The challenges and opportunities associated with deferred consent in time-sensitive pediatric emergency research: a systematic review

By

Jhalok Ronjan Talukdar

McMaster University

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Jhalok Ronjan Talukdar

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Author: Jhalok Ronjan Talukdar

Degree: Master of Science (MSc)

Department: Health Research Methodology

University: McMaster University, Hamilton, Ontario

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Thesis supervisor: Professor Lisa Schwartz

Thesis co-supervisor: Dr. Melissa J Parker

Thesis committee: Professor Lisa Schwartz

Dr. Melissa J Parker

Dr. Cynthia Lokker

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Abstract

Introduction

Obtaining informed consent is mandatory to involve human subjects in research. Researchers need to provide adequate information to the participants about the study including risks and benefits associated with the study in simple language so that the participants can comprehend the information. Informed consent has to be obtained from parents/guardians if the participants are children under 18. However, it is not feasible to obtain informed consent from parents/guardians in a time-sensitive pediatric emergency. In such situations, the clinicians may need to start the treatment immediately. The researchers often do not have time to provide adequate information to the parents/guardians to take informed consent. The parents may also not be in the right mental space to comprehend this information. Deferred consent is introduced to conduct studies in time-sensitive medical emergencies. It is also used to conduct studies in time-sensitive pediatric medical emergencies. It allows the researchers to enroll children in the study immediately and take consent as early as the health condition of the children is stabilized. Deferred consent is a new phenomenon in time-sensitive pediatric emergency research and there is a lack of evidence regarding the opportunities and challenges associated with this consent model. This review explored the challenges and opportunities associated with the application of this model in time-sensitive pediatric emergency research.

Methods

Four databases - MEDLINE, EBMASE, CINAHL, and PsycINFO were searched for the articles developing a comprehensive search strategy. The identified articles were deduplicated. The titles and abstracts of these articles were screened, the full-text articles were collected and read for final selection. The selected articles were imported to NVivo 12. These articles were coded using

NVivo 12 for thematic analysis of them. The identified themes explored the challenges and opportunities associated with deferred consent.

Results

The children, parents, and practitioners had positive impressions about deferred consent. They thought using deferred consent would allow the practitioners to start the treatment immediately and would give them enough time to discuss research participation later. However, there were some challenging situations for the practitioners to take deferred consent from the parents. It was difficult for them to understand when the appropriate time is to approach the parents for research discussion. The practitioners were also in a dilemma whether they should approach bereaved parents for deferred consent. They also faced ethical dilemma for collecting extra blood for study purposes only. Moreover, it was also challenging for them to address the concerns of the parents about the study.

Conclusion

Deferred consent in time-sensitive pediatric emergency research allows the clinicians to recruit the children immediately and take consent from the parents when their health condition is stable. The children, parents and practitioners had support for differed consent. However, it was challenging for the practitioners to find a suitable time to discuss research with the parents. It was difficult for them to approach the bereaved parents for deferred consent. There was a lack of studies on deferred consent especially studies which explored perspectives of children and bereaved parents on deferred consent. More studies on deferred consent in time-sensitive pediatric emergency research will guide future researchers to overcome their ethical dilemma in this situation and contribute more in pediatric emergency medicine.

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Chapter 1: Background

Informed consent: An overview

The research on human subjects has faced many challenges which include regulatory, scientific and ethical challenges. Many research studies, for example, those uncovered by the Nuremberg Trials and the Tuskegee Syphilis Study were harmful to the human subjects on which they were conducted. These past abuses in research encouraged governmental and medical organizations during the mid-twentieth century to take measures to protect the people who participate as subjects in research [1]. The Nuremberg Code, which was issued in 1947 [2], is the foundation of other guidelines developed later to protect human subjects during research [1, 2]. It has 10 basic principles. It introduces the concept of voluntary consent in the first principle [1-4]. The definition of voluntary consent has four major components which include legal competence of the person, voluntariness in nature, the person should be informed of the topic of the research and should comprehend the subject matter sufficiently to take an informed decision [3]. In principle 9 of The Nuremburg Code, it also allows the participants to withdraw themselves from the study [1-4].

Though the Nuremberg Code initiated fundamental principles for the protection of human subjects during research, it did not outline practical guidelines on conducting research on human subjects. The Declaration of Helsinki and The Belmont Report are two such documents which outlined guidance to conduct research on human subjects [1].

The Declaration of Helsinki expands the voluntary consent of the Nuremberg Code. It states that potential research participants have to be informed about the aims, methods, funding sources, potential conflicts of interest, researcher affiliations, and risks and benefits associated with the study [2, 5]. They must be informed that they can withdraw themselves from the study without

facing any punishment. If the researcher believes that the participants understood the provided information then, if possible, the consent can be taken in written form. Otherwise, the non-written consent has to be formally documented with an eyewitness. In the case of children, who are legally incompetent to give consent, assent should be taken from them beside seeking consent from their legal guardians [5].

However, the Declaration of Helsinki and the Nuremberg code did not provide enough protection for the participants of the infamous Tuskegee syphilis study [6, 7]. This study was conducted by the U.S. Public Health Service to understand the natural history of untreated syphilis [6]. This study was conducted from 1932 to 1972 [6] on 600 African-American males, among them, 400 were infected with syphilis [8]. The Nuremberg Code was adopted during the study period, in 1947, and the researchers should have applied this Code which includes the principle of voluntary consent to participate in research [2]. However, they did not apply the Code. Though penicillin was eventually understood to be a curative treatment for syphilis, participants were not informed about their disease and did not receive the treatment. A report on this study created a major public reaction which promoted the United States Congress to initiate the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [6]. The National Commission was assigned to develop a guideline identifying ethical principles to conduct studies involving human subjects [9]. The Commission published its report in 1979 which is called “The Belmont Report” [6, 8].

The Belmont Report identified three basic principles which should guide research involving human subjects. The principles are respect for persons, beneficence, and justice. The principle of respect for persons requires that individuals should be treated as autonomous agents. Participants should enter into the study voluntarily. They should be given enough information about the study

so that they can make their own decision to participate [9]. However, there are some people who are considered vulnerable populations for various reasons, including having diminished capacity to take their own decision on research participation. In this case, someone else can make decisions about research participation on their behalf. Such people need extra protection to ensure their interests are protected [7].

The principle of beneficence asks for maximizing the benefits and minimizing the risks for research participants. The principle of justice asks for distributing the risks and benefits fairly. The participants should be selected based on the problem being studied not based on the easy availability of the participants or their compromised position [9].

The Belmont Report outlines three requirements - informed consent, assessment of risks and benefits and selection of participants to apply Respect for Persons, Beneficence and Justice respectively in research involving human subjects [1, 8]. The research subjects must get enough information about the study in a way that they can comprehend the information and decide their research participation. Their consent to participate in research must be voluntary in nature. The researchers must assess the risks and benefits associated with research participation in a systematic way [8]. Moreover, the selection of study participants must be fair [8] so that everyone with a similar disease has equal opportunity of research participation[2].

The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, Second Edition (TCPS2) [10] recognises respect for human dignity when research is conducted involving human subjects. Three core principles – Respect for Persons, Concern for Welfare, and Justice are used to express respects for human dignity. These principles are similar to the core principles of the Belmont Report [9]. Respect for Persons demands recognizing every individual as an autonomous entity and protecting persons with diminished autonomy. The autonomy of a

person is recognized when the researchers obtain free, informed and ongoing consent from the research participants. The obtained consent should be based on participants' complete understanding of the predicted risks and potential benefits. Concern for Welfare demands protecting the welfare of research participants by the researchers and research ethics boards (REBs). The researchers and REBs must ensure that research participants do not face unnecessary risks. The researchers must provide enough information to them so that they can assess foreseeable risks and potential benefits associated with their research involvement. The participants must be treated fairly and equitably to ensure justice has been served. The foreseeable risks and potential benefits of research participation must be distributed in a way that does not overburden or favour any specific group(s). [10].

TCPS2 outlines detailed requirements for obtaining informed consent [10]. These include informing the participants that they are going to enroll in a study. The researchers need to provide information about the purpose of the study, researchers' affiliations, who is going to fund this study, how long they need to participate in this study, and what would be the responsibilities of the participants. They also need to inform the participants about the foreseeable risks and potential benefits associated with their participation. They must inform the participants that they can withdraw themselves from the study anytime, without providing any justification for their withdrawal. The researchers also need to inform the participants about the potential commercial use of their information and the possibility of revealing the identity of the participants and how this will be guarded against or mitigated. The researchers also need to provide contact details of a study team member who can clarify any information about the study, and contact information of someone else who is not a research team member but can clarify ethical issues related to this study. Moreover, the researchers also need to give an indication of

the information they are going to collect and how they will protect the privacy and confidentially of the information.

Pediatric emergency research and deferred consent

Acknowledging the importance of informed consent, it is not possible to implement in all research settings. If someone loses their ability to communicate because of their illness, it is still essential to conduct trials involving those persons to develop evidence based interventions for those conditions or diseases which caused such disability [11]. This is true for children as well. There are many medicines and devices which are used for the treatment of children, but are not licensed or tested [12]. Children have anatomical, physiological and developmental differences compared to adults, which demand different treatment options. There are also some diseases which are unique to children [13]. As a result, the medicines which are considered safe for adults might not always be safe for children. Thus, it is necessary to conduct pediatric trials to determine appropriate interventions for children [12, 14]. It is also important to conduct research involving children in the emergency setting, including of time-sensitive interventions, to develop evidence based interventions for children who have acute illness [15].

Though it is essential to conduct pediatric emergency research in certain circumstances, researchers face complex ethical challenges in doing so [16]. The principle of Respect for Persons is applied in part through obtaining informed consent of participants [8]. If the participants of a research study are children, then consent is normally obtained from their legally identified or appointed substitute decision makers (SDMs) – the parents or legal guardians of the children [15, 16]. Under normal conditions, it would be unethical for a study to be conducted involving children without seeking consent from SDMs , or they are denied participating in the research because their SDMs are unable to provide prospective consent [16].

As described above, obtaining proper informed consent requires providing adequate information about different aspects of the study like the purpose of the study, risks and benefits associated with research participation, confidentiality of participants' information as well as ensuring the participants that they can withdraw from the study whenever they want to do so. Researchers have to give required information to the participants in a way that they can comprehend [10]. In emergency care situations parents might be very distressed [15]; hence some literature suggests they might not comprehend the information provided during this time [12, 15]. So, taking consent during such times raises important questions about the validity of informed consent [12]. Moreover, the requirements for informed consent discussed earlier, can delay starting the treatment, especially if the parents or SDMs are not with the children during their admission to an emergency department [12]. Delaying treatment for a time-sensitive medical emergency situation can compromise patient care [12] and diminish children's chance of surviving [15]. It is therefore necessary to start the treatment immediately [12] and hence, the researchers may not have enough time to obtain informed consent for enrollment is this kind of study [11, 12].

The concept of Deferred consent (DC) was introduced by Fost and Robertson in 1980. DC is used to enroll participants without their consent for those who cannot communicate with researchers. Consent is obtained later for their continued participation from participants or their SDMs. If the researchers cannot obtain consent from the guardians then the participant may be discontinued from the study [11]. DC is also referred to as an initial waiver of consent, retrospective consent [16] and research without prior consent [17]. It is the approval by an REB for enrolling patients without prospective informed consent where consent is ideally sought and obtained later for continuation of their participation or permission to use the data already

collected from the participants [16]. DC is used to enroll and start the intervention to the participants immediately [18] when there is an urgent reason to do so.

Many countries allow using DC so that certain emergency care research can be conducted including United States of American [19-23], United Kingdom [19] and Canada [10]. The TCPS2 states the following conditions to be met to allow use of DC in Canada[10]:

1) Research participation does not pose more than minimal risk, it does not compromise the welfare of the participants and conducting research is impractical obtaining prospective informed consent (Articles 3.7 A),

2) Immediate intervention is required for the participant, there is no effective standard of care, the intervention poses less risk than standard of care or the intervention is potentially more beneficial than the standard of care, the participants have diminished capacity of understanding risks associated and research purpose, third party authorization can not be obtained and there is no prior instructions from the participants regarding study participation. (Article 3.8).

There are individual and population level medical emergencies. Our systematic review focused specifically on individual level time sensitive medical emergencies.

Though time-sensitive emergency research involving adults has been conducted using DC for many years, the use of DC in time-sensitive pediatric emergency research is a relatively recent phenomenon. There is a lack of evidence regarding the acceptability of the DC model in pediatric emergency research [12, 16], especially when a child has died after enrolling in a trial [12, 17]. It is essential to explore the perspective of parents and researchers on DC to inform future DC research in pediatric emergency research [16]. Considering this we wanted to

understand the perspective of pediatric patients (children onward), parents or substitute decision makers (SDMS) and researchers on DC specifically on challenges and opportunities associated with use of DC in time-sensitive pediatric emergency research (TPER). It is only possible if we systematically synthesize all the available evidence on the use of DC in TPER. Systematic review uses reproducible method to search, identify, select and summarize all available studies based on a specific research question which is not possible in other reviews including narrative, scoping and rapid reviews. As a result, we conducted a systematic review to explore the perspectives of children, parents or SDMs and researchers on opportunities and challenges associated with the use of deferred consent in TPER.

Researchers face ethical dilemmas conducting research with patients in this vulnerable situation. The findings of the current review were aimed to better prepare researchers to deal with ethical dilemmas which arise from the use of deferred consent models in pediatric emergency research. Researchers' knowledge of different aspects of this model can improve their skill and comfort to implement this consent model appropriately. Better implementation might improve the receptiveness of this model by parents or guardians. We hope it will inform practice and future research on the use of DC models in this situation and encourage researchers to conduct more pediatric emergency research thereby contributing to knowledge development for pediatric emergency patients.

Objectives:

The main objective of this review is to understand the challenges and benefits associated with the application of DC from the perspective of children, parents/SDMs, and practitioners in time-sensitive pediatric emergency research.

The specific objectives of the review are to understand

1. The challenges or problems associated with the use of DC model in time-sensitive pediatric emergency research
2. The benefits associated with using DC model in time-sensitive pediatric emergency research

Thesis outline

The outline of my thesis are as follows:

Chapter 1: Background

Here I set out to explore the guidance for ethics in human subject research, especially where it concerns informed consent. I explore the importance of conducting time-sensitive emergency research, even though consent is usually not possible in these contexts and establish the value of including children in evidence base development for this context. Finally, the notion of deferred consent is explained along with the restrictions required for its ethical use in practice.

Chapter 2: Systematic review protocol

This chapter outlines the methodology used to conduct the current systematic review. Here I describe the comprehensive search strategy used to conduct searches in MEDLINE, EMBASE, CINAHL and PsycINFO, and how the reference lists of the selected articles were hand-searched. The approach to developing the thematic analysis is also described.

Chapter 3: Systematic review article

This chapter outlines the result of the systematic review. The current review explored many opportunities and challenges associated with deferred consent. The children, parents and the practitioners supported deferred consent over prospective consent considering that it will allow practitioners to start treatment immediately in time-sensitive emergency care. However, the practitioners faced many challenges for the use of deferred consent in time-sensitive emergency research. They perceived challenges in obtaining consent from bereaved parents, and for the collection of additional blood samples for study purpose. They also described needing to manage misconceptions and fear of adverse events by the parents.

Chapter 4: Discussions and conclusions

This chapter outlines the implications of this review. The current review is the first to explore the challenges and opportunities associated with deferred consent in time-sensitive pediatric emergency research. There is a lack of studies which explore the perspectives of children and bereaved parents on deferred consent in time-sensitive pediatric research. The perspectives of these group of participants might be very different from other group of participants. We explore further areas for research and policy recommendations.

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Chapter 2: Systematic review protocol

The challenges and opportunities associated with deferred consent in time-sensitive pediatric emergency research: protocol for a systematic review

Jhalok Ronjan Talukdar[1, 2*], Lisa Schwartz[1, 4], Cynthia Lokker[1], Melissa J. Parker[1, 3]

*Corresponding author: Jhalok Ronjan Talukdar

Email: talukdaj@mcmaster.ca

Email:

Jhalok Ronjan Talukdar: talukdaj@mcmaster.ca

Lisa Schwartz: schwar@mcmaster.ca

Cynthia Lokker: lokkerc@mcmaster.ca

Melissa J. Parker: parkermj@mcmaster.ca

Author Affiliations

[1] Department of Health Research Methods, Evidence, and Impact, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada

[2] BRAC James P Grant School of Public Health, BRAC University, Dhaka -1212, Bangladesh

[3] Division of Pediatric Critical Care, Department of Pediatrics, McMaster Children's Hospital and McMaster University, HSC 3E-20,1280 Main Street West, Hamilton, ON L8S 4K1, Canada

[4] Department of Philosophy, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada

Abstract

Introduction

The process of obtaining prospective informed consent in time-sensitive pediatric emergency research is not always feasible given the small therapeutic window and inability of many children to give meaningful informed consent. Moreover, the focus and emotional state of substitute decision makers (parents or legal guardians) also acts as a barrier to discuss consent issues with them during this undesirable situation. Deferred consent is used to enroll children immediately without prior prospective informed consent, but with the requirement that children or their legal guardians are informed about the study as soon as possible or when appropriate. Deferred consent will offer an ethical and scientifically balanced approach to conduct time-sensitive pediatric emergency research, however, it might also pose challenges for the researchers who choose to implement this consent model. The current review aims to understand the challenges and benefits, or opportunities associated with deferred consent in time-sensitive pediatric emergency research.

Methods and analysis

We will conduct a systematic review of studies which aims to understand the application of deferred consent, especially the challenges and opportunities associated with deferred consent in time-sensitive pediatric emergency research. The participants of those deferred consent studies would be children who have the experience of emergency treatment or being enrolled in a study as part of their treatment, legal guardians or substitute decision makers of these children, clinical physicians or researchers who aim to better understand deferred consent. We will search MEDLINE, EBMASE, CINAHL and PsycINFO to identify research articles. We will screen the title and abstract of these articles, read the full text of initially selected articles, extract the data preparing a codebook and using NVivo. Finally, we will do thematic analysis of extracted data to

understand challenges and opportunities associated with deferred consent from the perspectives of children, parents and practitioners in time-sensitive pediatric emergency research.

Ethical consideration

We will use secondary data from published articles to conduct this review. Approval from local Research Ethics Board (REB) is not required.

Introduction

Research is conducted to gain knowledge about the unknown [1]. Medical research is conducted involving human beings to understand causes and consequences of diseases and improve interventions [2]. Medical research that is conducted with human participants to generate new knowledge [2], must ensure minimal risk to study participants [1]. Research ethics guidance worldwide is explicit that knowledge generation must never undermine the best interests of research participants [2].

The Belmont Report [3] outlined three basic ethical principles: respect for persons, beneficence, and justice to provide an analytical framework to guide researchers who are working with human subjects to resolve ethical conflicts. According to these principles, researchers have to acknowledge the autonomy of the participants and protect those who have limited autonomy. They have the responsibility of ensuring maximum benefit and minimum harms to research participants. Moreover, they have to ensure that no one is unjustifiably denied research participation and the associated benefits of this participation [3, 4].

One of the considerations when applying these principles is voluntary, informed and ongoing consent which protects research participants [5] and safeguards respect for their autonomy [6, 7]. Participants have the right to make their own decisions about their health care when they have the capacity to do so, and researchers must discuss the potential benefits and risks associated with any study to ensure that potential participants are well informed [5, 8, 9]. Obtaining consent from participants is mandatory in most circumstances, and researchers cannot include any participants who have refused to provide consent [1].

The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, Second Edition (TCPS2) [1] emphasizes respect for human dignity during research involving human

subjects through three core principles – Respect for Persons, Concern for Welfare and Justice which are similar to the core principles outlined in the Belmont Report. Respect for Persons puts an obligation to recognize every individual person as an autonomous person and obtain free, informed and ongoing consent during research. Concern for Welfare is associated with protecting the welfare of human subjects during their research participation. Researchers have to provide adequate information to the participants about the study so that they can understand potential risks and benefits associated with their research participation. Justice is facilitated when the participants are treated fairly and equitably by the researchers. The risks and benefits of the research have to be distributed in a way such that no specific population is overburdened by the harms of the research.

Pediatric emergency research is needed to advance pediatric emergency medicine in areas where sufficient evidence is lacking to inform treatment practices [10] and develop appropriate treatment for children [11]. Children are sometimes believed to be especially vulnerable in research because they might not have decision making capacity at this young age. It is necessary to find a balance between science and ethics to enroll these vulnerable groups of people in research [9].

In some emergency pediatric situations, the therapeutic window for an intervention being tested is very small. It is required to start the treatment immediately and as a result it is not feasible to follow usual informed consent procedures [5, 9, 12], for example in emergency resuscitation research where the intervention may be time-sensitive. The Declaration of Helsinki outlines the use of alteration of informed consent to recruit participants [2] when research interventions have to be started immediately. Deferred consent allows researchers to recruit participants without their informed consent, but consent is requested from the participants or substitute decision

makers (SDMs) as early as possible or when appropriate so that they can remain in the study or their data used for study purposes [1, 2, 13]. However, to implement this consent model, the reasons for using deferred consent in the study have to be outlined in the research protocol and approved by the research ethics committee [2].

Assent in pediatric research:

Assent from the children is obtained to respect their opinion on research participation. The assent process can also be considered as education to foster their autonomy and boost their confidence. The researcher needs to provide adequate information about the research to the children in a developmentally appropriate manner to help the child to understanding what is being presented and offer them an opportunity for input, ask questions and participate in the choice. This can promote trust towards the researcher and enhance the child-researcher relationship [14]. However, it can be impractical to receive prospective assent from children in time-sensitive pediatric emergency research as their medical condition might affect their decision-making capacity [15]. There is concern that receiving consent from the parents is also tricky at such times, since they may find themselves in a stressful situation, arguably unable to concentrate on anything but their child's health. It is therefore challenging to feel confident seeking consent during this time considering the relationship (or lack thereof) between researchers and the family. The time needed for the guardians to understand and decide whether or not to participate in the proposed study might delay [16] initiation of lifesaving treatment [1].

Deferred consent is allowed in some countries to conduct research in emergency care settings including Canada [1], United States of America (USA) [4, 8, 9, 12, 17] and United Kingdom (UK) [12]. The TCPS2 in Canada [1] introduced alteration of consent (deferred consent) under the following conditions [6]:

(1) when it is impractical to conduct research taking prospective consent and when potential benefits outweigh the associated risk (Articles 3.7 A),

(2) in medical emergencies when participants lack decision making capacity to participate in research or when the research is considered to be justified and recruiting after taking delayed consent from the legal authority might jeopardise the health of the participants (Article 3.8).

Though conditions are variable, deferred consent in USA and UK also require that the intervention is not more harmful to the participants compared to the current standard of care, and that it poses minimal risk [10].

Use of deferred consent in time-sensitive pediatric emergency research is a relatively recent development. There is a lack of research to help understand the challenges and opportunities associated with requesting deferred consent. This review aims to explore the challenges and opportunities associated with deferred consent taking perspective from children, parents and of practitioners. The findings of this review might prepare future researchers to deal with their own ethical conflicts that arise from the use of deferred consent in time-sensitive pediatric emergency research. The knowledge of these aspects might improve the comfort of researchers and receptiveness of parents or guardians. It might enhance ability to ask and answer important research questions which necessitate use of this consent model. It might also encourage researchers to conduct more pediatric emergency research using this model which will ultimately contribute to knowledge development in pediatric emergency care.

Review question

What is found in the literature about the perspectives of children, parents/substitute decision makers (SDMs) and practitioners on challenges and opportunities associated with deferred consent in time-sensitive pediatric emergency research?

Objectives:

This study aims to explore published literature to help understand the perspectives of researchers, parents and children on challenges and opportunities associated with deferred consent in time-sensitive pediatric emergency research.

The specific objectives of the review would be to understand

1. The problems or challenges associated with the use of deferred consent processes in time-sensitive pediatric emergency research
2. The benefits of using deferred consent in time-sensitive pediatric emergency research

Methods

We will conduct a comprehensive systematic review and report the review according to the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines [18]. The protocol of this review will be reported according to the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidelines [19].

Criteria for considering studies for this review

Type of studies

The review will include both qualitative and quantitative studies to understand the challenges and benefits associated with the use of deferred consent in emergency pediatric research. As a result, no articles will be excluded based on study design. There will be no language or publication date limits; studies in French, Spanish, Chinese, or German will be screened by

colleagues at McMaster University who speak and read those languages. Only published studies will be included.

Types of participants

To ensure representation of various experiences with deferred consent, participants will include children receiving pediatric emergency treatment as part of a research study, legal guardians or substitute decision maker of these children, and practitioners (clinicians and researchers).

Types of interventions

We will include studies about the application of deferred consent in time-sensitive pediatric emergency research. We will select those studies which address: 1. enrolling patients exclusively through deferred consent, 2. enrolling patients through deferred consent or prospective consent (mixed consent model), 3. future plans to enrol patients using deferred consent.

Types of outcome measures

The outcome of the studies might include challenges associated with implementation of deferred consent from the perspective of children, parents and practitioners. These might include challenges in approaching the parents or guardians of children for deferred consent after recruiting the children, reasons given for withdrawing the children when deferred consent is used, researchers' views regarding how to improve the use of deferred consent in pediatric emergency research. The outcomes could also include opportunities associated with deferred consent which might include discussion of how deferred consent can help recruit children which otherwise would not be possible or how it can be used to get a representative sample from the population.

Excluded studies

The current review will exclude articles which are not primary studies, include adult patients, or are not specifically on deferred consent. The articles which are not primary studies may include systematic reviews, workshop reports, poster presentations or discussion papers which use secondary data. Articles which only concentrate on community consultation aspects of deferred consent will also be excluded.

Search methods for identification of studies

Electronic searches

We will search MEDLINE, EMBASE, CINAHL and PsycINFO, developing a comprehensive search strategy to address our research question. We developed a draft search strategy for MEDLINE (Appendix - A) after consulting Stephanie Sanger, Clinical Services Librarian, McMaster University Health Science Library. We will customize this search strategy to make it suitable for EMBASE, CINAHL and PsycINFO.

Searching other resources

When needed, we will contact experts in this field to collect articles from them. We will also hand-search reference lists of selected studies.

Data collection and analysis

Selection of studies

After implementing the search strategies in different databases, we will combine the file into a single database and remove duplicate records. Three authors will independently screen the titles and abstracts for preliminary selection of articles based on inclusion criteria. Full text screening of preliminary selected articles will be done by two authors to determine the final inclusion of articles. Any disagreement will be resolved through discussion or if necessary, by consulting with the wider research team. Studies excluded at this stage will be listed in the characteristics of excluded studies lists with an explanation for exclusion.

Reference lists of the selected articles will be reviewed to identify any relevant study which meets our inclusion criteria but was not identified through the database searches. These will be screened and reviewed for inclusion.

Data extraction and management

A narrative synthesis of the articles will be done to explore the reported challenges and opportunities associated with deferred consent. We will import the selected articles to NVivo 12 for analysis. Two authors will read the full text to develop the codebook for this analysis. Then the codebook will be discussed with other study members and finalized. One author will code the articles and another author will cross-check the coding in NVivo. We will use the categorizing strategies, for example, coding and thematic analyse of the articles. Data displays will be used to organize emerging patterns thematically. These themes will help us understand the challenges and opportunities associated with deferred consent in emergency research.

Critical appraisal

The current systematic review identified mostly qualitive studies on the use of DC in TPER. Data triangulation is an important aspect of ensuring rigor in qualitative study [20]. To ensure triangulation of data we decided to include all the identified studies. As a result, we did not do critical appraisal of selected studies and did not exclude any of them.

Ethical consideration

The study will use secondary data from published research articles. Approval from local Research Ethics Board (REB) is not required.

Contributions

LS, MP and JRT conceptualized the systematic literature review protocol. JRT drafted the protocol and updated the protocol based on feedback from LS, CL, and MP. Supervising authors contributed to the development of the search strategy. The authors have reviewed and approved the final manuscript. JRT is the guarantor of the review.

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2. MJP is supported by a Canadian Blood Services/Canadian Institutes of Health Research New Investigator Salary Award (2015-2019) (Award: $300,000) – PI support for protected time for research. [CBS funding reference number: CIHRPA201309-MP-322414]

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Role of Study Funders

The funding sources noted will not be involved in the study design, conduct, analysis and interpretation of data. The funders will not be involved in manuscript preparation or influence any decisions around publication of findings. The authority for study conduct, analysis, interpretation, and dissemination of study findings will rest with the investigators.

Disclaimer

The views expressed herein do not necessarily represent the views of the federal government.

Competing interests

Not declared

Acknowledgement

We acknowledge the guidance and support of Stephanie Sanger, Clinical Services Librarian, McMaster University Health Science Library for helping us to develop the comprehensive search strategy for the review.

Abbreviations

SDM substitute decision maker

REB Research Ethics Board

Authors Information

JRT is a Master of Science candidate in the Health Research Methodology program at McMaster University. He is also a Senior Research Associate (on study leave) at BRAC James P Grant School of Public Health, BRAC University, Bangladesh.

LS is the Arnold L. Johnson Chair in Health Care Ethics in the Faculty of Health Sciences at McMaster University, Professor in the department of Clinical Epidemiology & Biostatistics, former Director of the PhD in Health Policy, co-Associate Director of the Centre for Health Economics and Policy Analysis (CHEPA), and associate member of the Department of Philosophy. She is formerly the Vice-Chair of the Standing Committee on Ethics at the Canadian Institutes of Health Research (CIHR), a member of the Expert Review Panel for non-pharmaceutical health technology assessment at the Canadian Agency for Drugs and Technologies in Health (CADTH) and member of the Ethics Committee at the Royal College of Physicians & Surgeons of Canada.

MJP is an Associate Professor of Pediatrics, and an Associate Member of Clinical Epidemiology and Biostatistics at McMaster University. She is a physician, Board Certified in both Pediatric

Critical Care and Pediatric Emergency Medicine. Her research interests focus on resuscitation interventions and algorithms and the ethical conduct of resuscitation research.

CL is an Assistant Professor in Health Research Methods, Evidence and Impact at McMaster University. She is also eHealth FHS Lead at McMaster University. Her research interests focus on the evaluation of mHealth applications and usability of eHealth applications (mobile, web-based, etc.), knowledge translation, and conducting reviews.

Appendices

Appendix - A: draft search strategy for MEDLINE (OvidSP)

1 exp PEDIATRICS/
2 exp CHILD/
3 exp Infant/
4 Adolescent/
5 (p?ediatric* or child* or infant* or toddler* or baby or babies or adolescen* or teen* or youth* or underage* or under age* or preteen* or young adult*).mp.
6 or/1-5
7 exp Informed Consent/
8 exp informed consent by minors/
9 exp parental consent/
10 ((waiv* or delay* or defer* or prior or retrospective or alteration*) adj2 (consent* or permission* or permit or assent or approv* or authoriz*)).ti,ab,kf.
11 or/7-10
12 Emergencies/
13 exp Emergency Medicine/
14 exp Emergency Medical Services/
15 exp Critical Care/
16 acute care.mp.
17 acute setting*.mp.
18 exp Resuscitation/
19 exp emergency treatment/
20 (emergenc* or intensive care or critical care or PICU or NICU or ICU).ti,ab,kf.
21 or/12-20
22 (challenge* or risk* or problem* or benefit* or limitation* or trust or trusting).mp.
23 professional-family relations/ or exp professional-patient relations/ or trust/
24 exp risk assessment/ or risk factors/
25 Patient Selection/
26 ((patient* or participant*) adj2 (recruit* or select*)).ti,ab,kf.
27 or/22-26
28 exp ethics, clinical/ or exp ethics, research/
29 ethics/ or bioethical issues/ or bioethics/
30 (ethic* or bioethic*).ti,ab,kf.
31 or/28-30
32 6 and 11 and 21 and 27 and 31 [Paediatric, deferred consent, emergency care, challenges, ethics]

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Chapter 3: systematic review article

The challenges and opportunities associated with deferred consent in time-sensitive pediatric emergency research: a systematic review

Jhalok Ronjan Talukdar[1, 2*], Melissa J. Parker[1,3], Roksana Hoque[2], Sayema Akter[2], Rachel Yantzi, Cynthia Lokker[1], Lisa Schwartz[1, 4]

*Corresponding author: Jhalok Ronjan Talukdar

Email: talukdaj@mcmaster.ca

Email:

Jhalok Ronjan Talukdar: talukdaj@mcmaster.ca

Roksana Hoque: roksana.hoque@bracu.ac.bd

Sayema Akter: sayema_akter@bracu.ac.bd

Rachel Yantzi: yantzir@mcmaster.ca

Melissa J. Parker: parkermj@mcmaster.ca

Cynthia Lokker: lokkerc@mcmaster.ca

Lisa Schwartz: schwar@mcmaster.ca

Abstract

Introduction

Children are anatomically and physiologically different compared to adults. As a result, treatments which are safe for adult patients might not necessarily be safe for pediatric patients. Research must therefore include children to assess interventions for them. It is also important to conduct pediatric emergency research to develop interventions in areas which lack sufficient evidence. Taking prospective informed consent is essential for conducting research involving human subjects. However, it is impractical to obtain informed consent during time-sensitive pediatric emergency research (TPER). Taking deferred consent in TPER can offer a scientific and ethical balance to conduct studies in this emergency setting. The current review explores opportunities and challenges associated with the use of deferred consent in TPER from the perspectives of children, parents and practitioners.

Methods

We comprehensively searched four databases - MEDLINE, EMBASE, CINAHL and PsycINFO. We deduplicated the identified records, selected the articles, and read the full text of the selected articles. We imported the articles into NVivo 12 and did thematic analysis for qualitative synthesis of selected articles.

Results

Deferred consent has many advantages over prospective informed consent in time-sensitive emergency pediatric research. It offers the opportunity to administer the intervention immediately and process informed consent later with the participants. However, researchers face many challenges when implementing this consent model in time-sensitive emergency research. They face ethical dilemmas discussing research participation for children with bereaved parents.

They are not sure when is the best time to discuss deferred consent. They also face challenge with collection of extra blood only for study purposes. They do not know how to respond when parents refuse to enroll their children into the study fearing adverse effects of the intervention.

Conclusion

There are few studies on use of deferred consent models in time-sensitive pediatric research especially studies which explore perspectives of children. Knowledge of deferred consent models will help guide researchers with ethical dilemmas. It may also encourage them to conduct more studies in this context and contribute in the development of emergency medicine for children.

Trial Registration: (Will be added after registering with PROSPERO)

Keywords: Consent, deferred consent, challenges, opportunities, pediatric emergency research, time-sensitive pediatric emergency research.

Background

An overview of informed consent

The history of research on human subjects has gone through many regulatory, scientific and ethical challenges [1]. The Nuremberg Code was developed in 1947 [2] which introduces voluntary consent in research [1-4]. It also directs that participants should be able to withdraw themselves from a study without the burden of providing any explanation [1-4].

The Declaration of Helsinki expands the guidance on voluntary consent in the Nuremberg code. It states that the researchers have to provide adequate information about the study to the potential research participants including aims and methods of the study, sources of funding, potential conflicts of interests, risks and benefits associated with a study [2, 5]. It is also mandatory to inform research participants that they can withdraw themselves from the study at any point of time without facing any penalty. In case of children, assent should be obtained from them besides taking consent from their legal guardians [5].

The Belmont Report was published in 1979 in response to the infamous Tuskeegee syphilis study in Alabama [6, 7]. This report outlines three basic principles- Respect for Persons, Beneficence and Justice to guide research involving human participants [8]. It also offers three requirements to apply these principles which include - informed consent, assessment of risks and benefits, and fair selection of participants[1, 7].

Likewise, The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, Second Edition (TCPS2) [9] by three federal research agencies of Canada states three core principles to express respects for human dignity. These core principles are – Respect for Persons, Concern for Welfare and Justice. The principle of Respect for Persons recognises every individual as a potentially autonomous entity, and also gives protection to persons with

diminished capacity to act autonomously. It is important to obtain free, informed and ongoing consent from research participants to recognise autonomy of the person. [9].

According to TCPS2, there are a number of requirements for obtaining informed consent [9]. Participants should be informed that they are going to enroll in a study. Researchers should provide adequate information about the study including study purpose, affiliation of researchers, sources of funding, duration of study participation as well as the responsibilities of the participants in the study. Moreover, the participants should be informed about the foreseeable risks and potential benefits associated with research participation. The participants should be informed that they do not need to provide any justification if they want to withdraw from the study at any point of time. They should be informed about how their confidential information will be protected, and the potential commercial use of their information. The contact information of a study team member should be provided to the research participants so that they can make contact with the researcher to clarify any information related to the study. It is also necessary to provide contact information of someone who is not a research team member so that they can clarify any ethical issues related to this study. Moreover, it is also essential to give an indication to the research participants of the information they are going to collect from them and how the privacy and confidentially of the information will be protected.

Pediatric emergency research and deferred consent

Children are anatomically, physiologically and developmentally different from adults. These differences demand different treatment options. Moreover, the children have some unique diseases[10]. As a result, it is obvious that medicines which are considered safe for adults might not be safe for children. Pediatric research, including emergency research, is essential to develop age appropriate evidence based interventions for children [11, 12].

Obtaining informed consent requires providing adequate information about the research to participants in a way that they can comprehend [9]. Consent is obtained from substitute decision makers (SDMs) - parents or legal guardians, if the research participants are children [13, 14]. When research is conducted in time-sensitive pediatric emergency settings then the parents might be very distressed [14] hence some people argue that they might not able to comprehend important study information provided during this time [11, 14]. As a result, the validity of informed consent might be questioned [11]. Moreover, it will take a significant amount of time to fulfill the requirements of informed consent, and might delay starting the treatment to the children immediately. [11]. If the treatment is delayed in time-sensitive emergency medical care then it can compromise patient care [11] and it can also diminish children's chance of surviving [14]. [11, 15].

The concept of deferred consent (DC) was introduced in 1980 by Fost and Robertson. It is used to enroll research participants without their prior consent. DC is an ethical means of enrolling patients to a study without obtaining prospective informed consent. The formal consent is obtained later but as soon as possible for continuation of research participation or to secure permission to use the data already collected from the participants [13]. So, DC is used in TPER to enroll the children and start the intervention for them immediately [16].

Many countries including United States of America [17-21], United Kingdom [17] and Canada [9] allow use of DC in TPER. The TCPS2 allows use of DC in Canada if the following conditions are met [9]:

1) Research participation does not pose more than minimal risk, it does not compromise the welfare of the participants and conducting research is impractical for? obtaining prospective informed consent (Articles 3.7 A),

2) Immediate intervention is required for the participant, there is no effective standard of care, the intervention poses less risk than standard of care or the intervention is more beneficial than the standard of care, the participants have diminished capacity of understanding risks associated with it and the research purpose, third party authorization can not be obtained and there is no prior instructions from the participants regarding study participation. (Article 3.8).

DC has been used in time-sensitive emergency research involving adults for many years. However, use of DC in TPER is relatively a recent phenomenon. There is a lack of evidence regarding use and acceptability of DC in TPER [11, 13] especially when children have died participating in a research study [11, 22].

The objective of this systematic review was to explore the opportunities and challenges associated with use of DC in TPER from the perspective of children, parents and practitioners. The findings from this systematic review may help the researchers to deal with ethical dilemmas which arise from the use of DC in TPER. Understanding the challenges and opportunities associated with DC in TPER might inform future research about the uses of DC in TPER and encourage the researchers to implement DC to conduct more TPER. Conducting studies in TPER will contribute to knowledge development for pediatric emergency patients.

Objectives:

The main objective of this review was to explore the challenges and benefits associated with application of DC in TPER from the perspective of children, parents and practitioners.

The specific objectives of the review were to explore

1. The challenges or problems associated with the use of DC in time-sensitive pediatric emergency research
2. The benefits associated with use of DC in time-sensitive pediatric emergency research

Methods

Protocol and registration

The detailed methods of this systematic review are outlined in the protocol section (Chapter 2) of this paper. This protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (record number will be provided after registering with PROSPERO).

Overview of the methods

We developed a comprehensive search strategy consulting with Stephanie Sanger, Clinical Services Librarian, McMaster University Health Science Library. We searched four databases - MEDLINE, EMBASE, CINAHL and PsycINFO using this search strategy. These databases were searched from their inception to December 15, 2018. We did not limit our search to any language or study design. We also searched the bibliographies of initially selected articles. We prepared a single database and included all the identified records from four databases. We deduplicated them before screening titles and abstracts of these articles. Three authors independently screened the titles and abstracts for preliminary selection of the articles based on study selection criteria. Full-text of initially selected articles were collected and screened independently by two authors. Any disagreement in this process were resolved through discussion. The final section of these articles was done after discussing with the wider research team.

Results

Result of the search

The following PRISMA diagram in figure 1 summarizes the flow of studies selected at different stages. We identified 1576 records from our database and hand searches published until December 2018. We screened 1413 records after removing 163 duplicates. We assessed 47 full-text articles for eligibility and 10 articles met selection criteria and were qualitatively synthesized.

PRISMA Diagram

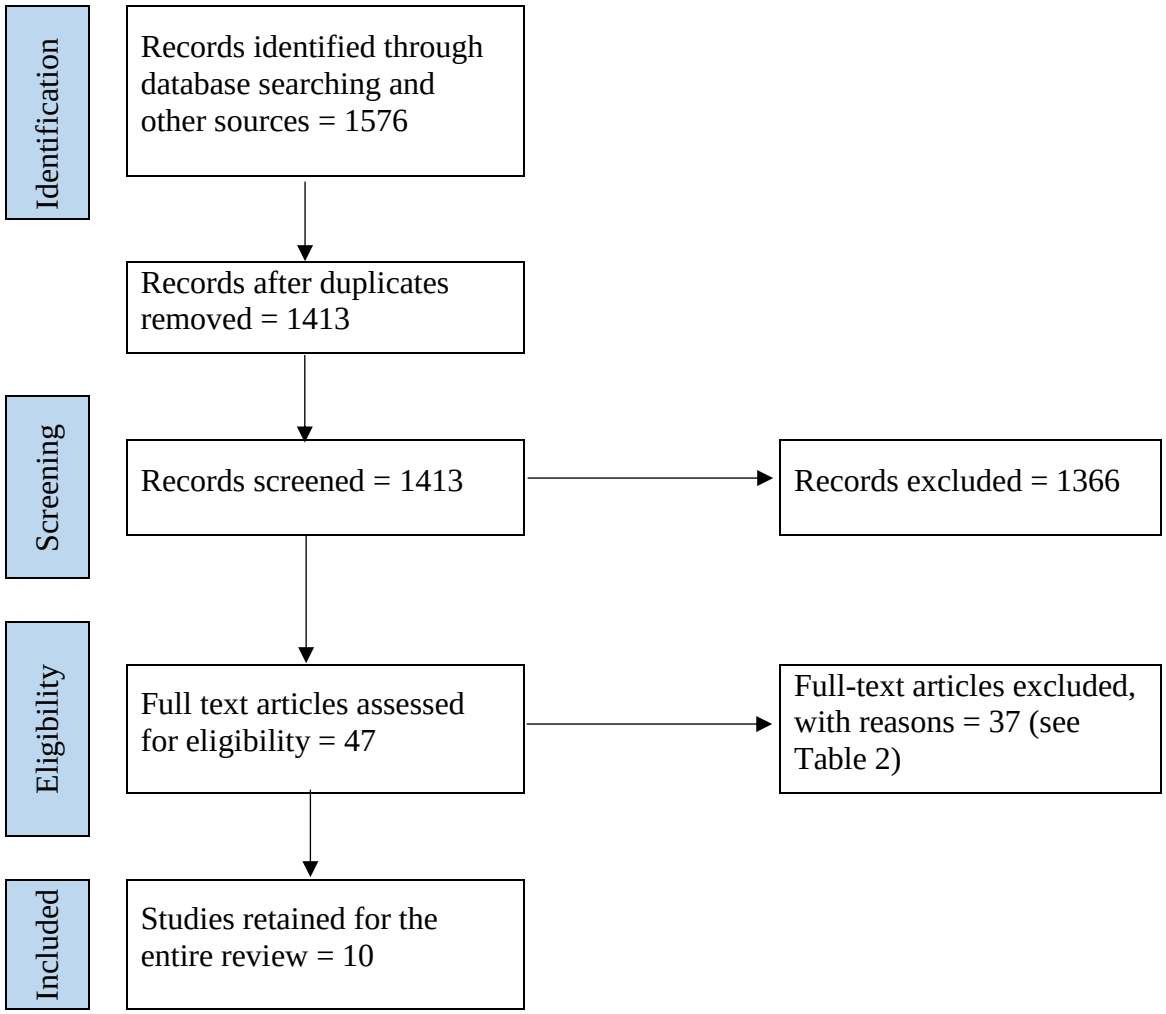

Figure 1: PRISMA diagram indicating flow of information in different phases of the review

Included studies

Our systematic review included those primary studies which explored the use of deferred consent models in TPER for children aged 0-18 years of age. The first and second reviewer identified 30 and 33 articles respectively from initial screening of titles and abstracts. They excluded 1383 and 1380 articles respectively. There were 47 unique articles in total among the selected articles by both reviewers. Among these 47 articles, 18 articles were common which were selected by both the reviewers. The reviewers agreed to read the full text of all these articles. The first reviewer prepared a data collection form using inclusion criteria for this systematic review. He collected data from all these articles using this data collection form. He cross-checked this form with the second reviewer. They agreed to exclude 34 articles from these 47 articles. Later 3 more articles were excluded discussing with the wider authors' panel. As a result, 10 articles were used for the qualitative synthesis of this systematic review.

Most of the included studies were conducted in high resource settings, including seven studies from the UK; while one study was conducted in a developing country [23]. Six of the studies involved parental perspectives on the conduct of deferred consent in TPER [16, 23-27] . Three studies each collected data from children [11, 28, 29] and health care practitioners [23, 24, 30]. Characteristics of the included studies are summarized in Table 1.

Table 1: Summary of included studies

Paper (reference)	Country /setting	Study design	Study participants	Study objective(s)
O'Hara et al., 2018[26]	UK, PICU	Semi-structured telephone interview	21 parents [18 mothers (5 bereaved), 3 fathers (2 bereaved)]	To explore acceptability of Fluids in Shock (FiSh) Trial including acceptability of deferred consent and recruitment barriers.
Roper et al., 2018 [29]	UK, hospital	Face-to-face interviews	16 children (9 males, 7 females: 7-15 years)	To explore children's perspective on deferred consent and how to involve them in research discussion.
Menon et al., 2017[28]	Canada, PICU	Semi-structured face-to-face interview	68 children (42 deferred consent, 26 prospective consent)	To explore the use of deferred and prospective consent in a randomized control trial.
Furyk et al. 2017 [25]	Australia, ED	Semi-sturctured telephone interview	39 parents (33 mothers, 6 fathers)	To explore parents' attitudes to deferred consent.
Woolfall et al., 2015[24]	UK, hospital	Postal survey, telephone/face-to-face interview, focus group discussion	275 parents surveyed, 23 parents interviewed, 17 practitioners participated in focus group discussion	To explore parents' and practitioners' views and experiences of deferred consent in a randomized control trial.
Harron et al., 2015 [11]	UK, PICU	Data collected using case report form	1358 children	To evaluate consent rates as well as reasons for non-consent in a randomized controlled trial.
Woolfall et al., 2014 [16]	UK, Emergency department (ED)	Telephone interviews and focus group discussion	17 parents (15 mothers, 2 fathers)	To explore parents' perspective on deferred consent in pediatric emergency care setting.

Woolfall et al., 2013 [30]	UK, PICU	Semi-structured online survey	45 practitioners (16 consultant and 29 nurses)	To explore practitioners' views and experience of taking deferred consent in pediatric emergency care research.
Molyneux et al., 2013 [23]	Uganda, Tanzania & Kenya, hospital	Face-to-face interview	30 trial team member, 15 health care providers and 51 parents	To explore views and experience of parents and practitioners regarding deferred consent process.
Gamble et al., 2012 [27]	UK, Research center	Postal survey	68 parents	To explore way of minimizing anxiety and distress related to involvement in randomized control trial and how to seek deferred consent in challenging circumstances.

PICU = pediatric intensive care unit; ED = emergency department.

Excluded studies

Our systematic review excluded those studies which were not primary studies, including review articles, analysis of secondary data, systematic review or those studies which included only the adult patients or only concentrated on community consultations. We excluded 37 studies after assessing their eligibility for the current review. Table 2 summarizes the reasons for excluding them from this review.

Table 2: Summary of excluded studies

Study name	Reason for exclusion
A comprehensive systematic review of stakeholder attitudes to alternatives to prospective informed consent in paediatric acute care research [13]	Systematic review
Waiver of informed consent in pediatric resuscitation research: a systematic review [31]	Systematic review
Retrospective Consent in a Neonatal Randomized Controlled Trial [32]	Used secondary data
Practitioner views and experiences of deferred consent in paediatric and neonatal emergency care trials: The connect study[33]	Poster presentation
Evidence-based guidance to inform consent seeking in children's critical care trials [34]	Poster presentation
Research in emergency situations: with or without relatives consent [35]	Adult patients
Ethics of Drug Research in the Pediatric Intensive Care Unit [36]	Review article
The battering of informed consent [37]	Review article
Use of deferred consent for severely ill children in a multi-centre phase III trial [38]	Review article
Ethics of Research in Pediatric Emergency Medicine [17]	Review article
Effectiveness of the informed consent process for a pediatric resuscitation trial [21]	Focused on community consultation
Consenting to pediatric critical care research: understanding the perspective of parents [39]	Not on deferred consent
Written versus verbal consent: a qualitative study of stakeholder views of consent procedures used at the time of recruitment into a peripartum trial conducted in an emergency setting [40]	Adult patients
Emergency research: only possible if consent is waived? [41]	Review article

Presumed consent in emergency neonatal research [42]	Review article
Challenges in the conduct of emergency research in children: a workshop report [43]	Workshop report
The use of delayed telephone informed consent for observational emergency medicine research is ethical and effective [44]	Adult patients
Ethical considerations in pediatric critical care research [45]	Discussion paper
Determinants of parental authorization for involvement of newborn infants in clinical trials [46]	Not on deferred consent
Informed consent in emergency care research: An oxymoron? [47]	Review article
More information, less understanding: A randomized study on consent issues in neonatal research [48]	Not on deferred consent
[Informed consent in emergency medicine] [49]	Review article
Complexities of Consent: Ethics in the Pediatric Emergency Department [50]	Review article
Implementation of community consultation for waiver of informed consent in emergency research: one Institutional Review Board's experience [51]	Focused on community consultation
Conducting ethical research in pediatric emergency medicine [52]	Review article
Consent for emergency medical services for children and adolescents [53]	Not on deferred consent
Perceived challenges to obtaining informed consent for a time-sensitive emergency department study of pediatric status epilepticus: results of two focus groups [54]	Not on deferred consent
Consent for clinical research in the neonatal intensive care unit...including commentary by Fenton AC... reprinted from Arch Dis Child Fetal Neonatal Ed 2003;88:F280-F286[55]	Not on deferred consent
The spectrum of informed consent in emergency psychiatric research [56]	Review article
In case of emergency: No need for consent [57]	Symposium report
Pediatric crash injury research: The challenge of informed consent [58]	Case study
Pediatric intravenous insertion in the emergency department: Bevel up or bevel down? [59]	Not on deferred consent
Informed consent in pediatric neurology [60]	Review article
Resuscitation research involving vulnerable populations: are additional protections needed for emergency exception from informed consent? [61]	Discussion paper

An approach to community consultation prior to initiating an emergency research study incorporating a waiver of informed consent [62]	Focused on community consultation
What gives them the right? Legal privilege and waivers of consent for research [63]	Discussed legal issues
Research in emergency situations: with or without relatives consent [35]	Adult patients

Identified themes from coding

We identified different themes from initial coding of the articles. The codebook used to code the articles is attached in Appendix 1. We divided these themes under two broad categories - *opportunities* and *challenges* associated with use of deferred consent in TPER.

We identified those themes as *opportunities of deferred consent* which indicate that using prospective consent instead of deferred consent will put the research participants at unnecessary risk. Findings under this category also indicate that use of deferred consent would be the better option in comparison to prospective informed consent in TPER. The themes under this category discussed deferred consent as a "logical solution" to conduct studies in this situation, support for deferred consent by children, parents and practitioners, administering study drug immediately and suggestions of children to improve deferred consent process.

The themes under *challenges* category covered those areas which make it difficult for researchers and participants to implement and accept this model in TPER. These themes raised questions about how to obtain deferred consent when a child dies after enrolling in a trial. Literature also asked about the proper time of obtaining deferred consent, how to address concerns the participants raise regarding a trial such as how trial participation would impact the health condition of their child or whether they can understand in which treatment arm their children are enrolled. Because of these, authors indicated respondents wondering how fear of adverse effects might impact study participation. Finally, specific challenges were raised related

to collecting blood sample from children before prospective consent as these extra blood samples were collected only for study purpose.

The following table gives a summary of codes used in the data analysis and respective participants from whom these codes were collected (Table 1).

Themes	**Codes**	**Perspectives collected from**
Logic of using DC	Parents' capacity	Parents
	Feasibility of PC	Practitioners
Support for DC	Support for DC typical	Children, parents and practitioners
	Support for DC atypical	Children, parents and practitioners
Children's opinion on DC	Who should approach children for DC	Children
	Whom should consult	Children
	Medium to provide study information	Children
Time to administer study drug	Time to administer study drug	Practitioners
Child's death during the research	Consent from bereaved parents	Practitioners
	Consent by bereaved parents	Parents
Timing of consent	Timing of consent	Parents, Practitioners
Concerns or questions about the trial	Concerns or questions about the trial	Parents
	Misconceptions about the study	Parents
Fear of adverse event	Fear of adverse event	Parents
Blood sample collection	Blood sample collection	Practitioners

DC = Deferred consent
PC = Prospective consent

Table 1: Codes and relevant participants

A. Opportunities associated with deferred consent

The current systematic review found a number of opportunities or benefits associated with application of deferred consent in TPER. We describe 5 here are as follows:

A1. "Logical solution" to conduct studies in challenging circumstances

Obtaining informed consent was not seen as feasible in time sensitive pediatric emergency care research. Conducting studies obtaining deferred consent was described as the "logical solution" by parents. During a pediatric emergency situation, the parents were perceived to be emotionally upset and hence respondents did not believe them to have full decision-making ability. They were not believed to be in a position to give meaningful informed consent and were perceived to be unable to understand the trial information [13, 25, 30].

Molyneux et al. [23] conducted a study taking short assent from the parents before coming back to them for full consent. The practitioners involved in this study raised concern about the validity of assent or full consent during this vulnerable situation. They felt that the parents were not in a situation to understand the information provided during that time. They indicate that parents wanted the doctors to start the treatment first and discuss the study later. The parents were very concerned about having their child's treatment started first. The parents also faced situations when nurses asked them to say "yes" or "no" to enroll the children in the study, otherwise they could not start the treatment. In this scenario, the parents might agree to enroll their children to the study start the emergency treatment as soon as possible. As the parents did not have enough time to comprehend the provided information respondedents wondered if it might not be valid informed consent.

This study [23] also found that the prospectivee assent process encouraged questions which also delayed treatment. The staff were not sure which information they needed to provide during this

time-sensitive emergency situation. They were also not sure whether they needed a straightforward “yes” answer to enroll the children. The parents were only concerned about the wellbeing of the children and sometimes they told the staff to do whatever they thought was best for the children. The staff also did not know how to deal with the situations when the father was not with the child and the mother wanted to wait for the father. The staff were confused whether it was a way for the mother to politely refuse enrolling her child to the study. All of these concerns and confusions demanded use of a deferred consent model which will allow the parents and practioners to discuss research participations later.

A2. Preference for deferred consent

The children, parents and practitioners across all the included studies preferred deferred consent in TPER.

The parents thought that taking deferred consent was a viable solution to conduct studies in challenging situations. They prioritized emergency treatment over spending time on consent processes [24]. They considered research participation could help other children and families in the future and wanted their children to participate in the study [26]. The parents also trusted the clinicians that they would do whatever was best for the children [16]. A study by Menon et al. [28] did not find any concern by parents regarding enrolling their children in a study without prospective consent. Even one bereaved guardian expressed how they felt better when they learned that their child died receiving the state of the art care as the child was enrolled in the study.

Though many children thought that research participation discussion should be done before conducting the study, deferred consent was acceptable to them in TPER, considering the fact that the study intervention should be given as early as possible. They also had full trust in clinicians.

They described that they would not be upset if they were enrolled in a study without consent from them or their guardians if the clinicians involved in taking care of them know about this enrollment [29] .

The practitioners who had experience of implementing deferred consent also had similar opinions [30]. They found that the families were receptive to deferred consent. The families found this consent process was ethically sound and wanted the practitioners to use the process more often. The practitioners also mentioned that they follow the same sequence of deferred consent to offer clinical care. In a time-sensitive emergency clinical setting, clinicians inform parents about their child's care after completing the treatment. In one study, the respondents reported that they did not face any trouble in obtaining deferred consent [24].

However, support for informed consent was not unconditional. The children were happy to give deferred consent if they were convinced that the intervention was safe [29] . They also wanted the treatment to be effective so that their recovery is quick and so it contributes to the development of pediatric medicine in the future.

The parents also had their own reservations. Deferred consent was more acceptable if it was related to observational studies than drug trials, especially if they did not know about the drug [16]. They also had reservations about deferred consent if they were not sure about the safety of trial drug [16]. Some practitioners felt that they should take at least verbal assent from the parents before enrolling their children in the trial [23]. The trial drug is not the standard of care and so, they wanted SDMs to be informed about this drug, which would give them an opportunity to opt out from the study. The practitioners also had concern that if they did not inform the parents about the trial drug and something happened to the children, then they might be blamed later [23] .

A3. Take less time to administer study drug

Deferred consent allowed the researchers to randomize the participants immediately and administer the study drugs in a timely manner. Menon et al. [28] compared time to randomize the children from meeting inclusion criteria to randomizing them with deferred consent and prospective informed consent. They found deferred consent took significantly less time to randomize and administer the first dose of study drug to the children in comparison with prospective consent.

A4. Children's opinion on consent processes

When DC has been employed, children still need to be informed of what took place and potentially involved in an assent process for continued research. The children had suggestions for researchers about deferred consent which would improve the deferred consent process. They had suggestions on who should follow up to obtain the deferred consent, who should be consulted for deferred consent and how to take deferred consent. In one study, children indicated wanting to receive information from a trusted and knowledgeable professional. The children expressed that it would be better if the doctors or nurses came to them to explain that they were enrolled in a study. One child even wanted to prioritize medical advice from clinicians rather than receiving it from their mother [29].

> "Tilly, aged 14: *'if it's a nurse who knows all about it and then also has studied kids, they can then help with that as well, help them do it, understand what's happened and go through it. But I don't think I'd listen if my mum told me. I would want it more, the medical advice really."*" [29]

The child expressed that children might have many questions like how the trial can affect them or what could be the consequences of enrolling in the trial, and doctors or nurses could be the best person to answer these kinds of questions. They wanted to talk to them face to face so that if they had more questions then they can ask them to clarify [29].

However, they also felt that doctors might not know how much information they need to explain about deferred consent to the young children. In this case, they suggested using animations, leaflets or other materials to help them understand these topics [29]

> "…most favoured an online animation that could be used either in hospital as part of a face to face discussion, or '*at some point when I was at home*' (Tom aged 13) to '*make sure they understand everything properly*' (Josh aged 11) to explain RWPC (research without prior consent)" [29].

The children, especially younger ones, wanted to consult their parents before making the enrollment decision [29]. They thought that they were too young to understand what research was and they would accept parent's decision regarding their study participation.

> "Participants of all ages echoed this by commenting that children younger than themselves, '*don't really understand […] what the research is about*' (Chloe aged 12) and '*might be a bit too young*' (Joseph aged 7) to make such decisions and that for such children it should be a parent's role to make a decision about the use of their information for research purposes." [29]

B. Challenges associated with deferred consent

There were also many challenges associated with taking deferred consent in pediatric emergency research. They are as follows:

B1. Child's death during research

Deferred Consent created anxiety for practitioners. It was "difficult" for them to approach bereaved parents for deferred consent as they did not want to "burden them" [24]. "Chasing" them for deferred consent was both "stressful" and "awful". They felt that they were the "worst person in the world" when the parents replied with "why are you asking this"? [24] In most of the cases the senior team member contacted the bereaved parents and they were not "particularly happy" doing this responsibility. Sometimes the practitioners personalized the letter they used to contact with the parents expressing the relationship they had with the family. Sometimes they did not contact the bereaved parents based on suggestions from the study consultant. Though the practitioners thought it would "not be good" or be "unethical" to contact them later, however, they also felt that it would be useful to obtain deferred consent to protect themselves from legal complications later [23].

The parents had diverse views on the use of deferred consent for the bereaved parents. The parents could understand that there was "no established right or wrong" with both interventions, that is, with usual care or study drug, so, they were happy if they were not informed about the study [27]. The information would remind them about the unfortunate event [16] and add distress to the grieving parents [25, 27]. They might become irrational because of their emotional disturbance. They might not understand that both treatments were safe and could take legal action against the practitioners. As a result, they thought it would be better if bereaved parents were not informed about the study [27].

However, some parents thought that bereaved parents should be consulted before using the data in the study [27]. The family has the "right to know the details of the circumstances" even if the outcome is "unfortunate" [25]. The practitioners should be prepared to answer any concerns they

might have had related to the trial. They might have questions like whether the trial intervention was the reason for the death of their child [16].

Many parents expressed support for medical research, which aims to improve the overall well being of a population and prevent child death. According to them, researchers need to do everything to prevent it from happening with other children [16]. The parents also stressed the importance of using the information already collected for the child who passed away. One parent suggested that the study team should use the data if they only look at "pure statistic numbers" without adding more burden to the parents [25].

B2. Timing of deferred consent

Parents thought the practitioners should contact the parents for deferred consent when the health condition of the child stabilized. They suggested the practitioners consult with the clinical team who were close to the family to understand the appropriate time for this discussion [16, 26]. The practitioners had to identify a time when they think that the parents would be able to talk about aspects of the deferred consent. If the practitioner approaches the parents and gets a negative response, then it is important that they give more time to those parents in discussing their consent [30].

The parents described how mistiming resulted in declining the consent. One parent mentioned that she would give approval of deferred consent if it would not happen in a time when the parent's only focus was on the critical situation of the child [24].

The bereaved parents had variations in their opinion about taking deferred consent from them. They expressed that practitioners should approach bereaved parents when they are not too upset to focus on the consent discussion [27]. The bereaved parents might be very angry at the initial phase of bereavement which could impact their decision-making abilities. Nevertheless,

bereaved parents did acknowledge the importance of medical research in order to contribute to the wellbeing of other children. Thus, it may be reasonable that the practitioners contact them later, once they have left the hospital[26]. One parent suggested initiating the deferred consent discussion during the organ donation discussion when she might "take in" the information. The parent would prefer a home visit by a nurse a few days after the bereavement. They wanted a responsive communication approach which would allow them time to ask questions [27].

B3. Concern about the trial

A qualitative study by O'Hara et al [26] identified a number of concerns by the parents about the trial. The information sheet used by the trial was missing important information which were impeding them from understanding the trial. For example, in one study parents had questions regarding whether the fluid amount would be changed if the child's condition does not improve, whether fluid amount will impact the outcome, whether they can identify the treatment group of the children or whether the fluid treatment is applicable to children of all ages. The parents acknowledged that they would not discuss these concerns with a trial recruiter. Some parents also had a misconception that standard of care is the best treatment option and so, using a trial drug might threaten the chance of survival for their children. All of these misconceptions impacted the parents' decision to allow their children to participate in the study [26].

B4. Fear of adverse events

The parents were afraid that if they allowed their children to participate in "research" then it would adversely impact the health of their children [24]. The parents prioritized whether the study drug was commonly used. They were concerned about associated "risks" or "unknown consequences" with research. They did not want to put their children at risk and want to be sure that the study drug was as safe as the standard of care [25]. The parents could not accept the "medical uncertainty" of research [27].

B5. Blood sample collection

A study by Woolfall et al. [24] explored concerns related to additional blood collection for research without prior consent. The practitioners, especially the doctors, thought collecting blood samples as part of the study without seeking consent is "insignificant" considering the overall emergency interventions. Thus, it was not a concern for them. However, the nurses had different views on collecting blood for study purposes without prospective consent. They thought if they do not have consent for blood collection from the parents prior then it would compromise the trust in the relationship between practitioners and parents. They also explained how they were not happy collecting additional blood which was a "huge difference" from the standard of care. The study also described how the nurses became "upset" when they needed to destroy the blood sample as the parents declined to give deferred consent later to use this sample. On the other hand, the study found the parents were not particularly unhappy regarding collecting a blood sample from the children without prospective consent. They thought it would not harm the children. However, they thought it would be "nice" if the practitioners would inform them before taking the blood sample for study purposes.

Discussion

This systematic review is the first of its kind which explored challenges and opportunities associated with deferred consent in pediatric emergency research. The current review included data only from deferred consent studies, the studies which aim to understand the deferred consent process in pediatric emergency research. Though there have already been two systematic reviews conducted on deferred consent processes in pediatric emergency research, the focus and selection of studies for those systematic reviews were different. The systematic review by Eltorki et al. [64] focuses on the ability to conduct pediatric emergency research using the deferred consent model. Most of the studies included in this systematic review focus on community

consultation and public disclosure. Community consultation and public disclosure are two extra requirements by U.S. Food and Drug Administration (FDA) to use deferred consent in time-sensitive emergency research. These requirements aim to involve community people in the study area before recruiting the study participants [64]. The systematic review by Furyk et al. [13] focuses on synthesizing empirical evidence on deferred consent in pediatric emergency research. All of the included studies were not specifically deferred consent studies. For example, one review included a proposed randomized control trial (RCT) on use of therapeutic hypothermia vs normothermia in UK emergency departments [65]. The study commented that it will be ethical to conduct the proposed RCT and deferred consent is acceptable to the majority of the participants. So, the focus of this review was not use of deferred consent in that trial. Our systematic review focused on those primary studies which focused mainly on use of deferred consent in TPER.

Summary of evidence

We identified 10 studies which discussed the conduct of deferred consent in pediatric emergency research. Our systematic review aimed to capture the opportunities and challenges associated with deferred consent in TPER. It uncovered that there are many opportunities as well as many challenges associated with DC.

One of the opportunities of using deferred consent is that children, parents and practitioners had support for using deferred consent in emergency care situations. The parents felt that the research participation of their children will contribute to the development of pediatric medicine and ultimately help other children and families in the future. This altruistic attitude towards research participation in RCTs has also been reported by other studies [46, 66]. The parents had a positive perspective about research [46] and they thought that research participation by their children will not only help their own children but children from other families [66]. The parents also trusted

the clinicians to always keep the best interest of their children in mind when conducting such studies [46, 66, 67]. The children and parents did have concerns regarding the safety issues related to the study drug. The clinicians need to clarify these safety issues related to the study drug, which is an important factor in determining if children can participate in RCTs [46].

Using deferred consent in TPER was also considered a "logical" solution to conduct research in this situation. The parents may be emotionally upset during these emergency situations and hence may not be well placed to give valid informed consent [13]. A study conducted by Harvey et al. [68] to understand informed consent in critical care found that only a small proportion of patients were able to give informed consent before randomization.

The parents were very concerned about the health condition of their children. They wanted the clinicians to start the treatment right away and discuss research participation later. Deferred consent would allow the clinicians to start administering the study drug immediately. The CRASH Trial Management Group [69], who conducted an RCT on adult head injury patients, found that randomization of patients takes less time if deferred consent is used.

Furthermore, children had specific suggestions to improve the deferred consent process. They wanted the doctors or nurses to discuss the consequences of research participation with them in detail when they approach them for DC. Some of them also preferred involving their parents in this discussion. They were also concerned about the safety issues of the study drug [46] and they were happy to give deferred consent if the study drug was safe and effective.

The practitioners faced many challenges to implement deferred consent in pediatric emergency research. One of the challenges of taking deferred consent includes when the practitioners needed to take deferred consent from bereaved parents. The practitioners were in a difficult position to take deferred consent from the parent of a child who died during the study period.

The practitioners did not want to burden the parents by reminding them of the death of their child when discussing research participation. Sometimes the parents were annoyed about this discussion and the practitioners avoided taking deferred consent [70].

The parents thought that they should be consulted even if the event was very unfortunate for them. They also had support for medical research, and they stressed the importance of using already collected data even if they were not informed about the use of data. There is consistent with evidence from others studies [68, 71] which used patient data from patients who died before obtaining deferred consent.

Timing of taking deferred consent was another challenge for practitioners. If the time for deferred consent was not appropriate for the parents, then they could decline to give deferred consent. The practitioners should approach the parent for deferred consent when the health condition of the child was stabilized, and the parents could focus of the consent discussion [14]. In case of bereaved parents, they might be very angry after the initial unfortunate event [72] which could impact their decision-making. The parents would prefer this discussion to take place when they returned home, and that a nurse visit their home to take deferred consent later [14].

The parents had different concerns regarding the trial itself which might impact their deferred consent decision. They also had misconceptions about the study drug that the study might be inferior than the standard of care. Moreover, they had fear regarding “risks” or “unknown consequences” of research [66]. The practitioners needed to address these fear and misconceptions to improve the deferred consent process [14].

Another challenge that the practitioners, especially the nurses, faced was related to collecting additional blood sample for study purpose. They thought that they were collecting a significant amount of additional blood as part of study. They would not collect this amount of blood when

providing standard of care. They expressed that they should not collect extra blood only for study purpose without consent from the parent and became very worried when they did not get permission from parents to use this extra amount of blood leading to it being destroyed. On the other hand, the parents were not very concerned about this extra blood collection. However, they felt that it would be better if the researchers would seek consent from them before collecting the extra blood from their children.

Conclusions

Deferred consent keeps scientific and ethical balance when conducting TPER. Our review explored challenges and opportunities associated with deferred consent. There is a lack of studies which specifically explored the perspective of children and bereaved parents on deferred consent. Knowledge about the application of deferred consent in this field might guide researchers to deal with their ethical dilemmas in this situation. It might encourage them to conduct more studies involving children and bereaved parents in the future and ultimately contribute to the development of pediatric emergency medicine.

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Appendix 1: codebook

Themes	Code	Description
Study information	Study ID	Last name of the first author and year of publication
	Country	The country or countries where the study was conducted
	Study setting	Description of the study settings
	Study design	Description of study design
	Participants	Information about the study participants
	Objective	The objective of the study
Logic of using DC	Parents' capacity	Any discussion regarding whether parents are capable of providing informed consent in TPER
	Feasibility of PC	Discussion on feasibility of taking informed consent by the practitioners from the parents in TPER
Support for DC	Support for DC typical	The typical reasons for supporting deferred consent by children, parents and practitioners
	Support for DC atypical	Discussion regarding support for DC which is not typical. This could include conditional support for DC or if the participants have any other reservations for supporting DC
Children's opinion on DC	Who should approach to children for DC	Perspectives of children regarding who should approach them for DC
	Whom should consult	Perspectives of children regarding whom the practitioners should consult for children's research participation apart from the children
	Medium to provide study information	Perspective of children on how the practitioners should provide study information to the children
Time to administer study drug	Time to administer study drug	Any discussion on comparing time to recruit the study participants and administering the study drug using DC versus PC
Child's death during the research	Consent from bereaved parents	Practitioner's perspective on obtaining consent from the bereaved parents
	Consent by bereaved parents	Bereaved parent's perspective on giving consent for their dead children
Timing of consent	Timing of consent	Any discussion on appropriate time to approach the parents for research discussion
Concerns or questions about the trial	Concerns or questions about the trial	Parent's concerns or questions related to the trial itself
	Misconceptions about the study	Discussion on parents' misconception about the study

Fear of adverse event	Fear of adverse event	Discussion on parents' fear on adverse event if they allow the children to participate in the study
Blood sample collection	Blood sample collection	Discussion on questions or concern related to blood sample collection as part of the study by the practitioners

DC = Deferred consent

PC = Prospective consent

TPER = Time-sensitive pediatric emergency research

Chapter 4: Discussion and conclusions

Pediatric emergency research is essential to develop interventions in areas where there is a lack of evidence to inform treatment practices for this group of people. However, it is not always feasible to seek prospective informed consent from the substitute decision makers (SDMs) of children experiencing a medical emergency which is one of the prerequisites for enrolling children in a study. Deferred consent can provide an ethical and scientific balance to enable conduct of studies involving children in an emergency situation. Deferred consent is used to enroll children into a trial immediately and take consent from the patients/SDMs when the health condition of the children is more stable.

The use of deferred consent in emergency research is a relatively new phenomenon, especially in pediatric emergency research. Our review explored the perspective of children, parents and practitioners regarding challenges of deferred consent model and benefits of using this model in pediatric emergency research. The children, parents and practitioners were optimistic of using deferred consent. Using deferred consent was considered a logical solution to conduct studies in time sensitive situation and start the treatment immediately.

Though deferred consent gives enough time to discuss research with the parents/SDMs, the researchers needed to identify best time to discuss this, consulting with the clinicians who were giving treatment to the children. The researchers also had confusion regarding whether they should approach bereaved parents and when. They also had mixed opinions regarding collecting blood sample solely for research purpose. Our review also explored that the parents had concerns and misconceptions regarding trial itself. Some of the parents/SDMs had misconception that trial drug is inferior to standard of care, which impacted their decision to allow their children to participate in the study.

Identified gaps in the literature

Our review has many implications. There was only one study which exclusively take perspective of children about deferred consent model. It is essential to understand the perspectives of children about their research participation as part of empowering them and respecting their dignity. More studies should be conducted involving children to explore perspective of children on deferred consent model. There were also less studies which explored perspective of bereaved parents. The bereaved parents have different experiences and it is essential to understand their perspectives to improve the deferred consent process for them and hence improve the chance of using data of deceased children. Excluding data from deceased children may lead to biased results. Our review also found that there was gap between the way study information was disseminated and how the parents or children received it. The parents expressed that the study information sheet provided to them did not answer all the questions they had about the study. Though they had many questions about the study, but they acknowledged that they would not ask these questions to the study team.

Recommendations to improve the use of DC model

The use of DC in TPER is a recent phenomenon. The current review found that there are a number of misconceptions around DC among the practitioners especially who do not have experience of implementing DC in TPER. However, the practitioners with experience of implementing DC did not find any problem with the conduct of studies in this situation. They found a positive response from the SDMs who experienced the conduct of studies using DC. The current review also found that understanding when to approach the SDMs for DC is an important factor for getting consent from the SDMs. It is always better to approach the SDMs when the health condition of their children is stable and hence the SDMs are less distressed. In this case, it is better to talk with the bedside doctors or nurses who are involved with taking care of the

children. These doctors or nurses could be the best person to understand the health condition of the children, and be aware of the emotional status of the SDMs. They can suggest to the researchers whether they should approach the SDMs for DC at a specific time or not.

The literature demonstrates that practitioners in general tend to perceive that it is unethical to communicate with the bereaved parents for study purposes as it might add more distress to the bereaved parents. However, this review found that many bereaved parents were positive about conducting studies using DC. They understood the importance of conducting emergency research involving pediatric patents. They were happy to give permission to the researchers to use their child's data. They also mentioned that the researcher should communicate with them when the situation is stable. In this case, it could be better to be visited at home by a doctor or nurse who were involved with the treatment of their children and hence developed a relationship with the family members.

The current review found many misconceptions among the SDMs about clinical trials. Many of the SDMs did not allow their children to participate in the study considering the trial might negatively impact the health of their children. The SDMs did not ask any questions of the study team if they were less clear about any information in the study information sheet. There is scope to explore this area to understand the concern or questions the parents or children might have about studies their children are enrolled in. Moreover, a feedback mechanism can be developed so that the parents or children can communicate their questions to the research team in an efficient way. The practitioners should find ways to seek feedback from the SDMs to understand their concerns and misconceptions about the study. The practitioners could talk with SDMs about their concerns or if they have any questions about the study information sheet. They can discuss with the SDMs whether the information provided is clear to them or whether they have any

suggestions to improve the study information sheet. Developing a feedback mechanism will help the SDMs to understand the study well and overcome some of their concerns or misconceptions about the study.

Providing study information to the children is another area to explore. The children mentioned that they are too young to understand what research is and what it means to participate in research. The children suggested the practitioners use specific tools to provide study related information to them. For example, most of them suggested the use of online animation to help them understand how research works and how they will be affected if they participate in the study. Using pre-tested tools to provide study related information for the children could be an efficient way to disseminate study related information to children.

To design a DC model, it is important to consider the aforementioned aspects related to DC. The practitioners should use the help of nurses or doctors involved in the treatment of the children to understand the health condition of the children and emotional status of SDMs before approaching SDMs for study discussion. It is also important to visit the home of bereaved parents by a clinician whom the parents know personally to discuss the study and seek permission to use the data already collected.

Practical enhancements to the application of DC could thus include some of the following: practitioners with experience of using DC should share their experience of using DC with other clinicians in different forums. Study teams need to understand the misconceptions or concerns of the SDMs about their study and take initiative to address them through face to face discussion. In the case of children, the clinicians who are involved with treatment of children should discuss research participation with them. They can use different tools like online animation or an app to

give them information about the study and how research is conducted. Using these strategies might improve the DC model and conduct the study in patient centered way.

The SQUEEZE trial, currently ongoing and being led from McMaster, aims to determine effectiveness of early goal directed fluid-sparing strategy versus usual care in quicker reversal of septic shock in children. This study is using deferred consent model to enroll the children in this study. The parallel qualitative study of this trial aims to understand perspective of children and SDMs on use of deferred consent implemented in SQUEEZE trial. The findings of this qualitative study might fill a number of gaps mentioned earlier in this review.