Consent in Pediatric Critical Care Trials: Duty or Burden?

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Clinical practice is highly variable. Some of our colleagues use more maintenance fluids than we would choose for our patients. Or we might continue antibiotics beyond when they would stop them. We suspect any reader could think of similar examples in their own teams.

We currently accept this variability as commonplace in a complex setting such as a PICU. After all there are tens, if not hundreds, of minor management decisions for each patient each day.(1) If there were no difference between clinicians our job could be replicated by robots or at least protocolized. There is a reasonable argument that this variability brings an additional level of safety. Practice regresses towards a mean such that over the duration of an admission any more extreme requests by one clinician will tend to be moderated by the colleague who takes over on the following shift.

While we share our decision making and plans with parents and patients where appropriate, we do not typically seek consent for these small variations in practice between staff.

All that changes if we want to systematize these same variations into a structure we can learn from. A clinical trial requires informed parental or patient consent. The World Medical Association declaration of Helsinki – ethical principles for medical research involving human subjects in 1964 made this unambiguous for all patients,(2) though was later amended to allow child subjects in research. This declaration was in response to numerous war, and peacetime, atrocities of experiments on people either against their will or with no knowledge of the potential harms.(3) With such a history, it seems incontestable that prospective, informed consent with an understanding of possible risks and benefits must be a precondition for any clinical research.

What are the implications of this for research in pediatric critical illness? This edition of the *journal* provides a novel insight into the complexity of this consent process in our setting. Armstrong and colleagues have reviewed the time involved, and success rate of, visiting the bedside of 201 potential subjects with a view to obtaining informed consent for trial participation across three Canadian PICUs. Their results are simple but compelling. Frequently legal guardians were not present at the bedside, and this represented a barrier to patient-participation in clinical trials with this consent model.

These are important factors to document. Trial delivery staff world-wide will absolutely recognize the need to return to the bedside on multiple occasions to ensure optimization of the consent discussion. A simple observation is that the complexity of this task is often underestimated in generic trial costings. To our disadvantage, timings are typically estimated from planned, outpatient discussions. This is very different from an emergency intensive care admission that can occur at any time of day.

We contend that there are much deeper problems with this type of consent for PICU trials. Armstrong and colleagues hint at this with a statement that this "*suggests that a model of deferred consent or implied consent would aid in the future of critical care research"*(4).

We agree but would state this even more strongly. Prospective, informed consent is not suitable for the majority of critical care research. (5) Nearly all critical care conditions are associated with a period of initial greater instability with very high associated risk. Therefore, most interventions that have the potential to change outcomes must be applied in the very earliest contact with critical care staff. A sepsis intervention that is applied after the first 24 hours is likely to miss most of the action (Figure). The consequence is that even an effective treatment is unfeasible to study because the required sample size is excessive.

To illustrate this point, we can refer to our description of the timing of death amongst children referred to our Children's Acute Transport Service regional retrieval team with a suspected diagnosis of sepsis or septic shock published in 2015.(6) In the unselected population the 1-year mortality was 21% (130/627). Most of these deaths, 55% (71/130), occurred within 24 hours of the referral phone call. If we had an intervention for sepsis associated with a 25% relative risk reduction for mortality, the required sample size for a two arm parallel group inclusive randomized controlled trial (with power 80% and alpha =0.05) in the whole population would be 851.(7) This is, just about, within the scale of what can be achieved by current PICU research networks.(8) However, if only the population who survive to have a prospective consent discussion with genuine time to digest complex information and to weigh options – estimated at 24 hours from referral - are included, this number increases to 1802. If we focus on previously healthy children only because of the confounding effect of significant underlying diseases this increases to 2551.

And of course, we have no treatment that is likely to reduce sepsis mortality by 25%. Perhaps 10% is a more credible effect size. Repeating the power calculation with previously healthy children gives us over 14279 with all included and more than 17221 with prospective consent.

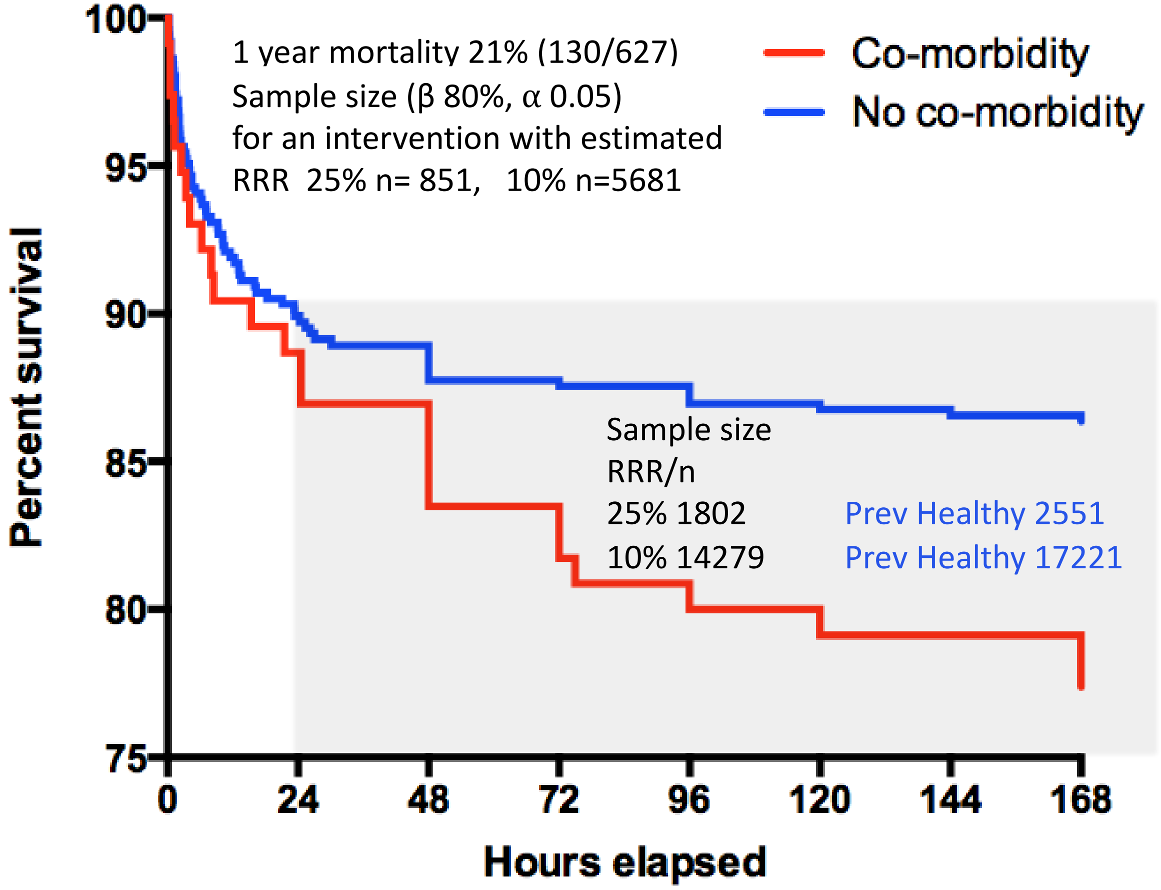
But there are perhaps even more important limitations to critical care research that follow prospective consent processes. Only families that have the time and resources to be at their child's bedside will be eligible for inclusion. The validity of a research finding includes a consideration of how similar the study population is to the population with the problem under review. Prospective consent in emergency studies may exclude patients who speak a different language or who are unable to attend the unit for prolonged periods of time. This is especially problematic for disadvantaged families. The non-specific benefits of research are well documented. Patients are, generally, better off being in a clinical trial than not, regardless of which group they are allocated to. (9–11) But also, the findings of the study may not apply equally to patients who have systematically, but unintentionally, remained unstudied.

So, how should we balance these risks and duties? Research without prior consent is acceptable in some jurisdictions. The United Kingdom Paediatric Critical Care Study Group (PCCS-SG) now has more than 15 years' experience across at least 10 randomized controlled trials in which research without prior consent or 'deferred consent' has been the primary model.(8) In this approach, intervention such the choice of non-invasive support, oxygen targets or blood pressure targets have been selected by trial randomization, rather than the near random influence of the on-call rota. Parental permission is then sought over the next few days to continue on the intervention, if relevant, and to collect data for the trial. Interventions for which this approach is suitable are those within the range of usual care and where there is a strong case that delay would reduce efficacy.(12, 13) We have monitored parents, carers and patient attitudes to this approach and they are overwhelmingly supportive to date.(14, 15)

We share the challenge of meeting the families to have the consent discussion described by Armstrong and colleagues, but this does not create a barrier to participation. Research without prior consent also helps ensure that trial population is representative of the real-world population for whom the intervention may be relevant. It also removes the time pressure on the consent discussion which may mean that the degree to which consent, or refusal, is informed is greater. This avoids the issue of trying to obtain prospective consent from those who may be affected by what has been termed situational incapacity reflecting the acute and disorienting stress of emergency admission of a child. (5)

Derek Angus and others recently bemoaned the division between the practice of medicine and clinical trials.(16) They call to 'repair the house divided' by included trial processes that resemble clinical care as closely as possible. Alternatives to a prospective consent model in appropriately selected trials is one step in this direction.

Figure. **Survival Curves for 627 children with sepsis or septic shock referred to the Children's Acute Transport Service in London, UK 2000-2011 and the potential impact on research feasibility** (previously presented data from (5)). The two curves are for previously healthy children (blue) and children who have been in hospital the last year (red). Added to the figure are simple sample size estimations for theoretical, parallel group, two-arm randomized controlled trials (80% power and alpha 0.05) with 1-year mortality as the primary outcome measure. Sample size indicated if all patients are included via a research without prior consent model or only those in whom a prospective informed consent model is used (assuming around 24 hours for this process). The benefits of research are denied to many of the highest risk cases in a prospective consent model, the study population is likely to be less representative of the real world and fewer studies are affordable or deliverable.


100
95
90
85
80
75
Percent survival
1 year mortality 21% (130/627)
Sample size (β 80%, α 0.05)
for an intervention with estimated
RRR 25% n= 851, 10% n=5681
Co-morbidity
No co-morbidity
Sample size
RRR/n
25% 1802
10% 14279
Prev Healthy 2551
Prev Healthy 17221
0
24
48
72
96
120
144
168
Hours elapsed

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