 16-year single-center experience based on 602 episodes of status epilepticus. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society 2015;19:584-90.
58. Momen AA, Azizi Malamiri R, Nikkhah A, et al. Efficacy and safety of intramuscular midazolam versus rectal diazepam in controlling status epilepticus in children. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society 2015;19:149-54.
59. Saz EU, Karapinar B, Ozcetin M, et al. Convulsive status epilepticus in children: etiology, treatment protocol and outcome. Seizure 2011;20:115-8.
60. Chin RF, Neville BG, Scott RC. Meningitis is a common cause of convulsive status epilepticus with fever. Arch Dis Child 2005;90:66-9.
61. Lewena S, Pennington V, Acworth J, et al. Emergency management of pediatric convulsive status epilepticus: a multicenter study of 542 patients. Pediatric Emergency Care 2009;25:83-7.
62. Citak A, Soysal DD, Ucsel R, Karabocuoglu M, Uzel N. Seizures associated with poisoning in children: tricyclic antidepressant intoxication. Pediatrics international : official journal of the Japan Pediatric Society 2006;48:582-5.
63. Seinfeld S, Shinnar S, Sun S, et al. Emergency management of febrile status epilepticus: results of the FEBSTAT study. Epilepsia 2014;55:388-95.
64. Hesdorffer DC, Shinnar S, Lewis DV, et al. Design and phenomenology of the FEBSTAT study. Epilepsia 2012;53:1471-80.
65. Dalmau J. Status epilepticus due to paraneoplastic and nonparaneoplastic encephalitides. Epilepsia 2009;50 Suppl 12:58-60.
66. Spatola M, Novy J, Du Pasquier R, Dalmau J, Rossetti AO. Status epilepticus of inflammatory etiology: a cohort study. Neurology 2015;85:464-70.
67. Holzer FJ, Seeck M, Korff CM. Autoimmunity and inflammation in status epilepticus: from concepts to therapies. Expert review of neurotherapeutics 2014;14:1181-202.
68. Nabbout R, Vezzani A, Dulac O, Chiron C. Acute encephalopathy with inflammation-mediated status epilepticus. The Lancet Neurology 2011;10:99-108.
69. Cock HR. Drug-induced status epilepticus. Epilepsy & Behavior : 2015;49:76-82.

70. Grill MF, Maganti RK. Neurotoxic effects associated with antibiotic use: management considerations. British journal of clinical pharmacology 2011;72:381-93.
71. Tome´ AM, Filipe A. Quinolones: Review of Psychiatric and Neurological Adverse Reactions. Drug Safety 2011;43.
72. Çaksen Hs, Odabas D, Erol M, Anlar Ö, Tuncer O, Atas Bl. Do not overlook acute isoniazide poisoning in children with status epilepticus. Journal of child neurology 2003;18:142-3.
73. Minns A. Isoniazid-induced status epilepticus in a pediatric patient after inadequate pyridoxine therapy. Reactions. 2010; 210:25-6.
74. Dunn D, Parekh H. Theophylline and status epilepticus in children. Neuropediatrics 1991;22:24-6.
75. Corey LA, Pellock JM, Boggs JG, Miller LL, DeLorenzo RJ. Evidence for a genetic predisposition for status epilepticus. Neurology 1998;50:558-60.
76. Bhatnagar M, Shorvon S. Genetic mutations associated with status epilepticus. Epilepsy & behavior : E&B 2015;49:104-10.
77. Barlow K, Spowart J, Minns R. Early posttraumatic seizures in non-accidental head injury: Relation to outcome. . Dev Med Child Neurol 2000;42:591-4.
78. Goldstein J, Leonhardt D, Kmytyuk N, al. e. Abnormal neuroimaging is associated with early in-hospital seizures in pediatric abusive head trauma. Neurocrit Care 2011;15:63.
79. Papavasiliou A, Vassilaki N, Paraskevoulakos E, Kotsalis C, Bazigou H, Bardani I. Psychogenic status epilepticus in children. Epilepsy & behavior : 2004;5:539-46.
80. Tuxhorn IEB, Fischbach HS. Pseudostatus Epilepticus in Childhood. Pediatr Neurol 2002;27:407-9.
81. Pakalnis A, Paolicchi J, Gilles E. Psychogenic status epilepticus in children: Psychiatric and other risk factors. Neurology 2000;54:969.
82. Geyer JD, Payne TA, Drury I. The value of pelvic thrusting in the diagnosis of seizures and pseudoseizures. Neurology 2000;54:227.
83. Welch RD, Nicholas K, Durkalski-Mauldin VL, et al. Intramuscular midazolam versus intravenous lorazepam for the prehospital treatment of status epilepticus in the pediatric population. Epilepsia 2015;56:254-62.
84. Eriksson K, ¨ranta PM, Huhtala H, Auvinen A, Kuusela A-L, Koivikko M. Treatment delay and the risk of prolonged status epilepticus. Neurology 2005;65:1316-18.
85. Gilbert D, Gartside P, Glauser T. Efficacy and mortality in treatment of refractory generalized convulsive status epilepticus in children: a meta-analysis. Journal of child neurology 1999;14:602-9.
86. Lacroix J, Deal C, Gauthier M, Rousseau E, Farrell CA. Admissions to a pediatric intensive care unit for status epilepticus: A 10-year experience. Critical Care Medicine 1994;22:827-32.
87. Santamarina E, Gonzalez M, Toledo M, et al. Prognosis of status epilepticus (SE): Relationship between SE duration and subsequent development of epilepsy. Epilepsy & behavior : 2015;49:138-40.
88. Scott R, Surtees R, Neville B. Status epilepticus: pathophysiology, epidemiology, and outcomes. Arch Dis Child 1998;79.
89. Hesdorffer D, Logroscino G, Benn E, Katri N, Cascino G, Hauser W. Estimating risk for developing epilepsy: a population-based study in Rochester, Minnesota. Neurology 2011;76:23-7.
90. Martinos MM, Yoong M, Patil S, et al. Recognition memory is impaired in children after prolonged febrile seizures. Brain : a journal of neurology 2012;135:3153-64.
91. Trinka E, Unterrainer J, Haberlandt E, al. e. Childhood febrile convulsions—which factors determine the subsequent epilepsy syndrome? A retrospective study. Epilepsy Res 2002;50:283-92.
92. Jafarpour S, Loddenkemper T. Outcomes in pediatric patients with nonconvulsive status epilepticus. Epilepsy & behavior : 2015;49:98-103.
93. Hocker S. Systemic complications of status epilepticus--An update. Epilepsy & behavior : 2015;49:83-7.

94. Freilich ER, Schreiber JM, Zelleke T, Gaillard WD. Pediatric status epilepticus: identification and evaluation. Current opinion in pediatrics 2014;26:655-61.
95. Frank LM, Shinnar S, Hesdorffer DC, et al. Cerebrospinal fluid findings in children with fever-associated status epilepticus: results of the consequences of prolonged febrile seizures (FEBSTAT) study. The Journal of pediatrics 2012;161:1169-71.
96. Johnson KB, Michelson KA, Lyons TW, et al. Pediatric status epilepticus: how common is cerebrospinal fluid pleocytosis in the absence of infection? Seizure 2014;23:573-5.
97. Michelson K, Lyons T, Johnson K, Nigrovic L, Harper M, Kimia A. Utility of Lumbar Puncture in Children Presenting With Status Epilepticus.
. Pediatric Emergency Care 2017;33:544-7.
98. Abend NS, Bearden D, Helbig I, et al. Status epilepticus and refractory status epilepticus management. Seminars in pediatric neurology 2014;21:263-74.
99. Lyons TW, Johnson KB, Michelson KA, et al. Yield of emergent neuroimaging in children with new-onset seizure and status epilepticus. Seizure 2016;35:4-10.
100. Le Gal F, Lebon S, Ramelli GP, et al. When is a child with status epilepticus likely to have Dravet syndrome? Epilepsy Res 2014;108:740-7.
101. Abend NS, Loddenkemper T. Pediatric status epilepticus management. Current opinion in pediatrics 2014;26:668-74.
102. Brophy GM, Bell R, Claassen J, et al. Guidelines for the Evaluation and Management of Status Epilepticus. Neurocritical care 2012;17:3-23.
103. Abend NS, Chapman KE, Gallentine WB, et al. Electroencephalographic monitoring in the pediatric intensive care unit. Curr Neurol Neurosci Rep 2013;13:330.
104. Abend NS, Wagenman KL, Blake TP, et al. Electrographic status epilepticus and neurobehavioral outcomes in critically ill children. Epilepsy & Behavior : 2015;49:238-44.
105. Wilson CA. Continuous electroencephalogram detection of non-convulsive seizures in the pediatric intensive care unit: review of the utility and impact on management and outcomes. Translational pediatrics 2015;4:283-9.
106. Yigit O, Eray O, Mihci E, Yilmaz D, Arslan S, Eray B. The utility of EEG in the emergency department. Emergency medicine journal : EMJ 2012;29:301-5.
107. Payne ET, Hahn CD. Continuous electroencephalography for seizures and status epilepticus. Current opinion in pediatrics 2014;26:675-81.
108. Patel M, Bagary M, McCorry D. The management of Convulsive Refractory Status Epilepticus in adults in the UK: No consistency in practice and little access to continuous EEG monitoring. Seizure 2015;24:33-7.
109. Abdel Baki SG, Omurtag A, Fenton AA, Zehtabchi S. The new wave: time to bring EEG to the emergency department. International journal of emergency medicine 2011;4:36.
110. Millikan D, Rice B, Silbergleit R. Emergency treatment of status epilepticus: current thinking. Emergency medicine clinics of North America 2009;27:101-13, ix.
111. Kobayashi K, Yunoki K, Zensho K, Akiyama T, Oka M, Yoshinaga H. Trend figures assist with untrained emergency electroencephalogram interpretation. Brain & development 2015;37:487-94.
112. Appleton R, Macleod S, Martland T. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. The Cochrane Database Of Systematic Reviews 2008:CD001905.
113. Abend NS, Loddenkemper T. Management of pediatric status epilepticus. Current treatment options in neurology 2014;16:301.
114. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. New England Journal of Medicine 1998;339 :792-8.
115. Aranda A, Foucart G, Ducasse JL, Grolleau S, McGonigal A, Valton L. Generalized convulsive status epilepticus management in adults: a cohort study with evaluation of professional practice. Epilepsia 2010;51:2159-67.
116. Smith DM, McGinnis EL, Walleigh DJ, Abend NS. Management of Status Epilepticus in Children. Journal of clinical medicine 2016;5 (47).

117. Tobias JD, Berkenbosch JW. Management of Status Epilepticus in Infants and Children Prior to Pediatric ICU Admission: Deviations from the Current Guidelines. South Med J 2008;101:268-72.
118. Arya R, Kothari H, Zhang Z, Han B, Horn PS, Glauser TA. Efficacy of nonvenous medications for acute convulsive seizures: A network meta-analysis. Neurology 2015;Neurology® 85:1859-68.
119. Holmes GL. Buccal route for benzodiazepines in treatment of seizures? The Lancet Neurology 1999;353:608.
120. McMullan J, Sasson C, Pancioli A, Silbergleit R. Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: a meta-analysis. Acad Emerg Med 2010;17:575-82.
121. Zhao ZY, Wang HY, Wen B, Yang ZB, Feng K, Fan JC. A Comparison of Midazolam, Lorazepam, and Diazepam for the Treatment of Status Epilepticus in Children: A Network Meta-analysis. Journal of child neurology 2016;31:1093-107.
122. Fernández IS, Abend NS, Agadi S, et al. Time from convulsive status epilepticus onset to anticonvulsant administration in children. Neuology 2015;84:2304-11.
123. Babl FE, Sheriff N, Borland M, et al. Emergency management of paediatric status epilepticus in Australia and New Zealand: practice patterns in the context of clinical practice guidelines. Journal Of Paediatrics And Child Health 2009;45:541-6.
124. Claassen J, Hirsch L, Mayer S. Treatment of status epilepticus: a survey of neurologists. J Neurol Sci 2003; 211:37–42.
125. Abend NS, Huh JW, Helfaer MA, Dlugos DJ. Anticonvulsant medications in the pediatric emergency room and intensive care unit. Pediatric Emergency Care 2008;24:705-18.
126. Knake S, Gruener J, Hattemer K, et al. Intravenous levetiracetam in the treatment of benzodiazepine refractory status epilepticus. Journal of neurology, neurosurgery, and psychiatry 2008;79:588-9.
127. Rossetti AO. Are Newer AEDs Better Than the Classic Ones in the Treatment of Status Epilepticus? J Clin Neurophysiol 2016;33:18–21.
128. Alvarez V, Januel JM, Burnand B, Rossetti AO. Second-line status epilepticus treatment: comparison of phenytoin, valproate, and levetiracetam. Epilepsia 2011;52:1292-6.
129. Mundlamuri RC, Sinha S, Subbakrishna DK, et al. Management of generalised convulsive status epilepticus (SE): A prospective randomised controlled study of combined treatment with intravenous lorazepam with either phenytoin, sodium valproate or levetiracetam--Pilot study. Epilepsy Res 2015;114:52-8.
130. Bleck T, Cock H, Chamberlain J, et al. The established status epilepticus trial 2013. Epilepsia 2013;54 Suppl 6:89-92.
131. Morrison G, Gibbons E, Whitehouse WP. High-dose midazolam therapy for refractory status epilepticus in children. Intensive care medicine 2006;32:2070-6.
132. Wilkes R, Tasker RC. Pediatric intensive care treatment of uncontrolled status epilepticus. Critical care clinics 2013;29:239-57.
133. Tasker RC, Vitali SH. Continuous infusion, general anesthesia and other intensive care treatment for uncontrolled status epilepticus. Current opinion in pediatrics 2014;26:682-9.
134. Abend NS, Dlugos DJ. Treatment of refractory status epilepticus: literature review and a proposed protocol. Pediatric neurology 2008;38:377-90.
135. Rossetti A, Milligan T, Vulliémoz S, Michaelides C, Bertschi M, Lee J. A randomized trial for the treatment of refractory status epilepticus. Neurocrit Care 2011;14:4-10.
136. Vohra TT, Miller JB, Nicholas KS, et al. Endotracheal Intubation in Patients Treated for Prehospital Status Epilepticus. Neurocrit Care 2015;23:33-43.
137. Owens J. Medical management of refractory status epilepticus. Seminars in pediatric neurology 2010;17:176-81.
138. Wheless JW. Treatment of refractory convulsive status epilepticus in children: other therapies. Seminars in pediatric neurology 2010;17:190-4.

139. Rosati A, Ilvento L, L'Erario M, et al. Efficacy of ketamine in refractory convulsive status epilepticus in children: a protocol for a sequential design, multicentre, randomised, controlled, open-label, non-profit trial (KETASER01). BMJ Open 2016;6:e011565.
140. Rosati A, L'Erario M, Ilvento L, et al. Efficacy and safety of ketamine in refractory status epilepticus in children. . Neurology 2012;79:2355-58.
141. Zeiler FA, Zeiler KJ, Teitelbaum J, Gillman LM, West M. Modern inhalational anesthetics for refractory status epilepticus. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques 2015;42:106-15.
142. Legriel S, Pico F, Tran-Dinh Y, et al. Neuroprotective effect of therapeutic hypothermia versus standard care alone after convulsive status epilepticus: protocol of the multicentre randomised controlled trial HYBERNATUS. Ann Intensive Care 2016;1.
143. Britton PN, Eastwood K, Paterson B, et al. Consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand. Internal medicine journal 2015;45:563-76.
144. Shah AS, Eddleston M. Should phenytoin or barbiturates be used as second-line anticonvulsant therapy for toxicological seizures? Clinical toxicology 2010;48:800-5.
145. Balasubramanian R, Agarwal D. Delphi Technique- A Review. International Journal of Public Health Dentistry 2012;3:16-25.
146. Rixon A, Smith TF, McKenzie B, Sample R, Scott P, Burn S. Perspectives on the art of facilitation: a Delphi study of natural resource management facilitators. Australian Journal of Environmental Management 2007;14:179-91.
147. Okoli C, Pawlowski SD. The Delphi method as a research tool: an example, design considerations and applications. Information & Management 2004;42:15-29.
148. Deane HC, Wilson CL, Babl FE, et al. PREDICT prioritisation study: establishing the research priorities of paediatric emergency medicine physicians in Australia and New Zealand. Emergency medicine journal : EMJ 2018;35:39-45.
149. Hartshorn S, O'Sullivan R, Maconochie IK, et al. Establishing the research priorities of paediatric emergency medicine clinicians in the UK and Ireland. Emergency medicine journal : EMJ 2015;32:864-8.
150. McIntyre S, Novak I, Cusick A. Consensus research priorities for cerebral palsy: a Delphi survey of consumers, researchers and clinicians. Developmental medicine & child neurology 2010;52:270-5.
151. Fatovich DM. Medical reversal: What are you doing wrong for your patient today? Emerg Med Australas 2013;25:1-3.
152. Hagihara A, Hasegawa M, Abe T, Nagata T, Wakata Y, Miyazaki S. Prehospital Epinephrine Use and SurvivalAmong Patients With Out-of-Hospital Cardiac Arrest. JAMA 2012;307:1161-68.
153. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. Resuscitation 2011;82:1138-43.
154. Lin S, Callaway CW, Shah PS, et al. Adrenaline for out-of-hospital cardiac arrest resuscitation: A systematic review and meta-analysis of randomized controlled trials. Resuscitation 2014; 85(6): 732-40.
155. Stub D, Smith K, Bernard S, et al. Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction. Circulation 2015;131:2143-50.
156. Hofmann R, James SK, Jernberg T, et al. Oxygen Therapy in Suspected Acute Myocardial Infarction. N Engl J Med 2017;377:1240-9.
157. Prasad V, Gall V, Cifu A. The frequency of medical reversal. Arch Intern Med 2011;171:1675–6.
158. Coats TJ. Consent for emergency care research: the Mental Capacity Act 2005. Emergency medicine journal : EMJ 2006;23:893-4.
159. Dutton RP, Stansbury LG, Hemlock B, Hess JR, Scalea TM. Impediments to obtaining informed consent for clinical research in trauma patients. The Journal of trauma 2008;64:1106-12.

160. Ellenberg SS. Informed consent:Protection or Obstacle? Some Emerging Issues. Controlled Clinical Trials 1997;18:628-36.
161. Eltorki M, Uleryk E, Freedman SB. Waiver of informed consent in pediatric resuscitation research: a systematic review. Acad Emerg Med 2013;20:822-34.
162. Cone DC, O'Connor RE. Are US informed consent requirements driving resuscitation research overseas? Resuscitation 2005;66:141-8.
163. The Oxford Textbook of Clinical Research ethics. New York: Oxford University Press; 2008.
164. Schmidt TA. The legacy of the Tuskegee syphilis experiments for emergency exception from informed consent. Ann Emerg Med 2003;41:79-81.
165. Foex BA. The problem of informed consent in emergency medicine research. Emergency medicine journal : EMJ 2002;18:198-204.
166. Beuchamp T. Informed consent. In: Veatch RM, ed. Medical Ethics Second Edition ed. Sunbury: Jones and Bartlett Publishers; 1997.
167. Hirshon JM, Hansoti B, Hauswald M, et al. Ethics in Acute Care Research: A Global Perspective and Research Agenda. Acad Emerg Med 2013;20:1251-8.
168. Coats TJ. Ethical and practical issues in trauma care research. The British journal of surgery 2012;99 Suppl 1:6-7.
169. Lecouturier J, Rodgers H, Ford GA, et al. Clinical research without consent in adults in the emergency setting: a review of patient and public views. BMC medical ethics 2008;9:9.
170. White B, McDonald F, Willmontt L. Health Law in Australia. Australia: Thomson Reuters; 2014.
171. Faden R, Kass N, Whicher D, Stewart W, Tunis S. Ethics and Informed Consent for Comparative Effectiveness Research With Prospective Electronic Clinical Data. . Med Care 2013;51.
172. Faden RR, Beauchamp TL, Kass NE. Informed Consent, Comparative Effectiveness, and Learning Health Care. NEJM 2014;370.
173. Platt R, Kass NE, McGraw D. Ethics, regulation, and comparative effectiveness research: time for a change. JAMA 2014;311:1497-8.
174. Baren JM, Fish SS. Resuscitation research involving vulnerable populations: are additional protections needed for emergency exception from informed consent? Acad Emerg Med 2005;12:1071-7.
175. Brierley J, Larcher V. Emergency research in children: options for ethical recruitment. Journal of medical ethics 2011;37:429-32.
176. CRASH. Research in emergency situations: with or without relatives consent. Emergency medicine journal : EMJ 2004;21:703.
177. Roberts I, Prieto-Merino D, Shakur H, Chalmers I, Nicholl J. Effect of consent rituals on mortality in emergency care research. Lancet 2011;377:1071-2.
178. Gammelgaard A. Informed consent in acute myocardial infarction research. The Journal of medicine and philosophy 2004;29:417-34.
179. Turner E. Substitute decision-making for participation in medical research. Australian Health Law Bulletin 2015:66-70.
180. Young WF. Change of Shift, informed consent. Ann Emerg Med 1997;30:350-1.
181. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Lancet 1986;8478:397-402.
182. An International randomized trial comparing four thrombolytic stratergies for acute myocardial infarction. The GUSTO Investigators. . NEJM 1993;329:674-82.
183. Tognoni G, Geraci E. Approaches to informed consent. Controlled Clinical Trials 1997;18:621-7.
184. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet 1988;2:349-60.

185. Ockene I, Miner J, Shannon T, Gore J, Weiner B, Ball S. The consent process in the thrombolysis in myocardial infarction (TIMI – phase I) trial. Clinical Research 1991;39:13-7.
186. Yuval R, Halon DA, Merdler A, et al. Patient comprehension and reaction to participating in a double-blind randomized clinical trial (ISIS-4) in acute myocardial infarction. Arch Intern Med 2000;160:1142-46.
187. Hunter D, Pierscionek B. Children, Gillick competency and consent for involvement in research. Journal of Medical Ethics 2007;33:659-62.
188. Neuman G, Shavit I, Matsui D, Koren G. Ethics of research in pediatric emergency medicine. Paediatric drugs 2015;17:69-76.
189. Franklin D, Dalziel S, Schlapbach LJ, et al. Early high flow nasal cannula therapy in bronchiolitis, a prospective randomised control trial (protocol): A Paediatric Acute Respiratory Intervention Study (PARIS). BMC pediatrics 2015;15:183.
190. Gray JD. The problem of consent in emergency medicine research. Cjem 2001;3:213-8.
191. Roberts I, Coats T, Edwards P, et al. HALT-IT--tranexamic acid for the treatment of gastrointestinal bleeding: study protocol for a randomised controlled trial. Trials 2014;15:450.
192. Harron K, Woolfall K, Dwan K, et al. Deferred Consent for Randomized Controlled Trials in Emergency Care Settings. Pediatrics 2015; 135:5.
193. Jansen TC, Kompanje EJ, Bakker J. Deferred proxy consent in emergency critical care research: ethically valid and practically feasible. Crit Care Med 2009;37:S65-8.
194. Maitland K, Molyneux S, Boga M, Kiguli S, Lang T. Use of deferred consent for severely ill children in a multi-centre phase III trial. Trials 2011;12:90.
195. Woolfall K, Frith L, Gamble C, et al. How parents and practitioners experience researh without prior consent (deferred consent) for emergency research involving children with life threatening conditions: a mixed method study. BMJ Open 2015;5.
196. Johnson LR, Siddaiah R. Use of deferred consent for enrolment in trials is fraught with problems. BMJ 2015;351:h4609.
197. Ripley E, Ramsey C, Prorock-Ernest A, Foco R, Luckett Jr S, Ornato JP. EMS Providers and Exception From Informed Consent Research: Benefits, Ethics, and Community Consultation. Prehosp Emerg care 2012;16:425-33.
198. Zelen M. A New Design for Randomized Clinical Trials. N Engl J Med 1979;300:1242-5.
199. Adamson J, Cockayne S, Puffer S, Torgerson D. Review of randomised trials using the post-randomised consent (Zelen's) design. Contemporary clinical trials 2006;27:305-19.
200. Schellings R, Kessels A, ter Riet G, Knottnerus J, Sturmans F. Randomized consent designs in randomized controlled trials: systematic literature search. Contemporary Clinical Trials 2006;27:320-32.
201. Torgerson D, Roland M. What is Zelen's design? BMJ 1998;316:606.
202. Abboud PA, Heard K, Al-Marshad AA, Lowenstein SR. What determines whether patients are willing to participate in resuscitation studies requiring exception from informed consent? Journal of medical ethics 2006;32:468-72.
203. Dickert N, Kass N. Patients' perceptions of research in emergency settings: a study of survivors of Sudden Cardiac Death. Soc Sci Med 2009;68:183-91.
204. Dionisio S, Brown H, Boyle R, Blum S. Managing the generalised tonic-clonic seizure and preventing progress to status epilepticus: a stepwise approach. Internal medicine journal 2013;43:739-46.
205. Semler MW, Self WH, Wanderer JP, et al. Balanced Crystalloids versus Saline in Critically Ill Adults. New England Journal of Medicine 2018;378:829-39.

Appendices

1.1 Supplementary Appendix – List of aetiologies that may cause status epilepticus

1 Cerebrovascular diseases
- a Ischemic stroke
- b Intracerebral bleeding
- c Subarachnoid bleeding
- d Subdural hematoma
- e Epidural hematoma
- f Sinus venous thrombosis and cortical venous thrombosis
- g Posterior reversible leukoencephalopathy syndrome
- h Vascular dementia

2 CNS infections
- a Acute bacterial meningitis
- b Chronic bacterial meningitis
- c Acute viral encephalitis (including Japanese B encephalitis, herpes simplex encephalitis, human herpesvirus 6)
- d Progressive multifocal leukoencephalopathy (PML)
- e Cerebral toxoplasmosis
- f Tuberculosis
- g Neurocysticercosis
- h Cerebral malaria
- i Atypical bacterial infections
- j HIV-related diseases
- k Prion diseases (Creutzfeldt-Jakob disease, CJD)
- l Protozoal infections
- m Fungal diseases
- n Subacute sclerosing panencephalitis
- o Progressive Rubella encephalitis

3 Neurodegenerative diseases
- a Alzheimer's disease
- b Corticobasal degeneration
- c Frontotemporal dementia

4 Intracranial tumors
- a Glial tumors
- b Meningioma
- c Metastases
- d Lymphoma
- e Meningeosis neoplastica
- f Ependymoma
- g Primitive neuroectodermal tumor (PNET)

5 Cortical dysplasias
- a Focal cortical dysplasia (FCD) II, tuberous sclerosis complex (TSC), hemimegalencephaly, hemihemimegalencephaly
- b Ganglioglioma, gangliocytoma, dysembryoplastic neuroepithelial tumor (DNET)
- c Periventricular nodular heterotopia (PNH) and other nodular heterotopias
- d Subcortical band heterotopia spectrum
- e Lissencephaly
- f Familial and sporadic polymicrogyria
- g Familial and sporadic schizencephaly
- h Infratentorial malformations (e.g., dentate dysplasia, mamillary dysplasia, etc.)

6 Head trauma

a Closed head injury
b Open head injury
c Penetrating head injury

7 Alcohol related
a Intoxication
b Alcohol withdrawal
c Late alcohol encephalopathy with seizures
d Wernicke encephalopathy

8 Intoxication
a Drugs
b Neurotoxins
c Heavy metals

9 Withdrawal of or low levels of antiepileptic drugs

10 Cerebral hypoxia or anoxia

11 Metabolic disturbances (e.g., electrolyte imbalances, glucose imbalance, organ failure, acidosis, renal failure, hepatic encephalopathy, radiation encephalopathy, etc.)

12 Autoimmune disorders causing SE
a Multiple sclerosis
b Paraneoplastic encephalitis
c Hashimoto's encephalopathy
d Anti-NMDA (N-methyl-D-aspartate) receptor encephalitis
e Anti–voltage–gated potassium channel receptor encephalitis (including anti–leucine–rich glioma inactivated 1 encephalitis)
f Anti-glutamic acid decarboxylase antibody associated encephalitis
g Anti–alpha–amino–3–hydroxy–5–methylisoxazole–4–propionic acid receptor encephalitis
h Seronegative autoimmune encephalitis
i Rasmussen encephalitis
j Cerebral lupus (systemic lupus erythematosus)
k CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) syndrome
l Adult-onset Still's disease
m Goodpasture syndrome
n Thrombotic thrombocytopenic purpura (Moschcowitz syndrome, Henoch Sch€onlein purpura)

13 Mitochondrial diseases causing SE
a Alpers disease
b Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)
c Leigh syndrome
d Myoclonic encephalopathy with ragged red fibers (MERRF)
e Neuropathy, ataxia, and retinitis pigmentosa (NARP)

14 Chromosomal aberrations and genetic anomalies
a Ring chromosome 20
b Angelman syndrome
c Wolf-Hirshhorn syndrome
d Fragile X syndrome
e X-linked mental retardation syndrome
f Ring chromosome 17
g Rett syndrome
h Down syndrome (trisomy 21)

15 Neurocutaneous syndromes
a Sturge-Weber syndrome

16 Metabolic disorders
a Porphyria
b Menkes disease

c Wilson disease
d Adrenoleukodystrophy
e Alexander disease
f Cobalamin C/D deficiency
g Ornithine transcarbamylase deficiency
h Hyperprolinemia
i Maple syrup urine disease
j 3-Methylcrotonyl Coenzyme A carboxylase deficiency
k Lysinuric protein intolerance
l Hydroxyglutaric aciduria
m Metachromatic leukodystrophy
n Neuronal ceroid lipofuscinosis (types I, II, III, including Kufs disease)
o Lafora disease
p Unverricht-Lundborg disease
q Sialidosis (type I and II)
r Morbus Gaucher
s Beta ureidopropionase deficiency
t 3-Hydroxyacyl CoenzymeAdehydrogenase deficiency
u Carnitine palmitoyltransferase deficiency
v Succinic semialdehyde dehydrogenase deficiency

17 Others
a Familial hemiplegic migraine
b Infantile onset spinocerebellar ataxia (SCA)
c Wrinkly skin syndrome
d Neurocutaneous melanomatosis
e Neuroserpin mutation
f Wolfram syndrome
g Autosomal recessive hyperekplexia
h Cockayne syndrome
i Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
j Robinow syndrome
k Malignant hyperpyrexia
l Juvenile Huntington’ s disease (Westphal variant)

1

1.2 Supplementary Appendix: Communiqué - Research involving patients who are unable to give consent 2017

Human medical research is a complex area which involves consideration of both legal and ethical principles. Any person undertaking human medical research is expected to comply with relevant policies and guidelines when conducting their studies, including the following:

National Statement on Ethical Conduct in Human Research (National Statement)
Queensland Health Research Ethics and Governance Health Service Directive and Research Management Policy
Queensland Health's Guide to Informed Decision-making in Healthcare

It is essential that anyone conducting research involving humans obtains informed consent from the patient (or authorised substitute decision-maker) before enrolling that patient in a research study. However, in specific circumstances, Human Research Ethics Committees (HREC) can grant a waiver of the requirement for patient consent to use the patient's personal information, including personal health information, in research, including medical research. The conditions associated with granting a waiver are strict and advice should always be sought from the HREC.

In some studies where a waiver has been granted, researchers may inform study participants or their substitute decision-makers about the study *after* the patient has been enrolled in the study. Some researchers have incorrectly referred to this practice as obtaining 'deferred' or 'delayed' consent for participation in the research study.

The concepts of 'deferred' or 'delayed' consent are not supported by the National Statement or by Queensland Health

The terms deferred or delayed consent are confusing. They do not exist in the National Statement and do not constitute any form of consent. This is because it is not possible to obtain a person's consent to something after that thing has already happened. Accordingly, the concepts of deferred or delayed consent are not recognised or supported by Queensland Health, and Queensland Health requires that the terms must not be used by researchers or HRECs operating in Queensland Health.

Waiver of consent for research using personal information in medical research or personal health information

When an HREC grants a waiver of the requirement for patient consent to participate in a research study, research participants will characteristically not know that they, or perhaps their tissue or data, are involved in the research. Once enrolled, researchers may inform the patient or substitute decision-maker about the inclusion of the patient in the research, but they would not be required to obtain consent at any stage.

Where an HREC has waived the requirement for researchers to obtain a patient's consent to be enrolled in a study, this does <u>not</u> mean that legal requirements regarding obtaining a patient's informed consent to *treatment* have been waived. Regardless of whether a waiver has been granted from a research perspective, treating health practitioners must always discharge their legal duties to the patient, which include:

to provide treatment only when a patient (or a substitute decision-maker) consents to that treatment, or where consent is not required (such as in an emergency situation);
to warn patients of the material risks attaching to the treatment; and
to exercise reasonable skill and care in the provision of services, including examination,

diagnosis and treatment.

Patients who require medical care who may be unable to give consent

When neither the potential research participant nor an authorised substitute decision-maker can consider the research proposal and give consent, such as in an emergency setting, an HREC may, having taken account of relevant jurisdictional laws, approve a research project without consent if the requirements of clause 4.4.13 of the National Statement are satisfied. If these requirements are satisfied, it may be open for health practitioners to decide (using reasonable professional judgement in the circumstances) to enrol a patient into a clinical research study, including research conducted in an emergency setting, without the patient's (or a substitute decision-maker's) consent to participate. However, it is Queensland Health policy that this may only occur where:

experimental treatments are not being tested as part of the research study; and
the health practitioner has satisfied their legal duties to the patient, which includes having exercised reasonable skill and care in the provision of the treatments being studied.

If the study involves researching, for example, the effectiveness of specific, randomly assigned clinical interventions, the study must involve an intervention where there is genuine uncertainty in the expert medical community over whether a treatment will be beneficial. If it is not known whether an intervention is effective, then it is Queensland Health policy that consent of the patient (or authorised substitute decision-maker) must be obtained.

More information

For more information, please contact the Health Innovation, Investment and Research Office, Department of Health on 3199 2973.

National Health and Medical Research Council, *National Statement on Ethical Conduct in Human Research 2007* (May 2015) < HYPERLINK "https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/e72_national_statement_may_2015_150514_a.pdf" https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/e72_national_statement_may_2015_150514_a.pdf>.

QHEPS, Research Ethics and Governance Health Service Directive # QH-HSD-035:2016 HYPERLINK "https://www.health.qld.gov.au/__data/assets/pdf_file/0025/494008/qh-hsd-035.pdf" https://www.health.qld.gov.au/__data/assets/pdf_file/0025/494008/qh-hsd-035.pdf

QHEPS, *Research Management Policy QH-POL-013:2015* (23 June 2015) HYPERLINK "https://www.health.qld.gov.au/system-governance/policies-standards/doh-policy/policy/qh-pol-013.pdf" https://www.health.qld.gov.au/system-governance/policies-standards/doh-policy/policy/qh-pol-013.pdf.

QHEPS, *Queensland Health Guide to Informed Decision-making in Healthcare* (February 2012) < HYPERLINK "https://www.health.qld.gov.au/consent/documents/ic-guide.pdf" https://www.health.qld.gov.au/consent/documents/ic-guide.pdf>.

For information regarding who can legally provide consent on behalf of patients who lack capacity to make decisions about a person's healthcare, consult the *Queensland Health Guide to Informed Decision-making in Healthcare*, available on QHEPS here: HYPERLINK "https://www.health.qld.gov.au/consent/documents/ic-guide.pdf" https://www.health.qld.gov.au/consent/documents/ic-guide.pdf.

For information regarding when it may be appropriate for an HREC to waive the requirement for informed consent to participate in a research study, consult clause 2.3.9 of the *National Statement on Ethical Conduct in Human Research.*

Just a note that, in taking this position, it means that Qld Health is determining that there is no way for emergency research that involves experimental treatments to take place (without consent of the patient).

We note that this is actually consistent with the National Statement because the combination of paragraphs 4.4.6 – and 4.4.1 and 2.3.6 (now 2.3.10) to which it refers – creates a situation in which an HREC can only consider a waiver of consent if the emergency care research is low-risk, which experimental treatment in an emergency care research context is unlikely to be. Some have argued that this outcome was not intentional and should be re-considered.

On this point, please note that NHMRC will be commencing with a full review of Section 4 of the National Statement in 2017.

Preferable definitions of clinical equipoise might be: "where there is genuine uncertainty in the expert medical community over whether a treatment will be beneficial" or "where there is no decisive evidence that the intervention being tested will be superior to existing treatments or effective at all."

This phrasing suggests that clinical researchers would use an intervention in research that they already consider to be *less effective than* standard treatment, whereas, in reality, if they suspected that, they would (or should) not do the research. Use of an intervention presumes that it is not known whether the intervention is *as effective as* or *more or less effective than* standard treatment.

2.1 Supplementary appendix - Medline search strategy

1 epilep$.mp.
2 seizure$.mp.
3 convulsion$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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5 tonic clonic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept
word, unique identifier]
6 status epilepticus.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
7 1 or 2 or 3 or 4 or 5 or 6
8 Animals/
9 Humans/
10 8 not 9
11 7 not 10
12 (child: or adolescent or infan:).mp.
13 11 and 12
14 exp Emergency Medical Services/
15 exp Military Medicine/
16 exp Emergency Medicine/
17 exp Emergency Treatment/
18 exp First Aid/
19 exp Emergency Medical Technicians/
20 exp Ambulances/
21 exp Air Ambulances/
22 prehospital.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
23 pre-hospital.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
24 paramedic$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
25 ambulance$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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34 emergency despatch$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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42 community support coordinator.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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45 physician assistant.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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47 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
48 13 and 46
49 13 and 47
50 limit 49 to yr="2014 -Current"

3.1 Supplementary appendix - Medline search strategy

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keyword heading word, protocol supplementary concept word, rare disease supplementary concept
word, unique identifier]
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5. tonic clonic.mp. [mp = title, abstract, original title, name of substance word, subject heading word,
keyword heading word, protocol supplementary concept word, rare disease supplementary concept
word, unique identifier]
6. status epilepticus.mp. [mp = title, abstract, original title, name of substance word, subject heading
word, keyword heading word, protocol supplementary concept word, rare disease supplementary
concept word, unique identifier]
7. 1 or 2 or 3 or 4 or 5 or 6
8. Animals/
9. Humans/
10. 8 not 9
11. 7 not 10
12. (child: or adolescent or infan:).mp.
13. 11 and 12
14. exp Emergency Medical Services/
15. exp Military Medicine/
16. exp Emergency Medicine/
17. exp Emergency Treatment/
18. exp First Aid/
19. exp Emergency Medical Technicians/
20. exp Ambulances/ 7336 Advanced
21. exp Air Ambulances/ 2146 Advanced
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keyword heading word, protocol supplementary concept word, rare disease supplementary concept
word, unique identifier]
23. pre-hospital.mp. [mp = title, abstract, original title, name of substance word, subject heading word,
keyword heading word, protocol supplementary concept word, rare disease supplementary concept
word, unique identifier]
24. paramedic$.mp. [mp = title, abstract, original title, name of substance word, subject heading word,
keyword heading word, protocol supplementary concept word, rare disease supplementary concept
word, unique identifier]
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unique identifier]
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concept word, unique identifier]
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supplementary concept word, unique identifier]
34. emergency despatch$.mp. [mp=title, abstract, original title, name of substance word, subject heading
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concept word, unique identifier]
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word, unique identifier]
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heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
37. emergency rescue.mp. [mp = title, abstract, original title, name of substance word, subject heading
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concept word, unique identifier]
38. emergency resus$.mp. [mp = title, abstract, original title, name of substance word, subject heading
word, keyword heading word, protocol supplementary concept word, rare disease supplementary
concept word, unique identifier]
39. emergency triage.mp. [mp = title, abstract, original title, name of substance word, subject heading
word, keyword heading word, protocol supplementary concept word, rare disease supplementary
concept word, unique identifier]
40. advanced life support.mp. [mp = title, abstract, original title, name of substance word, subject heading
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concept word, unique identifier]
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subject heading word, keyword heading word, protocol supplementary concept word, rare disease
supplementary concept word, unique identifier]
42. community support coordinator.mp. [mp = title, abstract, original title, name of substance word, subject
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45. physician assistant.mp. [mp = title, abstract, original title, name of substance word, subject heading
word, keyword heading word, protocol supplementary concept word, rare disease supplementary
concept word, unique identifier]
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or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47. 13 and 46

4.1 Supplementary appendix (Delphi study)

Table S5.1.1 Complete Delphi question rankings and scores.

Question	Round Two			Round Three		
	% ≥ 4*	Mean (SD)	Median (IQR)	% ≥ 4*	Mean (SD)	Median (QIR)
1. In **infants** with convulsive SE, is levetiracetam superior to phenytoin (or phenobarbitone) for efficacy (seizure termination) and safety (adverse effects)?	85%	5.3 (1.1)	5 (5-6)			
2. In children with convulsive SE, is levetiracetam superior to phenytoin for efficacy (seizure termination) and safety (adverse effects)?	82%	5.5 (1.3)	6 (5-6)			
3. In children with convulsive SE is the early use of anaesthesia associated with more rapid seizure terminations, less complications and better long-term outcomes, compared to anticonvulsant treatment alone?	82%	5.2 (1.2)	5 (5-6)			
4. In children with convulsive SE, is earlier administration of a second line agent (e.g. levetiracetam) more effective than standard protocols?	74%	4.9 (1.1)	5 (4.25-6)			
5. If EEG is not available, what are the most reliable clinical indicators of ongoing subtle SE?	73%	4.9 (1.4)	5 (4-6)			
6. In children with focal SE should the medical management proceed according to similar treatment pathways as for convulsive SE, and within the same time frames?	72%	4.7 (1.1)	5 (4-5)			
7. In children with convulsive SE, what is the most appropriate dose of levetiracetam as a second line agent?	68%	5.0 (1.2)	5 (4-6)	77%	4.9 (1.2)	5 (5-6)
8. In children with convulsive SE who require intubation, what induction agent is most effective for seizure termination, long-term outcome and complications (e.g. ketamine, propofol, thipentone, other)?	68%	4.8 (1.1)	5 (4-6)	81%	5.1 (1.2)	5 (5-6)
9. In children with convulsive SE, Is third line medical anticonvulsant drugs compared with induction of anaesthesia and intubation associated with improved long-term outcomes?	66%	4.9 (1.2)	5 (4-6)	81%	5.1 (1.0)	5 (5-5.75)
10. In children with recurrent convulsive SE, is home treatment with benzodiazepines associated less escalation of care?	66%	4.9 (1.3)	5 (4-6)	60%	4.6 (1.4)	5 (3.25-6)
11. In children with convulsive SE, is seizure duration a predictor of long-term outcome independent of aetiology?	65%	4.7 (1.3)	5 (4-5)	68%	4.7 (1.3)	5 (4-5.75)
12. In children with convulsive SE treated with benzodiazepines at home, how common is respiratory depression?	63%	4.7 (1.5)	5 (4-6)	48%	4.3 (1.4)	4 (3-5)

13. In children with non-convulsive SE should the medical management proceed according to similar treatment pathways as for convulsive SE, and within the same time frames?	61%	4.7 (1.3)	5 (4-5.5)	58%	4.2 (1.5)	5 (3-5)
14. In children with convulsive SE after two doses of benzodiazepines, is pre-hospital administration of levetiracetam superior to phenytoin or levetiracetam administered in the emergency department (ED) to achieve termination of seizure?	61%	4.5 (1.4)	5 (4-5)	56%	4.5 (1.2)	5 (4-5)
15. Is recognition of subtle SE or non-convulsive SE in the ED associated with improved outcomes in children with SE?	59%	4.7 (1.2)	5 (4-5)	60%	4.6 (1.3)	5 (4-5)
16. In children with convulsive SE treated in the pre-hospital setting, what is the most effective benzodiazepine to achieve seizure termination?	59%	4.6 (1.4)	5 (4-6)	37%	4.0 (1.3)	4 (3-5)
17. In infants with convulsive SE, is phenobarbitone superior to phenytoin for efficacy (seizure termination) and safety (adverse effects)?	55%	4.7 (1.1)	5 (4-5)	42%	4.3 (1.5)	4 (3-5)
18. In children with convulsive SE, does access to EEG in the ED change decision-making and improve outcomes?	54%	4.6 (1.5)	5 (4-6)	54%	4.4 (1.4)	5 (4-5)
19. In children with convulsive SE, what factors are associated with a delay to administration of a second line agent?	53%	4.7 (1.2)	5 (4-5.75)	55%	4.5 (1.3)	5 (4-5)
20. In children with convulsive SE, is sodium valproate superior to phenytoin for efficacy (seizure termination) and safety (adverse effects)?	53%	4.5 (1.4)	5 (4-5)	42%	4.2 (1.5)	4 (4-5)
21. In children with convulsive SE, is the utility of MRI superior to CT in the acute setting for accurate diagnosis and prognostication?	53%	4.3 (1.7)	5 (3-6)	39%	4.2 (1.5)	4 (3-5)
22. In children with convulsive SE due to prolonged febrile seizure, what is the yield of neuroimaging in the acute setting?	53%	4.2 (1.6)	5 (3-5)	47%	4.2 (1.3)	4 (3.25-5)
23. In children with prolonged febrile seizures, should the medical management proceed according to similar treatment pathways as for convulsive SE, and within the same time frames?	50%	4.6 (1.3)	5 (4-6)			
24. In children with convulsive SE who fail to recover fully between seizures, what time needs to elapse, before a third dose of benzodiazepine is appropriate, without the risk of respiratory depression?	47%	4.3 (1.4)	4 (3.25-5)			
25. In children with convulsive SE is iv lorazepam superior to iv midazolam for efficacy (seizure termination) and safety (adverse effects)?	46%	4.1 (1.4)	4 (3-5)			
26. In children with convulsive SE and a fever, does treatment with IV paracetamol, shorten the time to termination of seizure?	42%	4.3 (1.3)	4 (4-5)			
27. In children presenting with presumed convulsive SE, does early Neurologist review (either in person or through review of transmitted video of the SE features) improve diagnosis of the form of SE, management of the SE and outcome?	41%	4.2 (1.4)	4 (3-5)			

28. In children with suspected pseudoseizures, what is the best way to confirm the diagnosis, without the need to escalate management?	41%	4.2 (1.4)	4 (3-5)			
29. In children with convulsive SE, is there a role for the use of ketamine in the non-intubated patient?	38%	4.2 (1.1)	4 (4-5)			
30. In children with convulsive SE treated at home, is IM midazolam more effective than IN / buccal administration for seizure termination?	38%	3.9 (1.4)	4 (3-5)			
31. In children with convulsive SE, is IM fosphenytoin as effective to IV phenytoin for seizure termination?	37%	3.8 (1.4)	4 (3-5)			
32. In children with convulsive SE, Is there utility in end tidal CO2 as a predictor of the need for induction of anaesthesia and intubation?	32%	4.0 (1.3)	4 (3.25-5)			
33. Is failure to achieve IV access, associated with delay in second line drug administration?	32%	3.8 (1.5)	4 (3-5)			
34. In children with convulsive SE, are doses of benzodiazepines outside of published guidelines associated with better or worse outcomes, than children who are managed within current guidelines.	28%	3.9 (1.3)	4 (3-5)			
35. In children with convulsive SE, is there a role for the use of propofol in the non-intubated patient?	24%	4.0 (1.0)	4 (4-4)			
36. In children with convulsive SE, does the use of steroids decrease the rate of long-term complications?	19%	3.9 (1.1)	4 (3-4)			
37. In children with convulsive SE, does paradehyde still have a place in the management algorithm?	18%	3.5 (1.8)	4 (3-4)			

*Denotes proportion of respondents who ranked question fairly high priority (4 on scale) or higher. SD standard deviation.

	denotes questions achieving consensus high priority		denotes questions that did not reach consensus (or intermediate priority).		denotes consensus low priority

Table S5.1.2 Expert text comments on consensus High Priority questions in round 2 and 3.

1. In <u>infants</u> with convulsive SE, is levetiracetam superior to phenytoin (or phenobarbitone) for efficacy (seizure termination) and safety (adverse effects)?

"Three arm study feasible? PHT, PB, LEV"

"PHB is now known to be very toxic for infant brains and this study therefore has ethical concerns"

"in neonates this is an important question"

"Use of phenobarbitone is generally unethical given the impact on development/cognition and is therefore avoided"

2. In children with convulsive SE, is levetiracetam superior to phenytoin for efficacy (seizure termination) and safety (adverse effects)? *"Practice currently ahead of evidence which always concerns me"* *"Currently being undertaken in at least three countries. May need post marketing surveillance for true safety data"* *"Important, but happening now"* *"Current study needs completing before new one is planned"* *"Levetiracetam is rapidly becoming the standard second line agent in the absence of independent studies supporting this in either adults or children"*
3. In children with convulsive SE is the early use of anaesthesia associated with more rapid seizure terminations, less complications and better long-term outcomes, compared to anticonvulsant treatment alone? *"Would be important to clarify RSI agents and on-going sedatives/antiepileptics (e.g. midaz infusion) used"* *"this is concerning as a question and unethical"* *"Trend to use anaesthesia without EEG and without understanding the consequences"* *"increased aggressive treatment earlier may result in over treatment of many children"* *"unlikely to get ethics approval"* *"Noting that some participants considered this an unethical question, it should be mentioned that there is a heterogeneity in practice and some vocal individuals promote intubation at 15 minutes, while others are extremely reluctant to intubate. So with such polarised opinion clearly this question is ethical and important."*
4. In children with convulsive SE, is earlier administration of a second line agent (e.g. levetiracetam) more effective than standard protocols? *"would be interesting to know if should be given earlier if already had a prolonged period of SE prehospital"* *"No rigorous studies exist"* *"This could be a pre-hospital study – our ambulance service is already keen to use levetiracetam for SE"* *"Levetiracetam holds promise to be safer and more practical than PHT"*
5. If EEG is not available, what are the most reliable clinical indicators of ongoing subtle SE? *"There are no reliable clinical indicators, even for a neurologist"* *"EEG will probably never be widely available so this is important"* *"The utility of EEG has to be assessed prior to this PICO"* *"the rate of over diagnosis of seizures and movement disorders as CSE is high"* *"video capture of presenting seizures might be very valuable to subsequent diagnosis"*
6. In children with focal SE should the medical management proceed according to similar treatment pathways as for convulsive SE, and within the same time frames? *"Focal seizures are potentially more injurious than generalised ones"* *"most focal seizures you will be targeting will tend to settle or secondarily generalise anyway"*

"will include a heterogeneous group" *"Often focal SE may be associated with nasty underlying causes"* *"important to be incorporated into guidelines, as there is an ongoing belief in some places that focal seizures don't matter"*
7. In children with convulsive SE, what is the most appropriate dose of levetiracetam as a second line agent? *"wide safety range. Neurology tends to use lower doses than ED"* *"current trials should help answer that question"* *"20 mg/kg"*
8. In children with convulsive SE who require intubation, what induction agent is most effective for seizure termination, long-term outcome and complications (e.g. ketamine, propofol, thiopentone, other)? *"Anaethetists can do this bit"* *"This mandates EEG before and after intubation/induction agent."*
9. In children with convulsive SE, Is third line medical anticonvulsant drugs compared with induction of anaesthesia and intubation associated with improved long-term outcomes? *"Multicentre observational study/retrospective study in first instance may be of interest"* *"Rigorous studies are not available for this PICO"* *"Low dose propofol for SE?"* *"Would not ketamine, which preserves the airways and is not likely to increase intubation rate due to dosing issues in a heterogenous population be a better agent to consider at this point?"*

7.1 Supplementary appendix

Appendix 1. Medline (Ovid) Search

1. exp Emergency Medical Services/
2. exp Emergency Medicine/
3. exp Emergency Treatment/
4. ems.mp.
5. emt.mp.
6. emergency services.mp.
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8. emergency practitioner$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9. emergency triage.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
10. emergency care practitioner.mp.
11. exp Physician Assistants/
12. exp Emergencies/
13. emergenc$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
14. exp Resuscitation/ or exp Resuscitation Orders/
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
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34. "school child*".ab,ti.
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39. under*age*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
40. pubescen*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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42. "school*".ab,ti.
43. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44. exp Informed Consent/
45. deferred.ab,ti.
46. delayed.ab,ti.
47. waiver.ab,ti.
48. exception.ab,ti.
49. retrospective.ab,ti.
50. alternative.ab,ti.
51. 45 or 46 or 47 or 48 or 49 or 50

52. 44 and 51
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54. (delayed adj3 consent).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
55. (waiver adj3 consent).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
56. (exception adj3 consent).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
57. (retrospective adj3 consent).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
58. (alternative adj3 consent).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
59. 53 or 54 or 55 or 56 or 57 or 58
60. 52 or 59
61. 15 and 43 and 60

8.1 Supplementary appendix - EMA publication

Consent Social Survey – Manuscript - Appendices

Appendix 1.

Informed consent in hospital emergency room research

[READ STATEMENT IN FULL]

The following questions are about your opinion regarding research that is undertaken in hospital emergency departments and the issue of consent. Before ANY research happens within an emergency department, the research plan is reviewed and approved by a Human Research Ethics Committee and the hospital also reviews the research plan and monitors the research. It is also usual to get the patient's permission to include them in the research - this is known as consent. However, in certain emergency situations, treatment needs to be started immediately with no time for discussion with the patient or their family. This type of situation may also involve the need for the doctor to enrol the patient in a research study before a family member can be found or contacted. Examples include: patients requiring urgent treatment for severe head injury, stroke, and cardiac arrest.

QRF1: Would you support emergency research which has been approved by an ethics committee but involves starting treatment before consent can be obtained?

[READ OPTIONS 1-3]

1. Yes, I would support this
2. I might support this depending on the circumstances
3. No, I would not support this

DO NOT READ

4. Don't know/Unsure
5. No response

If (ans=1) skp QRF2
If (ans>2) skp QRF2

QRF1b: What types of circumstances or factors would influence your decision?
[PROBE FOR A RESPONSE - ENTER COMMENTS]

[READ STATEMENT IN FULL]

There are two main types of clinical research that occur in hospital emergency departments. The first type involves comparing a standard treatment that a patient would usually receive, with a newly developed treatment, in order to examine if the new treatment is as good as or better than the standard treatment. The second type involves comparing two treatments that are already used as standard practice to examine if one is better than the other.

For the purposes of the next few questions, please imagine that you are seriously injured or unconscious, and you and your relatives are unable to provide consent.

QRF2: What type of clinical research study would be acceptable for you to be automatically included as a participant, without your prior consent? Remembering that the studies would have the approval of the hospital and ethics committee.

[READ OPTIONS 1-4 IN FULL AND SELECT ONE RESPONSE]

1. Any type of research study would be acceptable
2. Only a study comparing two standard forms of treatment
3. Only a study comparing a standard treatment with a new form of treatment
4. None - Inclusion without consent would not be acceptable for any study

DO NOT READ

5. Don't know/Unsure
6. No response

QRF3: What type of clinical research study would be acceptable for YOUR CHILD to be automatically included as a participant, without your prior consent? (If you do not have children please answer hypothetically, as if you did have children).

[READ OPTIONS 1-4 IN FULL AND SELECT ONE RESPONE]

1. Any type of research study would be acceptable
2. Only a study comparing two standard forms of treatment
3. Only a study comparing a standard treatment with a new form of treatment
4. None - Inclusion without consent would not be acceptable for any study

DO NOT READ

5. Don't know/Unsure
6. No response

[READ STATEMENT]
We'd now like you to imagine that you were enrolled in a research study but you had been unable to give consent because of a condition such as a stroke or severe head injury.

QRF4: In this situation, how important would it be to you that you are told about the study as soon as you were able to understand? For example, if you were unconscious and then later regained consciousness?

[READ OPTIONS 1-4]

1. Very important
2. Important
3. Not very important
4. Not at all important

DO NOT READ

5. Don't know/Unsure
6. No response

[READ STATEMENT]
In clinical trials it is important to include both good and bad patient outcomes in order to obtain reliable information about how well the treatment works.

QRF5: If a patient who was part of a research study dies during their time in an emergency department and information about their treatment could be used in the study, do you think it would be acceptable to use the data without the families' consent?

1. Yes
2. No

DO NOT READ

3. Don't know/Unsure

4. No response

If (ans=1) end section
If (ans>2) end section

Q: QRF5b
What do you think is the best time to approach the family in these circumstances to seek consent?

1. Immediately
2. After a suitable period of time has passed
3. Never

DO NOT READ

4. Don't know/Unsure
5. No response

If (ans=1) end section
If (ans>2) end section

Q: QRF5c
Could you describe when you think it would be most suitable?

[PROBE FOR A RESPONSE - ENTER COMMENTS]

Appendix 2.

Table S1. Description of themes in qualitative analysis.

Question: What types of circumstances or factors would influence your decision? (Support for research before consent)	
Theme	**Description**
1. Clinical factors	Included qualifying statements from participants who were supportive of conducting emergency research without seeking prospective consent in the instance of a life-threatening event or in time-critical situations.
2. Perceived Personal benefit	Included statements from participants who indicated support on the expectation of personal benefit from research participation. This theme also included statements addressing the relative risks and possible harms to participants.
3. Patient factors	This theme included responses that indicated support for research without prospective consent, conditional on taking into consideration the patients' personal beliefs, preferences and values. This included prior wishes if expressed, religious or cultural factors, e.g. blood product transfusions for Jehovah's Witnesses.
4. Trust in medical teams	Support for research without prospective consent was associated for trust in medical teams, and concepts that medical judgment would protect their best interests.
5. Surrogate decision makers (SDM)	Included statement that highlighted the importance of SDM, and suggested that they should be involved in decisions if possible.
6. Altruism	Support for participation in research was associated with concepts of doing things for others, and for the benefit of society.
7. Deferred consent	Although the introductory stem included that consent would be sought later, respondents' statements about the importance of this concept was highlighted by comments in this theme
Question: In the case of a death as part of a research study, when is the best time to seek consent to use data already collected?	
Theme	**Description**
1. Depends on circumstances	Responses classified in this theme related the problems with attempting to generalise, indicating that it would depend on many factors
2. Time for grief	This theme participants stressed the importance allowing sufficient time for families to grieve, prior to being approached for consent. This was variably defined.