Intensive and Critical Care Nursing (2013) 29, 300—309

Available online at www.sciencedirect.com

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ORIGINAL ARTICLE

Enhancing the informed consent process for critical care research: Strategies from a thromboprophylaxis trial

Orla M. Smith[a,1], Ellen McDonald[b,1], Nicole Zytaruk[b,1], Denise Foster[c,1], Andrea Matte[d,1], France Clarke[b,1], Suzie Fleury[e,1], Katie Krause[f,1], Tracey McArdle[g,1], Yoanna Skrobik[h,1], Deborah J. Cook[b,i,*,1]

[a] *Critical Care Department and Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada*
[b] *Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Canada*
[c] *Division of Critical Care, Vancouver General Hospital, Vancouver, Canada*
[d] *University Health Network, Toronto, Canada*
[e] *Division of Critical Care, Kingston Hospital, Kingston, Canada*
[f] *Division of Critical Care, St John's Mercy Hospital, St Louis, USA*
[g] *Division of Critical Care, Ottawa Hospital, Ottawa, Canada*
[h] *Division of Critical Care, Hôpital Maisonneuve Rosemont, Montreal, Canada*
[i] *Department of Medicine, McMaster University, Hamilton, Canada*

Accepted 26 April 2013

KEYWORDS
Clinical research;
Critical care;
Informed consent;
Intensive care;
Randomized trials;
Studies;
Substitute decision-makers

Summary
Background: Critically ill patients lack capacity for decisions about research participation. Consent to enrol these patients in studies is typically obtained from substitute decision-makers.
Objective: To present strategies that may optimise the process of obtaining informed consent from substitute decision-makers for participation of critically ill patients in trials. We use examples from a randomised trial of heparin thromboprophylaxis in the intensive care unit (PROTECT, clinicaltrials.gov NCT00182143).
Methods: 3764 patients were randomised, with an informed consent rate of 82%; 90% of consents were obtained from substitute decision-makers. North American PROTECT research coordinators attended three meetings to discuss enrolment: (1) Trial start-up (January 2006); (2) Near trial closure (January 2010); and (3) Post-publication (April 2011). Data were derived from slide presentations, field notes from break-out groups and plenary discussions, then analysed inductively.

* Corresponding author at: Department of Medicine, McMaster University Health Sciences Center, Room 2C11, 1200 Main Street West, Hamilton, Ontario, Canada L8N 3Z5. Tel.: +1 905 525 9140x22162; fax: +1 905 524 3841.
E-mail address: debcook@mcmaster.ca (D.J. Cook).
[1] For the North American PROTECT Research Coordinators and the Canadian Critical Care Trials Group.

0964-3397
http://dx.doi.org/10.1016/j.iccn.2013.04.006

Results: We derived three phases for the informed consent process: (1) Preparation for the Consent Encounter; (2) The Consent Encounter; and (3) Follow-up to the Consent Encounter. Specific strategies emerged for each phase: Phase 1 (four strategies); Phase 2 (six strategies); and Phase 3 (three strategies).
Conclusion: We identified 13 strategies that may improve the process of obtaining informed consent from substitute decision-makers and be generalisable to other settings and studies.

Implications for clinical practice

- Informed consent for research is an ongoing process.
- Optimising informed consent for research participation is a multi-phase process that starts before a study is implemented and involves the inter-professional ICU clinical team.
- Implementation of these 13 strategies may help to improve the integrity of the informed consent process, minimise SDM decisional burden and maximise timely enrolment of eligible patients into clinical studies in the ICU.

Introduction

Clinical research in the intensive care unit (ICU) is essential to improve the outcomes of critical illness (Luce et al., 2004; McRae and Weijer, 2002; Yarborough, 1993). Timely completion of randomised trials and the generalisability of study results are contingent upon recruitment of the majority of eligible patients (Wade et al., 2009; Watson and Torgerson, 2006). While deferred or waived consent models have been employed in ICU trials of urgent interventions (Annane et al., 2002; NICE-SUGAR Investigators et al., 2009; Roberts et al., 2004), interventional trials typically require a priori informed consent. Most critically ill patients are incapable of research decision-making (Fan et al., 2008), such that substitute decision-makers (SDMs) are typically approached to consider research opportunities on their behalf (Arnold and Kellum, 2003). SDM consent to research is the preferred enrolment approach of ICU survivors (Chenaud et al., 2009; Scales et al., 2009), ICU family members (Barrett et al., 2012; Chenaud et al., 2009; Perner et al., 2010), research ethics board (REBs) (Duffett et al., 2011; Gong et al., 2010) and the public (Burns et al., 2011).

Ethical and procedural guidelines require research consent to be informed, voluntary, documented and ongoing (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, 2010; International Conference on Harmonisation, 1997; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979; Nuremburg code, 1996; World Medical Association, 1997). Researchers are obligated to disclose risks and benefits of participation to decision-makers, and to ensure understanding of the research purpose and procedures. Making a decision about research participation in the ICU may be difficult for SDMs for several reasons. First, enrolment is often time-sensitive, sometimes even requiring a decision within hours (Burns et al., 2009). For example, in two recently published international randomized controlled trials, the eligibility criteria dictated that patients be enrolled within 24 hours of demonstrating signs of septic shock (Guntupalli et al., 2013; Ranieri et al., 2012). Second, most SDMs are unaware of patient wishes regarding research (Chenaud et al., 2009; Ciroldi et al., 2007; Coppolino and Ackerson, 2001) and must balance their understanding of patient values with knowing how trial interventions may cause more harm than good, or introduce risk without benefit. Third, comprehension of SDMs regarding medical issues and research in the ICU is limited (Azoulay and Pochard, 2002; Rodriguez et al., 2008). Finally, SDMs are anxious, and involvement in research decision-making may increase psychological burden (Wendler and Rid, 2011) or induce post-traumatic stress (Azoulay et al., 2005). In this unique context, research coordinators approach SDMs, inviting their consideration of research opportunities for critically ill patients.

SDMs may agree to, or decline, a request for a critically ill patient to participate in research. High rates of refusal can decrease the generalisability of trial results if non-consenting participants are systematically different than consenting participants, even if the desired sample size is achieved (Chertow et al., 2003; Crowley et al., 2008). In observational research, it has been suggested that the requirement for informed consent can lead to biased results due to the systematic exclusion of some individuals (Gershon and Tu, 2008; Tu et al., 2004). Recruitment rates vary across studies; however, rates can also differ among centres recruiting patients into the same trial (Smith et al., 2012) underscoring how several factors may influence enrolment, just one of which is the informed consent process (Table 1). Although systematic reviews have addressed patient recruitment strategies outside the ICU setting (Caldwell et al., 2010; Mapstone et al., 2007; Watson and Torgerson, 2006), literature is sparse on how to improve the informed consent process for research involving critically ill patients.

The objective of this report is to present strategies that may optimise the process of obtaining informed consent from SDMs for participation of critically ill patients in randomised trials. To illustrate some strategies, we use the example of PROTECT (the Prophylaxis for ThromboEmbolism in Critical Care Trial) an international trial of heparin thromboprophylaxis for medical-surgical critically ill patients (clinicaltrials.gov NCT00182143).

Table 1 Factors potentially influencing enrolment into a clinical trial.

(1) Non-modifiable factors
Case-mix of patients
Number of beds
Availability of substitute decision makers
(2) Modifiable factors
Research culture
Support of the clinical team
Presence of research coordinators
Interpretation of the inclusion and exclusion criteria
Research coordinator workload
Approval of telephone consent procedures
Coenrolment procedures
Consent rate

In this table we outline the non-modifiable and modifiable factors that can influence enrolment of patients into a clinical trial. This article is focused on strategies to facilitate the last potentially modifiable factor, the informed consent process.

Methods

PROTECT was a concealed, randomised, stratified, blinded thromboprophylaxis trial of low-molecular weight heparin versus unfractionated heparin. Patients were considered for enrolment if they were ≥18 years of age, weighed ≥45 kilograms, and were expected to remain in ICU ≥72 hours. The primary outcome was proximal leg deep vein thrombosis. Secondary outcomes were venous thromboembolism at any site, the composite outcome of venous thromboembolism or death, major bleeding, minor bleeding and heparin-induced thrombocytopenia. This trial was completed on schedule, recruiting patients over 4 years from May 2006 to June 2010 in 67 ICUs in 6 countries. Methods and results of the pilot trial and full trial are available elsewhere (Cook et al., 2005; PROTECT Investigators, 2011).

Novice and experienced North American research coordinators involved in PROTECT attended three study meetings: January 2006 (before recruitment began), January 2010 (in the final year of recruitment) and April 2011 (after publication of the main results). In total, 98 persons attended these meetings (77 persons attended 1 meeting, 15 persons attended 2 meetings and 6 persons attended all 3 meetings). Overall, 71 persons participated in their capacity as a research coordinator.

At each of these multipurpose meetings of North American collaborators funded by the Canadian Institutes of Health Research, one session focused on screening, consenting and enrolling patients. The objective of these sessions was to develop a clear, concise, ethical approach to procuring consent for enrolling ICU patients into studies. These sessions were interactive, including an oral presentation facilitated by power-point slides and group discussion. At the first meeting, a role-playing video on obtaining consent for PROTECT was shown. At the second and third meetings, attendees formed small break-out groups for additional brainstorming. Each small group had a scribe who made field notes; each group had a rapporteur who verbally summarized discussion points in a plenary session of all attendees. The PROTECT Trial Manager collated plenary discussion points across meetings.

Research ethics of trial

The PROTECT protocol and consent forms were approved by each centre's Research Ethics Board. The consent form outlined the study purpose, procedures, possible risks and benefits and ranged from 2 to 10 pages across centres.

Written informed consent was obtained from SDMs or patients. The overall PROTECT consent rate was 82% (range 50—100%) across participating centres; 90% of the consents were obtained from SDMs.

Analysis

The foundational data for our analysis were derived from the initial slide presentations and expanded through critical discussion at each of the three research coordinator meetings. The slide presentations were created by the principal investigator (DJC) and the senior coordinators of the trial (EM, NZ) and included points on general ethical principles for research consent in the ICU, specific consent requirements for PROTECT, and suggestions for how to discuss consent for PROTECT with eligible patients and/or their designates. Field notes from the break-out groups and discussion points from the plenary sessions were analysed inductively by four of the authors (OMS, EM, NZ, DJC). This led to recognition of three distinct temporal phases of the informed consent process: Preparation for the Consent Encounter, The Consent Encounter and Follow-up to the Consent Encounter. Within these phases, we identified 13 specific strategies to optimize the informed consent process (Table 2).

Table 2 Strategies for informed consent from substitute decision-makers in an ICU trial.

Phase 1: Preparation for the Consent Encounter
(1) Brand the trial with key messages
(2) Train local research personnel
(3) Promote a culture of research
(4) Be familiar with the patient and family dynamics
Phase 2: The Consent Encounter
(5) Involve the bedside staff
(6) Introduce the idea of research in a professional, positive manner
(7) Present the facts about the research problem and the outcomes
(8) Explain all research-related activities
(9) Convey risks and benefits transparently
(10) Describe alternatives to participation and support the consent decision
Phase 3: Follow-up to the Consent Encounter
(11) Document the consent process
(12) Provide thanks and ongoing study updates to all stakeholders
(13) Follow-up with the patient to ensure ongoing consent

In this figure, we present three phases to the informed consent process, and the associated 13 strategies that may help to optimise the informed consent process when talking to SDMs.

Results

Phase 1: Preparation for the Consent Encounter

In all sessions, research coordinators identified the need for both the trial Methods Center and participating sites to engage in preparatory work prior to commencing recruitment. Four specific strategies were considered essential to successful preparation.

Strategy #1: brand the trial with key messages
To facilitate recruitment at the local sites, it is helpful for the study Methods Center to craft and disseminate key messages to be highlighted in educational sessions with bedside staff. These can also be touchstones for consent discussions with SDMs. An example from the PROTECT Methods Center is the 'top 10' talking points for PROTECT outlined in Fig. 1.

Strategy #2: train local research personnel
Before soliciting consent from an SDM, research coordinators need to be adequately prepared to explain the study and answer questions. Training exercises can include: attending the study start-up meeting; preparing a consent script including lay terms for complex concepts; practicing the consent dialogue with a colleague and lay person; soliciting input on techniques from an experienced coordinator; and sharing of both successful and non-successful strategies with colleagues. Practice exercises are especially important for novice coordinators and experienced coordinators new to the ICU.

Strategy #3: promote a culture of research
Engagement of ICU bedside staff in the trial was identified as key to successful recruitment. Consider study launch events; research updates as a standing agenda item during ICU staff meetings; posting study information on staff communication boards; and study newsletters. The visibility and accessibility of research personnel to the front line staff is crucial. Research coordinators can promote a research culture throughout the trial by providing staff with recruitment progress and soliciting feedback on addressing recruitment challenges. For the public, posters and brochures in waiting rooms can be used. Printed family information can explain the importance of research in general and details about specific studies, as permitted by local Research Ethics Boards. Information should be clear, simple and devoid of jargon. Posters should be eye-catching, presenting research as an integral part of hospital activities, but clearly optional.

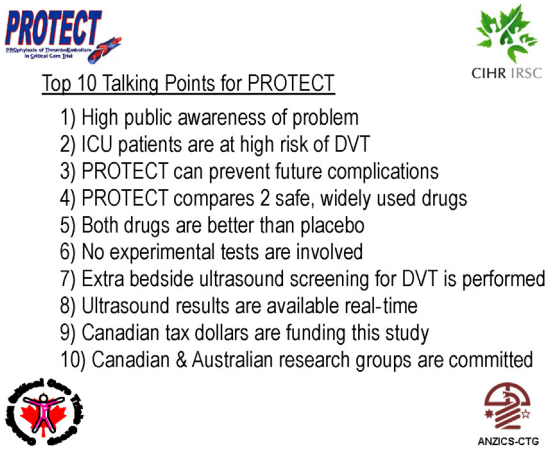

Figure 1 Top 10 PROTECT Talking Points. In this figure, we outline key points that served as touchstones for increasing familiarity with PROTECT. These 'Top 10 Talking Points' were useful to describe some features of the trial during initial bedside staff education, and during initial informed consent dialogue.

Strategy #4: be familiar with the patient and family dynamics
Before approaching the SDM, confirm patient eligibility for the study by reviewing the trial inclusion and exclusion criteria and the patient's medical history. Discuss the assessment of patient eligibility with the ICU staff and investigator. For safety reasons, when suitable, confirm with the physician that there are no medical contraindications to the patient's participation. Clarify the identity of the SDM with the medical staff, which is not always clearly documented. Ask the bedside nurse if the SDM is available and approachable. Inquire about familial issues requiring sensitivity. Ask about timing the consent encounter according to the SDM's visitation schedule and around medical updates. Before meeting the family, review the consent document to ensure comfort with the content, and to be able to easily direct the SDM to specific sections of the form, so that study information is portrayed consistently, verbally and in writing.

Phase 2: The Consent Encounter

Research coordinators identified six strategies to optimise the actual consent encounter with the SDM. The principles of ethical research conduct are embedded in these strategies. These also reflect professional behaviours of the research coordinator, teamwork and communication techniques.

Strategy #5: involve the bedside staff
The bedside nurse and physician should be aware that the patient is a candidate for research participation and why. Review the study procedures, risks and benefits with the staff before approaching the SDM. Knowledgeable bedside staff can introduce research coordinators to the family, having established that the family is interested in hearing about the study, particularly in those centres requesting that someone from the circle of care be involved in approaching the family. If appropriate or required by local policies, ask a member of the ICU team to introduce you to the family. If suitable, invite the bedside nurse or physician to be present during family discussions. After the consent encounter, bedside staff can also assist by answering family questions and reinforcing information shared by the research coordinator.

Strategy #6: introduce the idea of research in a professional, positive manner
Professionally state your name, professional designation and role in the ICU to the SDM. Explain that the ICU physician invited you to present an opportunity for the patient to participate in a study. Explain that the SDM is being asked to consider consent because the patient is not capable of

decision-making. If possible, provide a quiet and private place for discussion. However, if the SDM prefers the discussion to occur at the bedside, proceed according to their wishes. Inquire as to who else the SDM would like present. If multiple people are present, acknowledge each individual. Take a seat to converse at eye-level. Ensure that phones and pagers are turned off or on a silent mode to avoid interruptions. Focus the conversation on the patient and their individual suitability for the trial. Use clear and simple terms to explain the concept of research in general. Highlight the hospital and ICU's commitment to improving patient care through research. Be prepared for myriad reactions ranging from interest to disinterest, and enthusiasm to scepticism. Recognise that research may be a foreign concept. Be prepared to respond supportively if people become emotional. Acknowledge that decision-making can be burdensome.

Strategy #7: present the facts about the research problem and the outcomes

Use simple facts to convey the extent of the problem that the research is designed to address. In PROTECT, coordinators informed SDMs of the prevalence of blood clots in critically ill patients using published statistics, indicating that up to 3—5% of ICU patients are admitted with a pre-existing but typically unrecognized DVT, and up to 8—10% of ICU patients develop a DVT while in ICU. Personalise the discussion by highlighting the particular suitability of the patient for the study. In PROTECT, coordinators cited immobility, sedation and central venous catheters as risk factors for developing DVTs. Provide decision-makers with a clear rationale for the study interventions and explain the uncertainty amongst clinicians about which of the interventions is best, hence the need for the trial. In PROTECT, research coordinators educated families about the potential for leg DVTs to be undetected and to travel to the lungs in the form of pulmonary emboli, which can result in serious consequences such as prolonged mechanical ventilation or death.

Strategy #8: explain all research-related activities

It is important to be clear about what is 'standard of care' and what comprises research. If the study involves randomization, explain the number of study arms and process of randomisation in simple terms. If the study involves blinding, explain who will be blinded to what, and why. For example, in PROTECT, patients had an equal chance (i.e. 50/50 or 'flip of a coin') of receiving unfractionated heparin or low molecular weight heparin. Patients, families, ICU staff and research staff were all blinded; only the research pharmacist preparing the study medication was aware of what drug the patient was receiving. Research coordinators explained that the blinding method was the best scientific way to accurately evaluate the development of clots or bleeding. If the study involves diagnostic tests, explain when these tests will occur and what will happen with the results. In PROTECT, bilateral leg compression ultrasounds were performed at study entry and twice weekly thereafter until ICU discharge. Ultrasound results were shared with the bedside clinical staff to ensure timely treatment, if indicated. Tell families how often and for how long monitoring and data collection will continue. Assure them of the privacy and confidentiality of data collected.

Strategy #9: convey risks and benefits transparently

Be clear with families about the types and likelihood of adverse outcomes associated with the study. Clarify whether or not the risks of participation are greater than what would be expected as part of standard care. Be frank about whether or not there are any direct benefits to the participants or whether benefits pertain solely to generation of knowledge to help future patients, to avoid therapeutic misconception. Because routine screening ultrasounds are not part of standard care, bedside compression ultrasounds were considered a beneficial surveillance as part of participation in PROTECT, which allowed early detection of DVT if it was not clinically suspected. SDMs learned that critically ill patients rarely develop classic signs or symptoms of DVT because they are supine and receiving sedation and analgesia; therefore, ultrasound is generally necessary to detect DVT in the ICU.

Strategy #10: describe alternatives to participation and support the consent decision

Reinforce the voluntary nature of consent and inform the family that the patient will receive high quality care regardless of whether they participate. Remind the family that consent may be withdrawn at any stage without consequence. Ask the family if they have any unanswered questions and whether they would like to speak to the local investigator or bedside physician. Acknowledge that a lot of information has been presented about potentially foreign concepts. Suggest that the SDM reflect on what the patient would say if they were capable. Offer the family sufficient time to think and talk about the study privately, but be clear about any time restrictions on recruitment. If additional time is requested, specifically plan to re-connect to obtain their decision. Thank the family for their consideration, whether they ultimately agree or decline.

Phase 3: Follow-up to the Consent Encounter

After the consent encounter and a decision about participation has been rendered, the consent process continues. Research coordinators described three additional strategies following the actual consent decision.

Strategy #11: document the consent process

If the SDM has declined the study, communicate this to the ICU team and thank them for any help they provided. If the SDM has agreed to the study, ask them to sign, date and time the consent form. Place the original consent form in the study file and provide the SDM with a copy of the signed form. If suitable as per local standard operating procedures, insert a copy of the consent form in the patient's medical chart. Write a note in the patient's chart to document the consent discussion and enrolment of the patient in the study. Remember to include the name of the SDM and their relationship to the patient; the name of witnesses to the discussion; highlights of the consent discussion; and date and time that consent was received. Provide a brief summary of the study activities in your note for the bedside clinical team. Research coordinators suggested a standardized template as a source document to record the consent encounter, with space to insert patient-specific details.

Strategy #12: provide thanks and ongoing study updates to all stakeholders

As the study unfolds, to ensure that all parties feel included and appreciated in the research process, acknowledge each person's contribution verbally, in writing, or both if appropriate. Thank the SDM and patient (if capable) for the opportunity to include the patient in the study. Acknowledge the ICU team members who facilitated the consent encounter, and those who assist with study procedures. Remember contributions of staff outside the ICU such as those in the research pharmacy, laboratory and diagnostic imaging, expressing your gratitude frequently. Provide family members with updates about the patient's progress in the study as it evolves. It is important for them to know that research staff members are continuing to follow the patient's course in the ICU. Ongoing contact with research personnel may facilitate a positive research experience. Ensure that the ICU bedside team is aware of the patient's progress in the study by flagging pertinent diagnostic test results. In PROTECT, research coordinators provided updates to the ICU team on ultrasound results, and trends in coagulation tests and platelet counts, to alert them to potential problems such as heparin-induced thrombocytopenia.

Strategy #13: follow-up with the patient to ensure ongoing consent

In keeping with the context of this report, although the majority of consents for ICU research studies are obtained from SDMs, participants should be assessed regularly for research decision-making capacity over the study to the extent that this is possible to achieve. If the patient demonstrates capacity prior to completion of study activities, discuss consent with the patient directly. Ensuring that the patient is informed about enrolment and has the opportunity to make a decision about continued participation is an important aspect of patient autonomy in the ongoing consent process.

Discussion

Through soliciting and documenting the consenting experiences of North American research coordinators who worked on the PROTECT trial, we collated 13 strategies to optimise a 3-phase informed consent process when approaching SDMs regarding the enrolment of critically ill patients into randomised trials. The strategies suggested by research coordinators both reinforce requirements for informed consent outlined in existing legislation and/or guidelines, and also highlight additional processes that may enhance the integrity of the consent process.

Strategies outlined in Phase 1, Preparation for the Consent Encounter, represent suggestions to prepare both ICU and research personnel to begin a new study, starting with training, review of materials and key messages from the study Methods Center. The importance of multi-modal training for research coordinators is noted by others (Felsen et al., 2010). Difficulty explaining study details in simple terms can negatively impact on recruitment, as identified through qualitative analysis of screening logs, interviews of study personnel and audio-recordings in a urology—oncology trial (Paramasivan et al., 2011). Creating and sharing a 'study tool box' which includes simplified study messages for research personnel, clinicians and SDMs may increase recruitment, as suggested in a survey of 252 oncology investigators and coordinators (Ulrich et al., 2010). The PROTECT Methods Center provided consent tools and training to North American research coordinators in the form of workshops, sharing of the Top 10 Talking Points about PROTECT to help with initial dialogue and key messages (Fig. 1). The Methods Center developed slides on rigorous, transparent approaches to obtaining informed consent. A role-playing video of the consent encounter was also created to demonstrate ways to respond to various SDM reactions and questions. Simulation training, role-playing exercises, videos and workshops have been shown to enhance communication in the ICU (Berkenstadt et al., 2008) and improve recruitment, based on reports from 114 publically funded trials in the United Kingdom (McDonald et al., 2006).

In the clinical setting, bedside staff may have limited knowledge of, or minimal interest in research, or harbour concerns about it, which can contribute to recruitment challenges (Alt-White and Pranulis, 2006; Dale et al., 2010; Wiegand et al., 2008). Researchers should identify any bedside staff worries and address them pre-emptively. Engagement of staff champions, staff in-services and posting study advertisements can generate research support and help to discover and resolve staff concerns. Research coordinators should be cognisant of local ICU culture and tailor communication and education strategies accordingly to promote a favourable research environment (Chlan et al., 2009). Ideally, bedside staff members are aware of research initiatives for which their patients may be eligible; however, staff should at least understand the fundamentals of studies in which their patients are enrolled, particularly if they have key role(s) such as study drug administration.

Research coordinators recommended promoting a culture of research to families through printed materials in ICU admission packages, display of illustrative posters and research brochures where families congregate, such as the ICU waiting room (Fig. 2). Family members may not initially be aware that research is ongoing in the ICU as demonstrated in a recent Canadian survey (Dale et al., 2010). The majority of ICU family members report a desire to receive written information about research (Soltner et al., 2009).

Within Phase 2, the Consent Encounter, research coordinators had multiple suggestions to facilitate interactions with SDMs about patient participation in research. Professionalism and confidence of the research coordinator are key, as these attributes shape the SDM's first impression of research. In some settings, individuals report that their decision to consent to research was positively influenced by competent, personable and experienced research personnel (Felsen et al., 2010). In the ICU, research coordinators should express empathy, recognising the burden of having a family member or close friend who is critically ill, and acknowledging SDM uncertainty inherent in research decision making (Rose and Kasner, 2011; Sugarman et al., 2001). A common reason for SDM refusal of research in the ICU is stress (Grap and Munro, 2003; Mehta et al., 2012).

An SDM's uncertainty regarding research decision-making may be related to lack of familiarity with critical illness, and lack of familiarity with the patient's values regarding research (Azoulay et al., 2001; Rodriguez et al., 2008). SDMs

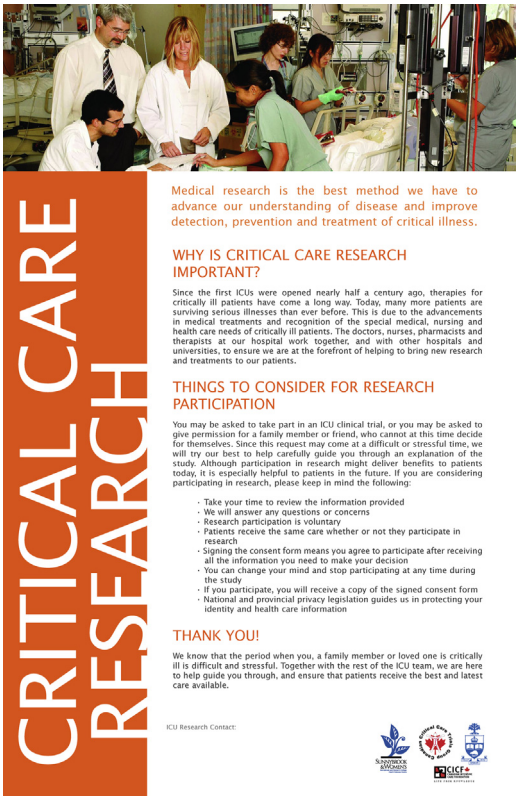

Figure 2 Example of research brochure or poster. In this figure, we present an example of a research brochure which may help to enhance the institutional research culture.

may sometimes equate a request for consent as permission to use the patient as a 'guinea pig' (Morgenweck, 2003). Research coordinators must spend sufficient time with SDMs to provide them with clear information about the purpose, risks, benefits and voluntariness of the study and to assess their comprehension (Chenaud et al., 2007). Clarity about the direct possible benefits to the patient, as compared to the benefits to future patients, is essential. Careful dialogue is required to avoid therapeutic misconception, or the mistaken belief that the primary intent of the study is to treat the patient as opposed to answer a research question (Appelbaum et al., 1982). SDMs in the ICU may be particularly susceptible to therapeutic misconception, given the high morbidity and mortality associated with critical illness (Flanagan et al., 2011; Mehta et al., 2012) and possible misunderstandings about research (Bigatello et al., 2003). An effective way to increase understanding of the consent process is through prolonged periodic engagement (Flory and Emanuel, 2004). SDMs may not understand key research concepts, such as blinding and randomisation (Snowdon et al., 1997), so research coordinators should individualise consent encounters, providing information in different formats if necessary (Wade et al., 2009).

SDMs should be encouraged to reflect on whether the patient would be agreeable to participate if they could decide themselves (Berger, 2011). Lack of SDM confidence regarding what the patient would decide can induce decisional burden (Wendler and Rid, 2011). The majority of ICU SDMs report the desire to engage others, including the ICU physician, in decision-making about research (Barrett et al., 2012; Mehta et al., 2012). Cultural factors may influence the decision-making process. To avoid errant assumptions, be aware that in some cultures, decision making may be based on family consensus or deferred to male family members (Braun et al., 2008; Charles et al., 2006; Kwak and Haley, 2005; Shrank et al., 2005).

In closing, ask SDMs if they have any remaining questions or concerns or if they desire to speak with the study investigator, then provide sufficient time for decision-making (Crowley et al., 2008; Ross et al., 1999; Wright et al., 2004). Research coordinators should thank the SDM for considering the study and support them, whatever the outcome. Lack of support in decision-making appears to increase the risk for adverse psychological outcomes for ICU SDMs (Siegel et al., 2008).

In Phase 3, Follow-up to the Consent Encounter, the ongoing nature of consent is underscored by several key activities. Patients and families involved in emergency research report a desire for more information after enrolment (Kamarainen et al., 2012). The need to engage in ongoing assessment of patient capacity for involvement in decision-making is crucial (Bigatello et al., 2003; Chenaud et al., 2007); however, only a minority of patients pass formal capacity screens both during their ICU stay and before hospital discharge which can preclude the ability of the research coordinator to obtain first-party consent (Fan et al., 2008; Scales et al., 2009). Furthermore, there is no clear guidance in the literature, or in existing ethical frameworks, as to how long the mandate for re-consent should apply. In Canada, re-consenting practices are variable and the time-frame for re-consenting tends to be dictated by local REB practices. Following initial SDM consent, concerns about the potential for the 're-consenting process' with patients to introduce bias as a result of post-randomisation withdrawals (Truog, 2007), especially in unblinded randomised trials, is the subject of active research (Duffett et al., 2011).

We encourage principal and local investigators to monitor consent rates and provide feedback and support to participating centres throughout a trial. In PROTECT, the informed consent rate was 82%; however, rates ranged from 50 to 100% across sites. We previously documented factors that were independently associated with high consent rates (Smith et al., 2012) including: research coordinator experience; ICU size (<15 beds compared to ≥15 beds); and the availability of >1 full-time research personnel. We also found that consent rates were lower in centres affiliated with formal research consortia compared to those that were not. Consent rates were highest during the PROTECT Pilot Trial; lowest during the initiation of the full trial; and increased each year of recruitment. To complement the foregoing analyses on the patterns and predictors of consent rates, we developed this report.

This report is limited in that we elicited consent strategies in the context of a low-risk trial testing two widely available drugs used to prevent blood clots. The problem of blood clots is one with which the public is generally familiar. Additional explanation may be required for trials of less familiar conditions, novel drugs or devices that confer higher risk, or trials involving more urgent interventions. We focused on the consent process with SDMs

rather than seeking initial consent from adult patients, since the latter is infrequently possible in the ICU. We did not discuss telephone consent, which was rare in PROTECT and not approved by most Research Ethics Boards. Our focus was the process of informed consent rather than all aspects of participant recruitment or reasons for non-enrolment, such as physician refusals, missed patients, or the unavailability of SDMs. Readers are referred elsewhere for literature underscoring the importance of a clear consent form and the influence of consent form length on understanding (Beardsley et al., 2007; Jefford and Moore, 2008; Silverman et al., 2005; Stunkel et al., 2010). Although PROTECT was an international trial, the strategies presented herein represent the views and experiences of North American research coordinators. Jurisdictional differences and legal requirements may decrease the applicability of some of our suggested strategies; however, strategies 7—10 reflect, in general, internationally accepted standards for informed consent in human subjects research that should be considered obligatory, not optional (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, 2010; International Conference on Harmonisation, 1997; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979; Nuremburg code, 1996; Rischbieth et al., 2005; World Medical Association, 1997).

While some randomised trials have examined recruitment and consent strategies for patient participation in research (Caldwell et al., 2010; Mapstone et al., 2007; Watson and Torgerson, 2006), no published study has examined the acceptability and effectiveness of different strategies targeting SDMs in the ICU. Additional quantitative and qualitative investigations are needed to better understand factors positively and negatively influencing recruitment into ICU trials. Two recent Canadian observational studies suggest that altruism and potential patient benefit may motivate SDMs to provide consent while fear, anxiety and risk-aversion may prompt refusal (Burns et al., 2010; Mehta et al., 2012). The role of patient decision aids to enhance understanding and improve research decision-making is currently being assessed (Brehaut et al., 2010). The utility of research decision aids in the ICU is worthy of investigation, given signals that not all SDMs desire an active role in decision-making (Anderson et al., 2009; Azoulay et al., 2004; Barrett et al., 2012; Heyland et al., 2003) and given that SDM research decision-making appears to increase the risk for post-traumatic stress (Pochard et al., 2005). Testing the impact of multiple rather than single strategies would be instructive.

Conclusion

In summary, we have presented 13 strategies to enhance the process of informed consent by SDMs for randomised trials in critically ill adults, based on the experiences of a large group of diverse North American research coordinators during an international trial of heparin thromboprophylaxis. We encourage research coordinators to comply with their own local requirements for informed consent, which may vary by jurisdiction within countries and across countries. We advocate practicing approaches to informed consent, and establishing or engaging in research networks that encourage sharing tips with colleagues. We hope that this third-phase interpretation of the process of informed consent from SDMs may help to improve the integrity of the informed consent process, minimise SDM decisional burden, and maximise timely enrolment of eligible patients into clinical studies. Further research on the impact of these strategies to achieve these aims is warranted.

Acknowledgements

We are grateful to the Canadian Critical Care Trials Group, the Australian and New Zealand Intensive Care Society Clinical Trials Group, and all participating centres for their collaboration on PROTECT. This report was prepared by North American PROTECT Research Coordinators attending trial meetings. We thank the following attendees for their thoughtful input: Nicole Marten, Nicole Marinoff, Suzie Logie, Kym Weibe, Kerri Porretta, Lisa Julien, Barbara Smithson, Christine Wynne, Anders Foss, Paulina Farias, Marie-Claude Ferland and Sandra Proulx. This work was funded by the St Joseph's Research Foundation. OM Smith is supported by a Doctoral Research Award from the Canadian Institutes of Health Research. D. Cook is a Research Chair of the Canadian Institutes for Health Research.

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