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REVIEW ARTICLE/BRIEF REVIEW

Consent models in Canadian critical care randomized controlled trials: a scoping review

Modèles de consentement dans les études randomisées contrôlées en soins intensifs canadiennes : une étude de portée

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Abstract

Purpose *Our primary objective was to describe consent models used in Canadian-led adult and pediatric intensive care unit (ICU/PICU) randomized controlled trials (RCTs). Our secondary objectives were to determine the consent rate of ICU/PICU RCTs that did and did not use an alternate consent model to describe consent procedures.*

Source *Using scoping review methodology, we searched MEDLINE, Embase, and CENTRAL databases (from 1998 to June 2019) for trials published in English or French. We included Canadian-led RCTs that reported on the effects of an intervention on ICU/PICU patients or their families. Two independent reviewers assessed eligibility, abstracted data, and achieved consensus.*

Principal findings *We identified 48 RCTs of 17,558 patients. Included RCTs had ethics approval to use prior informed consent (43/48; 90%), deferred consent (13/48; 27%), waived consent (5/48; 10%), and verbal consent (1/48; 2%) models. Fifteen RCTs (15/48; 31%) had ethics approval to use more than one consent model. Twice as many trials used alternate consent between 2010 and 2019 (13/19) than between 2000 and 2009 (6/19). The consent rate for RCTs using only prior informed consent ranged from 54 to 91% (ICU) and 43 to 94% (PICU) and from 78 to 100% (ICU) and 74 to 87% (PICU) in trials using an alternate/hybrid consent model.*

Conclusion *Alternate consent models were used in the minority of Canadian-led ICU/PICU RCTs but have been used more frequently over the last decade. This suggests that Canadian ethics boards and research communities are becoming more accepting of alternate consent models in ICU/PICU trials.*

Résumé

Objectif *Notre objectif principal était de décrire les modèles de consentement utilisés dans les études randomisées contrôlées (ERC) menées par des chercheurs canadiens dans les unités de soins intensifs adultes et pédiatriques (USI/USIP). Nos objectifs secondaires étaient de déterminer le taux de consentement aux ERC à l'USI et l'USIP qui utilisaient et n'utilisaient pas un autre modèle*

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de consentement pour décrire les processus de consentement.

Sources *À l'aide d'une méthodologie d'étude de portée, nous avons effectué des recherches dans les bases de données MEDLINE, Embase et CENTRAL (de 1998 à juin 2019) pour en tirer les études publiées en anglais ou en français. Nous avons inclus des ERC dirigées par des chercheurs canadiens qui rapportaient les effets d'une intervention sur les patients à l'USI/USIP ou leurs familles. Deux examinateurs indépendants ont évalué l'admissibilité, résumé les données et atteint un consensus.*

Résultats principaux *Nous avons identifié 48 ERC portant sur 17 558 patients. Les ERC incluses avaient obtenu l'approbation du comité d'éthique pour l'utilisation de modèles de consentement éclairé préalable (43/48; 90 %), de consentement différé (13/48; 27 %), de renoncement au consentement (5/48; 10 %) et de consentement verbal (1/48; 2 %). Quinze ERC (15/48; 31 %) avaient reçu l'approbation du comité d'éthique pour utiliser plus d'un modèle de consentement. Deux fois plus d'études ont utilisé un autre type de consentement entre 2010 et 2019 (13/19) qu'entre 2000 et 2009 (6/19). Le taux de consentement pour les ERC utilisant uniquement un consentement éclairé préalable variait de 54 à 91 % (USI) et de 43 à 94 % (USIP), contre 78 à 100 % (USI) et 74 à 87 % (USIP) pour les études utilisant un modèle de consentement alternatif/hybride.*

Conclusion *Des modèles de consentement alternatif ont été utilisés dans une minorité des ERC en USI/USIP dirigées par des chercheurs canadiens, mais ils ont été utilisés plus fréquemment au cours de la dernière décennie. Cela donne à penser que les comités d'éthique et les communautés de recherche canadiens acceptent de plus en plus les modèles de consentement alternatifs dans les études réalisées en USI et en USIP.*

Keywords intensive care unit · pediatric intensive care unit · critical care · informed consent · deferred consent

Randomized controlled trials (RCTs) in the intensive care unit (ICU) and pediatric intensive care unit (PICU) are often considered the gold standard of evidence to improve management of critically ill patients.[1] Despite their importance, conducting RCTs in the critical care setting can be fraught with challenges such as slow participant recruitment rates.[2] To participate in a trial, potential participants and/or their surrogate decision maker must provide their free and informed consent.[3] The standard model of obtaining consent for participation in medical research is informed and voluntary consent obtained from the participant prior to study enrolment (i.e., prior informed consent). Nevertheless, this approach to consent is not always feasible in the ICU/PICU setting. Patients in the ICU/PICU are critically ill, and timely treatment is required to avoid mortality and morbidity. As a result, many RCTs in this setting focus on time-sensitive interventions. However, time-limited enrolment windows create significant barriers to obtaining prior informed consent.[4,5] Moreover, critically ill patients often do not have the capacity to provide first person consent and thus, consent is more commonly obtained from the patient's legal guardian, legally authorized representative, or substitute decision maker (SDM).[6,7] At the same time, SDMs of critically ill patients can experience distress and anxiety during their loved one's ICU/PICU admission.[8,9] Substitute decision makers may not understand or retain consent or medical-related information imparted to them during this stressful time[10,11] and may be less likely to provide surrogate consent for participation in ICU research.[7,12]

These challenges highlight the importance of considering alternate consent models, particularly for studies that are "low risk" and require timely enrolment shortly after the patient is admitted to the ICU/PICU.[5,13] This is supported by the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS-2)*, which supports the use of alternate consent models such as deferred consent (seeking consent after intervention) or waiver of consent (consent not required) in emergency settings.[3] Previous ICU/PICU trials have successfully used alternate consent models,[12-15] and some have reported on participant experiences and perspectives towards the use of alternative consent models. For example, a multicentre RCT in seven tertiary level PICUs in Canada used both prior informed consent and deferred consent. The consent rate using deferred consent *vs* standard prior informed consent was significantly higher (83%; 35/42 *vs* 58%; 15/26; $P = 0.02$), permitted earlier enrolment, and was acceptable to healthcare teams and families, including families whose child had died.[13] While the use of alternate consent models has been evaluated within these single studies, we are not aware of any systematic or scoping review initiatives to evaluate the mode of consent across multiple ICU/PICU RCTs. Although some alternate consent models are currently used in Canadian ICU/PICU RCTs, details about the type of model, frequency, and impact their use has on overall trial enrolment is currently unknown.

The purpose of this scoping review was to provide an overview of consent in Canadian-led ICU and PICU RCTs. Our primary objective was to describe the consent models that have been used in Canadian ICU/PICU RCTs. Our

secondary objectives were to determine the consent rate of adult and pediatric RCTs using alternate consent models and RCTs that used traditional prior informed consent, and to describe consent procedures used in Canadian ICU/PICU RCTs.

Methods

We conducted a scoping review of Canadian-led RCTs in the ICU/PICU. The protocol and objectives were established *a priori* before commencing the systematic literature search and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews (PRISMA-ScR)[16] (Electronic Supplementary Material [ESM] eAppendix 1). The protocol (version 21 June 2019) is available on Open Science Framework at https://osf.io/cu7bt/, and was uploaded at the time of manuscript submission.

Eligibility criteria

We included published Canadian-led RCTs and quasi randomized trials that reported on the effects of an intervention on ICU/PICU patients or their families. Canadian-led was defined as a trial that was led or co-led by an investigator or investigative team based at a Canadian institution, regardless of whether or not the trial included international sites. Trials where ICU/PICU patients represented a subgroup of the whole trial cohort were included if consent data were reported separately for consent models used in the ICU/PICU population. We also included substudies of eligible RCTs if the consent process for the substudy was conducted separately. We excluded studies that focused solely on preterm infants or neonatal ICUs, and trials published in languages other than English or French. Trials conducted in the emergency room or operating room before ICU/PICU admission or trials that were initiated (i.e., consent was obtained) in another hospital unit following ICU/PICU admission were also excluded. We excluded trials conducted prior to 1998 (the year that the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, which guides the ethical conduct of research in Canada, was introduced).[3] Screening criteria are summarized in ESM eAppendix 2. These screening criteria were adapted from Duffet *et al.*[17] to include adult trials.

Search and selection

Two search strategies were developed to identify pediatric and adult ICU RCTs by a librarian experienced in systematic review searching (M.S.). We included articles indexed in MEDLINE, Embase, CENTRAL and ClinicalTrials.gov from 1 January 1998 to 27 June 2019 (ESM eAppendix 3). We also consulted the list of programs on the Canadian Critical Care Trials Group (CCCTG) website (www.ccctg.ca) to identify any RCTs not captured by the search strategy.

Eligibility assessment and data extraction

Before screening was initiated, each reviewer read the study protocol to familiarize themselves with the review objectives and study selection process. To ensure the reviewers understood the eligibility criteria, a test set of 50 citations (title and abstract of articles) was created by one study lead (K.O.) and verified by the second study lead (S.C.). The test set included five eligible citations and 45 ineligible citations.[18] During testing, each reviewer (K.K., V.S., R.P., J.G.) assessed the same 50 citations. To qualify for title/abstract screening, reviewers had to correctly identify at least four of the five eligible citations in the test set. Records were uploaded to insightScope (www.insightscope.ca; insightScope, Ottawa, ON, Canada) for title/abstract and full-text screening.[18] Records were assessed in duplicate by two independent reviewers, with discrepancies resolved by a third reviewer (K.O., S.C.). One investigator (K.O.) reviewed the reference lists of included trials for potentially relevant trials.

Three investigators (K.O., S.C., R.P.) developed a data extraction tool in REDCap[19,20] (REDCap Consortium, Vanderbilt University, Nashville, TN, USA) and piloted the form in duplicate using three eligible trials. Eligible trials were divided among the review team for duplicate, independent data extraction, followed by conflict resolution by one of the study leads. From each trial, we collected data pertaining to trial demographics, recruitment, consent model(s), the consent process, and the consent rate. The consent model(s) used in each trial was classified as one of two categories: (1) *prior informed consent* if the authors described that consent was obtained from the patient or SDM before trial procedures were initiated; or (2) *alternate consent models* such as waiver of consent (the requirement for participant consent was waived); deferred consent (trial procedures were initiated before consent was obtained, and consent was later obtained from the patient or SDM to continue trial procedures); integrated consent (streamlined consent process where consent for research and clinical care are obtained simultaneously by the care team); or verbal consent (consent was obtained verbally before trial procedures were initiated). Trials were classified as using an alternate consent model if they reported using an alternate consent model to enrol some or all trial participants.

We contacted authors of included studies only if data related to the primary outcome (consent model used) was missing.

Study analysis and statistics

Results are presented overall and for adult and pediatric RCTs separately. We calculated kappa (κ) values for title-abstract and full-text screening using the Fleiss approach.[21] Data are presented as median and interquartile range [IQR] or counts with frequencies. Descriptive analysis was conducted using IBM SPSS for Windows version 27 (IBM Corp., Armonk, NY, USA). We calculated the trial consent rate by dividing the number of participants/SDMs who provided consent by the number of participants/SDMs approached for consent. If patients/SDMs who were approached for consent were not enrolled in the trial for a reason other than consent refusal (e.g., eligibility changed, physician refusal), we removed them from the both the numerator and denominator. Studies using a waiver of consent were removed from the consent rate calculation.

We created forest plots illustrating the proportion with 95% Clopper–Pearson confidence intervals of those who consented using R statistical software version 3.62 (R Foundation for Statistical Computing, Vienna, Austria).[22] We assessed for statistical heterogeneity using the I^2 test.[23] The I^2 statistic was estimated by the metaprop function in the R package meta, which also reports an estimated tau^2, the between-study variance.[24]

Changes from the original protocol

The protocol was developed *a priori* and made available on Open Science Framework at the time of manuscript submission. There was one change from the original study protocol. Originally, we planned to statistically compare RCTs using traditional prior informed consent and RCTs using an alternate consent model. Nevertheless, given that there are specific criteria to be met to use alternate consent models[3] and criteria within trials for when alternate consent models can be employed, it is likely that these differences would introduce confounding variables into such a comparison. As a result, we instead elected to present, but not compare, the pooled consent rate for trials that did and did not use alternate consent.

Results

Identification of eligible trials

For pediatric RCTs, the search identified 296 unique citations (290 from the database search and six through review of other sources). During screening, we excluded 273 citations (κ = 0.6). At the full-text level, reviewers excluded 12 records (κ = 0.63), leaving 11 eligible pediatric trials[25-31] (Fig. 1). The most common area of disagreement during full-text screening was related to the study setting.

For adult RCTs, we identified 1,030 unique citations. Of these, we excluded 903 during screening (κ = 0.57). Ninety-one articles were subsequently excluded at the full-text level (κ = 0.62), leaving 36 fully eligible adult trials. One paper reported the results of two separate trials; therefore, we included 37 adult trials in the analysis (Fig. 1). The most common areas of disagreement during full-text screening were study design and country of origin.

The included trials are summarized in ESM eAppendix 4.

Characteristics of included trials

The characteristics of the included trials are presented in Table 1. A total of 17,558 patients were enrolled across the 48 trials. Most RCTs were published after 2010 (Fig. 2). Of the 48 included ICU/PICU RCTs, 30 (63%) were pilot feasibility trials (23/37 [62%] adult RCTs and 7/11 [64%] pediatric RCTs). Eighteen (38%) trials included sites outside of Canada, most commonly in the USA, Europe, and/or Australia/New Zealand. The median [IQR] sample size was 94 [48–519] for adult ICU RCTs and 49 [30–97] for pediatric ICU trials. Most trials (42/48; 88%) were funded by a public agency, such as a hospital or government grant. Trials most commonly focused on a general ICU/PICU population (25/48; 52%), followed by populations with a respiratory condition (7/48; 15%) or infection/sepsis/septic shock (7/48; 15%). One pediatric trial was an ancillary study within an RCT.[27] A total of 25/48 (52%) RCTs specified an eligibility time window during which a participant could be enrolled, including 19/37 (51%) adult and 6/11 (55%) pediatric RCTs. In 12/48 (25%) RCTs, the eligibility time window was $\leq$ 24 hr, seven (58%) of which had approval to use an alternate consent model and five (42%) of which used solely prior informed consent. Enrolment time windows typically began at ICU/PICU admission or when a specific treatment was initiated. The shortest reported time window for enrolment was six hours in one adult[32] and one pediatric trial,[30] and the longest enrolment window was 336 hours in two adult trials (published in one manuscript).[33]

Consent models used in Canadian adult and pediatric ICU RCTs

Most trials (43/48; 90%) used prior informed consent (Table 2). Seventeen of the 37 (46%) adult RCTs and 2/11 (18%) pediatric RCTs employed an alternate consent model. Four adult trials used an alternate consent model

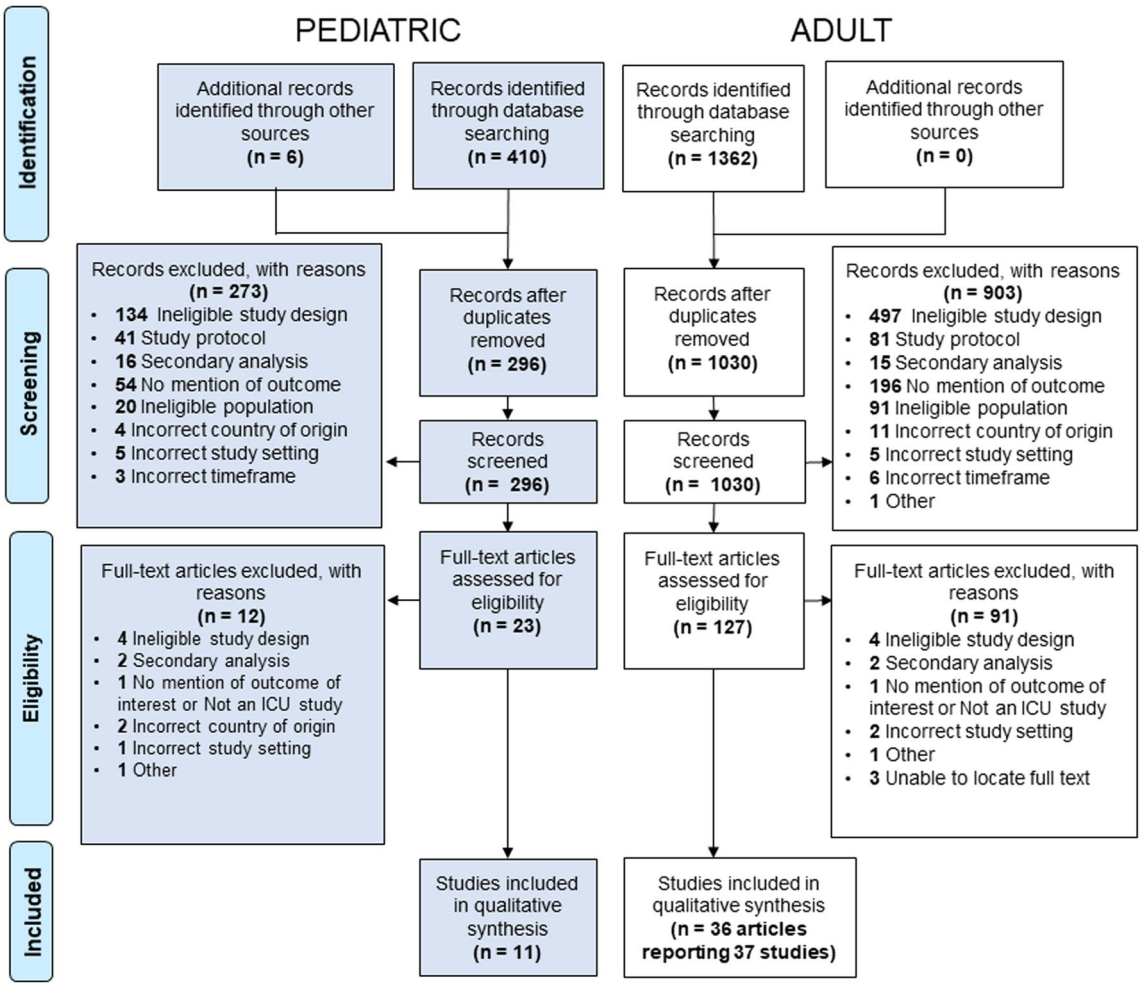

Fig. 1 PRISMA diagram

as the sole consent model, with approval to use a waiver of consent[34-36] or deferred consent.[37] Two adult trials had approval to use a waiver of consent at all participating sites except one, which required informed consent before starting data collection but not to initiate the intervention.[38,39] All other adult and all pediatric trials that utilized alternate consent models had ethics approval to use either model as the situation dictated. Of the trials using an alternate consent model, deferred consent was the most common method used for both adult (11/17; 65%) and pediatric trials (2/2; 100%).

Characteristics of RCTs using alternate consent models

We present the characteristics of the 17 adult and two pediatric RCTs that used an alternate consent model in Table 1. There were twice as many trials using an alternate consent model published between 2010 and 2019 (13/19; 68%) than published between 2000 and 2009 (6/19; 32%) (Fig. 2). Trials using alternate consent models were most commonly adult trials (17/19; 90%), pilot trials (13/19; 68%), endorsed by the CCCTG (13/19; 68%), unblinded (11/19; 58%), and with a time constraint on enrolment (15/19; 79%). The most common conditions evaluated in trials using an alternate consent model were general ICU/PICU admissions (9/19; 47%) followed by infection/sepsis/septic shock (4/19 21%). Of the five trials that used waived consent, three were cluster RCTs with randomization occurring on a site level.[34,38,39] In the remaining two trials, randomization was on the patient level.[35,36]

Rationale for the use of alternate consent

Seven trials provided a rationale for why the investigative team sought approval from the research ethics board (REB) to use an alternate consent model. Two trials provided the

Table 1 Characteristics of included trials

Trial characteristic	All trials			Trials using an alternate consent model		
	Adult *N* = 37	Pediatric *N* = 11	All *N* = 48	Adult *N* = 17	Pediatric *N* = 2	All *N* = 19
Pilot trials, *n*/total *N* (%)	23/37 (62%)	7/11 (64%)	30/48 (63%)	12/17 (71%)	1/2 (50%)	13/19 (68%)
International trials, *n*/total *N* (%)	15/37 (41%)	3/11 (27%)	18/48 (38%)	6/17 (35%)	1/2 (50%)	7/19 (37%)
International trials - locations (in addition to Canada) where patients were recruited, *n*/total *N* (%)						
USA	9/37 (24%)	1/11 (9%)	10/48 (21%)	2/17 (12%)	0/2 (0%)	2/19 (11%)
Europe	3/37 (8%)	3/11 (27%)	6/48 (13%)	1/17 (6%)	1/2 (50%)	2/19 (11%)
Australia/New Zealand	6/37 (16%)	0/11 (0%)	6/48 (13%)	3/17 (18%)	0/2 (0%)	3/19 (16%)
Middle East	4/37 (11%)	1/11 (9%)	5/48 (10%)	2/17 (12%)	0/2 (0%)	2/19 (11%)
Central and South America	2/37 (5%)	0/11 (0%)	2/48 (4%)	0/17 (0%)	0/2 (0%)	0/19 (0%)
Asia	1/37 (3%)	0/11 (0%)	1/48 (2%)	0/17 (0%)	0/2 (0%)	0/19 (0%)
Sample size, median [IQR][a]	94 [48–519]	49 [30–97]	79 [40–225]	98 [51–719]	49, 225[c]	98 [51–209]
Number of study arms, *n*/total *N* (%)						
Two	34/37 (92%)	11/11 (100%)	45/48 (94%)	17/17 (100%)	2/2 (100%)	19/19 (100%)
Three	1/37 (3%)	0/11 (0%)	1/48 (2%)	0/17 (0%)	0/2 (0%)	0/19 (0%)
Four	2/37 (5%)	0/11 (0%)	2/48 (4%)	0/17 (0%)	0/2 (0%)	0/19 (0%)
Funding, *n*/total *N* (%)[b]						
Public agency (e.g., government) or hospital grant	31/37 (84%)	11/11 (100%)	42/48 (88%)	13/17 (77%)	2/2 (100%)	15/19 (79%)
Industry	7/37 (19%)	2/11 (18%)	9/48 (19%)	4/17 (24%)	0/2 (0%)	4/19 (21%)
In-kind support	5/37 (14%)	3/11 (27%)	8/48 (17%)	1/17 (6%)	0/2 (0%)	1/19 (5%)
Private	4/37 (11%)	0/11 (0%)	4/48 (8%)	3/17 (18%)	0/2 (0%)	3/19 (16%)
Author stated unfunded	1/37 (4%)	0/11 (0%)	1/48 (2%)	1/17 (6%)	0/2 (0%)	1/19 (5%)
Unclear	2/37 (5%)	0/11 (0%)	2/48 (4%)	0/17 (0%)	0/2 (0%)	0/19 (0%)
CCCTG trial, *n*/total *N* (%)	22/37 (60%)	7/11 (64%)	29/48 (60%)	11/17 (65%)	2/2 (100%)	13/19 (68%)
Time limit on enrolment, *n*/total *N* (%)						
Yes	19/37 (51%)	6/11 (55%)	25/48 (52%)	13/17 (77%)	2/2 (100%)	15/19 (79%)
No	5/37 (14%)	5/11 (46%)	10/48 (21%)	1/17 (6%)	0/2 (0%)	1/19 (5%)
Not reported/unclear	13/37 (35%)	0/11 (0%)	13/48 (27%)	3/17 (18%)	0/2 (0%)	3/19 (16%)
Blinded, *n*/total *N* (%)						
Yes	12/37 (32%)	5/11 (46%)	17/48 (35%)	5/17 (29%)	1/2 (50%)	6/19 (32%)
Partial	5/37 (14%)	2/11 (18%)	7/48 (15%)	1/17 (6%)	1/2 (50%)	2/19 (11%)
No	19/37 (51%)	4/11 (36%)	23/48 (48%)	11/17 (65%)	0/2 (0%)	11/19 (58%)
Not reported/unclear	1/37 (3%)	0/11 (0%)	1/48 (2%)	0/17 (0%)	0/2 (0%)	0/19 (0%)
Trail described as pragmatic, *n*/total *N* (%)						
Yes	5/37 (14%)	3/11 (27%)	8/48 (17%)	4/17 (24%)	1/2 (50%)	5/19 (26%)
No	32/37 (87%)	8/11 (73%)	40/48 (83%)	13/17 (77%)	1/2 (50%)	14/19 (74%)
Trial described as evaluating interventions that are standard of care, *n*/total *N* (%)						
Yes	5/37 (14%)	4/11 (36%)	9/48 (19%)	3/17 (18%)	1/2 (50%)	4/19 (21%)
No	32/37 (87%)	7/11 (64%)	39/48 (81%)	14/17 (82%)	1/2 (50%)	15/19 (79%)
Study terminated early, *n*/total *N* (%)						
Yes	4/37 (11%)	1/11 (9%)	5/48 (10%)	2/17 (12%)	0/2 (0%)	2/19 (11%)
No	33/37 (89%)	10/11 (91%)	43/48 (90%)	15/17 (88%)	2/2 (100%)	17/19 (90%)
Population, *n*/total *N* (%)						
Adults	36/37 (97%)	0/11 (0%)	36/48 (75%)	16/17 (94%)	0/2 (0%)	16/19 (84%)

Table 1 continued

Trial characteristic	All trials			Trials using an alternate consent model		
	Adult $N = 37$	Pediatric $N = 11$	All $N = 48$	Adult $N = 17$	Pediatric $N = 2$	All $N = 19$
Children	0/37 (0%)	10/11 (91%)	10/48 (21%)	0/17 (0%)	2/2 (100%)	2/19 (11%)
Older adults	1/37 (3%)	0/11 (0%)	1/48 (2%)	1/17 (6%)	0/2 (0%)	1/19 (5%)
Children and families	0/37 (0%)	1/11 (9%)	1/48 (2%)	0/17 (0%)	0/2 (0%)	0/19 (0%)
Condition of interest, *n*/total *N* (%)						
General PICU admissions	19/37 (51%)	6/11 (55%)	25/48 (52%)	9/17 (53%)	0/2 (0%)	9/19 (48%)
Respiratory	6/37 (16%)	1/11 (9%)	7/48 (15%)	1/17 (6%)	0/2 (0%)	1/19 (5%)
Infectious/sepsis/septic shock	5/37 (14%)	2/11 (18%)	7/48 (15%)	3/17 (18%)	1/2 (50%)	4/19 (21%)
Cardiac—surgical	3/37 (8%)	0/11 (0%)	3/48 (6%)	0/17 (0%)	0/2 (0%)	0/19 (0%)
Renal/GU	3/37 (8%)	0/11 (0%)	3/48 (6%)	2/17 (12%)	0/2 (0%)	2/19 (11%)
Trauma	1/37 (3%)	1/11 (9%)	2/48 (4%)	1/17 (6%)	1/2 (50%)	2/19 (11%)
Cardiac—nonsurgical	1/37 (3%)	1/11 (9%)	2/48 (4%)	1/17 (6%)	0/2 (0%)	1/19 (5%)
Hematology	1/37 (3%)	0/11 (0%)	1/48 (2%)	0/17 (0%)	0/2 (0%)	0/19 (0%)

[a] Sample size for one adult RCT reported as number of ICUs instead of number of patients, not included in average

[b] Numbers add up to more than the number of trials, as some trials had funding from multiple sources

[c] Actual sample size of each study

CCCTG = Canadian Critical Care Trials Group; GU = genitourinary; PICU = pediatric intensive care unit; RCT = randomized controlled trial

rationale for waiving consent. These included infeasibility of obtaining consent prior to enrolment[35] and implementing a study protocol that represented a variation of normal practice standards that did not impart additional risks.[36] For trials that used deferred consent, five trials provided a rationale. These rationales included a minimal risk study with a narrow time window for enrolment;[33] feasibility of deferred consent in the pilot trial for the full RCT;[40] to enable recruitment of patients with a higher illness acuity and a study design that met the TCPS-2 requirements for deferred consent;[41] to allow recruitment of incapacitated patients when the SDM was not available;[42] and to allow rapid enrolment.[43]

Consent procedures

Of the RCTs with REB approval to use deferred consent, 7/11 (64%) adult and both pediatric (100%) trials reported specific criteria when deferred consent could be used. For adult RCTs, the most common criteria were that the patient lacked capacity to give consent themselves (6/11; 55%) and/or the SDM was not available (5/11; 46%). In one of the two pediatric RCTs, the criterion for deferred consent was that the SDM was not available within the eight-hour enrolment window.[31] The other pediatric RCT had broader criteria for using deferred consent, which included the SDM not being available and/or insufficient time remaining in the enrolment window, and/or if the SDM was overwhelmed and/or if SDM had not been informed of the patient's medical condition.[30] Most adult and pediatric trials did not report who was responsible for obtaining consent (27/48; 56%). Among those that did, consent was most commonly obtained by a member of the study team (16/48; 33%) (Table 2). All pediatric trials, and most adult trials (30/37; 81%) reported that consent could be obtained from someone other than the patient, including the parent/legal guardian, SDM, or power of attorney.

Assent

Only one pediatric RCT,[26] and the ancillary study within the same RCT,[27] reported information related to assent. Both reported that assent was obtained from children older than seven years, when appropriate, in addition to informed consent from the child's legal guardian. Neither reported the number of children who were asked for, provided, or refused assent.

Consent rates in Canadian adult and pediatric ICU RCTs

The consent rates for adult RCTs that did and did not use an alternate consent model are presented in Fig. 3. There were 17 adult RCTs that solely used prior informed consent with available information to determine the trial consent rate. The consent rate for these 17 trials ranged from 54 to 91%. Seven adult RCTs used an alternate consent model to enrol some or all participants and reported information to

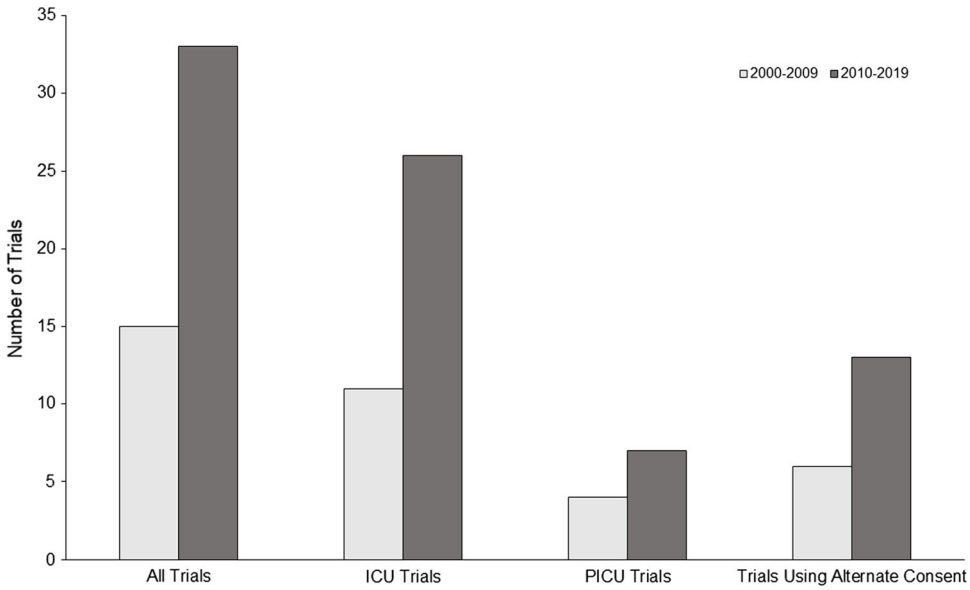

Fig. 2 Overall number of ICU/PICU RCTs and number of RCTs using an alternate consent model published prior to and after 2010. All trials included in this review initiated recruitment after 1998 and were published between 2003 and 2019. ICU = intensive care unit; PICU = pediatric intensive care unit; RCT = randomized controlled trial

determine the consent rate. The consent rate for these seven trials ranged from 78 to 100%. There was large heterogeneity between trials using prior informed consent (I^2 = 96%) and alternate consent (I^2 = 85%).

Figure 4 summarizes the trial consent rates in pediatric RCTs. Nine pediatric RCTs solely used prior informed consent and two pediatric RCTs used an alternate consent model that reported information to calculate the trial consent rate. The consent rate for pediatric RCTs using prior informed consent ranged from 43 to 94%. The consent rates for the two pediatric RCTs that used alternate consent were 74%[30] and 87%.[31] There was large heterogeneity between trials that used prior informed consent (I^2 = 90%) and between trials that used alternate consent (I^2 = 80%).

Use and perspectives of deferred consent

Nine RCTs (eight adult, one pediatric) reported the number of participants enrolled using deferred consent (Table 3) and the deferred consent rates were 20–88% of the final trial sample size. Seven trials reported the number of participants who subsequently refused ongoing study participation following enrolment with deferred consent. In four trials, all patients enrolled with deferred consent agreed to continue participating in the study.[33,42,44] In the remaining three trials, the percentages of patients enrolled with deferred consent who later refused consent were 2%,[45] 14%,[30] and 16%.[40] Only the pediatric trial included information on SDM perspectives of deferred consent. Although SDMs were not specifically asked if they had any issues with the deferred consent model, no SDM expressed concern that their child was enrolled without their prior informed consent, including four children who passed away before consent for ongoing participation was obtained.[13,30]

Discussion

To our knowledge, this is the first scoping review to summarize the consent models used in Canadian-led ICU/PICU RCTs. We found that the use of alternate consent models was higher in the last decade than in the previous decade, and that they were more commonly used in adult ICU RCTs than in pediatric ICU RCTs. Deferred consent was the most common alternate consent model used, and all but one trial that used deferred consent were granted approval to use a hybrid approach where consent was obtained using either deferred consent or prior informed consent as the situation dictated. There was high heterogeneity in consent rate among trials that used prior informed consent, and also among trials that used an alternate consent model to enroll some or all participants. Trials did not consistently report information on overall consent rate. Some trials reported consent information separately for participants enrolled using deferred consent.

Consent has long been recognized as a challenge in the ICU/PICU setting, given that participants are rarely able to provide consent for themselves,[6] and both patients and SDMs experience a significant amount of distress, particularly early in ICU/PICU admission when many studies are initiated.[8,9] In addition, the SDM may not always be present at the bedside and often cannot be contacted during the study enrolment window.[6] Deferred consent delays the timing of the consent conversation, and

Table 2 Approved consent models and consent procedures

Consent model and procedures	Adult trials $N = 37$	Pediatric trials $N = 11$	All trials $N = 48$
Approved consent models, *n*/total *N* (%)[a]			
Prior informed consent	32/37 (87%)	11/11 (100%)	43/48 (90%)
Alternate consent model	17/37 (46%)	2/11 (18%)	19/48 (40%)
Not reported/unclear	1/37 (3%)	0/11 (0%)	1/48 (2%)
Who obtained consent, *n*/total *N* (%)			
Study team member	12/37 (32%)	4/11 (36%)	16/48 (33%)
Study team or any member of the care team	0/37 (0%)	1/11 (9%)	1/48 (2%)
Not reported/unclear	20/37 (54%)	7/11 (64%)	27/48 (56%)
Not applicable (waiver of consent)	5/37 (14%)	0/11 (0%)	5/48 (10%)
Other than the patient, consent could be provided by, *n*/total *N* (%)			
Legal guardian/parent	0/37 (0%)	11/11 (100%)	11/48 (23%)
Surrogate decision maker	28/37 (76%)	0/11 (0%)	28/48 (58%)
Power of attorney	2/37 (5%)	0/11 (0%)	2/48 (4%)
Trials using alternate consent	$N = 17$	$N = 2$	$N = 19$
Alternate consent model(s) used, *n*/total *N* (%)			
Waiver of consent	5/17 (30%)	0/2 (0%)	5/19 (26%)
Deferred consent	11/17 (65%)	2/2 (100%)	13/19 (68%)
Verbal consent	1/17 (6%)	0/2 (0%)	1/19 (5%)
Integrated consent	0/17 (0%)	0/2 (0%)	0/19 (0%)
Criteria stated for when an alternate consent model could be used, *n*/total *N* (%)			
Waiver of consent	0/17 (0%)	0/2 (0%)	0/19 (0%)
Deferred consent	7/17 (41%)	2/2 (100%)	9/19 (47%)
Verbal consent	0/17 (0%)	0/2 (0%)	0/19 (0%)
No criteria reported	10/17 (59%)	0/2 (0%)	10/19 (53%)
Trials using deferred consent	$N = 11$	$N = 2$	$N = 13$
Criteria to use deferred consent[b], *n*/total *N* (%)			
SDM not available	5/11 (46%)	2/2 (100%)	7/13 (54%)
Patient lacked capacity for consent	6/11 (55%)	0/2 (0%)	6/13 (46%)
SDM not available plus 2-physician waiver	1/11 (9%)	0/2 (0%)	1/13 (8%)
Prior informed consent was not feasible	1/11 (9%)	0/2 (0%)	1/13 (8%)
Insufficient time remaining in enrolment window	0/11 (0%)	1/2 (50%)	1/13 (8%)
SDM overwhelmed	0/11 (0%)	1/2 (50%)	1/13 (8%)
SDM had not been informed of patient's medical condition	0/11 (0%)	1/2 (50%)	1/13 (8%)
No criteria reported	3/11 (27%)	0/2 (0%)	3/13 (23%)

[a] Numbers add up to more than the included number of trials, as trials could have more than one approved consent model

[b] Numbers add up to more than the number of trials who had criteria for consent, as more than one criterion could be selected for a given trial

SDM = substitute decision maker

has been proposed as a solution to the consent challenges in critical care research. The benefits of using deferred consent in critical care research have been shown in several studies and include a higher consent rate, earlier initiation of the trial intervention,[13,30] improved recruitment, and shorter study duration.[14,46] In addition, the use of deferred consent in critical care and emergency research is acceptable to most patients and/or SDMs,[13,14,47] and to the general public in a Canadian city.[48] Notwithstanding, less than 30% of Canadian-led adult RCTs and less than 20% of pediatric RCTs used deferred consent, even though ~52% of adult and pediatric RCTs

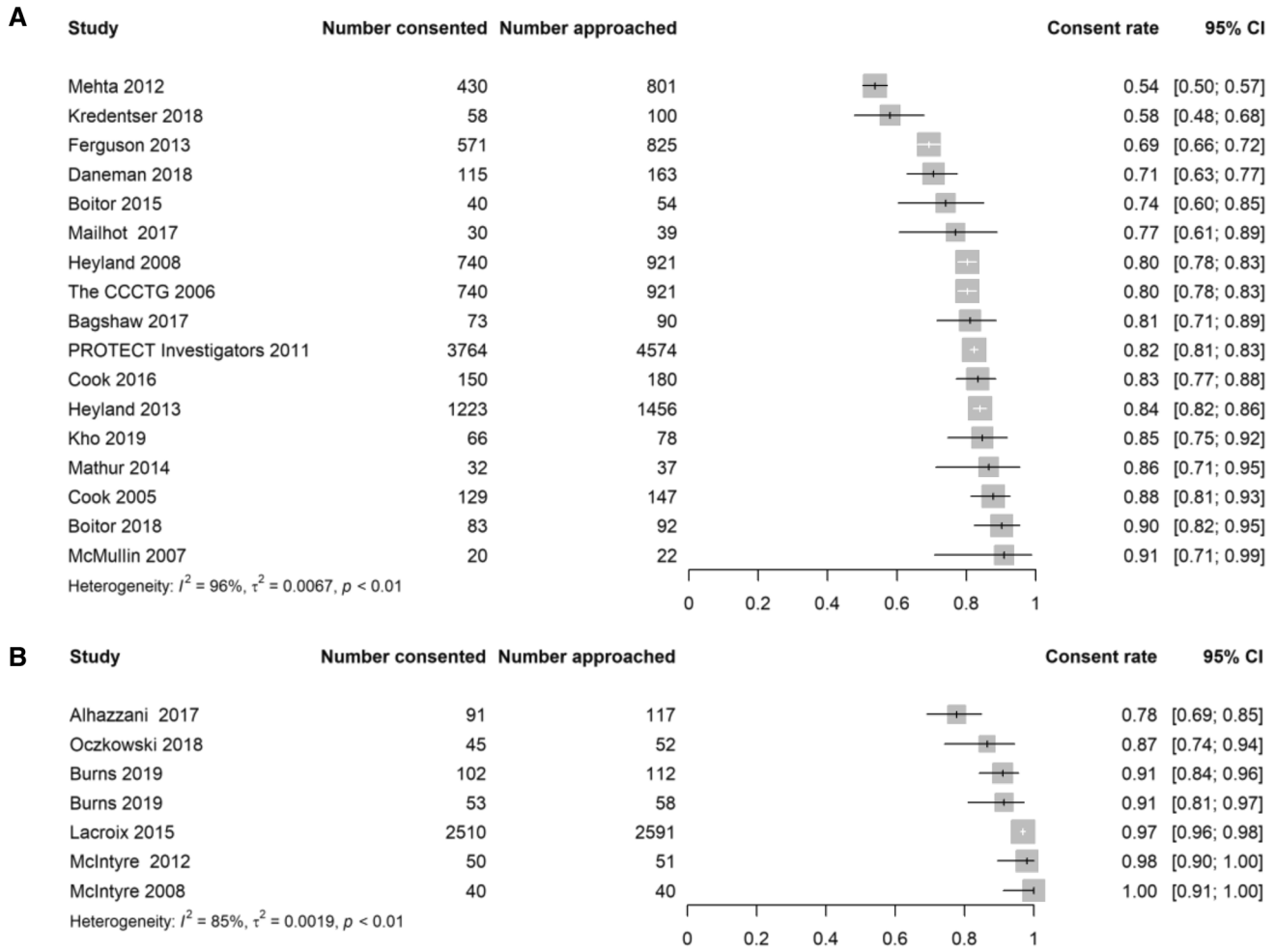

Fig. 3 Consent rates (with 95% confidence intervals) in adult Canadian-led critical care randomized controlled trials using prior informed consent (A) or using an alternate consent model (B)

had a time constraint on enrolment. Further, deferred consent was not always approved by the REB at each participating centre, resulting in some sites within a trial using deferred consent while others could not.[30,41,42,44,45] This indicates that, despite the benefit of deferred consent for critical care trial recruitment and acceptability of deferred consent to SDMs, the use of alternate consent models is limited by differences in practice across institutional REBs.

Many of the trials that provided a rationale for using deferred consent focused on the time-sensitive nature of enrolment into critical care research. Several RCTs in this review had a narrow enrolment window of < 8 hr or < 24 hr[25,49-51] but did not employ a deferred consent model. In three of these trials, the consent rate was lower than trial consent rates observed in adult (78–100%) and pediatric (74–87%) RCTs using alternate consent (44%,[25] 75%,[51] 77%[50]). It is important to note that the consent rate is based on the number of participants/SDMs actually approached for consent. Two of these trials report excluding eligible participants because an SDM was not available during the enrolment window. In one trial, 471 patients were not enrolled because the SDM was not available, representing ~39% of the target sample size of 1,200.[49] In the second trial, 214 patients were excluded because an SDM was not present, representing 710% of the target sample size of 30 patients.[50] These trials could have benefited from using deferred consent to enrol patients whose SDM was not present within the recruitment window. In addition to the effect these exclusions would have on study duration and cost, there are also significant scientific concerns about excluding eligible patients because of the requirement for prior informed consent, and the limitation this places on the generalizability of study results.[5]

There is some apprehension in the Canadian research community towards the use of deferred consent. This may explain why deferred consent is not more widely used in Canadian critical care research. A 2011 survey by Duffet *et al.*

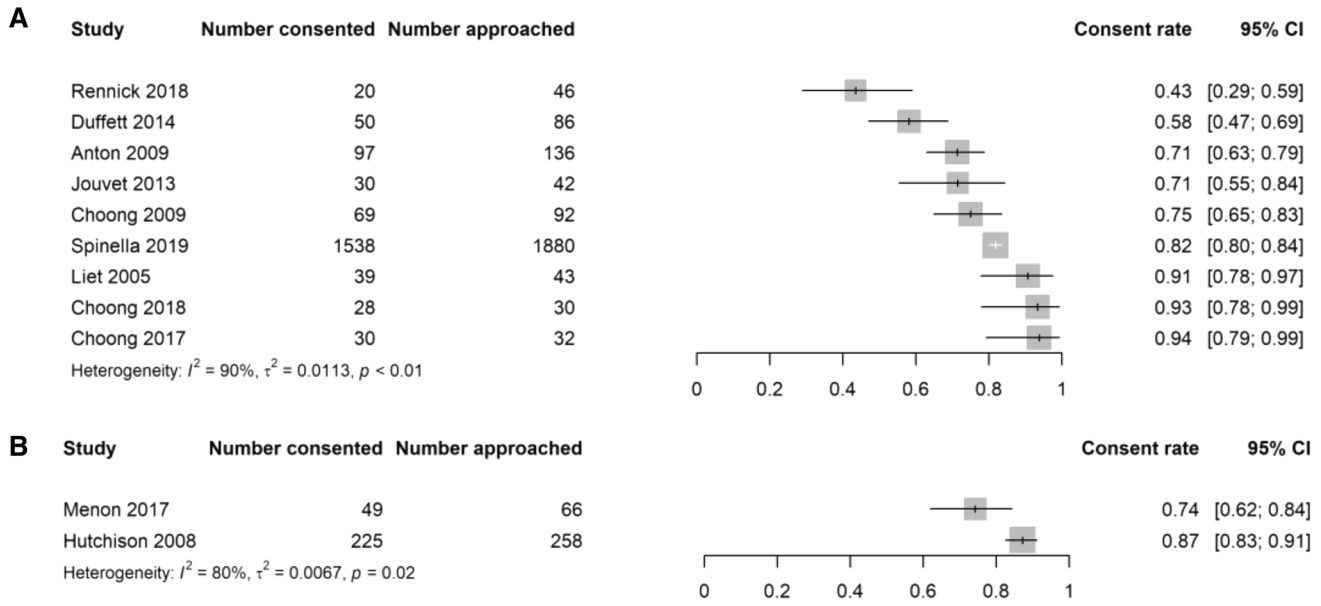

Fig. 4 Consent rates (with 95% confidence intervals) in pediatric Canadian-led critical care randomized controlled trials using prior informed consent (A) or using an alternate consent model (B)

Table 3 Number of patients enrolled using deferred consent, and who refused ongoing participation

Trial	Number of patients enrolled, *N*	Number of patients enrolled using deferred consent, *n* (%)	Number of patients who refused further participation following enrolment via deferred consent, *n* (%)
RELEASE	53	24 (45%)	0 (0%)
SENIOR	102	42 (41%)	0 (0%)
REVISE	91	19 (21%)	3 (16%)
STARRT-AKI	100	20 (20%)	0 (0)
OMAKI	79	NR	0 (0)
PRECISE	50	44 (88%)	NR
FINESS	40	29 (73%)	NR
OVATION	120	82 (68%)	2 (2%)
STRIPES	49	42 (86%)	6 (14%)

NR = not reported

found that only 8% of REBs in Canada and 43% of Canadian critical care researchers were comfortable or very comfortable with deferred consent when the SDM was not available.[52] Experience with deferred consent has been shown to result in positive perceptions of deferred consent, whereas lack of experience is associated with negative perceptions of deferred consent.[53] Given that the use of alternate consent models, including deferred consent, has increased in Canadian critical care RCTs over the last decade (thus increasing REB and researchers' experience with deferred consent), we expect that the comfort with, and perceptions of, deferred consent in Canada have also increased.

Opponents of deferred consent have suggested it does not consider the ethical principle of autonomy because the study is initiated before consent is obtained, or that it has the potential to be coercive (i.e., the patient is already enrolled and therefore the patient/SDM provides consent to continue the trial when they normally would not have provided a priori informed consent). Nevertheless, critically ill patients are rarely able to provide first-person consent and practice autonomy; consent is usually provided by an SDM.[5,6] Substitute decision makers do not always have good understanding or recall of medical or research information provided during their loved one's ICU admission.[10,11,35] Accordingly, it is challenging to accept that prior informed consent obtained during this distressing time is truly "informed", particularly when SDMs have to make a decision about study participation in a limited time frame. By delaying the consent conversation, the SDM/patient may have less distress, allowing a more

comprehensive understanding of the research study, and a decision to continue participation that truly is informed and based on an actual desire to continue the study.

Outside of deferred consent, waiver of consent and verbal consent were the only alternate consent models used in Canadian critical care RCTs since 1998. Of note, in two multicentre trials using a waiver of consent, a single centre required the use of prior informed consent for data collection, despite consent being waived in all other sites. This again highlights that alternate consent models are not consistently accepted by the ethics community. To date, no published Canadian-led critical care RCTs have used integrated consent. This streamlined approach to consent is of particular interest for critical care research, as it allows the patient or SDM to be part of the decision-making process regarding research participation,[54,55] while reducing the burden of the consent process and increasing clarity.[56] The feasibility of integrated consent in critical care RCTs should be investigated.

Strengths and limitations of this review

The strengths of this scoping review are that this manuscript is reported according to PRISMA-ScR guidelines, the search strategy was developed by an experienced health information specialist, and the review team was trained and tested on the review eligibility criteria prior to screening. In addition, this scoping review focuses specifically on consent models in Canadian-led RCTs. Consent policies, practices, and uptake of alternate models are expected to vary across countries, thus focusing specifically on Canadian-led trials allows an analysis of the consent models used within the policies of a single country.

This scoping review also has some limitations. We did not perform a statistical comparison of the consent rate between RCTs that did and did not use an alternate consent model. This was a deviation from the a priori established protocol. Nevertheless, given that specific criteria need to be met to use alternate consent models[3] and there are criteria within trials for when alternate consent models can be employed, it is likely that these differences would introduce confounding variables into such a comparison. This scoping review focused solely on RCTs, and did not consider consent models used in other types of ICU/PICU research or in trials led by countries other than Canada. Additional research focused on evaluating consent in ICU/PICU RCTs led primarily by other countries would be beneficial to the field.

Conclusion

Deferred consent was the most common alternate consent model used, and there was a low rate of withdrawal following enrolment with this consent model. While alternate consent models are used in the minority of Canadian-led adult and pediatric ICU RCTs, the use of alternate consent models has increased over the last decade. This suggests that Canadian ethics and research communities are becoming more accepting of alternate consent models in ICU/PICU trials. We recommend that future research be focused on increased engagement of key stakeholders (public, patients, caregivers, clinicians, and researchers) to determine the optimal consent model(s) for ICU/PICU RCTs based on risk level of the study, among other factors.

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