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Factors affecting consent in pediatric critical care research

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Abstract *Purpose:* Consent for research is a difficult and unpredictable process in pediatric critical care populations. The objectives of this study were to describe consent rates in pediatric critical care research and their association with patient, legal guardian, consent process, and study design-related factors. *Methods:* A prospective, cohort study was conducted from 2009 to 2010 in six tertiary care pediatric intensive care units (PICU) in Canada with legal guardians of patients who were approached for consent for any ongoing PICU research study. Data were recorded on details of the consent process for all consent encounters. *Results:* We recorded 271 consent encounters. The overall consent rate was 80.1% (217/271). We observed higher consent rates when the research assistant was introduced by a member of the clinical team prior to approaching the family (89.7 vs. 77.7%; $P = 0.04$). Legal guardians of cardiac surgery patients were less likely to provide consent than those of all other patients (75.3 vs. 86.0%; $P = 0.03$). There was no difference in consent rates between therapeutic (117/145, 80.7%) versus non-therapeutic studies (100/126, 79.4%; $P = 0.88$). *Conclusion:* This study provides future researchers with consent data for determination of recruitment rates, sample sizes, budget estimations, and study timelines. Future pediatric critical care studies should consider incorporating the lower consent rates in cardiac surgery patients and routine introduction of the research assistant to the family by a member of the patient's care team into their study designs. The potential influence of parental factors on consent rates in pediatric critical care studies requires further research.

Keywords Ethics · Consent · Informed consent · Pediatric critical care

Introduction

Informed consent is an integral part of clinical research and is an especially difficult process in vulnerable populations such as critically ill children. The need for surrogate decision makers [1] and the level of parental anxiety [2, 3] in pediatric critical care populations compound these difficulties. Obtaining informed consent for research in critically ill patients involves a complex interplay between patient, legal guardian, consent process, and study-related factors. A review of the literature showed limited data on the consent process and consent rates in pediatric critical care research which have varied from 42 to 94% in recent large trials [4–8]. The factors that affect these consent rates are poorly understood and may lead to delays in trial completion and obtaining results that may influence patient care [6], difficulty with planning and financing of clinical studies [4], and questions about the reliability and generalizability of trial results [7].

The neonatal intensive care unit (NICU) literature suggests that infant size [9], perceptions of risk or benefit [10–12], parental attitudes towards research [10, 12], and illness severity [12] may influence consent rates in neonatal intensive care research. However, a single-center pediatric intensive care unit (PICU) study evaluating factors that may influence consent rates [13] found that the presence of pre-existing medical conditions was associated with a lower parental consent rate, whereas patient illness severity was not. A recent large trial in PICU [7] also did not find a difference in illness severity between those in whom consent was and was not obtained. Furthermore, studies suggest that the PICU is a unique environment [14], and that PICU families prioritize their needs differently than those in NICU families [15]. Prior studies also suggest a difference between adult and pediatric informed consent processes [16, 17]. These differences make it difficult to extrapolate findings from research on the consent process in other settings to the PICU.

The limited research on factors that influence consent rates in pediatric research and the importance of pediatric critical care research in advancing patient care underscores the need for more investigations on the consent process in pediatric critical care research. The objectives of this study were to describe associations between consent rates in pediatric critical care research and factors related to patients, legal guardians, consent processes, and study designs. This study will provide important information for the conduct of future pediatric critical care research by (1) documenting consent rates to inform sample size calculations, recruitment rates, study budgets, and timelines; (2) identifying patient groups that are more or less likely to participate; (3) exploring potentially modifiable factors that affect legal guardians' willingness to participate; and (4) describing the effect of specific study designs on consent rates.

Methods

Studies and sites

We conducted a large, prospective, observational study in six university-affiliated PICUs from June 2009 to May 2010. All participating sites were members of the Canadian Critical Care Trials Group and represented the majority of pediatric critical care research being conducted in Canada. We included all studies for which informed consent was required and therefore excluded surveys and chart audits. All PICU studies screening patients for enrollment during the study period were included and written permission for their inclusion was provided by each study's principal investigators. Research ethics approval was obtained at all sites.

Study protocol

A consent encounter was defined as any time a legal guardian/patient was approached for consent for participation in a PICU study. Data were recorded on the consent process for all consent encounters during the study period by the site-specific research assistant for this study. The dedicated research assistant for this study contacted the individual (research assistant, physician, nurse, etc.) who had approached the legal guardian for consent for the primary study after the consent encounter to obtain the necessary data. We recorded patient and study demographic data and the unsolicited reasons stated by legal guardians for consent refusal. Training of the research assistants for this study was conducted during a multicenter start-up meeting with the primary investigator and the study research coordinator during which the *Study Procedures Manual* was reviewed in detail. This was followed by monthly phone calls from the research coordinator at the coordinating center to answer questions and provide feedback from already received case report forms.

Using a visual analogue scale, we recorded the level of parental anxiety on a scale of 0–10, based on the impression of the individual obtaining consent for the primary study. This method was chosen as we were not permitted to solicit information on guardians' reasons for their consent choices by any of the six involved research ethics boards.

We defined a therapeutic study, a priori, as either a randomized controlled trial or an observational study that had the potential to change management (and therefore have a potential benefit for the patient) and similarly, non-

therapeutic studies as those which were purely observational in nature.

Statistical analysis

Factors associated with consent rate were assessed using a Fisher's exact test for dichotomous variables or a logistic regression model for continuous variables. We used descriptive statistics to describe therapeutic and non-therapeutic types of studies. Homogeneity of consent rates between study groups and across participating centers was tested using a Breslow–Day test [18]. When a significant design effect was observed, the overall consent rate and 95% confidence interval (CI) for both therapeutic and non-therapeutic study samples was calculated using the Laird and Mosteller formula [19] and compared using a Z test. Otherwise, we pooled consent rates over centers and calculated 95% CIs using the Wilson score. In this case, pooled consent rates were compared using a χ^2 test. We compared observational studies and randomized controlled trials similarly.

Results

Participating study factors

There were 12 randomized controlled trials (32 patients), 15 observational therapeutic studies (113 patients), and 18 observational non-therapeutic studies (126 patients). Eight studies had a time limit for enrollment of less than 48 h. Twenty-five studies were PICU investigator initiated, 13 were non-PICU investigator initiated, four studies were industry initiated, and three studies were initiated by others (not specified). There was no difference in consent rates between PICU initiated, non-PICU initiated, industry sponsored, or other studies ($P = 0.89$) (Table 1).

A total of 271 patients (286 consent encounters) were approached for 45 different studies across the six participating sites. There were a total of 54/271 consent refusals (19.9%; 95% CI 15.5, 25.0). Two hundred and seventy-one families participated in one consent encounter, 13 families participated in two, and two families participated in three. The consent rate for the 15 repeat consent encounters was 66.7% (10/15). The site-specific recruitment and consent rates are shown in Table 2. There was no statistically significant difference in overall consent rates across the sites ($P = 0.70$).

Table 1 Effect of the source of study sponsorship on consent rates

Study sponsor	Was consent obtained?		Consent rate* (%)
	Yes	No	
PICU initiated	59	12	83
Non-PICU initiated	84	18	82.3
Industry	68	23	74.7
Other	6	1	85.7

* $P = 0.89$

There was no significant difference in the consent rates between therapeutic studies (studies with a potential for benefit to the child), 80.7% (117/145; 95% CI 73.5, 86.3) and non-therapeutic studies (studies with no potential benefit to the child), 79.4% (100/126; 95% CI 71.5, 85.5; OR 1.0, 95% CI 0.7, 1.5; $P = 0.88$, homogeneity test $P = 0.69$). There was also no difference in consent rates for observational studies (therapeutic plus non-therapeutic), 78.6% (95% CI 73.3, 83.5) versus 81.8% (95% CI 44.7, 99.8) for randomized controlled trials (OR 1.42, 95% CI 0.37, 5.44; $P = 0.93$, homogeneity test $P = 0.04$).

Patient factors

The demographics of patients enrolled in the study are shown in Table 3. Forty-eight percent of patients (131/271) were less than 1 year old and 55% (149/271) of consent encounters were with legal guardians of patients having cardiac surgery. The consent rate was lower in patients admitted after cardiac surgery, and trended lower in younger patients (Table 3).

Legal guardian factors

One or both parents were the legal guardians in 265/271 cases. In the remaining 6 cases the legal guardians were the aunt (2/271), the sibling (1), the grandparent (2/271), or child protection services (1/271). Consent was successfully obtained in all six of these cases.

There was no significant difference in consent rates as provided by mothers alone versus fathers alone (79.3% vs. 88.2%; OR 0.51, 95% CI 0.11, 2.44; $P = 0.52$) or mothers alone versus both parents together (79.3% vs. 79.7%; OR 0.98, 95% CI 0.52, 1.85; $P = 1.00$).

Increased legal guardian anxiety, as assessed by the person involved in the informed consent process, using a visual analog 1–10 scale was associated with a lower likelihood of providing consent (mean anxiety score 5.3 ± 3.0 for non-consenters vs. 3.1 ± 2.4 for consenters; OR 0.73, 95% CI 0.64, 0.83; $P < 0.001$). The main reasons for consent refusal as verbalized by the legal guardians during the consent encounter are shown in Table 4. Other stated reasons for consent refusal included poor timing, the risk of a central line infection, loss of confidentiality, more time needed to make the decision, concerns regarding the study procedure, and inability to understand the study.

Table 2 Overall consent rates by site

Site	Eligible for any participating study	Number of consent encounters	Number of patients who consented	Recruitment rate (% of eligible encounters enrolled)	Consent rate* (%)
1	99	57	49	49.5	83.1
2	34	21	15	44.1	70.8
3	44	43	35	97.7	80.0
4	16	14	11	68.8	78.6
5	30	28	26	86.7	92.9
6	163	108	81	49.7	75.5
Total	386	271	217	67.2	80.1

* Eligibility rates not associated with consent rates, $P = 0$

Table 3 Effect of patient-related factors on consent rate

Characteristic	All patients ($n = 271$)	Consenters ($n = 217$)	Non-consenters ($n = 54$)	OR (95% CI)	P value
Age (year), median (IQR)	1.3 (0.3, 5.9)	1.5 (0.3, 7.5)	0.6 (0.2, 3.6)	1.06 (0.99, 1.14)	0.088
Pre-existing condition[a], no. (%)	217 (80.4)	171 (78.8)	46 (86.8)	0.57 (0.24, 1.34)	0.214
PRISM score, median (IQR)	1 (0, 13)	0 (0, 12)	5.5 (0, 15)	0.99 (0.96, 1.02)	0.145
Mechanical ventilation, no. (%)	153 (56.9)	122 (56.5)	31 (58.5)	0.92 (0.50, 1.69)	0.877
Diagnosis[b]					
Trauma, no. (%)	12 (4.4)	11 (5.1)	1 (1.9)	2.83 (0.36, 22.41)	0.470
Sepsis, no. (%)	12 (4.4)	8 (3.7)	4 (7.4)	0.48 (0.14, 1.65)	0.265
Surgical, no. (%)	31 (11.4)	30 (13.8)	1 (1.9)	8.50 (1.13, 63.82)	0.009
Cardiac surgery, no. (%)	149 (55.0)	112 (52.1)	37 (68.5)	0.50 (0.27, 0.94)	0.033

IQR interquartile range

[a] This is defined as any condition that requires ongoing follow-up by a specialist and/or recurrent hospitalization as per the list provided on the case report form

[b] The four most common diagnostic categories are reported. Of the remaining 66 patients, 63 had other diagnoses and a diagnosis was missing for 3 patients

Table 4 Effect of consent encounter-related factors on consent rates

Consent-related factors	Consenters ($n = 217$)	Non-consenters ($n = 54$)	OR (95% CI)	P value
Consent from mother alone, no. (%)	40 (18.4)	7 (13.0)	1.52 (0.64, 3.60)	0.424
Physician obtained consent, no. (%)	28 (12.8)	12 (22.2)	0.52 (0.24, 1.10)	0.090
Research assistant introduced, no. (%)	52 (24.0)	6 (11.3)	2.48 (1.01, 6.14)	0.042
Consent asked for at bedside, no. (%)	65 (30.1)	18 (34.0)	0.84 (0.44, 1.59)	0.624
Consent asked for within 24 h of admission, no. (%)	112 (51.6)	32 (59.3)	0.73 (0.40, 1.34)	0.196

Consent process factors

One institution allowed a telephone consent process (for four studies) which was used in only five cases. Co-enrollment of one patient in more than one study was allowed in 44/45 studies. The median number of pages of the informed consent form was 5 and 6 for English and French, respectively. Eleven studies (11/45, 24%) had information sheets in addition to consent forms. Assent was required for eight studies at four different sites and was obtained in 14/17 (82.4%) of patients from whom it was asked. The consent form was not in the primary language of the legal guardian in 22/271 (8.1%) consent encounters and a translator was used in 7/271 (2.6%) encounters. Amongst these 22 patients, there was no difference in the consent rate between those in whom a translator was and was not used (85.7% vs. 80%).

For consent process-related factors see Table 5. A total of 21 research assistants were involved in approaching families for consent across the six centers. Introduction of the research assistant by any member of the patient's care team was associated with a higher

Table 5 Reasons for consent refusal as volunteered by the legal guardian during consent encounter

Reasons given for declining consent	Number of guardians providing this reason
Guardian too stressed	24
Blood taking required for study	13
Medication administration required for study	3
Radiation required for study[a]	2
Guardian does not agree with research	8
Already in another study	6
Discord between guardians	2
Child has been through enough	7
Other	28

Based on a total of 45/54 non-consenters who volunteered a reason for refusal to the research assistant. Some legal guardians provided more than one reason for refusal

[a] Radiograph or CT scan required for study

Table 6 Effect of location of the consent encounter on consent rates

Location of consent process	Frequency	Consent rate (%)
Bedside	83	70.4
Hallway	23	91.5
Family or conference room	69	74.5
Clinic	34	87.5
PICU waiting room	51	81.0
Other	9	96.7

Data were missing in 2 cases

consent rate than if the research assistant independently approached the legal guardian ($P < 0.001$). The location of the consent encounter (Table 6) did not appear to influence the consent rate ($P = 0.624$). Research assistants approached legal guardians for consent in 192/271 (70.8%) of cases with a median number of six consent encounters (IQR 1.75–13.25) per research assistant. The majority of the remaining consent encounters were obtained by physicians (69/271, 25.5%). Thirty-six of these (52.2%) were conducted by a single physician for one study at one site. The remaining 10 consent encounters were conducted by nurses (5/271) and other allied health personnel (5/271).

Discussion

In this large, multicenter observational study in six Canadian PICUs, we found that the overall consent rate for pediatric critical care research was 80.2% which is higher than what has been previously reported in several studies [4, 6, 7, 20]. Many pediatric critical care studies have, in fact, not reported the consent rate in their manuscripts [21, 22] making it difficult for researchers to obtain this information. The consent rates provided in this study will allow researchers to estimate sample sizes, recruitment rates, budgets, and timelines for future pediatric critical care studies.

When compared with parents of children admitted to the PICU for all other reasons, parents of children undergoing anticipated or minor surgery were more likely to consent whereas legal guardians of children undergoing cardiac surgery were less likely to provide consent for research. The lower consent rate of cardiac surgery patients is important as these patients comprise 20–40% of participants recruited into previous pediatric critical care research studies [6, 7] and 50% of the participants in this study. It will be important for researchers using the cardiac surgery population to incorporate the lower consent rate into their sample size estimation, recruitment processes, and anticipated trial duration. Similarly, the knowledge of higher consent rates in patients undergoing anticipated or minor surgery will provide justification for higher recruitment rates, shorter trial durations, and lower budgets in studies using these populations.

We found that introduction of the research assistant to the legal guardian by a member of the health care team prior to the encounter significantly improved consent rates. In an NICU study Zupancic et al. [12], found that 32% of parents preferred to have their physician advise them whether to volunteer their infants for a clinical trial suggesting that endorsement of the research study by the primary care team is important to families. This is an important finding for future researchers as it is easily implementable and could make a tangible difference in consent rates.

We found no difference in the informed consent rates between studies with and without a potential direct benefit to the child (randomized controlled trials plus observational therapeutic studies versus observational non-therapeutic studies) and no parent volunteered lack of benefit to their child as a reason for non-participation. In the only other study to spontaneously record parents' stated reasons for non-consent [10], lack of benefit to their newborn was also not volunteered as a reason. Previous studies on participation in pediatric acute care research for purely altruistic reasons have focused mainly on parental opinion surveys. In these studies parents stated a variable willingness to participate ranging from 30.2% [11] and 31% [23] to 53% [10] and 72% [24]. In 1997, Pierro and Spitz [25] reported an increasing rate of parental refusal for non-therapeutic studies in their surgical unit which they attributed in part to lack of benefit for the individual. We also found that the originator of the study (PICU physician vs. non-PICU physician vs. industry sponsored) had no effect on the consent rate which is useful information in the determination of collaborations for future studies.

This study uncovered several areas for future research. We found a trend towards a lower consent rate when

physicians attempted to procure consent compared with personnel from any other background. However, since 80% of physician consents were from one center this finding may simply reflect either a center- or physician-specific effect but does also raise the question of who the best person is to approach families for consent. Secondly, the trend towards lower consent rates in younger children has not been previously reported in the research ethics literature and again raises an important question for future exploration.

Finally, we found an association between perceived parental anxiety and lower consent rates for research. There were several limitations to this finding. First, we were not able to solicit information directly from the legal guardians regarding their anxiety levels and/or their thoughts on the consent process during the actual consent encounter. Our use of a subjective, non-validated tool for the assessment of parental anxiety limits the interpretation of our finding of lower consent rates with increased parental anxiety ($P < 0.001$, OR 0.73, 95% CI 0.64, 0.83). Another limitation is that the determination of the anxiety score occurred after the result of the consent encounter was already known. However, the associated tight CIs and the fact that the anxiety assessments were conducted by 30 different individuals with differing backgrounds in six different centers makes it less likely that a systematic bias is responsible for this finding. Furthermore, in our study, being too stressed was the most common reason volunteered by the legal guardians for declining participation which again suggests that parental anxiety may play a role in parental decision making around research. While we cannot make any definitive recommendations based on our findings on parental anxiety, they do provide a potentially important area for future qualitative research. Another limitation of this study is that it was conducted in a setting where consent is primarily obtained by research assistants rather than members of the patient's health care team. Therefore it may not be possible to extrapolate our findings to jurisdictions where this is not the case.

When patients are incapacitated or developmentally unable to provide consent, as is the case in critically ill children, surrogate decision makers or legal guardians are typically sanctioned as their legal representative. Thus factors that affect the legal guardian's decision to provide consent become especially important in such cases. Although several studies have attempted to tease out these factors using hypothetical case scenarios [26, 27] or parental recall of previous consent encounters [12], to date no study has examined real-time consent encounters in order to explore the reasons behind parental decision making around research. The spontaneously volunteered reasons for consent refusal in our study suggest that parents are focused on potential harms, and may not understand the potential benefits of research. Interestingly, although research ethics boards were not comfortable with asking families to provide a rationale for consent refusal, 83% (45/54) of legal guardians spontaneously volunteered a reason for non-participation. This suggests that guardians may either feel a need to or appreciate the opportunity to explain why they did not consent, and this should be examined in future studies.

Strengths of this study include the large, prospective, multicenter design. Data generated provide a unique perspective on informed consent in pediatric critical care studies. We examined real-world approaches to enrolling patients in studies, rather than relying on hypothetical scenarios, retrospective interviews or self-report of research personnel or legal guardians. Consent encounters were recorded over a wide variety of studies which adds greatly to the generalizability of our findings. This initial environmental scan of some of the factors that may affect consent rates in pediatric critical care research provides a rich foundation for further research in this area, including previously unavailable data for sample size calculations and factors to consider for study design and implementation in future pediatric critical care trials.

Conclusion

The consent rates described in this study provide pediatric critical care researchers with a source of data for determination of recruitment rates, sample size calculations, budget estimations, and study timelines. Future studies in pediatric critical care patients will need to take into account the lower consent rates in the cardiac surgery population and should consider incorporating routine introduction of the research assistant to the family by a member of the patient's care team prior to attempting consent. The effect of age, the background of the individual obtaining consent, and parental anxiety on consent rates in pediatric critical care studies requires further research.

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Conflict of interest All authors declare that they have no competing interests and therefore have nothing to declare.

Appendix

Canadian Critical Care Trials P-Consent Study Group
Institutions, site investigators, research coordinators, and research assistants (numbers of enrolled patients are shown in parentheses): Edmonton, AB (110)—A. Joffe, C. Sheppard, C. Gresiuk; McMaster Children's Hospital, Hamilton, ON (28)—K. Choong, N. Smigielski; Hospital

for Sick Children, Toronto (14)—J. Hutchison, R. Gaitiero, J. Van Huyse, Children's Hospital of Eastern Ontario, Ottawa, ON (45)—K. Menon, R. Ward; Montreal Children's Hospital, Montreal, QC (65)—R. Gottesman, J. Gaudreault, M. Dagenais; St. Justine Hospital, QC (24)—J. Lacroix, N. Poitras, M. Dumitrascu, A. Fontaine.

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