Deferred consent in a minimal-risk study involving critically ill subarachnoid hemorrhage patients

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INTRODUCTION: Alterations from first-party and surrogate decision-maker consent can enhance the feasibility of research involving critically ill patients.
OBJECTIVE: To describe the use of a deferred-consent model to enable participation of critically ill patients in a minimal-risk biomarker study.
METHODS: A prospective observational study was conducted in which serum biomarker samples were collected three times daily over the first 14 days following aneurysmal subarachnoid hemorrhage. Sample collection was initiated on intensive care unit admission and consent was obtained when research personnel could approach the patient or the patient's surrogate decision maker.
RESULTS: Twenty-seven patients were eligible for the study, of whom only five were capable of providing informed consent. Full consent was obtained for 21 (78%) patients through self- (n=4) and surrogate (n=17) consent. Partial consent or refusal (only permitting the collection of blood samples as a part of routine care or use of data) occurred in three patients. Among the 22 consents sought from surrogates, three (11%) refused participation. The refusals included the sickest patients in the cohort. Once consent was provided, no patient or surrogate withdrew consent before study completion.
DISCUSSION: Use of a deferred consent model enabled participation of critically ill patients in a minimal-risk biomarker study with no withdrawals.
CONCLUSIONS: Further research and enhanced awareness of the potential utility of hybrid models, including deferred consent in addition to patient or surrogate consent, in the conduct of low-risk and minimally interventional time-sensitive studies of critically ill patients are required.

Key Words: *Critical care; Ethical aspects; Informed consent; Research design*

Le consentement différé dans une étude à risque minime auprès de patients gravement malades ayant une hémorragie sous-arachnoïdienne

INTRODUCTION : Des modifications au consentement des patients et des décideurs substituts peuvent accroître la faisabilité d'une recherche auprès de patients gravement malades.
OBJECTIF : Décrire l'usage d'un modèle de consentement différé pour permettre la participation de patients gravement malades à une étude à risque minime sur des biomarqueurs.
MÉTHODOLOGIE : Les chercheurs ont mené une étude d'observation prospective au cours de laquelle ils ont colligé des échantillons de biomarqueurs sériques trois fois par jour pendant les 14 premiers jours suivant une hémorragie sous-arachnoïdienne anévrismale. La collecte des échantillons a commencé à l'admission à l'unité de soins intensifs, et le consentement a été obtenu lorsque le personnel de recherche a pu en parler au patient ou à son décideur substitut.
RÉSULTATS : Vingt-sept patients étaient admissibles à l'étude, mais seulement cinq étaient en mesure de donner leur consentement éclairé. Vingt et un patient (78 %) ont accordé un plein consentement eux-mêmes (n=4) ou par l'entremise d'un substitut (n=17). Trois patients ont donné un consentement partiel ou ont refusé (n'autorisant que des prises de sang dans le cadre des soins habituels ou que l'utilisation des données). Parmi les 22 consentements obtenus auprès de substituts, trois patients (11 %) ont refusé de participer. Les refus incluaient les patients les plus malades de la cohorte. Après avoir accordé leur consentement, les patients et les substituts l'ont maintenu jusqu'à la fin de l'étude.
EXPOSÉ : Le recours à un modèle de consentement différé a permis de faire participer des patients gravement malades à une étude à risque minime sur des biomarqueurs, sans s'associer à des retraits de l'étude.
CONCLUSIONS : D'autres recherches et une meilleure sensibilisation à l'utilité potentielle de modèles hybrides, y compris le consentement différé en plus du consentement des patients ou des substituts, s'imposent pour la tenue d'études à faible risque comportant peu d'interventions et devant êtres effectuées dans un délai précis auprès de patients gravement malades.

A key tenet of the conduct of ethically sound research is that individuals have the opportunity to provide free and informed consent to participate. A priori, first-party informed consent is difficult to operationalize in the intensive care unit (ICU) because most patients lack decision-making capacity as a result of their critical illness, concurrent chronic illness or interventions including sedation, analgesia and mechanical ventilation (1). However, the conduct of clinical research is imperative in this environment to ensure timely identification of effective and ineffective therapies to mitigate morbidity and mortality in this seriously ill population (2). The inability to obtain consent directly from potential participants in the ICU presents important challenges to investigators, especially during conduct of studies in which patient identification and inclusion are time sensitive. Currently, investigators are left with few options including: not to conduct research involving patients who are incapable of providing autonomous consent; to only approach surrogate decision makers (SDMs) for proxy consent; or to conduct the research using alternative consent models, such as delayed/deferred consent (Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans [TCPS 2] section 3.8 [3]) (Appendix 1) or waived consent (TCPS 2 section 3.7 [3]) alone or in combination with traditional consent models (4,5). Whereas consent is not sought in waived-consent studies, deferred or delayed consent refers to the intent to obtain consent from either the patient or their SDM at a later time, typically after research-related activities have commenced for ongoing study participation (6).

In addition to the general principles for the conduct of clinical research outlined in the International Conference on Harmonization Good Clinical Practice Guidelines (7), national regulations have been developed in many jurisdictions to ensure the protection of participants involved in clinical research. However, these regulations are subject to interpretation and can be implemented in different ways (8). For example, some types of clinical research can be conducted with a waiver of consent in several European countries (Belgium, Germany, France, The Netherlands) and in Canada (TCPS 2; departures from consent) but not in other countries (Denmark, Italy, Poland, Portugal) (9). While these regulations were primarily developed to guide

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TABLE 1
Characteristics of the study sample

Participant characteristic	Entire cohort (n=27)	Full consent (n=21)	Partial consent (n=2)	Partial refusal (n=1)	Complete refusal (n=3)
Age, years, mean (range)	55.8 (28–81)	55.2 (28–81)	35.5 (35–36)	73	67.7 (50–81)
Female sex	20 (74)	15 (71)	1 (50)	1 (100)	3 (100)
World Federation of Neurological Surgeons grade					
I-II (good to fair grade)	18 (66)	15 (71)	2 (100)	1 (100)	0 (0)
III-V (tending to poor grade, poor grade, or moribund)	9 (33)	6 (29)	0 (0)	0(0)	3 (100)

Data presented as n (%) unless otherwise indicated

implementation of experimental drug trials, they are often uniformly applied to all studies, including minimal-risk studies (10). Even within jurisdictions, classification of a research study as 'minimal risk' is left to the discretion of individual institutional review boards and evaluated on an individual basis. Emerging data, however, indicate that there is significant variability in institutional review board practices in ascribing risk (11). In most circumstances, minimal-risk studies are held to the same standards as interventional drug trials.

While studies suggest that ICU survivors prefer the conventional approach of a priori SDM consent for enrollment in a research study if they cannot consent for themselves (12-14), involvement in the research decision-making process may be burdensome for some SDMs (15). Symptoms of post-traumatic stress, fear and anxiety in family members involved in consent discussions for research participation have been documented (16-18). Moreover, in a recent multicentre cross-sectional study of research recruitment processes, more than one-half of all opportunities to include critically ill patients in research studies were either missed or infeasible due to operational reasons (19). Meanwhile, another study demonstrated that few patients enrolled in a trial with SDM or deferred consent withdrew after regaining decision-making capacity (5). Furthermore, in a survey of 57 of 210 (27.1%) patients and 152 of 210 (72.4%) SDMs who provided deferred consent to participate in the Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation (NICE-SUGAR) study (6), 195 of 204 (95.6%) would have consented to participate in the NICE-SUGAR study if asked before enrollment. Implementation of a waiver of consent has been shown to increase study recruitment rate and facilitate study completion (20,21). We present our experience in using a deferred-consent model to enable participation of critically ill patients in a minimal-risk study.

METHODS

A prospective, observational study of serum biomarker levels over the first 14 days following aneurysmal subarachnoid hemorrhage (aSAH) to ascertain whether biomarkers herald the development of cerebral vasospasm before documentation on clinical examination or imaging was conducted. Adult patients were entered into the study if they were admitted to the ICU within 48 h of a suspected aSAH and were to undergo treatment of their aneurysm within 48 h of hospital admission. Patients with non-aSAH, life expectancy <24 h from hospital admission and with renal failure were excluded. Cerebral vasospasm typically presents three to five days post-hemorrhage. The authors endeavoured to obtain an immediate blood specimen to establish baseline serum biomarker levels. Blood samples were collected from indwelling venous or arterial catheters three times daily, from admission to day 14 or ICU discharge, whichever occurred first. When feasible, study sample collection coincided with the collection of blood for the patient's routine clinical care. Approximately 5 mL of blood was collected at each sampling for a maximum of 210 mL over the 14-day study period. Selected data elements were abstracted (age, sex, admission World Federation of Neurological Surgeons [WFNS] grade and hospital vital status) from the patient's medical records. The Institutional Review Board of St Michael's Hospital (Toronto, Ontario) approved the study protocol and use of a hybrid model of consent prioritizing patient or SDM if available, and deferred consent if neither the patient nor the SDM were able to provide consent before the first blood sample.

When they could approach the patient or their SDM to discuss study participation, research personnel asked for consent to retain the samples and data already collected, and to ongoing participation in the study including subsequent blood draws and the use of their data. Patients/SDMs were then provided with four options:

1. Full consent: Agree to continue in the study and to analyses of samples already collected;
2. Partial consent: Agree to continue in the study but with samples being collected only in conjunction with clinical sampling;
3. Partial refusal: Consent to analyses of samples already collected but withdrawal from further participation; or
4. Complete refusal: Refusal to continue participation and to analyses of samples already collected.

In circumstances for which the SDM provided initial consent and the patient regained decision-making capacity while in the ICU, research personnel held an additional consent discussion with the patient.

RESULTS

Thirty-two patients were screened at ICU admission over the 4.5-month study period and 27 eligible participants were identified (Table 1). Only five (19%) patients were capable of providing first-party consent at first contact. The majority of study samples coincided with the collection of blood for the patient's routine clinical care; however, nearly one in every six collections did not. The demographic characteristics of study participants are presented in Table 1.

'Complete refusal' occurred in three (11%) cases (all involving SDMs). The admission WFNS scores of these patients were significantly higher (indicating higher severity) than those of 'Full consent' patients (P=0.042 [Fisher's exact test]), with two patients ultimately dying during their ICU admission and one experiencing a protracted hospital course. After initial consent was provided by the patient or SDM, no patient or SDM withdrew consent before study completion (Figure 1).

The mean (± SD) time to obtaining consent from ICU admission was 2.6±2.5 days (range 0.3 to 11.2 days) for those providing either 'Full or partial consent' (n=23) and 5.9±4.4 days (range 1.8 to 12.0 days) for those 'Partially or completely refusing' participation (n=4). Patients regained decision-making capacity (n=10) within 7.7±4.1 days of ICU admission.

DISCUSSION

Our data support previous findings indicating that few patients or SDMs withdraw consent when included in research using a deferred-consent model (5,22). Only three SDMs (11%) completely refused participation. For patients enrolled with SDM consent initially, no patient withdrew consent after regaining decision-making capacity. The three SDMs who completely refused participation in the study took longer to make their decision compared with the SDMs who provided consent. These SDMs were aware that we continued to draw

protocol-defined blood samples while we awaited their decision, suggesting that reasons for refusal may not have been related to the perceived risk of the study to the patient. All three complete refusals were for patients with more severe aSAH. We postulate that severity of illness may have played an important role in SDMs decision to decline participation. At the time they were approached, these SDMs may have been overwhelmed with the clinical condition of the patient and, consequently, were unable or unwilling to consider participation or additional information. Previous research suggests that most SDMs of critically ill patients (68%) report symptoms of anxiety and many (38%) report symptoms of depression (23). Moreover, involvement in the research decision-making process has been associated with symptoms of post-traumatic stress in some SDMs (16,17).

Given that no patients withdrew their consent after enrollment in our study using deferred consent and noting that making consent decisions may be burdensome for SDMs, waived consent could be regarded as an alternative consent model for minimal-risk studies involving patients with high illness acuity. Waived consent may help preserve study validity and limit selection bias by limiting postenrollment withdrawal of study data by deferred-consent participants that may, in turn, compromise the contributions of the other study participants (5,24). In our study, consent for participation was refused for three patients who were among the most severely ill in our cohort; it is conceivable that the exclusion of their data may have altered the study findings, as has been noted in some trials (24).

While based on a small sample size (n=27), our prospective study provides novel insights into the use of a deferred-consent model, in addition to patient and SDM consent, for a low-risk, time-sensitive biomarker study of critically ill patients. While hypothetical scenarios are integral to understanding research recruitment involving SDMs (25,26), their comparability with patient and SDM preferences in real-time is largely unknown. Whereas others have documented that 15% to 24% of 240 survivors of critical illness rated deferred consent as unacceptable or highly unacceptable in hypothetical scenarios (13), no patient withdrew consent in our prospective biomarker study involving a deferred-consent model. Low withdrawal rates after enrollment have been documented in several other studies involving critically ill patients (5,6,27). Scenario-based studies often evaluate clinical trials associated with greater than minimal risk and this may, in part, explain the discordant study findings. Moreover, agreement between patient and SDM decision making regarding research participation has been shown to decline as study risk increases in hypothetical research scenarios (26). Notwithstanding, no data are available to evaluate the 'acceptability' of participation under deferred consent in minimal-risk studies for critically ill patients and their surrogates. Future studies with larger sample sizes involving multiple sites and other critically ill populations are needed to further explore the use of deferred consent in clinical research. Another potential limitation of our study was that it pertained to consent models currently used in Canada and, therefore, may not be generalizable to other countries and jurisdictions.

Use of deferred-consent models may be justified in low-risk, time-sensitive observational studies involving critically ill patients acknowledging the time-sensitive nature for inclusion in some research studies, the potential for selection bias and the burden imposed on SDMs by consent discussions. In our study, the use of a hybrid consent model, including traditional and deferred consent, enabled participation of critically ill patients in a minimal-risk, time-sensitive serum biomarker study with no study withdrawals. Currently, the TCPS 2 (3) does not make allowance for strictly observational studies or minimally interventional studies wherein the risk is not greater than that involved with standard care or is justified by the prospect for direct participant benefit. Further research and enhanced awareness of the potential utility of deferred-consent models or hybrid consent models (that prioritize SDM consent when SDMs are available, but enable research to be conducted under deferred consent when SDMs are not available) in the conduct of low-risk and minimally interventional, time-sensitive studies of critically ill patients are required.

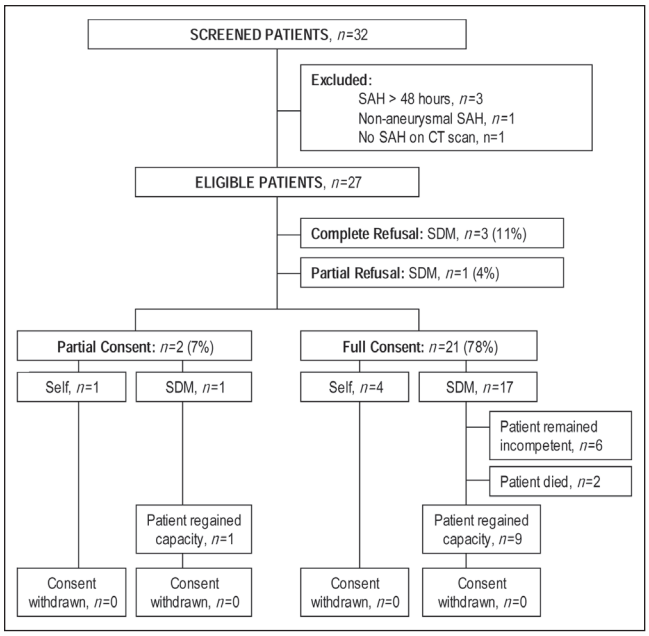

Figure 1) *Patient and surrogate decision maker (SDM) consents and refusals. CT Computed tomography; SAH Subarachnoid hemorrhage*

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APPENDIX 1

From TCPS-2:

Article 3.7: The REB may approve research without requiring that the researcher obtain the participant's consent in accordance with Articles 3.1 to 3.5 where the REB is satisfied, and documents, that all of the following apply:

(a) the research involves no more than minimal risk to the participants;

(b) the lack of the participant's consent is unlikely to adversely affect the welfare of the participant;

(c) it is impossible or impracticable to carry out the research and to answer the research question properly, given the research design, if the prior consent of the participant is required;

(d) whenever possible and appropriate, after participation, or at a later time during the study, participants will be debriefed and provided with additional pertinent information in accordance with Articles 3.2 and 3.4, at which point they will have the opportunity to refuse consent in accordance with Article 3.1; and

(e) the research does not involve a therapeutic intervention, or other clinical or diagnostic interventions.

Article 3.8: Subject to all applicable legal and regulatory requirements, research involving medical emergencies shall be conducted only if it addresses the emergency needs of the individuals involved, and then only in accordance with criteria established in advance of such research by the REB. The REB may allow research that involves medical emergencies to be carried out without the consent of participants, or of their authorized third party, if all of the following apply:

(a) a serious threat to the prospective participant requires immediate intervention;

(b) either no standard efficacious care exists or the research offers a realistic possibility of direct benefit to the participant in comparison with standard care;

(c) either the risk is not greater than that involved in standard efficacious care, or it is clearly justified by the prospect for direct benefits to the participant;

(d) the prospective participant is unconscious or lacks capacity to understand the risks, methods and purposes of the research project;

(e) third-party authorization cannot be secured in sufficient time, despite diligent and documented efforts to do so; and

(f) no relevant prior directive by the participant is known to exist. When a previously incapacitated participant regains capacity, or when an authorized third party is found, consent shall be sought promptly for continuation in the project, and for subsequent examinations or tests related to the research project.

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