Pediatric clinical research in the PICU: Ethical challenges and solutions

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Ethics of drug research in the pediatric intensive care unit.
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ABSTRACT

Critical illness and treatment modalities change pharmacokinetics and pharmacodynamics of medications used in critically ill children, in addition to age-related changes in drug disposition and effect. Hence, to ensure effective and safe drug therapy, research in this population is urgently needed. However, conducting research in the vulnerable population of the pediatric intensive care unit (PICU) presents with ethical challenges. This chapter addresses the main ethical issues specific to drug research in these critically ill children and proposes several solutions.

The extraordinary environment of the PICU raises specific challenges to the design and conduct of research. The need for proxy consent of parents (or legal guardians) and the stress-inducing physical environment may threaten informed consent. The informed consent process is challenging because emergency research reduces or even eliminates the time to seek consent. Moreover, parental anxiety may impede adequate understanding and generate misconceptions. Alternative forms of consent have been developed taking into account the unpredictable reality of the acute critical care environment.

As with any research in children, the burden and risk should be minimized. Recent developments in sample collection and analysis as well pharmacokinetic analysis should be considered in the design of studies.

Despite the difficulties inherent to drug research in critically ill children, methods are available to conduct ethically sound research resulting in relevant and generalizable data. This should motivate the PICU community to commit to drug research to ultimately provide the right drug at the right dose for every individual child.

INTRODUCTION

Drug research in children balances between the advancement of knowledge – and consequently improvement in clinical care – and protection of this vulnerable population susceptible to harm and exploitation. Children are relatively incapable of protecting their own interests and therefore need additional protection as recognized in many international ethical and legal documents concerning research with humans.[1-4] Specific provisions for minors, for example relating to the informed consent process and the acceptability of burden and risk have recently been reviewed by our group.[5] These provisions pose challenges to research in children. Failing to conduct clinical trials in minors turns children into '*therapeutic orphans*' because the level of protection is not balanced with the need of generating knowledge to improve care.[6]

THE NEED FOR DRUG RESEARCH IN CHILDREN

We need to be aware that every medication used in clinical practice that has not been studied in clinical trials can be considered an experiment. Clinical drug trials in children are essential because data on effectiveness and safety often cannot reliably be derived from data in adults. Major changes in pharmacokinetics (PK) and pharmacodynamics (PD) occur with increasing age due to changes in body composition, ontogeny of drug metabolism and transport and renal function.[7] The relative lack of knowledge on drug disposition can lead to treatment failure[8 9] and adverse events as serious as fatalities.[10 11] It is known that extrapolation from adult data has caused harm in the past. For example, a lack of knowledge on ontogeny of enzymes responsible for conjugation caused grey baby syndrome in neonates treated with doses of chloramphenicol derived from adult studies.[12 13] Similarly, drug choice and dosing for patients in the pediatric intensive care unit (PICU) cannot always be derived from research in the general pediatric population because PK/PD is influenced by critical illness [e.g. inflammation, liver and renal failure)[14-17] and its treatment modalities (e.g. extra corporeal membrane oxygenation (ECMO), hypothermia, continuous renal replacement therapy).[18-20]

Some drugs (such as vasoactive and sedative drugs) are almost exclusively used in critically ill children, and therefore can only be researched in these patients. However, a large proportion of drugs used in pediatric practice has not been systematically tested in the pediatric population. To stimulate pediatric drug research the Best Pharmaceuticals for Children Act in the US and a similar directive in Europe offered incentives to pharmaceutical companies to generate data in children.[21 22] Regrettably, fewer than 50% of these studies and 26% of those focusing on safety were published in peer-reviewed journals. Moreover, studies on safe and efficient drugs were more likely to be published than studies resulting in negative labelling change, putting children at risk of inefficient

or unsafe prescriptions.[23] Although these stimulating measures generated some useful safety and prescribing information in children, they did not result in the expected reduction of off-label use.[24 25] Estimates of off-label use in the pediatric population still range from 10-65%.[26] In the PICU, even up to 70% of drugs are unlicensed or off-label, which reflects the lack of knowledge on drug efficacy and safety in the PICU population.[27-29]

CHALLENGES OF DRUG RESEARCH IN THE PICU

The previous paragraph has made clear that drug research in the PICU is essential. But research in this population of critically ill children is precarious and raises specific ethical challenges. These challenges may be specific to culture and legislation of each individual country; this chapter focuses mainly on research in high income countries. The ethical dilemma of conducting research in the PICU is recognized by pediatric intensivists themselves; in a survey of 415 pediatric intensivists, over 95% found randomized controlled trials (RCTs) on potentially life-saving therapies ethically acceptable, but at the same time almost all were in ethical conflict with these studies.[30] The specific challenges faced by researchers in the PICU are, first, the extraordinary physical environment of the PICU that presents challenges to the design and conduct of research and its ability to generate useful results. Second, the children themselves may be too young to consent or incapable of it due to acute illness and sedation. Then, parents or surrogates are responsible for the decision to involve their child in research, with consequences for the informed consent process, notably under the stressful conditions of the admission. Last, patients in the PICU already undergo many painful and invasive procedures as part of clinical care. Therefore, additional burden and risk of research procedures must be minimized.

Improving care of the critically ill child implies generating reliable knowledge with research widely endorsed by caregivers and families. This chapter addresses the main ethical issues specific to drug research in the PICU and proposes several solutions.

OPTIMAL STUDY DESIGN AND CONDUCT IN THE PICU

Research subjects included in research of poor quality are exposed to risk and burden without benefit, neither for themselves nor for others. Therefore, only methodologically sound research that can generate new results should be proposed to possible research subjects. This requirement was already laid down in the Nuremberg Code in 1949, and consequently in all other important ethical and legal documents concerned with research with humans.[1-4] The specific study population, recruitment method, outcome measures, use of rescue medication and protocol adherence can influence the validity

of research in the critically ill child and consequently influence the usefulness of the generated results. Table 1 presents an overview of these issues.

Table 1: Challenges to quality of clinical drug studies in critically ill children

Theme	Challenge	Impact on results of trial
Study population	Heterogeneous, small patient populations and relative lack of multicenter research networks	Risk of inconclusive trials due to limited sample size
Recruitment	Risk of selective recruitment: the sickest patient may not be enrolled	Risk of bias and reduced generalizability
Outcome measure	Selection of clinical relevant outcome measures may be jeopardized by small sample sizes	Outcome may be clinically irrelevant
Rescue medication	Allowing rescue medication with the study drug in placebo arm, as not doing so may be perceived as unethical	True efficacy of study drug cannot be determined
Protocol adherence	Protocol violations due to ethical conflicts e.g. when a child's condition deteriorates and physician is biased towards the, potential life-saving, study intervention	May severely impact the validity of study results

STUDY POPULATION

Children in the PICU represent a wide age range and a broad case mix of underlying diseases and ICU diagnoses. Moreover, the critically ill child receives many drugs simultaneously and combinations differ between centers. Therefore, while studying a single drug, the interactions with co-medications and type of underlying diagnosis and care may interfere with outcomes. More than 80% of randomized controlled trials (RCT) are single-centred.[31] This reduces generalizability of the results from these trials. Data sharing and collaboration in larger international PICU research networks could overcome this limitation. Examples of pediatric critical care networks are the Canadian Critical Care Trials Group (Pediatric Interest Group) and the NICHD Collaborative Pediatric Critical Care Research Network. Europe and the other continents are lagging behind: to our knowledge international PICU networks are non-existent to date.

RECRUITMENT

An underestimated limitation to the generalizability of PICU trial outcomes could be the difficulty with recruitment. One third of RCTs in the PICU is terminated before the needed sample size is achieved, often due to recruitment problems.[31] One of the reasons for recruitment problems could be reluctance to approach potential research subjects, also known as 'gate-keeping', which attitude may be due to the clinicians' fear of excessive patient burden.[32] This usually means that the sickest patients are less likely to be included in research. To our knowledge, the study by Menon and colleagues is the only addressing barriers to the recruitment process in the PICU. This was an observational trial implying an ACTH stimulation test, blood sampling on an existing line and recruitment within 26 hours of admission. Almost 50% of 1707 eligible research subjects were not

approached due to unavailability of legal guardians, language issues, lack of agreement of treating physician or prior enrolment in another study.[33] Thus, we need to be aware of possible selection bias and its effects on generalizability of research results in the PICU. One solution to recruitment issues could be co-enrolment of patients in multiple studies.[34] Research shows that participation rates do not decline when parents are asked to have their child participate in two studies simultaneously. This is only possible, however, if it does neither effect study outcome (e.g. simultaneous inclusion in two RCTs with potential influence on outcome of the studies) nor increases patient burden and risk to unacceptable levels (e.g. additive blood sampling volume increases above safety margins).

OUTCOME MEASURES

Appropriate outcome measures in PICU research are another challenge. It is difficult to identify good outcome measures due to the combination of low prevalence of major adverse events (e.g. severe morbidity, mortality) and small sample size of many studies (median of 49 patients).[31] While the majority of trials report laboratory or physiological primary outcomes, mortality was the primary outcome measure in 2% of trials.[31] Data from a recent feasibility trial of clonidine for sedation suggest that at least 190 patients are needed to show a 1.5 day difference in days of ventilation and many more to show relevant differences for other outcomes such as length of PICU and hospital stay.[35] Laboratory or physiological outcomes should be clinically relevant, otherwise the research cannot result in improvement of patient outcome.[36] Relevant outcome measures and validated assessment tools are therefore essential. The latter is not always the case. For example, Vet and colleagues showed that two thirds of the many different sedation scores used in studies on ventilated children receiving a continuous infusion of sedatives were not validated for PICU patients.[37] Regarding the effect of a medication, it must be kept in mind that adverse effects may not become apparent until years after PICU stay. A major concern in this regard is the possible effect of sedative and analgesic medication on longer-term neurological outcome.[38] Enrolling former PICU patients in follow-up programs can broaden our knowledge on long-term outcomes. This should be encouraged, as currently very few units provide care and research beyond the ICU stay.

RESCUE MEDICATION

The use of rescue medication in a randomized trial for a potential life-saving intervention with a placebo group presents additional ethical and scientific challenges.[39] Full equipoise regarding the efficacy of the study drug contrasts with the clinician's perceived need to administer the study drug as a rescue therapy despite the inclusion of the patient in the placebo group. When rescue therapy is allowed, only 'early' versus 'late' effects can be determined when analyzing data on an intention to treat basis. More

children are needed to show a beneficial effect of the drug. As a consequence, overall more children will receive placebo and be at risk for a negative outcome, including death, provided the study drug is really effective. Holubkov and colleagues present an interesting hypothetical study, i.e. steroids for pediatric septic shock, and use sample size simulations to illustrate this challenge.[39] A solution to avoid misuse of rescue medication is to educate physicians, nurses and other staff involved in the care of research participants on the rationale and clinical equipoise in research.

PROTOCOL ADHERENCE

Protocol adherence may be jeopardized if the treating physician is biased towards the study drug and may decide to violate the study protocol when a patient's situation is deteriorating. In the survey of Morris and colleagues, discussed above, a large majority of physicians admitted that they may be biased toward the study arm on the basis of published data from uncontrolled studies.[30] Moreover, two thirds indicated that they do not fully adhere to the study protocol when the patient's condition deteriorates and parents ask for the study drug. There was a strong correlation between the occurrence of an ethical conflict and the likelihood of protocol violations, compassionate use of the study drug or alterations to the protocol. These violations are an important risk factor for bias in these studies and consequently may affect the validity of the findings. A way of avoiding protocol violation is to inform everyone involved in the care of the research subjects about the rationale for the study, the existing equipoise motivating its conduct and the potential benefits of the study.

INFORMED CONSENT PROCESS IN THE PICU

Informed consent is one of the ethical cornerstones of performing research with human subjects. It represents the implementation of the ethical principle of respect for persons. Respect for persons means that persons are treated as autonomous agents, and that persons with diminished autonomy have a right to protection.[3] Informed consent has been incorporated in many ethical and legal guidelines concerned with research with humans.[1-4 40 41] Five elements are distinguished, which are all essential for a valid consent: transmission of information; understanding of this information; no coercion by others; competence; and actual consent.[42] These requirements cannot always be met in research with children in the PICU, due to the vulnerability of the population and extraordinary surroundings. Besides that, children in the PICU generally are not able to participate in the decision as they may be too young, too ill or too heavily sedated. In these cases their parents (or legal guardians) need to consent for them, a process that is known as proxy consent.[43]

FACTORS INFLUENCING INFORMED (PROXY) CONSENT IN THE PICU

A qualitatively good consent process prepares future research subjects for the trial, is free and informed. In the PICU, quality of consent is threatened by several factors.

ANXIETY

The stressful PICU environment has great impact on parents and children. Many parents of acutely ill children suffer from acute and post-traumatic stress disorder and this often lasts for months after discharge.[44 45] Practitioners asking consent for trials in emergency situations reported that some parents are unable to focus on anything else than the health of their child and will not be able to take any decision about research, whereas others will still be receptive.[46] The most important reason for refusal to consent as spontaneously provided by parents in the PICU is anxiety or being overwhelmed.[33 47] In contrast, in a study by Thomas and colleagues parents mentioned being anxious, but said that this did not influence their decision regarding research participation.[48] These parents provided useful suggestions. For example, tell parents about ongoing trials prior to PICU admission if possible (e.g. in the case of planned surgery) and do not approach parents when their child is in the operating room, but before *or* after surgery.[48]

BURDEN OF RESEARCH

In a large study by Hulst and colleagues, 421 parents who declined informed consent to a nutritional assessment study implying additional procedures were asked for their reasons. Two-thirds wanted to avoid additional burden to their child.[49] In two multicenter studies, Menon and colleagues analyzed parents' reasons to decline informed consent. One study was an observational study involving blood sampling, the other concerned different kinds of PICU research. In both studies, the burden of blood sampling was a major reason for declining participation.[33 47] A small qualitative interview study was conducted by Thomas and colleagues among parents who accepted or declined consent in an undefined PICU trial. The interviews identified added pain, discomfort and additional diagnostic testing as factors discouraging participation.[48] Overall, it would seem that limiting the burden of research procedures is essential to increase participation. This is further elaborated on in the next paragraph about burden and risk in pediatric research.

ILLNESS SEVERITY

Interestingly, severity of illness does not seem to influence consent rates in the PICU. Two studies done in the PICU could not identify a difference in severity of illness between children of consenting and non-consenting parents.[33 49] Still it should be borne in mind that the life-threatening nature of illness in the PICU can make parents more susceptible to the idea that the trial might convey a therapeutic benefit, when this is very unlikely.[50]

UNDERSTANDING

Parents reach a good understanding of their child's health condition within 24 hours after admission in PICU,[51] but this need not be true for research participation. Studies in the neonatal intensive care unit (NICU) suggest that the conditions for a valid consent are often unmet.[52 53] Understanding and recalling of information is difficult for parents in a research context and they also overestimate their understanding.[54 55] Written information and posters are identified by parents in the PICU as useful information tools in the informed consent process.[48 56]

ALTERNATIVE FORMS OF INFORMED CONSENT

The life-threatening and acute nature of illness in the PICU puts great pressure on the validity and process of informed consent. It is not always possible to achieve written informed (proxy) consent before start of the study in emergency settings. Alternative consent processes should balance the respect for the decision of future research participants and the benefit trial participation might bring them. Two different alternative consent processes are available to deal with these time constraints: a waiver of consent or deferred consent.

WAIVER OF CONSENT

A waiver of consent, also known as exemption from informed consent, means that no consent is required for inclusion of research participants in research. It is sometimes allowed for studies in life-threatening conditions for which available treatments are unproven or unsatisfactory and the study intervention needs to be applied urgently to be effective. The conditions under which a waiver (or) is acceptable vary between countries. For example in the US, additional requirements are community consultation and public disclosure.[57] They favor dialogue with the community, which is informed about the project beforehand and its results afterwards.[58] Raymond and colleagues describe an efficient way of in-hospital community consultation for a trial of vasopressin added to adrenaline in cardiac arrest in the PICU. All parents were informed about the trial through posters, written information, a website and the research team, and were offered the possibility to opt-out of the study. 80% of parents were aware of the trial and knew how to opt out. The authors suggested this approach could increase recruitment while preserving freedom of choice.[56]

DEFERRED CONSENT

Another way of dealing with the acute nature of decisions in emergency research, but still taking into consideration parental decision, is the use of deferred consent. This form of consent implies that patients are recruited without consent and that after enrolment consent is asked for use of already collected information and ongoing participation.

Just like a waiver of consent, deferred consent is an alternative in emergency situations where obtaining prior informed consent is not possible and postponing the intervention would potentially harm the child. The conditions under which deferred consent is acceptable vary between countries, too. An example of conditions can be found in the upcoming new EU regulation on clinical trials.[40]

Research suggests that parents favor deferred consent over waived consent and consider it an acceptable alternative to informed consent for emergency situations.[59 60] In a study by Woolfall and colleagues parents suggested it would be advisable for the researchers to seek advice from the bedside nurse to establish the moment when the child's condition was stable and then ask consent.[60] Practitioners with experience in asking deferred consent were generally positive about parental acceptance of this method of consent. They highlighted the importance of explaining the purpose of its use.[46] A systematic review on waiver of informed consent in pediatric resuscitation trials concluded there is a general endorsement of research in life-threatening situations, but that parental preferences for waiving of consent or deferred consent vary depending on the approach and population.[61] Opinions of children about being enrolled in studies with a waiver of consent or deferred consent have not yet been addressed in research.

Interpretation of approval of alternative forms of consent by researchers and research ethics committee (REC) members may differ. It has been shown that REC members may be less prone to accept alternative forms of consent than are researchers.[62] This may be a barrier to conduct trials with alternative forms of consent. Documenting parental acceptance of deferred consent process could provide insight into its acceptability.

Questions still remain on how to handle consent when a child dies before deferred consent from parents or proxies is asked. Problems arise with use and storage of the collected data. Excluding data from deceased patients (for whom no deferred consent was obtained) may impair validity of the results.[63 64] Still, although seeking deferred proxy consent for a deceased child can burden parents, the majority of parents wish to be informed.[59] Bereaved parents said it was important to adapt to their needs on a case-by-case basis and to allow time after the child's death.[60]

COMBINED FORMS OF CONSENT

The waiver of consent and deferred consent methods are justified only in life-threatening situations where postponing trial inclusion would harm to the research subject.

If the required conditions should not be met, full informed (proxy) consent needs to be given prior to inclusion. Practitioners have suggested that an approach taking the reality

of parents into account would be ideal.[46] Combining different forms of consent could be a useful way of adapting to the unpredictability of acute care environment. The FEAST trial, which studied the effect of fluid resuscitation on mortality, is an example of such a combination.[65] Informed consent was asked only if the child was stable enough and the parents not too distressed. Otherwise, verbal assent was sought prior to inclusion and full written consent after child's stabilization.

IMPROVEMENTS TO THE INFORMED CONSENT PROCESS

It would be worthwhile to study alternative consent approaches in pediatric intensive care, taking into account that approaches in different situations cannot be uniform. Although we should be wary about adding burden to parents (which an informed consent conversation and decision can be), parents must be given the opportunity to make a decision. The approaches to obtaining informed consent in different situations cannot be uniform. The solutions to practical problems may never be a permit for exploitation and harm of the vulnerable population at the PICU.

Getting informed consent is not a one time achievement: informed consent is a continuous process, especially in the PICU. After improvements in health or decrease of sedation, children can regain the capacity to consent or assent; and they are entitled to do so after reaching legal age of consent. They should then be informed about the study they were involved in and their assent or consent should be sought when feasible – usually when the acute phase of the disease is over or after transfer to the ward. It is advisable to consider this re-consent process in the design of the study because the research team needs to plan for the resources needed to allow this important follow-up. There are no studies on this re-consent process in critically ill children.

To our knowledge the amount of empirical research on preferences and motivations of parents and children to participate in drug research in the PICU is small. These preferences have been assessed more extensively in other pediatric populations, but data from the PICU are lacking. It would be relevant to study factors that shape the decision to consent or dissent to drug research in the PICU– for example with a focus on altruism, hope and loyalty. Having this information would enable us to better tailor the process of recruitment and informed consent to the needs of the parents (or legal guardians) and children.

BURDEN AND RISK OF DRUG RESEARCH IN THE PICU

According to the principle of proportionality, risk and burden of research participation should be balanced against the possible benefit of the trial. The principle of subsidiarity entails that research can only take place if there are no other less burdensome and less risky methods of generating the same results. In other words: burden and risk for the research participant need to be minimized, irrespective of the possible benefits of the trial for the individual or society. These principles of proportionality and subsidiarity underlie important ethical guidelines concerning research with humans.[1-4] Children are vulnerable and therefore need additional protection against the risk and burden of research participation. Recent progress in drug research can decrease burden and risk for children participating in research in the PICU. Some of these new techniques are illustrated in the next paragraphs.

METHODS TO DECREASE BURDEN AND RISK BY USE OF NEW TECHNIQUES

PK studies traditionally implied collecting many 1-2 mL blood samples from a patient at scheduled intervals up to 12 times in 24 hours, which means a considerable burden to research subjects. Recent progress in sampling methods, data analysis and outcome measurement tools can decrease this burden while rational evidence-based drug regimens can still be derived. As an example, a solution to oversedation with morphine, which is often observed in neonates, was found using a three-step approach. First, PK data were collected during two RCTs.[66 67] Second, the data were analyzed with population PK, and it was found that same dosing guidelines of morphine resulted in much higher plasma concentrations in neonates than older infants.[68] Third, a new dosing guideline was created on the basis of this finding, and validated.[69] The following paragraphs detail how limited blood sampling schedules, novel drug concentration assays and data analysis methods can decrease burden and risk.

OPPORTUNISTIC OR SPARSE BLOOD SAMPLING METHODS

PICU patients usually have an arterial or venous central line from which blood can be drawn. To avoid accessing lines just for research purposes, sampling for research purposes can be combined with regular blood work. In the absence of a line, samples can be collected during routine heel pricks.[70] Opportunistic studies determine levels of the drug received as part of the patient's treatment and no study drug is given.[71] Another strategy is to measure drug concentration in blood left over from routine analysis.[70 71] Population pharmacokinetics make use of randomly collected and limited blood samples per patient. Maximum allowed amounts of blood for research purposes vary between hospitals and countries, but generally the maximum is set at 3-5% of total blood volume within 24 hours and 5-10% of total blood volume over 8 weeks.[72]

LOW VOLUME DRUG ASSAYS

High performance liquid (LC-MS) or gas (GC-MS) chromatography allows simultaneous analyses of many low concentration substances in small plasma volumes (10-100 µL) or left-overs.[70 73] This is of particular interest for studies in neonates and small children, whose total blood volume is small.[71] New emerging technologies such as digital microfluidics will further decrease the sample volume needed and may represent the future of PK studies.[74-76] If combined with sampling using micro needles sharp enough to minimize nerve contact,[77] these technologies will further decrease the burden and risk of clinical drug trials in children.

DRIED MATRIX SPOTS

Dried matrix spot analysis requires no more than a minimal volume (5-30 µL) of biological fluids (urine, plasma, blood) on blotting paper, allowing for easy and cost-effective sample processing, storage and shipping.[71 78] These samples can be used in PK studies and pharmacogenetic tests.[78-82] Dried blood spots obtained during routine new-born screening can be used for genetic (DNA) and epigenetic (DNA methylation) analysis until 30 years later if stored at -20°C, as is routinely done in some countries.[82 83]

PK-PD MODELLING TOOLS

Population PK-PD analysis using non-linear mixed effect models allows using samples derived from different dosing regimens with random timing and only few samples per patient to estimate PK parameters and the PK-PD relationship and to optimize dosing recommendations.[84] Sparse sampling is a strategy by which just 2-3 samples per individual allow deriving PK parameters from a group of 25-100 infants.[85] This enables studies in which the patient already receives the drug for clinical reasons and even the use of left-over material from regular blood work. Population PK calculates both the inter- and intra-individual variability. The effects of different covariates like age and weight are tested by delineating their effects on inter-individual variability. Particularly relevant to PICU patients, the effect of disease and its treatment can be taken into account (e.g. renal function, inflammation, ECMO).[86] PK-PD parameters in particular populations, such as patients on ECMO, can be estimated.[87] A next step is to validate the obtained PK data and the dosing guidelines derived from these data in a prospective trial performing the same sample analysis. In an efficient new dosing regimen, inter-individual variability should be greatly reduced and dose-effect relationships should remain unchanged or improve. Regrettably, this validation is rarely performed.[71 85]

MICRODOSING STUDIES

Microdosing is an elegant new method to minimize burden and risk in PK-studies in children.[88] It uses a sub therapeutic, extremely low dose of drug, known as a microdose

(e.g. 1/100th of the therapeutic dose).[89 90] Microdosing is ideal for non-therapeutic pharmacokinetic studies in critically ill children because therapeutic or adverse effects will not occur. Microdosing also enables knowledge gain on drug metabolism or excretion, using probe drugs for these specific pathways. Radioactive labelling allows detection of the extremely low dose and carries very minimal risk, because the level of radioactivity is well below international cut-offs for radiation safety.[91] It cannot be excluded, however, that parents and health care providers perceive this differently, and it is recommended therefore to underline in the informed consent process the minimal risk of microdosing.

Table 2: Examples of ethical challenges of clinical drug trials in critically ill children

Example of drug trial*	Ethical challenge**
RCT with daily sedation interruption[92]	Risk of 'gate-keeping' during recruitment and non-adherence to protocol during study for fear of accidental extubation or line removal.
RCT with corticosteroids for pediatric septic shock[39]	Potential life-saving medication: rescue medication in placebo arm may reduce validity of trial.
RCT with vasopressin add-on for cardiopulmonary resuscitation[93]	Emergency treatment leaves no time for informed consent: acceptability of deferred consent or waiver of consent.
Pharmacokinetic study with drug already prescribed to patient[70]	No potential benefit to patient. Multiple catheter accesses may increase risk of infection. Blood sample volume may compromise health, especially in small children.
Dose-finding study for new drug, e.g. Imatinib for pulmonary arterial hypertension	Risk of off-label prescription without any trial, ethical barriers may be perceived too high to perform a 'non-therapeutic trial'.
Microdosing pharmacokinetic study with radio-active labelled drug[94]	No potential benefit to patient despite safe radiation dose: 'gate-keeping' by physicians and/or nursing staff out of fear for radiation-related negative outcomes. And possible misunderstanding of minimal risk by parents.

*Examples are illustrative and based on trials and experiences of researchers in the PICU. **Ethical challenges are examples that researchers could face when performing these kinds of studies but are of course not limited to these examples.

CONCLUSION

Drug research in the PICU is essential because there is a great need of evidence-based dosing guidelines. Conducting drug research in critically ill children is a precarious enterprise because of the vulnerability of the research population and the specific circumstances in the PICU – which present specific ethical challenges. Examples of these challenges are presented in table 2.

Characteristics of the specific study population, recruitment issues, challenging outcome measures, use of rescue medication and sub-optimal protocol adherence, stand in the way of obtaining useful results. Gatekeeping does not only limit recruitment but is also an underestimated source of bias especially with acutely ill children. Collaboration

of intensive care units is bound to improve quality of research and to increase the likelihood of producing generalizable data.

Informed consent for research in the PICU implies almost invariably proxy consent by the parents or legal guardians. Documenting informed consent does not imply, however, that parents know what they signed for. Indirect evidence shows that informed consent may not be achieved in the stressful situation of the PICU due to parental anxiety and misunderstanding. The informed consent process does not stop when the consent is signed but is rather a continuous process. Continuous dialogue between researchers, parents, and children when possible, is the only way to do justice to the unpredictable and changing reality of the PICU. 'One size fits all' is not always possible for structuring informed consent in the PICU therefore alternative approaches to consent need to be developed and evaluated.

Drug research carries burden and risk for the subjects and it is only logical that we should prevent or minimize these, especially in the vulnerable population in the PICU. New techniques allow us to generate evidence with decreased burden and risk to the research subject and deserve to be widely used and systematically evaluated. The different types of studies (e.g. dose-finding studies, PK studies, RCTs) each present specific challenges. Dealing effectively with these challenges is an essential step towards evidence for dosing and drug choice in pediatric intensive care practice.

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