**Title:** Research without prior consent in paediatric emergency and critical care medicine

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**Abstract**

Children and young people’s healthcare should be evidence-based yet many treatments are unlicensed or prescribed off-label. Research is needed, but prospective informed consent for many emergency and critical care trials is neither feasible nor ethical - treatments are time critical, and delays for research discussions may cause harm. Research without prior consent (RWPC) is a practical approach which facilitates such research. Trial interventions are administered immediately to eligible patients, and consent for ongoing study involvement is sought after the emergency situation has passed. This has been permitted in the United Kingdom since an amendment to legislation in 2008, and subsequently employed by several trials. Studies demonstrate that most parents are supportive of this approach provided their child’s safety is not compromised, and research discussions are appropriately timed. Practitioners with no experience of RWPC often initially report anxiety about taking this approach, but study experience and training helps change perspectives. Sadly, some children enrolled into such studies will die. Approaching bereaved families for consent requires a bespoke approach, conducted with care and sensitivity. Future research should explore the acceptability of higher risk trials, the viewpoints of children with first-hand experience of this method, and international perspectives.

**Introduction**

The healthcare of children and young people (CYP) should be based on robust evidence derived from paediatric studies, as their anatomy, physiology and development are different to adults. However, less than half of all medicines administered to CYP have been studied in this age group, and many are unlicensed or prescribed off-label. Developing paediatric-specific evidence requires new research.

Prospective informed consent for clinical trial participation is a cornerstone of ethical research. This process involves an individual voluntarily making a decision for themselves or their child to participate in a trial, having received all the relevant information. Seeking informed consent in emergency and critical care situations presents numerous practical and ethical challenges. Unlike elective settings, it is generally not possible to predict which children may be eligible for a given trial prior to their attendance. Treatments are time-critical, and delay for research discussions could lead to harm. Parents may be absent or unable to absorb the information required to make the ‘informed’ component of consent a reality, due to concerns over their child’s health.When faced with a critically ill child or young person, how can clinicians practically and ethically obtain consent for trial participation?

One approach is conducting research without prior consent (RWPC), also known as deferred consent or exception from informed consent (EFIC) in the United States. RWPC prevents delays in administration of time critical interventions by enrolling patients immediately, before discussing the trial with families at a later stage. Consent for ongoing study involvement is obtained after the emergency situation has passed.

RWPC has been permitted in UK adult and paediatric settings since an amendment to the Medicines for Human Use (Clinical Trials) Regulations in 2008. Regulations are supported by General Medical Council guidance and stipulate which criteria are required for the use of RWPC in a clinical trial, including: *treatment must be needed urgently, it is not practicable to obtain consent prospectively and a research ethics committee (REC) has given approval.*

Paediatric medical and nursing staff should be familiar with RWPC, particularly those working in Paediatric Emergency Medicine (PEM) and Paediatric Intensive Care (PIC).

**Research with vulnerable populations**

CYP are vulnerable research participants due to their cognitive, emotional, and physical developmental differences to adults. In the UK, CYP under 16 years of age, or 16-18 year olds who lack capacity, cannot legally consent to trial participation.Responsibility for providing consent lies with their parent or legal guardian. However it is a formal requirement in Medical Research Council guidelines that if a child is mature enough, their assent should be sought to respect their developing autonomy.

CYP in emergency and critical care may be particularly vulnerable due to very young age, distress, or impaired conscious levels. Additionally, some CYP may present without a parent or guardian. This can occur for example in major trauma cases resulting from road traffic collisions, where the child’s parents may also sustain significant injuries. In neonatal intensive care, parents are often separated from their baby during the initial resuscitation and stabilisation process.

Vulnerability is context-dependent and arises from the interaction between an individual’s characteristics and their environment. Parents can be vulnerable in emergency settings due to the psychological distress of seeing their child acutely unwell. Although they are not the patient or research participant, parents are the main decision makers in regards to providing consent for their child’s involvement in research. They may find it difficult in this situation to absorb information or make a fully informed decision about research - termed ‘situational incapacity’. Qualitative research corroborates these findings, and the concept of situational incapacity rings true for parents whose child has been acutely unwell.

Historically, these vulnerabilities were acknowledged by minimising involvement of CYP in research. Recognition of the need for evidence-based medicine has increased the number of clinical trials which include CYP as participants, but considerable challenges remain. Guidance, including the need for those involved in delivering research to attain Good Clinical Practice in research training, and gaining approval for trials from a REC, is in place to protect such groups. RECs act to safeguard participants, and fall under the remit of the Health Research Authority (HRA).

**Examples of RWPC studies**

In 2013, the CATheter infections in CHildren Trial (CATCH) was one of the first UK trials to use RWPC since UK legislation change. This study assessed the effectiveness of impregnation with heparin or antibiotic, compared to standard central venous catheters, in preventing bloodstream infections in CYP requiring intensive care. Between March 2010 and November 2012, 1859 participants were randomised across 14 UK hospitals and one emergency transfer service. CATCH used prospective informed consent for elective surgery admissions and RWPC for emergency admissions. Consent rates were higher for emergency (76%) than elective admissions (69%).

Following CATCH, further National Institute for Health Research (NIHR) funded trials and feasibility studies have been conducted:

* Emergency Treatment with Levetiracetam or Phenytoin in Status Epilepticus in Children (EcLiPSE trial, 2019), comparing second line treatments for convulsive status epilepticus
* Fluids in Shock (FiSh trial, 2018), comparing fluid bolus volumes in suspected sepsis
* FEVER study (2019), examining optimal temperature thresholds in children with a fever and suspected infection

These studies have shown that RWPC can facilitate the conduct of much needed clinical trials in this challenging setting. Findings have been used to develop guidance to inform future trials (see CONNECT study guidance, further reading list).

Internationally, the Fluid Expansion As Supportive Therapy (FEAST, 2011) trial of fluid bolus volumes in sepsis took place across three African countries. This study employed staged consent, a modified form of RWPC. In staged consent, parents provide brief verbal assent at the point of enrolment followed by informed written consent after the emergency situation has passed. In an embedded study staff and parents viewed the verbal assent as a way of protecting the interests of researchers and parents. However the authors questioned the validity of verbal assent due to concerns about parents’ understanding and voluntariness at the height of their child’s critical illness.

**Perspectives of parents and CYP on RWPC**

The studies described above have included embedded research led by one of the authors (KW) that explored stakeholder views on the acceptability of RWPC, including optimal ways of approaching families to discuss research participation when CYP are critically ill. Most parents whose children experience emergency care will not have heard of RWPC, but as this quote illustrates, most are supportive provided safety is not compromised and trial discussions are appropriately timed:

‘*I do genuinely feel that in 99 percent of the cases…if you approached them in the right way and at the right time then there wouldn’t be a problem.’* (P5, father, CONNECT study)2

Parents understand the need for research and support the use of RWPC to inform best treatment for other CYP in the future: *‘if it helps other children then that’s brilliant’* (P9, mother, CONNECT study).2

A minority of parents may initially describe surprise or shock at discovering their child has been entered into a trial without their consent. However most parents support RWPC once practitioners explain the reasons for its use, including why informed consent could not be sought prospectively.

‘*I was initially surprised that this had happened, because obviously the consent happened afterwards, but I wasn’t sort of concerned or anything. They explained everything really clearly and the information leaflet was very good as well’* (P12, mother, FiSh trial).3

Some may still find RWPC difficult to accept after an appropriately timed explanation, but this is very rare: ‘*it’s effectively already been done…it takes away your power as a parent to make that decision’* (P16, mother, CATCH study).4

The Voices study explored views on RWPC amongst CYP who had recent experience of emergency care.1 They were keen to be included in research - *‘it’s quite cool to be part of like a scientific medical thing’* (‘Josh’, aged 11) and felt RWPC was acceptable in an emergency if trial interventions were deemed safe: *‘I think they can do that (research) without asking for permission because it’s an emergency and you have to give the medicine’* (‘Chloe’, aged 12). CYP wanted to discuss the trial when they felt better.

**Practitioners’ perspectives on RWPC**

Opportunities for clinical staff to get involved in RWPC trials and processes are somewhat limited, as the incidence of conditions requiring this approach is low. Practitioners with no experience of RWPC may have negative perceptions of this model, and report anxiety about approaching families for consent, voicing concerns about the impact on the parent-practitioner relationship.For example: *‘the first time I did approach a parent* (to discuss RWPC) *I remember feeling really nervous about their reaction’* (P7, female nurse, CATCH study).4

However evidence demonstrates that experience of RWPC can alter viewpoints and allay practitioner anxiety. After RWPC study involvement, those with no prior experience often change their perspective. First-hand experience helps staff acknowledge that prospective informed consent is not feasible in an emergency, and that most families are receptive to RWPC if conducted sensitively and at an appropriate time. RWPC enables practitioners to approach parents *‘at a time when we feel that they are able to absorb the information’* (P5, male nurse, CATCH study).4

Several acute research-active sites offer RWPC training as part of a standard program for clinical staff who may be expected to undertake this as part of their job role. An evaluation of RWPC training in the EcLiPSE trial showed that an interactive training package alleviates anxiety and negative perceptions in those unfamiliar with this approach. Interactive training incorporating videos and simulations can improve practitioners’ confidence in recruitment discussions for RWPC studies. Clinicians value parental perspectives being incorporated into training; this helps engage practitioners in trials that are at risk of being deemed too challenging to conduct. Trial teams should therefore ensure that bespoke written and video training materials are provided for clinical staff, alongside simulation scenarios for the critical care episode and the RWPC conversation with families.   
**Death of a child or young person**

**Scenario**

Sam is a twelve year old boy who is brought to ED following a road traffic collision. His father Peter was driving and is brought to the same ED but is unconscious whilst Sam is being assessed.

Sam has multiple injuries and catastrophic bleeding. The ED is currently recruiting to a RWPC trial investigating tranexamic acid versus placebo in the management of major haemorrhage. Sam is enrolled in the study and receives tranexamic acid alongside standard resuscitative measures. Sadly, despite the best efforts of the clinical team, Sam dies.   
  
*Should the research team tell Sam’s parents that he was recruited into a research trial? If so, when and how should this be done?*

Sadly, some CYP enrolled into emergency care trials die during their admission. In a review of UK neonatal and PICU research, 16% of CYP enrolled into studies died before discharge, mostly in neonatal settings. UK legislation does not stipulate what should happen to research data of CYP in these circumstances.

Inclusion of data from enrolled CYP who die is important; excluding these data risks introducing systematic bias, and contradicts the principle of intention to treat analysis.However, discussing research participation with a bereaved family is a daunting prospect even for experienced researchers and clinicians, and opinions vary on the best approach.

Interviews with bereaved parents suggest that most favour inclusion of their child’s data in RWPC trials, though a minority oppose such disclosure.Parents’ responses may be unpredictable due to grief:

*‘You have to understand that you’re dealing with a completely irrational time…nothing really makes sense…it has to be approached with care, but…I certainly wouldn’t mind it’* (P17, bereaved mother, CONNECT study)2

Guidance based on bereaved parents’ perspectives advises that this topic is best introduced by a member of the clinical team who knows the family rather than a researcher. Research discussions should take place a reasonable amount of time after events and ideally be face-to-face. If face-to-face discussions are deemed inappropriate, letters are a more acceptable form of contact than phone calls. Approaches to consent in these circumstances should be personalised and conducted with considerable care and sensitivity.

**Planning a RWPC study**

When planning any trial, the attention given to consent and trial processes should be equivalent to that traditionally applied to the study rationale, selection of interventions, and statistical modelling. Planning of consent methodology should therefore occur early in the development phase. This is especially the case for RWPC, as there are a number of factors to take into consideration, not least of which is whether RWPC is appropriate.

Although RWPC may be intimidating for those not experienced in its use, it is often subsequently a very attractive approach. It obviates the need to have research staff available all the time, allows clinicians to focus on clinical care and key trial processes without the cognitive burden of informed consent discussions, and results in very high trial participation rates. However it must only be used in trials which fulfil the regulatory guidance relating to urgency of treatment, ethical approval, and practicalities of obtaining prospective informed consent.

Trial success is dependent on the ability of staff to perform all trial processes whilst delivering clinical care in a high stakes, low frequency situation. Trial interventions should therefore follow standard clinical care as closely as possible. Clear nomograms should be provided in trials using medications. Essential information such as eligibility criteria should be clear and readily available, randomisation must be rapid and reliable, and case report forms should be brief with essential data fields highlighted. Clinical care will always predominate in critical care situations, and the impact of this on sample size calculations should be factored in to trial development; for example, in the case of patient deterioration, clinicians may need to institute non-trial therapies which affect the primary outcome rate.

**Involvement of stakeholders**

Early engagement of families, CYP, and clinical staff is crucial for the success of any study using RWPC. Providing assurance that the trial has their support is important to participants, parents, and those taking consent. Patient and public involvement (PPI) must be relevant, meaningful, and robust; formal pre-trial research with families may be necessary if there are aspects which have not been explored previously. PPI groups are often accessible via clinical trials units, local institutions, and Royal Colleges.

Discussions should explore any special circumstances relating to trial participation. For example, are participants potentially vulnerable due to underlying conditions, and are there any particular risks? Is the intervention an established or new treatment? Do any predictable side effects preclude its use in certain groups? Are any tests involved, and are these invasive? Do they need to be done before trial participation discussions, and are they reasonable and essential? Opinions should be sought from CYP and their parents, and trial materials such as information leaflets should be co-designed. This approach will ensure that any such materials are clear to families, and explain the rationale for the trial, and the use of RWPC, in easy to understand language. It is also important to acknowledge and incorporate the opinions of clinicians, especially regarding the importance of the trial and the existence of equipoise in relation to treatment options.

**Consent discussions**

Timing is crucial for consent discussions. These should only be undertaken once the patient’s clinical condition has stabilised, and ideally within 24 hours, as supported by CONNECT guidance and RWPC trial experience to date. Discussions must happen early enough to ensure transparency, whilst not being so soon as to increase family distress (or risk lack of understanding); engagement between research staff and clinical teams is essential in order to strike this balance. Parents and CYP enrolled into RWPC trials must feel safe voicing any objections, and to withdrawing from any further involvement in the trial. Trial processes must make this clear to families, and allow them sufficient time to ask any questions and go through any concerns. Planning availability of practitioners to discuss the trial with families is therefore key, especially if there may be rapid clinical improvement resulting in hospital discharge within a short time frame of the trial intervention. This is particularly relevant over weekends, traditionally seen as non-standard hours for research practice.

Despite this, CYP may be discharged before RWPC discussions can take place. Processes for seeking consent for ongoing involvement in this situation should therefore exist, or there should be ethical approval for opt-out consent; any such procedures must comply with the General Data Protection Regulation 2016/679.

Finally, it is inevitable that families will occasionally notice that something “unusual” is being done while critical care is being delivered. Whilst this is more likely in cases where a condition necessitates multiple emergency attendances (such as epilepsy), it may also occur if clinicians discuss “the trial” or appear overly secretive. Staff must therefore be alert to this, and address any issues which arise transparently and succinctly. To support any such discussions trial teams should also provide a short information leaflet, co-designed with families, summarising the trial and RWPC prior to full consent discussions taking place. If the family wish to not take part in the research, even without knowing trial-specific details, then this must be respected.

**Areas for future research**

As can be seen, our experience and knowledge around RWPC in paediatric emergency care as a community has grown markedly in recent years. Exploration of the acceptability of this approach with families, CYP, and practitioners, has also helped identify key areas for future study. Research is required to establish the acceptability of conducting RWPC within trials that involve higher risk, such as trials of medicinal products and interventions not used in standard clinical care. Similarly, future diagnostic studies involving additional invasive procedures or an opt-out only approach to consent would benefit from exploring parent and clinician views at the pre-trial stage.

Future work should study the views of CYP with personal experience of RWPC and whether there are alternative ways of involving young people in decisions about their participation in critical care trials. These might include contacting them at their local hospital, at home or through their general practitioner when they have recovered.

To date, there has been relatively limited research involving bereaved parents who have first-hand experience of RWPC. Further studies should be conducted to inform recruitment and consent-seeking when a child has died. Bereaved parents’ views should be sought on the inclusion of CYP data in a trial if practitioners have made attempts to seek deferred consent but parents have not responded.

Research is required to look at the transferability of current RWPC guidance to other healthcare settings, including neonatal units and adult critical care, as less is known in these areas. Paediatric emergency research is also well recognised for its efforts in national and global collaboration; moving forward, exploration of international legislation and perspectives will be essential in order to inform trials conducted in multiple geographical regions via research networks such as the Pediatric Emergency Research Networks.

**Practice points**

* Prospective informed consent is neither feasible nor ethical in time-critical situations, leading to the need for research without prior consent (RWPC)
* RWPC is acceptable to most parents, children and young people, provided it is done sensitively and in a time-appropriate manner
* Approaching bereaved families to discuss RWPC requires a bespoke approach, and is often best introduced by the clinical team
* Further research is required to explore perspectives of CYP and bereaved parents with first-hand experience of RWPC

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**Further reading list**

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