Evaluation of Informed Consent Documents used in Critical Care Trials

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Abstract

The literature suggests that informed consent documents (ICDs) are not well understood by research participants. The patient decision aid model may suggest improvements for the informed consent process, particularly in the critical care setting (ICU) because of patient capacity issues. Our goal was to evaluate the extent to which existing ICDs used in ICU research adhere to standards and recommendations for high quality informed consent. Eighteen items from recommendations specific to ICU trials were added to a previously developed ICD evaluation tool. A sample of ICU trials was identified from clinicaltrials.gov database and the investigators contacted for their trial ICD.

Conformity to the recommendations was variable. Some information are found routinely in consent documents for critical care research and some are not. Efforts should aim to establish tools for measuring decision quality in the ICU with the goal of facilitating and helping patients and surrogates work through trial participation decisions.
Acknowledgement

This work could not have been completed without the guidance of my supervisors, help from friends and the support of my family.

My deepest gratitude to my supervisors, Dr Jamie Brehaut and Dr. Lauralyn McIntyre. You provided a great atmosphere within which to do this research. Your continuous guidance, suggestions, questions, understanding and patience have been exceptional throughout this journey. Thank you!

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<tr>
<td>AAPOR</td>
<td>American Association for Public Opinion Research</td>
</tr>
<tr>
<td>BC</td>
<td>British Columbia</td>
</tr>
<tr>
<td>CBC</td>
<td>Canadian Broadcasting Corporation</td>
</tr>
<tr>
<td>CFR</td>
<td>US Code of Federal regulations</td>
</tr>
<tr>
<td>CIHR</td>
<td>Canadian Institutes of Health Research</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Council for International Organizations of Medical Sciences</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>ICD</td>
<td>Informed Consent Document</td>
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<tr>
<td>ICMJE</td>
<td>International Committee of Medical Journal Editors</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit/critical care setting</td>
</tr>
<tr>
<td>IPDAS</td>
<td>International Patient Decision Aid Standards</td>
</tr>
<tr>
<td>IPDASi</td>
<td>International Patient Decision Aid Standards Instrument</td>
</tr>
<tr>
<td>LAR</td>
<td>Legally Authorized Representative</td>
</tr>
<tr>
<td>N/A</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>NBAC</td>
<td>National Bioethics Advisory Committee</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NSERC</td>
<td>Natural Sciences and Engineering Research Council of Canada</td>
</tr>
<tr>
<td>OHSN-REB</td>
<td>Ottawa Health Science Network Research Ethics Board</td>
</tr>
<tr>
<td>PIPEDA</td>
<td>Personal Information Protection and Electronic Documents Act</td>
</tr>
<tr>
<td>PP/PPT</td>
<td>Potential Participant</td>
</tr>
<tr>
<td>PTSD</td>
<td>Post-Traumatic Stress Disorder</td>
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<tr>
<td>REB</td>
<td>Research Ethics Boards</td>
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<tr>
<td>SDM</td>
<td>Surrogate Decision Maker</td>
</tr>
<tr>
<td>SPIRIT</td>
<td>Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial</td>
</tr>
<tr>
<td>SSHRC</td>
<td>Social Sciences and Humanities Research Council</td>
</tr>
<tr>
<td>TCPS</td>
<td>Tri-Council Policy Statement</td>
</tr>
<tr>
<td>TRALI</td>
<td>Transfusion Related Acute Lung Injury</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<td>WMA</td>
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INTRODUCTION

Ethical principles of health research inform how researchers account to the public with respect to funding, conduct of the research, adherence to applicable laws and welfare of research participants. Guidance around ethical conduct of research date back to the Hippocratic Oath (which, though not specifically about research, could be interpreted to be relevant to it), when medical practitioners are to ‘use methods of treatment that are beneficial, avoid mischievous activity’ and to ‘give no deadly medicine’.

Research is different from medical care. Medical care is individualized for the optimal care of a patient; it is designed to benefit the individual patient. In contrast, research is designed primarily to test a hypothesis about an intervention using scientific methods. The care of a research participant is thus dictated by a protocol administered by a research investigator. Even with participants in a given research study, different levels of care may be administered, depending on the group they are randomized to: different monitoring, different treatments (unproven intervention, conventional intervention or placebo) or different doses of the same therapy. The knowledge gained from research may help to improve medical practice, but is often primarily to the benefit of future patients, not the research participants themselves. More commonly than is the case with medical care, risk(s) and side effect(s) associated with a research intervention may not always be known or fully understood. Any associated risk(s) to participants must therefore be carefully weighed and managed.
Research investigators need to be responsible for the welfare of their participants, in order to maintain public trust in their work. Failure to conduct research ethically has far reaching consequences, often leading to major legislative changes. For example, in what has commonly become known as the Doctor’s Trial, twenty Nazi-sponsored doctors stood trial for medical experiments conducted on prisoners (causing disability, disfigurement and death, among others) in their concentration camps without the prisoners’ consent. The doctors were tried for murder and torture by the international military tribunal at Nuremberg in 1946. The experience gave rise to The Nuremberg Code, the first international blueprint for ethical conduct of research involving human beings. To date, controversy exists as to whether the data and results from these experiments should be used in current scientific queries because of the manner in which the experiments were conducted.

A second example of ethical research conduct failure occurred between 1932 and 1972, when the US Public Health Service conducted the Tuskegee Syphilis study on African-American sharecroppers in Macon County, Alabama. These men, who had contracted syphilis prior to enrolment, were deceived about the purpose of the trial, and were purposefully left untreated even after penicillin became available as an effective cure for the disease. The National Research Act of 1974, which established the National Commission for the Protection of Human Subjects in Biomedical and Behavioural Research (and subsequently the Belmont Report in 1978, discussed below), was passed after this study became public.
From the late 1950s to the early 1960s, thalidomide was commonly prescribed to expectant mothers to alleviate nausea. Having only been previously tested on rodents, the drug was found to have caused birth defects to more than 10,000 babies within this period, in Canada, Japan, Australia and US. The Kefauver-Harris Bill in the US was born out of this tragedy, requiring drug manufacturers to keep records of any adverse events, safety and effectiveness associated with a drug, through well conducted trials 12-14.

Recently, between 2010 and 2012, personal health data of some British Columbia (BC) residents collected by the Ministry of Health, were compromised. Information on their lifestyle, physical and mental health was shared with unauthorised 3rd party entities. More than 38,000 individuals were affected and had to be notified. In its investigations of the breach, the office of the BC Privacy Commissioner noted the “indirect harm of loss of assurance and public trust arising from the unauthorized disclosures” 15-17. The office released the Accountable Privacy Management in BC’s Public Sector document, to guide entities in implementing privacy programs that comply with Freedom of Information and Protection of Privacy Act of British Columbia.

Research that went beyond what was publicly acceptable lead to wide scale policy and legal changes. Research investigators need to be mindful of these as they take responsibility for the welfare of their participants, without whom their work cannot be performed. When research investigators conduct quality research with integrity, balance the interest of participants with that of the society’s need to improve care, and avoid ethical breaches, public support and trust in research is maintained.
Published Directives on the Ethical Conduct of Medical Research

While guidance around clinical care dates back to the Hippocratic Oath, similar guidance around medical research is a modern phenomenon. In the 1920s, Claude Bernard was the first to publish the notion that individual patient care cannot be sacrificed in the cause of medical science: ‘never performing on man an experiment which might be harmful to him in any extent even though the results might be highly advantageous to science’.

Two decades later, following the Nuremberg Doctor’s Trial, ten guiding principles (APPENDIX I) for the conduct of medical research were recommended. These 10 principles have become widely accepted, and are thought to embody many of the core concepts around ensuring that the rights of individuals who participate in research are not violated. The first and arguably most important of these principles is the voluntary consent of research participants. That researchers acquire the ‘informed, voluntary, competent and understanding consent’ of research participants is the basis and focus of the modern informed consent process.

The Nuremberg code, while a good start, is not very detailed. Subsequent documents by various health organizations (such as the World Health Organization-WHO, the World Medical Association-WMA and the US Department of Health, Education and Welfare) have used it as a blueprint to specify the principles for the ethical conduct of research, and specifically informed consent, more completely.

The WHO broadened the code in establishing the Council for International Organizations of Medical Sciences (CIOMS) in 1949. The council, made up of various
national and international biomedical research bodies, explored guidelines to govern and facilitate international biomedical research. Their guidelines for obtaining consent from research participants came out in 1982, with subsequent revisions in 1993 and 2002.

The WMA, at its 18th assembly in 1964, issued the Declaration of Helsinki. It expanded on the Nuremburg code by highlighting the difference between medical research and medical care, requiring its members to seek consent from research participants for what is commonly referred to as non-therapeutic research\textsuperscript{20,21}. Some research activities (for example, drawing blood, skin tissue donation) are conducted to gain insights into and understand a health condition in order to develop procedures and or treatments for future patients with similar conditions. Such activities, considered non-therapeutic, require consent from recruited participant, who may not benefit directly from research involvement.

The National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research established in 1974 by the US Department of Health, Education and Welfare, expanded on the notion of a participant’s capacity to consent. A research participant whose capacity was compromised needed additional protection. The work of the commission resulted in the publication of the Belmont Report issued in 1978\textsuperscript{22}.

The Belmont Report set out three principles for ethical research conduct:

1. Respect for persons: research participants should be treated as autonomous beings (capable of making decisions and acting on those decisions). Persons with diminished
autonomy should be protected. Respect for persons ensures that research participants are given the opportunity to decide and choose what happens to them in the research they are involved in.

2. **Beneficence:** research should maximize benefit(s) to participants while minimizing any possible harm(s).

3. **Justice:** research burdens and benefits must be shared among those who partake of it- risks of research must be weighed with its proposed benefits.

The principles discussed above are enshrined in the Tri-Council Agency of Canada research guidelines. Comprising the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Social Sciences and Humanities Research Council (SSHRC), the agency is responsible for ensuring responsible conduct of health research in Canada. It requires researchers to conduct their activities in an ethically responsible manner, protecting research participants while complying with all applicable laws/regulations. Funded institutions are required to set up research ethics boards (REBs) to oversee research activities and ensure compliance with ethical principles outlined in its Tri- Council Policy Statement (TCPS). An REB must review the ‘ethical acceptability’ of each proposed research study to ensure its respect for voluntary and informed consent, benefit(s) outweigh any potential risk(s), and its respect for privacy and confidentiality of research participants information while complying with any applicable regulatory/legal requirements concerning privacy and confidentiality. The TCPS views informed consent
as a “dialogue, information sharing..... through which prospective participants choose to participate in research involving themselves” (Article 2.1(d)).

Informed Consent Documents

Information sharing between researchers and participants is a process with both an in-person/conversational component and a more formal documentation component usually referred to as the informed consent document (ICD). The process involves identifying a prospective participant, explaining the benefits, risks and discomforts and providing him/her with the consent document associated with the trial. Procedures and interventions used in the trial, as well as alternates to trial participation are also explained. The prospective participant is given the opportunity to ask questions and seek clarification as they think about trial participation. Once a prospective participant agrees to participation, the consent document is signed and copies retained by both parties.

The ICD encompasses the written documentation of what transpires between a researcher and a participant. Details about a study are conveyed to potential participants using the ICD, readily available to participants, for consultation on various valuable aspects of the research through the entire period of the study. Through the ICD, participants are intended to get a clear insight and understanding of what a study is about and what participation entails. Participants then choose freely whether to participate in the research, knowing the potential benefits/risks associated with their decision. The ICD serves as an informational document that contains elements that addresses informed consent, namely,
- Full disclosure- all the relevant information needed to make the decision. The study should be clearly identified as a research study and its purpose disclosed. It should also disclose what the study involves (protocol, randomization, allocation, the investigational intervention(s)), duration of the study, known risks, potential benefits, and how confidentiality of all collected data would be maintained

- Adequate understanding of the information presented. Information should be presented/ written in easy to understand language

- Voluntary participation- make a decision freely (without coercion) and voluntarily, to participate in a research study. The consent document should clearly state that participation is voluntary, provide any known alternatives to participation, and contact information for addressing any concerns or questions (of the research team, in case of illness, and for additional questions /clarifications)

- Competence- the capacity and capability to make the decision. Where the capacity to understand is lacking, measures are put in place to protect research participants.

The ICD is the chief mechanism by which detailed information gets disclosed to participants. Because of requirements for some elements in ICD (from various guidelines and regulations, some of which are provided in Table 1), extensive oversight by ethics board members, and increased public attention to research participant issues, more and more information is being disclosed in ICDs. Horng and colleagues (2002) note that emphasis and details about potential risks in consent documents takes more space than discussions about benefits. Disclosure of information has also increased with such
government regulations as The Personal Information Protection and Electronic Documents Act (PIPEDA) of 2000 in Canada. Under PIPEDA, organizations are expected to collect, use and disseminate health information in an appropriate manner and for reasonable purposes, with the consent of individuals whose information they hold. REBs require information on how participant health data is to be used, disseminated, protected and kept confidential, be presented to research participants through the ICD. Under the Food and Drug Act (C.R.C., c.870) of Health Canada, researchers must keep documentation on each trial participant, to protect prospective research participants while ensuring that the highest ethical standards are maintained by research investigators. As well, researchers are required to keep a record of the ICD signed by each participant enrolled in a trial. Consent documents have been used by courts of law as constituting legal duties between researchers and participants, an agreement between a researcher and a participant. The ICD has therefore been viewed by organizations as a legal document designed to protect the institution/sponsor against civil litigation; the legal aspects are accentuated at the expense of communicating to promote participant understanding.
Table 1: Evolution of Modern Informed Consent

<table>
<thead>
<tr>
<th>Regulation</th>
<th>Key Event</th>
<th>Resulting Influence on Informed consent</th>
<th>Some required details in ICD</th>
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| Nuremberg Code of 1947          | Doctor’s Trial after World War II (1935-1945)  | • Voluntary consent of research participants is essential  
• Favourable risks/benefits  
• Scientifically necessary study  
• Participant withdrawal without penalty |                                                  |
| CIOMS 1982                      | Guidelines to govern international biomedical research commissioned in 1949 | • Voluntary consent  
• Clarification of research and clinical care  
• Participant right to study data/results | • Duration of study  
• Risks/benefits  
• Steps to ensure data privacy |
| Declaration of Helsinki 1964    | World Medical Association’s 18th Assembly      | • Independent review of research involving humans                                                      | • Participant right to withdraw  
• Description and goal of study  
• Benefits/risks |
| Kefauver-Harris Bill of 1962    | Thalidomide scandal with pregnant women (late 50s-early 60s) | • Evaluation of safety and effectiveness of drugs before marketing  
• Documentation of adverse effects through well-conducted randomized control trials | • Identify study as research  
• Voluntary consent of research participants involved in drug testing  
• Description of risks and benefits |
| Belmont Report of 1979          | Tuskegee Syphilis Study (1932-197)             | • Established the principles of autonomy, beneficence and justice                                       | • Alternatives to participation  
• Opportunities for participants to ask questions about study |

**Concerns with the Informed Consent Document**

Evidence suggests that participant understanding of ICD content is often poor.\(^\text{32, 36-40}\) There are many documented examples of research participants not adequately understanding information presented in the consent document. In a tuberculosis trial, 70% of participants did not understand that participation was voluntary, and that they
could terminate participation at any time. Another survey of trial participants who had already given consent for various cancer studies showed that about 70% believed that “the treatment being researched in my clinical trial has been proven to be the best treatment for my type of cancer”. Dathatri (2014) and colleagues noted that trial participants in a cardiac procedure did not fully understand the risks, benefits and alternatives to participation presented in the ICD. For example, in a study to access consent forms used in oncology trials, it was noted that none of the 107 forms evaluated was written at or below the recommended grade 8 reading level. They also noted that the average ICD contained more than 10 pages; the increasing length of consent documents prevents some participants from reading them at all. ICDs are often lengthy documents, often written with technical and medical jargon, and in a language that is much higher than the recommended 8th grade reading levels. There is therefore the need to help participants understand information disclosed in the ICD.

Many interventions to improve participant understanding of consent documents have been studied. A systematic review of interventions to improve understanding of ICDs by Flory and Emmanuel (2004) showed that various approaches adopted to enhance informed consent have yielded limited improvements in participant understanding. Multimedia interventions such as supplemental videos, power point presentations and interactive computer programs in place of the consent document, yielded limited improvement in participant understanding of informed consent. Enhanced informed consent document interventions, including lowering the document’s readability to 6-7 grade reading levels, simplifying the language, using pictures and bolding text, did not appear to improve understanding. The review noted that extended discussions like
additional phone conversations and extra meetings of participants and research team members, seem to improve participant understanding of informed consent. This suggests that efforts to improve the consent process should focus on emphasising this face-to-face communication aspect over improvements to the informed consent document.

**Patient Decision Aids**

Patient decision aids have been suggested as a means to address research participant understanding of the informed consent document.\(^{41-43}\) Decision aids are decision support tools. They are designed to allow a user to work through a specific decision in a careful and deliberate way, and to explicitly weigh the risks and benefits of the different available decision options. They often do this through in-person facilitated discussions, providing information about the health condition together with available intervention, as well as risks, benefits and uncertainties of each intervention to users, assisting users in clarifying values they place on these risks and benefits, and guiding users in communicating these preferences to others involved in the decision.\(^{43, 44}\)

Decision aids were originally developed to help patients work through difficult treatment and screening decisions.\(^{45}\) Such decisions are difficult because there is no clear clinically correct option, and figuring out what a ‘good’ decision is can be tricky. In situations where there is known to be more than one equally effective option, or where there is no clear, clinically preferable treatment approach to the health condition, decisions about the course of action must be decided according to individual preferences of the patient; i.e. the decision ultimately depends on the individual’s needs, preferences and values, and is considered a ‘preference-sensitive’ decision.\(^{45, 46}\) Decision aids are
designed with these kinds of preference sensitive decisions in mind. They have been utilized extensively, with over 500 decision aids currently available for various health treatment and screening decisions.\textsuperscript{47}

In research, participants must make the often difficult decision about whether to participate in a study or not. A common reason participants provide for engaging in trials is to help others,\textsuperscript{48-50} a reason that could be considered to be based on values. Participants might therefore benefit from making such decisions with the help of a decision aid. The decision aid approach emphasises better understanding, careful presentation and enumeration of risks to help participants make trial participation decisions. A decision aid approach to informed consent might be worthwhile in improving the consent process as it focuses more on the decision making process (not just documentation), has internationally accepted standards for its development (IPDAS), as well as a method to objectively identify when a good decision has been made.\textsuperscript{51}

Decision aids have been extensively evaluated. A systematic review by Stacey et al. (2014) identified more than 100 studies where decision aids were compared to other information strategies such as information pamphlets and consultations.\textsuperscript{44} In all, decision aids were shown to improve a user’s knowledge of available options, and increase his/her accuracy in perception of risks compared to the other methods. Decision aid users were also more comfortable with their choices, compared to those who made their decision without a decision aid. Patients who made decisions with the help of a decision aid were more knowledgeable about the various aspects of their treatment, had better perceptions about risks/benefits of available interventions, felt more informed, and were more likely
to make decisions with their healthcare providers that matched their personal values. Thus decision aids not only provide information, but also provide guidance in making a decision based on a patient’s values and preferences, and promoting patient autonomy.\textsuperscript{43, 44, 51-53}

Decision aids have the advantage of being developed on a sound framework, providing clear concept of a ‘good decision’ where there is no clinically correct answer, and an approach to measure the quality of the decision\textsuperscript{54}. This framework, known as the International Patient Decision Aid Standards (IPDAS) was based on a rigorous evidence-based consensus process among 122 participating stakeholders (patients, researchers, practitioners and policy makers) from 14 different countries\textsuperscript{52, 55}. With the aim of establishing a set of quality criteria for decision aids, the IPDAS steering committee identified twelve core quality dimensions, and 12 working groups, each assigned to one quality dimension, were formed. Each group was tasked with establishing a definition for the quality dimension, a theoretical rationale for considering that dimension as important to decision aid quality, relevant evidence base for that dimension, as well as relevant theoretical and empirical references for that dimension. Stakeholders familiar with or aware of decision aids were then invited to rate these dimensions, resulting in a checklist consisting of 74 criteria in 11 domains pertaining to

- content (providing information about options, clarifying and expressing values, presenting probabilities, guiding/coaching),

- development process (systematic development process, disclosing conflicts of interest, using plain language, balanced presentation of options, basing information on up to date evidence, [use of patient stories and access to internet where applicable]) and
effectiveness (match between chosen option and values of a user)

These standards also describe how to have a good decision making process, while ultimately, encouraging good quality decision making.

The IPDAS collaboration later developed and validated an instrument, International Patient Decision Aid Standards Instrument (IPDASi), to quantitatively assess the quality of decision aids; its development is described by Elwyn and colleagues. The original 74 items on the checklist were refined to 47, based on their measurability and applicability to a wide variety of decision aids, and validation studies with different decision aids conducted. The IPDASi measures the quality of an individual decision aid using 47 items in 10 domains: information, probabilities, values, guidance, development, evidence, disclosure, plain language, evaluation and test. It represents an internationally accepted standard for tools designed to encourage a good decision making process.

Application of the decision aid approach to research participation decisions is new. Brehaut et al. (2012) were among the first to examine whether the decision aid approach could usefully inform issues of informed consent in research. They assessed the extent to which consent documents can serve as decision aids, and how consent documents conform to standards similar to those in the IPDASi. They hypothesised about using IPDASi standards to improve the informed consent process for research participation and evaluated a random sample of existing consent documents against the IPDASi standards. These documents failed to meet a range of IPDASi criteria, suggesting that they may be sub-optimal in helping patients make good decisions. Wallace and
colleagues (2006) reported on using a decision aid approach to boost participant accrual in the SPIRIT trial. Prostate cancer patients, who were equally suitable for brachytherapy and surgery, were introduced to the idea of being randomized to receive either as another treatment option. In other words, three options were presented to patients; choose brachytherapy, choose surgery, or allow researchers to choose either option through randomization. A video approach to consent yielded no participants, but a face-to-face consultation, together with the video, resulted in 34 participants agreeing to be randomized. Jurascova (2007) reported using a decision aid approach to informed consent for post-menopausal women at high risk of developing breast cancer. Though consent in this scenario was hypothetical, 90% of the women who compared the decision aid to the standard information booklet would have agreed to research participation. More recently, a decision aid approach to consent is being considered for palliative care patients in Switzerland. Use of decision aid approach to research participation decisions is new, but is expanding.

The Critical Care Environment

The intensive care setting presents particular challenges with respect to informed consent and decision making. Patients in intensive care are critically ill; in some sort of medical crisis, usually as a result of an after surgery procedure, severe illness and or serious accident, and require constant medical attention and the support of specialized equipment. Delirium, though not the primary reason for admission to the intensive care unit (ICU) is often present, and patients are at risk of single or multiple organ system failure as a result of their underlying injury/condition. Medical conditions can also
worsen rapidly without warning, incapacitating an otherwise conscious and alert patient.\textsuperscript{61-63} Patients are therefore cared for and managed by a multidisciplinary team of specialists (physicians, nurses, respiratory therapists, nutritionists and physiotherapists, among others) who aim to find and use lifesaving interventions for patients who might otherwise die under existing therapies.\textsuperscript{64}

Critical illness is associated with significant mortality, morbidity and costs. Globally, mortality in the ICU is estimated to be between 8-18\%.\textsuperscript{65} In the United Kingdom, about 140,000 patients are admitted to the ICU each year, 50,000 of whom die within a year.\textsuperscript{66} One in 5 deaths in the US occur in the critical care setting, and the annual cost is estimated to be 180 billion dollars.\textsuperscript{67,68} For patients who survive a critical illness, physical and psychological complications have been reported\textsuperscript{69,70}. The in-hospital cost of survival for a general ICU patient has been estimated at $282,618 per year in the US.\textsuperscript{61,71} More than 50\% of ICU resources are utilized by patients 65 years or older.\textsuperscript{72} With this population expected to increase in the coming decades (in part due to aging baby boomers), critical care expenditure is projected to increase and research is needed to inform allocation of resources accordingly.

Critically ill adults are a vulnerable population, lacking “sufficient power, strength, or other needed attributes to protect their own interests”.\textsuperscript{73} From an ethical perspective, this has specific implications for their protection. Additional safeguards (e.g. special monitoring, additional REB consultations, and therapeutic or minimal risk procedures) must be put in place to ensure that vulnerable participants are treated fairly, justly and respectfully when they are involved in research activities.\textsuperscript{23,73}
Research in the critically ill is essential, as it is important that this vulnerable population receive the benefits to be derived from research. The principle of justice (from the Belmont report, and considered a key component for ethical research conduct) makes explicit this notion that critically ill patients should be involved in research. Exclusion implies that such patients may be denied access to new potentially life-saving therapies, and or given therapies based on poor evidence because the therapy was not originally intended for this patient population. When there is no specific treatment for a condition, (e.g. acute kidney injury), or where no effective treatment is available, (e.g. critical illness myopathy), research is needed to establish effective agents for future patients and their families. Research in the critically ill is not only necessary, but also needed to improve the effectiveness and safety of existing therapies, and ultimately, to optimize the care of critically ill patients.

**Challenges in ICU Research**

Protocol implementation and obtaining consent have been noted as major barriers to research in critical care. To control for co-interventions and attain high internal validity, complex protocols are often employed in this setting. For example, delirium management requires the collective input of physicians, nurses, physiotherapists and pharmacists. Any research on delirium must bear this in mind and consult the needed disciplinary experts in order to design and implement an ICU trial that would effectively address the objectives of the trial. This might result in a complex protocol, and communicating such protocols to severely ill patients may be difficult or impossible to do.
Narrow time windows within which a therapeutic/investigational agent must be administered also add to the difficulty of obtaining consent in this setting. Some therapies in the ICU (for example, thrombolytic therapy for acute myocardial infarction) need to be administered in a timely manner to optimize benefits to a patient. This time includes time within which to locate a surrogate decision maker to make participation decisions for incapacitated patients. As an example, if an intervention needs to be administered within a 24 hour period, and a surrogate is identified 14 hours after the fact, the time is effectively reduced to 10 hours (within which to explain the trial to a surrogate, obtain consent, enrol the patient and administer the intervention).

Most research conducted in the ICU requires consent from legally authorized representatives (LAR) or surrogate decision makers- SDMs. Patients who are critically ill, however, are not able to understand the information presented, easily communicate their wishes, or make decisions, adding to the challenges of conducting research in the ICU. Wendler et al. (2011) note that about 95% of adults who are critically ill cannot make decisions for themselves. In a prospective observational study conducted in Canadian ICUs, Burns et al. (2013) observed that less than 10% of critically ill adult patients were able to provide consent for themselves.

Health Canada identifies the LAR as ‘the legal guardian, or any individual with power of attorney who is authorized to consent on behalf of a prospective participant’. The LAR is usually identified in advance, in a written directive (legal document detailing a person’s designations/wishes/preferences about their care in case the unexpected happens and they are unable to communicate them personally), before a person is
incapacitated. Surrogates are individuals who can make decisions on behalf of an incapacitated person, particularly when there is no LAR.  

**Surrogate Decision Making in the Research Context**

While the Nuremberg code is silent on third party authorization for human research, the 1964 Declaration of Helsinki notes that informed consent can be sought from a legal guardian for research participants who are legally incapacitated. The Belmont report introduced the notion of surrogate consent for social research that affects an entire community, giving such responsibility to a local/state government representative(s). The Tri-Council Policy Statement recognizes the need for surrogate consent where the research does not ‘expose the participants to more than minimal risk’. It also makes provisions for a waiver of consent to research participation in personal medical emergencies. These criteria are 1) a participant is incapacitated, and the condition requires immediate treatment, 2) the existing standard of care is ineffective, and there is a possible direct benefit to the individual, 3) the risk involved is no greater than that with the existing care, or justified by the expected direct benefit, 4) the participant does not have an advanced directive, and a third party consent cannot be obtained in time. These provisions, however, do not extend to consent situations in the ICU where a potential participant may lack capacity, but is not in a crisis.

The practice of asking surrogates to make decisions for incapacitated patients is common in legal and medical circles, particularly after the 1990 Patient Self Determination Act in the US. Surrogacy is an extension of an adult patient’s autonomy, and a mechanism to protect patients with diminished autonomy who do not
have advanced written directives. Surrogates normally make decisions based on what they believe the patient would have made had he/she been able to (substituted judgement) and or make decisions based on what is in the best interest of the patient. 76, 93, 94

Introduction of surrogates brings additional complexity into the discussion around informed consent. It is not always known who can act as a surrogate. In Canada, no federal identification of surrogates exists, but different provinces have ways of identifying surrogate decision makers (SDMs) where an advance directive of a prospective participant does not exist. In Ontario for example, a spouse, child, parent, brother/sister or other relative (in order of importance) may consent in lieu of an LAR. 95 Such individuals can consent to treatment on another person’s behalf, though it is unclear if that consent extends to research enrolment.

Another issue is the extent to which surrogates know participants’ desire(s) and preference(s). Surrogates do not always know their loved ones preferences, and therefore do not accurately predict patients’ desires for treatment or to participate in research. Shalowitz (2006), in a systematic review of how accurately surrogates predict patients’ treatment preferences, noted (after analysing more than 19,000 patient-surrogate pair responses to hypothetical trial scenarios) that in a third (32%) of situations, surrogates did not accurately predict a patient’s end of life treatment preferences. 96 Coppolino and colleagues (2001) provided cardiac surgery patients and their designated surrogates with previously conducted study protocols. In later face to face interviews with the patient surrogate pairs, they observed that approximately 16-20% of surrogates would enrol participants who would have declined research participation.93 Ciroldi et al. (2007), in a
prospective multicentre trial involving 100 patient/surrogate pairs given hypothetical study protocols, observed a 32% rate of discrepancy between patients and their surrogates; 11% of patients would have been enrolled against their wishes. These rates increased when the research involved greater than minimal risk. 97 Newman (2012) noted a 46% discrepancy between patients desire to enrol in a hypothetical research and their surrogates’ decisions. 98

A third issue is that surrogates themselves might not understand information pertaining to their loved one’s condition in the ICU.99-102 Of 76 designated surrogates, 20% did not understand their loved one’s diagnosis (primary organ involved in the disease process), 43% did not understand their loved one’s prognosis (whether their loved one was expected to survive or not) and 40% did not understand their loved one’s treatment (knowledge of at least one of the 10 major treatments used). 99 It has also been noted that surrogates are often stressed about making decisions for their loved ones. 99-102 Azoulay et al. (2005) noted that about 82% of surrogates were at risk of post-traumatic stress disorder, PTSD, 90 days after patient death/discharge from the ICU. Doubt, unease, regret and guilt have all been reported to be associated with surrogates making decisions for loved ones.87 Decision makers in the ICU, be they patients or surrogates need help in making these complex trial participation decisions.

**Summary**

The evolution of informed consent for research participation suggests that current standards of consent were not made with the critical care setting in mind. The Society of Critical Care Medicine, established in 1970, was still in its infancy when the National
Commission for the Protection of Human Subjects of Biomedical and Behavioural Research commissioned the Belmont Report in 1974. Limited understanding of consent documents may be even more pronounced in the intensive care setting, where patient capacity is compromised and surrogates are likely to be in distress. In addition, many of the recommendations for informed consent in the ICU are relatively recent, and their rate of implementation is not known. Decision aids have been shown to improve a user’s knowledge of an intervention, improve users’ satisfaction with their decision, and also help users have a more realistic expectation of outcomes.\textsuperscript{54, 103} These may be particularly important in the ICU research context, where the right information needs to get to participants and or surrogates in an efficient manner, while still upholding the ethical principles of clinical research. To our knowledge, no interventional studies conducted with critically ill participants have used the patient decision aid approach to informed consent, and the evaluation by Brehaut and colleagues excluded trials in critical care settings as well as trials involving proxy consent.\textsuperscript{54} A decision aid approach to consent in the ICU (informed by modern recommendations for informed consent in the ICU gathered during this work) might be the way forward in helping critically ill patients and their surrogates as they make decisions about research participation.

**Research Question and Thesis Objectives**

How well do existing informed consent documents used in critical care research adhere to recommendations for helping patients (and/or surrogates) through tough trial participation decisions?
The extent to which existing consent documents used in adult ICU research adhere to standards and recommendations for informed consent and decision making will be evaluated. In particular, this work will

- Assess how well consent documents from ICU research adhere to standards of informed consent taken from existing informed consent guidelines.

- Assess how well ICU consent documents adhere to standards for encouraging high quality decision making recommended by the shared decision making and decision aids literature.

- Assess how these ICDs from ICU research adhere to recommendations made by the ICU research community about obtaining consent in this especially challenging setting.
METHODS

This project was reviewed by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) prior to data collection.

Study Design

The design of this project involves three major components. A search on Medline was performed to find recommendations for informed consent documents used in critical care. A search was also performed on clinicaltrials.gov for trials conducted with critically ill patients. We then sent out a survey to critical care study investigators, requesting the actual consent documents used in their trials.

This work is an extension of work originally published by Brehaut et al. (2012). They obtained a broad sample of 139 informed consent documents through email contact of principal investigators of randomized controlled trials registered with clinicaltrials.gov. They assessed how these documents conformed to standards for supporting decision making using an evaluation tool comprised of 59 items. The evaluation tool had two sections. The first part was developed based on recommendations from the International Patient Decision Aid Standards Instrument-IPDASi, to assess the extent to which the informed consent document created the conditions for good quality decision making (e.g. describing the health condition, providing information on probability of intervention advantages/disadvantages, providing clear citations to the scientific evidence used). The second part was developed based on recommendations and guidelines specific to informed consent documents (e.g. stating rational for the study,
describing all procedures, stating that participation is voluntary and participants can withdraw at any time).

The original project excluded consent in the critically ill and proxy decision makers. In the critically ill, an intervention is administered to a severely ill patient who may not necessarily be the one giving consent for research participation. Thus, there might be a need for third party consent, and a patient must be given the opportunity to revisit consent when they are able to, in deference to the patient’s autonomy. The consent document used in critical care trials, therefore has to address different issues than the more general informed consent documents used in the original project. 54

Guided by Brehaut’s method,54 also employed by Resnik104 in examining consent documents used in oncology trials, this thesis examined consent documents used in critical care research. In particular, three sets of issues were addressed: 1) the general principles of informed consent as addressed in the previous work, 2) standards for encouraging high quality decision making taken from the shared decision making literature, also addressed previously, and 3) recommendations made specifically for consent in the critically ill population and developed de novo as part of this thesis.

Recommendations for consent in the critically ill population were sought and used to develop a series of items. A sample of consent documents from critical care clinical trials, where most decisions involve a surrogate/proxy decision maker were examined. Trials conducted with critically ill patients were identified from the clinicaltrials.gov website, and contact information for the PI extracted. The principal investigator of each trial was then contacted by email and asked to provide an example of the actual consent
document used for the trial. These documents were then evaluated based on the three sets of items. In the following sections putting together our evaluation instrument, obtaining consent documents and analysing these documents are addressed.

**Evaluation Instrument**

An evaluation instrument to assess consent documents used in critical care trials was developed. The evaluation tool comprised 77 items in 3 parts. Brehaut et al. (2012) designed the first two parts, which are summarised in this work. The third part was developed de novo and the development process will be described in detail below.

**Part 1- Decision Quality Standards**

Part 1 of this instrument contained 32 items on measuring decision quality taken from the International Patient Decision Aid Standards instrument (IPDASi). A complete description of their development is given elsewhere. To summarise, items from the IPDASi (47 items), developed by Elwyn and colleagues, were reviewed by Brehaut and colleagues for their applicability to informed consent. Items from the domains on development, evaluation, test and plain language in the original IPDASi were excluded. Items on plain language were excluded because they coincided with those from guidelines for consent documents. Those from the domains on development, evaluation and test were dropped because they did not apply to informed consent. Items were included after expert deliberation and subsequent consensus on their relevance to informed consent. The final set of 32 items were organised into 6 descriptive categories. These included
• 8 items about presenting outcome probabilities; e.g. specifying probabilities in natural frequencies, specifying period within which probability applies, using the same denominator in presenting probability information.

• 2 items about clarifying and expressing values; e.g. describing clearly how an intervention impacts a participant’s life, and asking participants (and surrogates by extension) to think about how these matter to them.

• 2 items on structured guidance; e.g. describing specific decision making steps, including a tool to facilitate further discussions with study personnel.

• 4 items about using evidence; e.g. citing scientific evidence, describing the quality of the scientific evidence.

• 12 items on information about options; e.g. describing the health condition, describing advantages and disadvantages of both participation and non-participation in a consistent manner.

• 4 items about disclosure and transparency; e.g. providing information on funding sources credentials and contact information for research personnel.

**Part 2 - General Informed Consent Guidelines**

Part 2 of the evaluation instrument developed by Brehaut and colleagues\(^5^4\) consists of 27 items, derived from consent form guidelines and regulations from Canada, UK, and the US, specifically key documents from major funding agencies, and select research ethics board guidance\(^1^0^5\). These documents included the Tri-Council Policy, Health Canada Good Clinical Practice, US Code of Federal Regulations (45 CFR 46.116), Food and Drug Administration (FDA; 21 CFR 50.20-27) guidelines, the 2009 recommendations from the US National Cancer Institute, the Hamilton Integrated Research Ethics Board consent checklist (March 2008 version), and the Ottawa Health Science Network Research Ethics Board sample consent form (January 2009 version).
These documents were examined for recommendations that were applicable to a wide range of health conditions. For example, disease-specific recommendations and recommendations for compensation (in case of injury) were excluded. After an iterative process of design and pilot testing, Brehaut and colleagues settled on 27 items that were deemed to be applicable to a wide range of clinical disciplines and studies. These were then organized descriptively into 4 categories:

- 10 items on key regulatory statements; e.g. providing information on the nature of the research, study procedures, voluntariness of participation.
- 5 items on ethical issues; e.g. describing any effect(s) of participation on foetus (for expectant participants), describing how personal health information is protected.
- 5 items on study design - e.g. explaining randomization, providing information on study duration and number of participants.
- 7 items on formatting and style; e.g. presenting information in clear understandable language, avoiding spelling and grammatical errors.

Part 3: ICU-specific Recommendations for Informed Consent Documents

Below, efforts to assemble and itemize a new set of recommendations for informed consent documents around issues specific to critical care research are outlined.

Search for Sources of ICU-specific Recommendations for ICDs

A systematic search of the literature was done to find guidelines and recommendations for research investigators and ethics boards dealing with protocols that involve vulnerable populations, including intensive care patients. Documents were
eligible for inclusion if they specified guidelines and or recommendation(s) for some aspect of the informed consent process used in adult critical care trials.

The search was conducted in Medline database on March 12, 2014. The search terms used, based on keywords and Medical Subject Headings (MeSH), and with the help of a research librarian, are listed in APPENDIX II. Of the total citations retrieved, duplicates were removed and limits to language applied to obtain English language articles only. As well, citations pertaining to paediatric/adolescent/child were excluded. The remaining citations, including those with unclear titles, were retained.

Title and abstract screening were performed, followed by full text data extraction. Two reviewers (JB, PA) searched through the title and abstract citations. Articles that were primarily reviews, commentaries, regulations or recommendations for specific groups or diseases but not critical illness, were excluded. For those citations retained, two reviewers (JB, PA) obtained the full text of the article and considered whether any recommendation(s) or guideline(s) for the informed consent document were made, with respect to research done in the critically ill population. Articles that provided guidelines and or recommendations for informed consent in vulnerable populations and the critical care setting, in particular, were considered relevant. A hand search was made of the references of the retained documents to find any other documents with recommendations/guidelines for consent in the critically ill.

**Itemizing Recommendations for ICU-specific Recommendations for ICDs**

Once the core sources were identified, two reviewers searched through them for recommendations about information to include in the informed consent document,
recommendations that were thought to be unique to or particularly important for studies conducted in the ICU. Some texts were lifted directly from the recommendations, and others were rephrased for clarity. The individual recommendations then went through a process of itemization. Three reviewers (JB, LM, and PA) examined the recommendations. JB has experience and expertise in evaluating cognitive theories relevant to health care decision support, with extensive research work and publications on informed consent. In addition to surveys and observational studies, LM, an ICU physician, also conducts clinical trials with critically ill patients. PA is a graduate trainee. Similar ideas were combined into a single item. Recommendations that overlapped with those from consent and IPDAS items were excluded to avoid duplication and also because they were not specific to the ICU.

Some recommendations related to ICU-specific issues were excluded because they did not lend themselves to evaluation in the consent document. Thus, recommendations on capacity assessment and surrogate availability were excluded as items from our evaluation as they would not reasonably be expected to be included within the informed consent documents being evaluated. For example, it has been advocated that researchers formally evaluate participants’ capacity to consent before and during a trial for a more meaningful informed consent process.\textsuperscript{106-108} A patient’s capacity may become compromised as a result of their condition, administration of sedatives and or the presence of delirium. Whether a patient has the capacity to consent or not cannot be ascertained from examining the ICD. Another example is surrogate availability. It is not feasible to ascertain surrogate availability or otherwise from the informed consent
document since the consent document does not indicate how, or the time frame within which a surrogate was located.

With these items our hope was to capture how important ICU-specific elements of trial participation are laid out in ICDs for critically ill patients and their surrogates.

**Piloting the Items**

Six (6) consent documents used in prior critical care trials from the Ottawa Hospital were obtained to pilot-test the ICU-specific items with 4 reviewers (JB, KC, TH, PA). To maintain consistency with previous work, response categories ‘strongly agree’, ‘agree’, ‘disagree’ and ‘strongly disagree’ were employed. ‘Strongly agree’ was used when there was no reservation on the presence of the item in the ICD. ‘Agree’ was employed when the ICD complied with the item, but there was room for improvement. ‘Disagree’ was used when the ICD was unclear on an item or when there was considerable room for improvement. When an item was completely lacking, ‘strongly disagree’, was used. A ‘not applicable’ (NA) option was provided for some items. For example, items on randomization had N/A for trials that did not randomize participants. For a particular item, responses for rating, with anchors, would be similar to this:

- **SA** = clearly provide this information.
- **A** = fulfills the criterion, but there is room for improvement.
- **D** = does not fulfill the criterion, or unclear.
- **SD** = does NOT provide this information.
- **N/A** = document for patient only (if rating surrogate specific document)
Responses for each item were converted to a Likert-like scale (0=strongly disagree, 1=disagree, 2=agree, 3= strongly agree, 9= N/A) for analysis.

During piloting, four raters (JB, KC, TH, and PA) independently assessed and scored each consent document on items from all three parts of the evaluation instrument. Raters were trained on how to score each individual item. The training was conducted by trained raters of the two previously developed sets of items (JB and KC), to ensure consistency. All raters were provided with the same ICDs to score independently, before coming together to discuss ratings. In the case of IPDAS and general informed consent guideline items, specific examples from previously evaluated ICDs were drawn on during the training process when an item needed further clarification.

Two raters agreed on an item if there was no more than a one point difference between their ratings-

- Strongly agree/strongly agree- average score of 3;
- Strongly agree/agree- average score of 2.5;
- Agree/agree- average score of 2;
- Disagree/disagree- average score of 1;
- Disagree/strongly disagree- average score of 0.5;
- Strongly disagree/strongly disagree- average score of 0;
- NA/NA.
The average of the two ratings was taken as the final item score. Items that raters agreed were not applicable were not analyzed.

A difference of more than one point between reviewers on an item was considered a disagreement (strongly agree/disagree; strongly agree/strongly disagree; agree/strongly disagree N/A with any other rating). A rating of agree/disagree (2/1) was also considered a disagreement. Disagreements triggered consensus discussions. Discussions focused on achieving concordance and how item specific responses/anchors could be clarified and improved. The consensus score was taken as the final item score. Items where both reviewers agreed on a N/A score were not included in analyses.

From these discussions, some items were reworded for clarity and ease of coding and one item was split into two items. Similarly, a ‘not applicable’ category was added to rate surrogate (or patient) specific items. For example, when an ICD was intended for the patient only, an item on whether surrogates have discussed participation decisions with the patient was evaluated as ‘not applicable’. Newly worded items had to be judged to be reasonable, practical, evaluable and applicable to the ICU.

Identification and Selection of Consent Documents for Evaluation

Studies with critically ill participants registered with clinicaltrials.gov were identified and selected as potential sources of ICDs. Clinicaltrials.gov is a website of the US National Library of Medicine, a part of the National Institutes of Health (US Department of Health and Human Services). The site has been available since 2000 and is a database of ongoing and completed clinical trials using various interventions—drugs, devices and other biologics. Trials regulated by the FDA are required to be registered
with databases such as clinicaltrials.gov; the FDA Modernization Act of 1997 requires clinical trials (be they privately or publicly funded) for “serious or life threatening diseases and condition” to be registered in a publicly accessible data bank. 110 The International Committee of Medical Journal Editors (ICMJE) require that a trial be registered if it is to be considered for publication in any of its member journals 111. On June 20, 2013, the site had over 147,000 registered trials from over 180 countries. Each registered trial provides information on the condition under investigation, design, sponsors, date of registration and outcome measures, as well as any exclusion and inclusion criteria for participation. Contact information of the trial team coordinator/investigator and where the study is being conducted are also usually provided.

Inclusion and exclusion of studies were limited to fields within the database, and based on our selection criteria:

- Setting- trials conducted in an ICU facility, as well as trials with patients with health conditions typically presented in the ICU were considered (e.g. acute kidney injury, liver failure, stroke)
- Participants- intervention targeted at critically ill patients. Studies with interventions aimed specifically at surrogates in the ICU were excluded.
- Informed consent- the trial required consent from the participant and/ or a proxy. Trials that waived consent were excluded.
- Language of ICD- study conducted in an English and or French speaking population (based on country of recruitment). It is reasonably that the consent document would be in the French or English language.
• Time period from 2006- important documented recommendations around consent documents for critical care were published around 2004.\textsuperscript{80, 111, 112} We limited to studies that might reasonably have been expected to abide by the recommended standards.

• Phase 2 and phase 3 studies- phase 1 studies were excluded because they tend to be dose escalating trials usually done in healthy volunteers, and phase 4 studies were excluded because they are often post marketing surveillance to assess long term effects; both of these have different informed consent practices. Combined phase1/2, 2/3and phase 3/4 trials were considered.

• Non-Industry trials- studies were excluded if they were funded and conducted solely by industry. If a trial was collaboration between an institution and an industry, and PI contact information was provided, the trial was included. Concerns over inappropriate analysis and an effort to maintain competitive advantage, among others, make it difficult to obtain industry data;\textsuperscript{113} it might not be possible to obtain documents from industry within the time frame of this project.

• Trial Status- all trials, regardless of recruitment status (completed, recruiting, unknown, not yet recruiting, terminated) were considered. Studies with unknown status (unverified/not updated in 2 years) were included if their last known status was recruiting. For trials with terminated or withdrawn status, a study was included if it recruited any participant before being terminated or withdrawn. If no reason was given for the withdrawal/termination, the trial was included.

• Non-paediatric- our focus was on critically ill adults and the consent documents used in trials with this population. Children’s capacity for judgement and self-direction are still maturing, and parents generally act on their behalf. Parental permission, together with child assent, is usually required when children are involved in research\textsuperscript{23, 114}. This assent document might be a pared- down version of the adult consent document, which might not include all the information we’d
expect of an adult consent document. Trials with both adult and child participants were included.

To ensure as many studies as possible are captured, a basic search of the database was performed. A wide net was cast to try and capture as many trials as possible that were researching conditions expected to be conducted with the ICU population. The search terms “critical care OR intensive care OR critical illness” were used in the ‘search for studies’ field. The search was conducted on March 17th, 2014 in the clinicaltrial.gov database. Limits to age group (adults and seniors), trial phase (2 and/ or 3) and time of registration (First received 01/01/2006 or later) were applied. The resulting trials were selected and downloaded into an excel spreadsheet before further exclusions were made. Duplicates were removed based on the unique trial numbers provided to each trial by the database. Trials conducted in French and English speaking locations were selected. International multi-country trials were included if trials were conducted in an English/French speaking population.

The same definitions provided by clinicaltrials.gov to classify trial characteristics were employed. The database defines intervention as the ‘process or action’ under investigation in the trial. Four general categories are provided; drugs, devices, procedures and behavioural. For this work, drugs are substances that go directly into the body, by injection, ingestion, infusion or any other means. Giving blood and other biological components were classified under drugs. Mechanical and electrical equipments under study were classified as devices. Such devices include monitors, filters, and electrical stimulating devices. When a trial was focused on establishing a more efficient approach to improve outcomes, the intervention was considered a procedure. For example,
comparing early and late introduction of the same intervention to patients (physical therapy started on day one compared to therapy started at a later day), and alternating protocols (using mouthwash before breathing tube insertion compared to using mouthwash after tube insertion), were classified under procedures. Any intervention that did not fall under the first 3 was grouped under Behavioural. Such interventions included surveys, interviews and educational sessions.

Investigators describe the ‘disease or illness’ being studied as the condition, using MeSH terminology. The problem or situation that the study sought to address (treat, evaluate, control, improve, compare or monitor a condition) and to which the intervention was applied was considered. The place where the trial was being conducted, whether in the ICU (general, medical, surgical ward) or not (other hospital wards, clinics or in the community) was also considered in classifying conditions as within an ICU or outside the ICU. Conditions within the ICU were further grouped according to the major body systems:

- **Gastrointestinal/Metabolic System** - bowel movement, colonic perforation, gut bleeding, intrabdominal hypertension, pancreatic necrosis, bowel integrity, blood sugar control, hypoglycemia, hyperglycemia, enteral feeding, nutritional delivery, supplemental feeding, liver failure.

- **Cardiovascular/Circulatory System** - heart failure, heart surgery, high blood pressure, MI, shock, oxygen delivery, abdominal aortic aneurysm, circulatory function, hypovolemia.

- **Nervous/Neuromuscular System** - brain/head injury, subarachnoid haemorrhage, delirium, stroke, seizures, sedation, sleep, spinal cord injury, physiotherapy, exercise, intraventricular haemorrhage.
• Renal system - acute kidney failure, renal failure, kidney injury, haemodialysis,

• Respiratory system - acute lung injury, ARDS, endotracheal intubation, respiratory failure, transfusion related acute lung injury (TRALI), ventilator failure, lung disease.

• Sepsis/Infection - catheter related infection, hospital acquired infection, pneumonia, septic shock, fever, urinary tract infection, and ventilator associated infections.

Studies were coded into industry involved, government involved and others, with respect to funding sources. Trials with any industry involvement were classified under industry. Such trials included hospital/industry and government/industry collaborations. Trials with provincial, state or federal funding were classified under governmental. These include funding by the National Institute of Health NIH (USA), Canadian Institute for Health Research CIHR (Canada), National Health Service NHS (England), Fund for Scientific Research FSR (Belgium) and the National Health and Medical Research Council NHMRC (Australia/New Zealand). Trials funded by hospitals, universities and other interest groups (such as the critical care trials group) were classified under “Others”.

Studies were coded into early (Phase II and Phase 1/2 trials) and late (Phase III and phase 2/3 trials) phase trials. When a trial did not provide phase, it was categorized into either early or late phase after considering the intervention and the population to which the intervention was applied.
Sample Size

The aim was to obtain and assess 100 consent documents. Since our primary goal for this work is descriptive, this number of consent documents was considered large enough (considering timely consent document collection and evaluation as well as available resources), and is consistent with previous work. Other studies of consent forms have used similar sample size ranging between 92-139 documents.\textsuperscript{54, 104, 115} Informed by the 32.4\% response rate reported by Brehaut et al. (2012), a response rate of 25\% was conservatively estimated. Thus the target was to obtain a sample frame of 400 unique studies from the clinicaltrials.gov database, randomly selected from obtained search results.

Contacting prospective Principal Investigators and Obtaining Consent Documents

For each study, the principal investigator contact details (mainly name and email) were noted. If a trial provided no contact information on the PI but was published, the correspondence address from the publication was used. Failing that, a first author search in Pub Med and Google were conducted and the author correspondence email information used. If a PI had more than one registered trial, only one of his/her trials was included. For trials with more than one PI, the first listed PI was selected and, if no response was received, the next PI was contacted.

Requests to PIs for their consent documents were done in 2 stages. On April 14\textsuperscript{th} 2014, 76 PIs (20\% of our sample for whom valid emails had been obtained, randomly selected) were emailed and their consent document(s) requested. This initial run was to assess the feasibility of obtaining ICDs from PI, the time it took to obtain these ICDs and
the number of ICDs that would be in the French language. In particular, we needed to determine

- length of time it took to obtain ICDs
- resources needed to translate French documents into English
- clarity of email communication with PI (whether a draft, study material, etc., or actual ICD was received and any concerns raised by PI),

As well, any information that would suggest refining inclusion criteria of selected trials needed to be determined. The aim was to attain a 25% response rate within 4 weeks of contact with PI- approximately 20 ICDs, after which the remaining PIs will be contacted.

Email requests were sent in both English and French (Appendix III). A reminder email was sent two weeks after the first, on April 28th, 2014 (Appendix IV).

From this initial mail out, PIs from Switzerland (official languages of German, French, Romansh and Italian) for whom valid emails were obtained, were added to the sample of remaining PIs. The second batch of PIs was emailed on May 2nd, 2014 and their consent documents requested. Reminder emails were sent out on May 16th, 2014.

For emails that were undelivered, an alternate email for the PI was searched for and used to contact them again. After 2 bounced addresses, no further contact was made.

**Analyses**

Response rate was reported using the American Association for Public Opinion Research (AAPOR) guidelines. The AAPOR is an organization of professional researchers founded in 1947 that upholds a code of ethics and professional standards for survey researchers. AAPOR’s detailed method for calculating outcome rates for mail
surveys, with its accompanying Excel spreadsheet, was employed. The distribution of
language of ICD and trial phase (2, 3, combined), funding sources, type of intervention,
as well as health condition of interest was reported using percentages. Studies were also
summarised with percentages based on who was required to provide consent for research
participation (patient only, patient and or surrogate, surrogate only). Non-responder
analysis was also conducted.

The complete evaluation instrument consisting of parts 1, 2 and 3 described
above (pages 24-29) is presented in APPENDIX VII. Three raters (PA, TH and KC, all
trained in reviewing and rating consent documents) were involved in rating qualifying
consent documents received from trial investigators. Ratings were done using the same
strategy employed during the item piloting stage. PA rated all qualifying consent
documents. TH translated the French documents into English and rated them, together
with other English documents. KC rated the remaining English language consent
documents with PA. Each consent document was rated by two raters (PA/TH or PA/KC).
Final item score was the mean rating between 2 raters, or where there was a
disagreement, the consensus score. Not applicable items were not rated. Agreement
between the raters on each item was determined using Cohen’s Kappa with linear
weights, which tend to be more conservative, and less affected by the number of
categories. 117-119 Kappa also has clear established benchmarks that communicate the
strength of agreement between raters. 119-121 Percentages were used to describe how each
of the consent documents conformed (strongly agree, agree, disagree and strongly
disagree) to each individual item in our instrument. This enabled a detailed description of
the strengths and weaknesses of consent documents used in the critical care setting in
terms of general informed consent standards, ICU-specific standards and decision aid standards. The items were grouped into 3 parts described above: items on general informed consent guidelines, items measuring decision quality-IPDAS and items on ICU-specific recommendations. These helped in identifying ICDs that were of high quality and aid patients in their decisions on trial participation.
RESULTS

Our goal for this work was to evaluate the extent to which existing consent documents used in ICUs trials adhere to standards and recommendations for high quality informed consent and decision making. Section 1 of the results summarizes the key sources contributing ideas that led to items. Section 2 describes our process of extracting items from these sources, the iterative process leading to the final list and the final list of items. Section 3 describes our search for relevant clinical trials and response from study investigators. Sections 4 and 5 show non-responder analysis and descriptive analyses of included studies. Section 6 outlines agreement between raters and Section 7 describes adherence of these consent documents to the standards and recommendations for informed consent documents used in critical care clinical trials; details of item ratings for each of the 3 sets of items from the 3 parts of the evaluation instrument are provided.

Section 1: Summary of the Sources for ICU-specific Recommendations for Informed Consent Documents used in ICU Trials

The search for articles that provided guidelines and or recommendations for informed consent in vulnerable populations and the critical care setting, in particular yielded 10 such recommendations, is presented in Table 1 and Appendix V. The search on Medline yielded 927 articles, of which 763 abstracts were reviewed (after excluding duplicates, non-English articles and articles concerned with children). Commentaries and reviews on specific diseases and groups were excluded, leaving 21 articles with recommendations for informed consent in the ICU for which a full text reading was done. Of these, 7 articles with recommendations for the consent document used in ICU research
were retained. A hand search of the references of these 7 articles yielded 3 additional articles for a total of 10 articles with recommendations for the consent document used in ICU research. A brief description of the source articles and specific issues for ICU consent discussed is presented below.

Coppolino and Ackerson (2001), noting a high discrepancy between patient and surrogate preferences for medical research, recommended assessing the practice of surrogate consent for critical care research, and implementing strategies that allows for patients and their surrogates to openly discuss their views on critical care research enrolment. They made these recommendations after a cross sectional face to face (paired) interview with a 100 cardiac surgery patients and their surrogates to ascertain how accurately surrogates predict patients’ preference to research participation.

McRae and Weijer (2002) reviewed the ethics of conducting research with the critically ill and the laws that govern such work. They justified research in this area that uses non therapeutic interventions which aim to improve outcomes, and call for risk-benefit assessments in research protocols that involve this population. They proposed a framework to assess research risks, establishing thresholds that still allow conducting quality research.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Article</th>
<th>Title</th>
<th>Originating Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coppolino, M and Ackerson, L., 2001</td>
<td>Empirical-cross sectional</td>
<td>Do surrogate decision makers provide accurate consent for intensive care research? 93</td>
<td>USA</td>
</tr>
<tr>
<td>McRae, A. D. &amp; Weijer, C., 2002</td>
<td>Review</td>
<td>Lessons from everyday lives: a moral justification for acute care research 122</td>
<td>Canada</td>
</tr>
<tr>
<td>NBAC*, 2002</td>
<td>Consensus</td>
<td>Research involving persons with mental disorders that may affect decision making capacity 107</td>
<td>USA</td>
</tr>
<tr>
<td>Bigatello et al., 2003</td>
<td>Review</td>
<td>Ethical considerations for research in critically ill patients 94</td>
<td>USA</td>
</tr>
<tr>
<td>Alzheimer's Association, 2004</td>
<td>Consensus</td>
<td>Research consent for cognitively impaired adults: recommendations for institutional review boards and investigators 106</td>
<td>USA</td>
</tr>
<tr>
<td>Luce et al., 2004</td>
<td>Consensus</td>
<td>The ethical conduct of clinical research involving critically ill patients in the United States and Canada: principles and recommendations 71</td>
<td>USA</td>
</tr>
<tr>
<td>Silverman et al., 2005</td>
<td>Consensus</td>
<td>Recommendations for informed consent forms for critical care clinical trials 80</td>
<td>USA</td>
</tr>
<tr>
<td>Chenaud et al. 2007</td>
<td>Review</td>
<td>Research in critically ill patients: standards of informed consent 123</td>
<td>Switzerland</td>
</tr>
<tr>
<td>Burns et al., 2009</td>
<td>Review</td>
<td>The 'Consent to Research' paradigm in critical care: challenges and potential solutions 76</td>
<td>Canada</td>
</tr>
<tr>
<td>Silverman, H., 2011</td>
<td>Review</td>
<td>Protecting vulnerable research subjects in critical care trials: enhancing the informed consent process and recommendations for safeguards 108</td>
<td>USA</td>
</tr>
</tbody>
</table>

*NBAC- National Bioethics Advisory Commission
In an effort to bridge the gap that exists in protecting incapacitated research participants, and to provide ‘practical guidance’ to those working with them, the National Bioethics Advisory Commission drafted recommendations for research with the mentally incapacitated adult (with delirium, dementia and depression, among others). The commission, established to look into the welfare of research participants, comprised experts in the fields of law, medicine, psychology and ethics. Their recommendations came after a review of the relevant federal laws, and consultation with practicing clinicians. Guidelines for REBs and proxy consent were discussed. Among other things, they expounded on mechanisms of withdrawal of an enrollee by a surrogate should the need arise.  

Bigatello and colleagues (2003) reviewed the literature on regulations pertaining to research participants’ protection. They discussed the uniqueness of the critical care environment with regards to conducting quality research and the problem of asking surrogates for consent. They proposed different mechanisms for optimising informed consent to protect the welfare of critically ill patients enrolled in research in light of these regulations.  

The Alzheimer’s Association made recommendations for researchers and REBs working with adults with cognitive impairments (such as delirium) or those who might lose cognition in the course of a research (as may be the case with critically ill patients). The Medical and Scientific Advisory board of the association, in collaboration with the Attorney General’s office (Maryland State), select REB and the National Institutes of Health Clinical Center, drafted a consensus paper in an effort to operationalize the safeguards necessary for the protection of vulnerable research participants.
Recommendation for identifying a surrogate, capacity assessment and instructions to surrogates in the consent document were proposed. In response to calls to educate its members on ethical conduct of clinical research with the critically ill, the American Thoracic Society proposed a checklist approach to ensure that the design, implementation and monitoring of research done with this population is ethically sound. In collaboration with the National Institute of Health, and the National Heart, Lung and Blood Institute, experts in ethics, clinical investigations and patient advocacy explored many aspects of critical care research. They made specific recommendations for ICU research based on the principles that govern ethical clinical research in Canada and the US.

Following concerns from the Office for Human Research Protection about the trial of ventilator therapy in acute respiratory distress syndrome (ARDS), the Acute Respiratory Distress Syndrome Clinical Trials Network (ARDSNet) formed an ad hoc informed consent working group to look into consent in the critical care setting. This group used a consensus process to come up with recommendations and a template for ICD specific to the ICU. Recommendations for including death as a risk (when applicable) and regulatory status of an intervention, among others, in the consent document, are presented.

Chenaud et al. (2007) provided a review of the critically ill patient condition and obtaining consent from this population. They noted that current consent standards were not set up with the critically ill in mind. They suggested revisiting consent requirements and procedure for the critically ill to better respect their autonomy, while alleviating any
anxiety the request for consent might induce in patients and surrogates in this environment.  

Burns and colleagues (2009) expounded on the challenges faced by investigators conducting research in the ICU. They provided a review of the critical care environment, identifying a proxy for an incapacitated patient and the various methods of obtaining consent for research participation. They called for alternate consent models for this patient population.

Silverman (2011) looks at the issues of proxy consent and additional safeguard measures put in place to protect research participants in the ICU. A review of these safeguards, assessing participant capacity and obtaining consent (assent /re-consent when necessary) was presented. Safeguards for different risks, based on individual research protocols, were proposed.

Section 2: Summary of Items extracted from ICU-specific Recommendations for Informed Consent Documents

The 10 sources described above and summarized in Table 1 yielded 40 items (Appendix VI). As detailed in the Methods section under Itemizing recommendations for ICU-specific consent, items that overlapped with those from consent and IPDAS items were dropped, as were those on surrogate availability and patient capacity assessment. This left us with 18 items for studies conducted in the ICU. Three items were modified for inclusion in the final list of 18 items. Items 5 and 6 (ICD describes standard of care, ICD describes how each arm differs from standard of care) originated from the recommendation about describing the control arm in terms of usual care. Item 9
(ICD includes a statement about whether or not the intervention is expected to change/influence risk of death/survival) is not a direct recommendation for consent documents from the sources, but the authors underscore the importance of survival in the ICU environment. How this concept of survival was reflected in the consent document was explored.

The final list of 18 items are described below and summarized in Table 2.

**Item 1 - The ICD clearly indicates the time period within which the decision must be made.** The ICU is a fast paced environment, with rapidly changing health conditions as well as interventions that need to be administered often in short time frames if they are to be effective. A patient who meets the inclusion criteria for a study can become ineligible within a short period. Consent for research participation is thus often sought with important time constraints. The authors suggested educating the public on these ICU time limits, which can be communicated to patients/surrogates through the consent document 71, 76, 122. Though the authors did not frame this as something to be put in the consent document, we considered the ICD to be a way in which such communication could be made.
<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Source(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The ICD clearly indicates the time period within which the decision must be made</td>
<td>Burns et al., 2009; McRae and Weijer, 2002; Luce et al., 2004</td>
</tr>
<tr>
<td>2</td>
<td>The ICD avoids the use of treatment terminology to describe investigational components of the study</td>
<td>Silverman et al., 2005; AA, 2004</td>
</tr>
<tr>
<td>3</td>
<td>The ICD makes a clear distinction between therapeutic and non-therapeutic interventions</td>
<td>Luce et al., 2004; McRae and Weijer, 2002; AA, 2004; Chenaud et al., 2007; Bigatello et al., 2003</td>
</tr>
<tr>
<td>4</td>
<td>The ICD makes explicit that non-standard of care study components may not be tailored to the individual patient’s specific needs</td>
<td>Silverman, H. 2011; Luce et al., 2004</td>
</tr>
<tr>
<td>5</td>
<td>The ICD clearly describes what standard of care is for the health condition</td>
<td>Luce et al., 2004; McRae and Weijer, 2002</td>
</tr>
<tr>
<td>6</td>
<td>The ICD clearly describes how each arm of the trial differs from standard of care for the condition</td>
<td>Luce et al., 2004; McRae and Weijer, 2002</td>
</tr>
<tr>
<td>7</td>
<td>The ICD indicates that the decision not to participate will not affect the quality of care</td>
<td>Silverman et al., 2005; NBAC, 2002</td>
</tr>
<tr>
<td>8</td>
<td>The ICD clearly indicates whether or not the intervention has or needs regulatory approval in the context of the health condition/problem</td>
<td>Silverman et al., 2005</td>
</tr>
<tr>
<td>9</td>
<td>The ICD includes a statement about whether or not the intervention is expected to change/influence risk of death/survival</td>
<td>Silverman et al., 2005; Alzheimer’s Association, 2004</td>
</tr>
<tr>
<td>10</td>
<td>The ICD addresses the fact that when a patient is too sick or unable to make a decision, a proxy can make decisions for them</td>
<td>Burns et al., 2009; Coppolino et al., 2001; AA, 2004</td>
</tr>
<tr>
<td>11</td>
<td>The ICD clearly states who has been identified as the proxy for the patient</td>
<td>Burns et al., 2009; AA, 2004; Bigatello et al., 2003</td>
</tr>
<tr>
<td>12</td>
<td>The ICDs clearly acknowledge that the decision/situation may be stressful</td>
<td>Burns et al., 2009; Luce et al., 2004; Chenaud et al., 2007</td>
</tr>
<tr>
<td>13</td>
<td>The ICD asks the proxy to consider whether they have discussed with the patient their wishes with respect to participation in research</td>
<td>Coppolino et al., 2001; AA, 2004; Bigatello et al., 2003</td>
</tr>
<tr>
<td>14</td>
<td>The ICD explains the criteria the proxy should base their participation decision on</td>
<td>Burns et al., 2009; AA, 2004; Coppolino et al., 2001; Bigatello et al., 2003</td>
</tr>
<tr>
<td>15</td>
<td>The ICD specifically indicates that the proxy can revisit or withdraw informed consent at anytime throughout the trial</td>
<td>AA, 2004; NBAC, 2002; Chenaud et al., 2007; Luce et al., 2004</td>
</tr>
<tr>
<td>16</td>
<td>The ICD indicates that informed consent will also be obtained from the patient if/when they are well enough to do so</td>
<td>Luce et al., 2004; AA, 2004; Bigatello et al., 2003</td>
</tr>
<tr>
<td>17</td>
<td>The ICD explains HOW to withdraw consent</td>
<td>NBAC, 2002</td>
</tr>
<tr>
<td>18</td>
<td>The ICD addresses any personal/financial interests of study investigators (conflict of interest)</td>
<td>Luce et al., 2004; Bigatello et al., 2003</td>
</tr>
</tbody>
</table>

*AA- Alzheimer’s Association; NBAC- National Bioethics Advisory Commission*
Item 2- The ICD avoids the use of treatment terminology to describe investigational components of the study. Critically ill patients and their families are often desperate for life-saving interventions. In an effort to curb their ascribing therapeutic intent to an investigational intervention, the Alzheimer’s association (2004) and Silverman et al. (2005)suggested that consent documents avoid using medical jargons and words like ‘doctor’, ‘therapy’, ‘medication’ and ‘treatment’ to describe study components.

Item 3- The ICD makes a clear distinction between therapeutic and non-therapeutic interventions. This is particularly important for ICU studies because critically ill patients and their surrogates may be more susceptible to therapeutic misconception. The authors recommended that consent documents should distinguish procedures for study purposes only from those that may benefit the patient or standard treatment options to avoid confusion about the efficacy of an intervention. For enrolled participants, whether a procedure was of benefit to the participant, or the procedure was solely for research purposes, was explored. In other words, if one is enrolled in the study, will this procedure benefit the participant in anyway, or is it solely for scientific purposes? With this item, consideration was given to whether the procedure had any prospect of direct benefit to the patient. For example, a blood sample to monitor a patient’s glucose level in order to instigate appropriate treatment would be considered therapeutic. The same procedure, whose purpose is to ascertain whether blood type influences response to treatment, would be considered non-therapeutic. This is similar to, but distinct from item 5 under the general informed consent guidelines in Section B (The ICDs describe which procedures are solely for research purposes). Again, using blood
draws, this item in Section B answered the question of whether the blood sample would have been taken at all had the patient not enrolled in the trial (would one have to go through this procedure if not enrolled in the study?).

**Item 4** - The ICD makes explicit that non standard of care study components may not be tailored to the individual patient’s specific needs. Silverman (2011) and Luce (2004) noted that research participants do not always understand some research procedures, believing that researchers act as their physicians. This is usually the case when a research investigator also serves as a physician to the participants. They argued that patients need to be clear that the decision on what intervention would be received in the trial was not made based on patients’ medical needs. In the ICU setting where decision makers are rushed and stressed, this would further help patients and surrogates to not ascribe any therapeutic meaning to the study intervention.

**Item 5** - The ICD clearly describes what standard of care is for the health condition. For any health condition in the ICU, there exist routine practices that usually entail some risk. Luce et al. (2004) and McRae (2002) suggested that a clear description of usual care/best practice would help participants better understand which procedures are extra, or if they may be denied individualized care in the course of the study. They noted that this is especially important as rapidly changing health conditions can necessitate changes to what standard of care entails.

**Item 6** - The ICD clearly describes how each arm of the trial differs from standard of care for the condition. McRae (2002) and Luce (2004) noted that a description of how the different arms of a trial relate to current practice can help patients and their surrogates
to better weigh the benefits/risks of participation, and also give a participant a clear picture of what to expect from his/her commitment to the trial. For example, if time-consuming follow up activities such as interviews are expected, a participant may be better able to commit to the study if this is clearly laid out from the outset\textsuperscript{71,122}.

\textbf{Item 7- The ICD indicates that the decision not to participate will not affect the quality of care.} Critically ill patients and their families are very dependent on their physicians/clinicians\textsuperscript{71}. Family members are in a stressful situation and would do anything for their sick loved ones. When the investigator is also the physician, it might be difficult to refuse trial participation. Silverman (2005) and the National bioethics advisory committee (2002) suggested that such a statement in the consent document may reduce any perceived coercion, improving the voluntariness of a participant’s decision\textsuperscript{80,107}.

\textbf{Item 8- The ICD clearly indicates whether or not the intervention has or needs regulatory approval in the context of the health condition/problem.} To further emphasize the experimental nature of a trial, Silverman et al. (2005) recommended mentioning the intervention’s status with the regulatory authorities, rather than relying only on words like “study” or “research”\textsuperscript{80}. Knowing whether the intervention one is about to receive has been in use for years, or is experimental, might impact a participant’s decision to enrol in a study.

\textbf{Item 9- The ICD includes a statement about whether or not the intervention is expected to change/influence risk of death/survival.} Various authors underscore the importance of survival in the ICU environment, sometimes used as the outcome of a trial.
Silverman et al. (2005) noted that some experimental interventions used in critical care trials affect mortality rates, some actually increasing mortality. It becomes important to distinguish between mortality due to a participant’s underlying condition, and mortality due to the study intervention. Such a statement is expected to factor into a patient’s or surrogate’s decision to participate in a trial.

**Item 10- The ICD addresses the fact that when a patient is too sick or unable to make a decision, a proxy can make decisions for them.** The nature or progression of a condition could render a patient incapable of making decisions. To respect the principle of autonomy, surrogates are routinely asked to provide consent on behalf of incapacitated patients in the ICU. Such a statement in the consent document would help surrogates understand why they are being asked to make a decision about study participation for their loved one.

**Item 11- The ICD clearly states who has been identified as the proxy for the patient.** Different jurisdictions have different ways of identifying who can act as a surrogate decision maker (family member/next of kin/legally authorized representative) for an incapacitated person. Surrogates need to know that they can make trial participation decisions on their loved ones behalf. Whether an identified relationship between proxy and patient was mentioned in the consent document was ascertained with this item.

**Item 12- The ICDs clearly acknowledge that the decision/situation may be stressful.** Burns (2009), Luce (2004) and Chenaud (2007) noted that the ICU environment is laced with uncertainties, including quickly changing conditions and short period within
which consent decisions must be made.\textsuperscript{71, 76, 93, 123} The frequency with which consent documents acknowledged the context within which trial participation decisions were being sought was examined. Acknowledgement of the stressful situation might alleviate some of the stress, reinforce that participants and surrogates can choose not to make any decision, help patients/surrogates put the trial into context and have realistic expectations from trial participation.

\textbf{Item 13- The ICD asks the proxy to consider whether they have discussed with the patient their wishes with respect to participation in research.} A capable participant can lose and regain competence during the course of a study. The Alzheimer’s Association suggested that patients and proxies be encouraged to talk about research participation any time the opportunity presents itself so that a proxy would know what to do in a given circumstance. A proxy who has had such deliberations with a participant is more likely to make a decision aligned with those of the participant, and be confident in the trial participation decision\textsuperscript{93, 94, 106}.

\textbf{Item 14- The ICD explains the criteria the proxy should base their participation decision on.} In lieu of an advanced directive that clearly states the wishes of an incapacitated participant, the practice in most ICUs is to ask a proxy to base trial participation decisions on substituted judgement (the decision the participant would take if he/she was capable of doing so), or failing that, best interest (the decision that is rational, practical and realistic under the circumstance), when making such decisions\textsuperscript{71, 76, 94, 106}. The Alzheimer’s Association recommended communicating this to surrogates through the informed consent document.
Item 15- *The ICD specifically indicates that the proxy can revisit or withdraw informed consent at anytime throughout the trial.* Informed consent is a process, which must be assessed regularly as the study progresses. With changing conditions in the ICU, an incapacitated participant can become capable or vice versa, which necessitates revisiting consent. For example, if an enrolled patient regains capacity and decides not to participate, the consent of the proxy should be withdrawn.

Item 16- *The ICD indicates that informed consent will also be obtained from the patient if/ when they are well enough to do so.* Different approaches are used to obtain consent for research in the ICU. Respect for a person’s autonomy is paramount, and should be exercised if and when a patient is capable of doing so in the course of the research. If an otherwise incapacitated participant becomes capable, he/she should be allowed to make the decision on trial participation, regardless of any prior decision taken on his/her behalf.

Item 17- *The ICD explains how to withdraw consent.* Critically ill patients and their surrogates may feel indebted to their clinicians and believe that they cannot withdraw their prior consent even if the informed consent document states that their care would not be affected either way. The consent document should indicate who to talk to should one wish to withdraw from a trial. Such a statement in the consent document would reflect the continual nature of informed consent, enable participants to exercise their right to withdraw any prior consent, and reduce any perceived coercion.

Item 18- *The ICD addresses any personal/financial interests of study investigators (conflict of interest).* The consent document should be clear on any
advantages (compensations or benefits) that the trial has for the research investigator(s)\textsuperscript{71,94}. Luce (2004) suggested that when a physician is also the researcher, a third party should be tasked with the request for patient consent. For researchers who are also physicians, involvement with other parties must be declared so as not to compromise the integrity and independence of the research. For patients and surrogates, declaring any conflicts of interest would convey that the research is being conducted in an unbiased manner and maintain their trust that their interests are considered. This item is different from item 15 under the general informed consent guidelines in Section B \textit{(There is a statement about whether study investigators or institutions receive compensation for patient enrolment)}, which is interested in any compensation that researchers receive for participant enrolment in particular, and not the study as a whole.

\textbf{Section 3: Sample Frame of ICU Trials}

This section describes the results of our search for relevant trials in the ICU within the Clinicaltrials.gov database. Figure 1 shows the results of our search on the clinical trials database. The search yielded 3685 studies. After applying limits to age (adults and seniors), phase (2 and 3) and time of registration (first received from January 1\textsuperscript{st}, 2006), 789 studies were retrieved and downloaded into an excel spreadsheet for further refinement to meet pre-defined inclusion criteria.

No duplicates (from the unique trial number given to each study) were found. Based on the country from which participants were recruited into the studies, 466 studies were in English (mainly from Australia/New Zealand, Canada, UK and USA), 98 studies were in French (Canada, France, Switzerland, Belgium), and 2 studies did not provide a
location. For 5 studies, the language could be either French or English. As per our inclusion criteria, 218 studies (in other languages such as Dutch, Spanish, Mandarin and German) were excluded. Of the remaining 571 studies, email contact information could be found for 412 unique principal investigators (PIs).

Figure 1: Search of Clinicaltrials.gov Database for Critical Care Trials on March 17, 2014 using the search terms ‘critical care OR intensive care OR critical illness’
Section 4: Response Rate and Non-responder analyses

Figure 2 presents the responses of investigators to our request for their informed consent documents. Of the 412 PIs contacted, 30 emails were undelivered, 192 PIs did not respond to our request at all, 11 PIs declined participation, 11 automatic responses (“I am away between this dates” message types that come back immediately after sending mail) were received, and 31 PIs provided other responses (will/may send, confidential, no enrolment, waived consent, will discuss with others); 137 PIs provided a consent document (respondent). These consent documents were received between April 14th, 2014 and August 20, 2014. The unadjusted response rate (proportion of PI who provided a consent document) was 33.3% (137/412).

Based on the standards set by the AAPOR, the contact rate (number of PI reached as a proportion of all eligible and likely-eligible PI) for this study was 40% (161/402*).

\[ Contact\ Rate = \frac{I + R + O}{I + P + R + O + NC + e(\text{UI} + UO)} \]

\[ = \frac{137 + 12 + 12}{137 + 12 + 12 + 0.976(42 + 204)} \]

\[ = \frac{161}{402.1} = 40.04\% \]

Where

I = Complete response, PI provided a consent document (n=137)

P = Partial Response, (not applicable as only one question was asked; n=0)

R = Refusals, PIs who declined participation (confidential, declined, n=12)

NC = Non-contacts (wrong PI address, undelivered, automatic responses, n=42)

UI = Unknown eligibility (no response to request, contact someone else but no response from them, n=204)

O = other non-refusals (may/will send but no document received, n=12)

e = proportion of PIs of unknown eligibility that are eligible, automatically calculated by AAPOR as e = 0.976

*Not eligible and out of sample (waived consent, no patient enrolment, non-critical care trial n= 5; hence the denominator of 402).
The response rate (number of principal investigators who provided consent forms as a proportion of all eligible and likely-eligible PI, Response Rate# 3) was 34.1% (137/402).

\[
\text{Response Rate} = \frac{I}{I + P + (R + O + NC) + e(UH + UO)}
\]

\[
= \frac{137}{402.1} = 34.07\%
\]

Figure 2: Investigator Response to Informed Consent Document Request
Table 3 describes and compares the characteristics of respondent and non-respondent studies. Although 137 ICDs were received, two documents were in Dutch and German and excluded from analysis. Language in which consent form is written was not related to the likelihood of receiving a consent document. Among respondents, 78.5% (106/135) consent documents were in English; for non-respondents, there were 85.1% (234/275) English documents. Non respondents did not differ significantly from respondents in terms of language of consent document (p= 0.10, $\chi^2 = 2.76$).

Table 4: Characteristics of 412 Respondent and Non-Respondent Studies

<table>
<thead>
<tr>
<th>Trial Characteristics</th>
<th>Respondents (n=135*)</th>
<th>Non-Respondents (n=275)</th>
<th>$\chi^2$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>106 (78.5%)</td>
<td>234 (85.1%)</td>
<td>2.7626</td>
<td>0.096</td>
</tr>
<tr>
<td>French</td>
<td>29 (21.5%)</td>
<td>41 (14.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within an ICU Facility</td>
<td>88 (65.2%)</td>
<td>125 (45.5%)</td>
<td>14.122</td>
<td>0.000</td>
</tr>
<tr>
<td>Outside the ICU</td>
<td>47 (34.8%)</td>
<td>150 (54.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial Interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>68 (50.4%)</td>
<td>164 (59.6%)</td>
<td>6.162</td>
<td>0.104</td>
</tr>
<tr>
<td>Devices</td>
<td>19 (14.1%)</td>
<td>24 (8.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedures</td>
<td>29 (21.5%)</td>
<td>42 (15.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioural</td>
<td>19 (14.1%)</td>
<td>45 (16.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial Phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Phase</td>
<td>62 (45.9%)</td>
<td>126 (45.8%)</td>
<td>0.000</td>
<td>0.984</td>
</tr>
<tr>
<td>Late Phase</td>
<td>73 (54.1%)</td>
<td>149 (54.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding Sources</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Industry</td>
<td>23 (17.0%)</td>
<td>85 (30.9%)</td>
<td>8.984</td>
<td>0.011</td>
</tr>
<tr>
<td>Governmental</td>
<td>45 (33.3%)</td>
<td>77 (28.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>67 (49.6%)</td>
<td>113 (41.1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Although 137 ICDs were received, two documents were in Dutch and German and excluded from analysis.

Investigators conducting trials in an ICU were more likely to respond to our request for a consent document compared to those conducting trials outside an ICU facility (p< 0.01, $\chi^2 = 14.14$) probably because those working outside an ICU facility
(though their patients were very sick) thought the request did not apply to them. About 65.2% (88/135) of respondent trials were conducted within an ICU facility, whereas among non-respondent trials, only 45.4% (125/275) were conducted in an ICU.

Overall, type of study intervention was not related to a PI’s tendency to provide us with a consent document (p-value = 0.104), indicating equal likelihood of receiving consent documents from investigators regardless of the intervention being used in their trials. Among respondent trials, 50.4% (68/135) used drug interventions, while for non-respondent trials, this was 59.6% (164/275).

Investigators working on early phase trials were as likely to provide us with a consent document as those working on late phase trials. Among respondent trials 45.9% (62/135) studies were early phase trials. For non-respondent trials this was 45.8% (126/275). Non-respondents did not differ significantly from respondents with respect to trial phase (p = 0.10, \( \chi^2 = 0.98 \)). Study phase was independent of response for consent documents.

Industry funded trial investigators were less likely to respond to our request compared to investigators with other sources of funding (p-value = 0.011). Among respondents 17% (23/135) of studies had some industry funding. For non-respondents 30.9% (85/275) of studies had some industry funding.

**Section 5: Descriptive Analyses of Informed Consent Documents**

Thirty seven percent (51/137) of documents received were excluded from analysis; 2 were in languages other than French and or English (these were not excluded earlier, or from response rate calculations because they were conducted in multi lingual
countries and could have been in either included languages), 1 was a template looking at health conditions in newborns, 1 document was targeted at healthy volunteers, 4 documents targeted surrogates of critically ill patients, and the remaining 43 documents were targeted at other diseases not typically observed in the ICU (substance abuse, diabetes, HIV, cancer, obesity, community-based interventions; one of these documents was in the German language). Eighty six informed consent documents were therefore assessed in how they help participants make trial participation decisions.

Table 4 describes the characteristics of the 86 rated informed consent documents. About 72% (62/86 documents) were written in English. Most of the study conditions had to do with infections (29.1%; 25/86) and drugs represented the majority of trial interventions at 59.3% (51/86). The majority of trials, (52.3%, 45/86) were late phase trials. Only 18.6% (16/86) of trials had any industry funding; the remaining were funded by various government authorities (such as CIHR, US National Institute of Health, NHS) and other health organizations/institutions (hospitals, universities, medical centres, individuals). Most trials (88.4%; 76/86) involved the patient in trial participation decisions whenever possible.
Table 5: Characteristics of Rated Informed Consent Documents

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Informed Consent Document N=86</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language</td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>62 (72.1%)</td>
</tr>
<tr>
<td>French</td>
<td>24 (27.9%)</td>
</tr>
<tr>
<td>Health Condition</td>
<td></td>
</tr>
<tr>
<td>Sepsis/Infections</td>
<td>25 (29.1%)</td>
</tr>
<tr>
<td>Nervous/Neuromuscular</td>
<td>22 (25.6%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>12 (14.0%)</td>
</tr>
<tr>
<td>Cardiovascular/Circulatory</td>
<td>10 (11.6%)</td>
</tr>
<tr>
<td>Gastrointestinal/Metabolic</td>
<td>9 (10.5%)</td>
</tr>
<tr>
<td>Renal</td>
<td>8 (9.3%)</td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>51 (59.3%)</td>
</tr>
<tr>
<td>Procedures</td>
<td>21 (24.4%)</td>
</tr>
<tr>
<td>Devices</td>
<td>14 (16.3%)</td>
</tr>
<tr>
<td>Phase</td>
<td></td>
</tr>
<tr>
<td>Early Phase</td>
<td>41 (47.7%)</td>
</tr>
<tr>
<td>Late Phase</td>
<td>45 (52.3%)</td>
</tr>
<tr>
<td>Funding</td>
<td></td>
</tr>
<tr>
<td>Industry</td>
<td>16 (18.6%)</td>
</tr>
<tr>
<td>Governmental</td>
<td>20 (23.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>50 (58.2%)</td>
</tr>
<tr>
<td>Consenting to Trial Participation</td>
<td></td>
</tr>
<tr>
<td>Surrogate only</td>
<td>10 (11.6%)</td>
</tr>
<tr>
<td>Patient only</td>
<td>16 (18.6%)</td>
</tr>
<tr>
<td>Either or Both</td>
<td>60 (69.8%)</td>
</tr>
</tbody>
</table>

Section 6: Rater Agreement

The evaluation instrument is presented in Appendix VII. Together with the items previously developed, a total of 77 items, in three parts, were evaluated. Agreement between raters is described in Table 5. Overall agreement between raters across all items and consent documents was 91.6% (item-specific agreement ranging from 73.3% to 100%). Inter rater reliability (Kappa) was found to be 0.77 (95% CI 0.76-0.79). Agreement on general informed consent guidelines items was 92.7%. The inter rater reliability 0.79 [ (p <0.01), 95% CI (0.77-0.81)].
Similarly, agreement on IPDAS standards items was 94.3%, consistent with the 95.1% noted by Brehaut and colleagues\(^4\). The inter rater reliability was 0.78 (\(p < 0.01; 95\%\) CI of 0.76-0.80). Agreement on ICU-specific guideline items was 84.9%. The inter rater reliability was 0.63 (\(p < 0.01; 95\%\) CI 0.59-0.67). Item specific agreement scores are presented in Appendix VIII.

**Table 6: Agreement among Raters**

<table>
<thead>
<tr>
<th>Rater Agreements</th>
<th>Percent Agreement</th>
<th>Weighted Kappa (CI)</th>
<th>Kappa Interpretation*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>91.6</td>
<td>0.77 (0.76-0.79)</td>
<td>Substantial agreement</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Set 1: Informed Consent Guidelines (27 Items-Section B of Appendix VII)</td>
<td>92.7</td>
<td>0.79 (0.77-0.81)</td>
<td>Substantial agreement</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Set 2: IPDAS Standards (32 Items-Section A of Appendix VII)</td>
<td>94.3</td>
<td>0.78 (0.76-0.80)</td>
<td>Substantial agreement</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Set 3: ICU-specific Recommendations (18 Items-Section C of Appendix VII)</td>
<td>84.9</td>
<td>0.63(0.59-0.67)</td>
<td>Substantial agreement</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Raters PA/KC</td>
<td>92.8</td>
<td>0.81(0.80-0.82)</td>
<td>Almost perfect agreement</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Raters PA/TH</td>
<td>88.8</td>
<td>0.70(0.67-0.73)</td>
<td>Substantial agreement</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Interpretation based on Landis and Koch (1977) cut-offs

Language differences might be responsible for the lower agreement score between PA and TH, who rated the translated French consent documents received. For example, item 19 in Section B (The term ‘randomization’ is explained) was consistently rated Disagree or strongly disagree by one rater, and agree and strongly agree by the other rater, because the meaning of randomization was lost in translation. Subsequently, PA
deferred to TH’s judgement (he could understand both languages) whenever there were any such disagreements.

On the 32 IPDAS items, 6 items attained an agreement score of 100% (the ICDs specify the time period over which the probabilities apply, the ICDs provide information about the levels of uncertainty around probabilities, the ICDs describe probabilities in multiple frames to limit framing biases, the ICDs ask PPs to think about which intervention advantages and/or disadvantages matter most to them, the ICDs provide guidance on a step-by-step way to decide whether or not to participate in the trial, the ICDs provide citations to the scientific evidence referenced). On the 27 general ICD items, agreement scores for 2 items (abbreviations and acronyms are minimally used and well-defined, all font sizes are 11 point or greater) was 100% and for 17 other items was over 90%. On the 18 ICU specific items, no item had an agreement score of 100%, and only 5 items scored over 90%. This might explain why the overall ICU- specific section agreement score was lower than that of the other 2 sets; the higher number of items scoring high percentages in these 2 sets might have drawn those averages upwards.

Section 7: Item Ratings

Figures 3, 4 and 5 present the percent ratings (strongly agree, agree, disagree, strongly disagree) for each of the 3 sets of the items in our evaluation instrument. Corresponding tables (Tables 6, 7 and 8) provide the same information in numerical format for each of the 3 sets of items. The diagonal red portion of the bar indicates the percentage of the 89 ICDs for which the final rating was Strongly Agree. Similarly, the vertical blue represents Strongly Disagree.
**General Consent Guideline Items**

Overall percent conformity scores for general informed consent guidelines items (Figure 3, Table 7) ranged from 7% on 1 item (states whether PI/organization receive compensation for participant enrolment) to 100% on 7 items (no grammatical errors, no spelling errors, non-repetitive text, state that study involves research, readable font sizes, explains rationale for the research, clearly labelled graphics). Compared to ICU-specific and IPDAS items, there was little variability within this range; most items (24/27) scored over 50%. Two items had agree and strongly agree scores under 30% (describes duration of the study, describes potential risk(s) to embryos, foetus or nursing infants). Conformity was low (7% strongly agree and agree scores) for the item on outlining compensations that PI and or their organization received for participant enrolment.
Figure 3: Informed Consent Guideline Items-Percent of ICDs rated as Strongly Agree, Agree, Disagree or Strongly Disagree
Table 7: Percent (n) of ICDs rated as Strongly Agree, Agree, Disagree or Strongly Disagree on Set 2 27 General Informed Consent Guidelines Items

<table>
<thead>
<tr>
<th>Item Description</th>
<th>Percent Strongly Agree (n)</th>
<th>Percent Agree (n)</th>
<th>Percent Disagree (n)</th>
<th>Percent Strongly Disagree (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key Elements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State that study involves research</td>
<td>90.7 (78)</td>
<td>9.3 (8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Explains rationale for the research</td>
<td>93 (80)</td>
<td>7 (6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>States why the PP is being asked to participate in the study</td>
<td>46.5 (40)</td>
<td>36 (31)</td>
<td>14 (12)</td>
<td>3.5 (3)</td>
</tr>
<tr>
<td>Explains all procedures to be carried out</td>
<td>58.1 (50)</td>
<td>37.2 (32)</td>
<td>4.7 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Describes procedures that are solely for research purposes</td>
<td>33.7 (29)</td>
<td>48.8 (42)</td>
<td>15.1 (13)</td>
<td>2.3 (2)</td>
</tr>
<tr>
<td>Describes other options aside from participation</td>
<td>41.9 (36)</td>
<td>14 (12)</td>
<td>22.1 (19)</td>
<td>22.1 (19)</td>
</tr>
<tr>
<td>States that participation is voluntary</td>
<td>90.7 (78)</td>
<td>8.1 (7)</td>
<td>0 (0)</td>
<td>1.2 (1)</td>
</tr>
<tr>
<td>States that participant can withdraw at any time</td>
<td>97.7 (84)</td>
<td>1.2 (1)</td>
<td>0 (0)</td>
<td>1.2 (1)</td>
</tr>
<tr>
<td>Describes reasons for which PP’s participation may be terminated</td>
<td>22.1 (19)</td>
<td>29.1 (25)</td>
<td>20.9 (18)</td>
<td>27.9 (24)</td>
</tr>
<tr>
<td>State that new information will be conveyed to PP</td>
<td>62.8 (54)</td>
<td>4.7 (4)</td>
<td>0 (0)</td>
<td>32.6 (28)</td>
</tr>
<tr>
<td><strong>Ethical Issues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Describes potential risk(s) to embryos, foetus or nursing infants*</td>
<td>10.7 (9)</td>
<td>17.9 (15)</td>
<td>4.8 (4)</td>
<td>66.7 (56)</td>
</tr>
<tr>
<td>States that participation may benefit society</td>
<td>54.7 (47)</td>
<td>10.5 (9)</td>
<td>1.2 (1)</td>
<td>33.7 (29)</td>
</tr>
<tr>
<td>Indicates how personal information will be protected</td>
<td>33.7 (29)</td>
<td>19.8 (17)</td>
<td>43 (37)</td>
<td>3.5 (3)</td>
</tr>
<tr>
<td>Indicates which organizations/individuals have access to personal information</td>
<td>45.3 (39)</td>
<td>38.4 (33)</td>
<td>8.1 (7)</td>
<td>8.1 (7)</td>
</tr>
<tr>
<td>States whether PI/organization receive compensation for PP enrolment</td>
<td>4.7 (4)</td>
<td>2.3 (2)</td>
<td>1.2 (1)</td>
<td>91.9 (79)</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Describes duration of the study</td>
<td>12.8 (11)</td>
<td>4.7 (4)</td>
<td>5.8 (5)</td>
<td>76.7 (66)</td>
</tr>
<tr>
<td>Describes duration of PP’s participation</td>
<td>50 (43)</td>
<td>29.1 (25)</td>
<td>19.8 (17)</td>
<td>1.2 (1)</td>
</tr>
<tr>
<td>Describes the number of participants</td>
<td>76.7 (66)</td>
<td>2.3 (2)</td>
<td>0 (0)</td>
<td>20.9 (18)</td>
</tr>
<tr>
<td>Explains randomization*</td>
<td>55.1 (43)</td>
<td>32.1 (25)</td>
<td>7.7 (6)</td>
<td>5.1 (4)</td>
</tr>
<tr>
<td>Describes the different groups to which PP can be assigned*</td>
<td>55 (44)</td>
<td>42.5 (34)</td>
<td>1.3 (1)</td>
<td>1.3 (1)</td>
</tr>
<tr>
<td><strong>Formatting and Style</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Spelling errors</td>
<td>82.6 (71)</td>
<td>17.4 (15)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No grammatical errors</td>
<td>80.2 (69)</td>
<td>19.8 (17)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Minimally used and well defined acronyms</td>
<td>72.1 (62)</td>
<td>25.6 (22)</td>
<td>2.3 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Readable font sizes</td>
<td>90.7 (78)</td>
<td>9.3 (8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Clearly labelled graphics*</td>
<td>100 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Non-technical Language</td>
<td>68.6 (59)</td>
<td>25.6 (22)</td>
<td>5.8 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Non-repetitive text</td>
<td>82.6 (71)</td>
<td>17.4 (15)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*For items not applicable to all trials, n was less than 86
IPDAS Items

Figure 4 and Table 8 illustrate conformity with IPDAS standards, with conformity (strongly agree and agree) ranging from 0% for 8 items (describes disadvantages of NON-participation in a consistent order, comparison of advantages & disadvantages for participation & non-participation, specifies time period over which probabilities apply, provides information about levels of uncertainty around probabilities, describes probabilities in multiple frames to limit framing biases, asks PPs to think about which advantages and/or disadvantages matter most to them, provides a step-by-step way to decide whether or not to participate, describes that there are different levels of quality of evidence) to 91.9% for 1 item (name & contact information of someone to whom questions can be asked). Aside from the 8 items with zero conformity mentioned above, another 7 items scored under 10% (describes disadvantages of NOT participating, describes advantages of NOT participating, includes a tool designed to facilitate further discussion, provides citations to scientific evidence referenced, describes quality of research evidence used, specifies probabilities in natural frequencies, specifies population(s) that yielded the probabilities) and a further 6 items scored under 20% (provides more than one way of viewing probabilities, comparison of probabilities using same denominator, describes time of onset of side effects of participation, provides information on probabilities for all advantages/disadvantages, describes reversibility of side effects of participation, describes advantages/disadvantages with enough detail to help imagine impact on life). Slightly more than half of the ICDs (57%, 49/86 strongly agree and agree) indicated that a decision needed to be made about trial participation. The remaining 10 items showed conformity with over 60% of ICDs.
Figure 4: IPDAS Items - Percent of ICDs rated as Strongly Agree, Agree, Disagree or Strongly Disagree: IPDAS Items - Percent of ICDs rated as Strongly Agree, Agree, Disagree or Strongly Disagree
Table 8: Percent (n) of ICDs rated as Strongly Agree, Agree, Disagree or Strongly Disagree on Set 1 32 IPDAS Items

<table>
<thead>
<tr>
<th>Item Description</th>
<th>Percent Strongly Agree (n)</th>
<th>Percent Agree (n)</th>
<th>Percent Disagree (n)</th>
<th>Percent Strongly Disagree (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Describes that a participation decision needs to be made</td>
<td>22.1 (19)</td>
<td>34.9 (30)</td>
<td>36 (31)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Describes health condition or problem</td>
<td>43 (37)</td>
<td>36 (31)</td>
<td>18.6 (16)</td>
<td>2.3 (2)</td>
</tr>
<tr>
<td>Describes intervention</td>
<td>48.8 (42)</td>
<td>37.2 (32)</td>
<td>14 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Describes advantages of participation</td>
<td>70.9 (61)</td>
<td>17.4 (15)</td>
<td>5.8 (5)</td>
<td>5.8 (5)</td>
</tr>
<tr>
<td>Describes disadvantages of participation</td>
<td>58.1 (50)</td>
<td>31.4 (27)</td>
<td>9.3 (8)</td>
<td>1.2 (1)</td>
</tr>
<tr>
<td>Describes advantages of NOT participating</td>
<td>1.2 (1)</td>
<td>0 (0)</td>
<td>9.3 (8)</td>
<td>89.5 (77)</td>
</tr>
<tr>
<td>Describes disadvantages of NOT participating</td>
<td>0 (0)</td>
<td>1.2 (1)</td>
<td>1.2 (1)</td>
<td>97.7 (84)</td>
</tr>
<tr>
<td>Describes disadvantages of participation in a consistent order</td>
<td>19.8 (17)</td>
<td>43 (37)</td>
<td>23.3 (20)</td>
<td>14 (12)</td>
</tr>
<tr>
<td>Describes disadvantages of NON-participation in a consistent order</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.2 (1)</td>
<td>98.8 (85)</td>
</tr>
<tr>
<td>Comparison of adv. &amp; disadv. for participation &amp; non-participation</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>83.7 (72)</td>
<td>16.3 (14)</td>
</tr>
<tr>
<td>Describes reversibility of side effects of participation</td>
<td>1.2 (1)</td>
<td>17.4 (15)</td>
<td>17.4 (15)</td>
<td>64 (55)</td>
</tr>
<tr>
<td>Describes time of onset of side effects of participation</td>
<td>2.3 (2)</td>
<td>11.6 (10)</td>
<td>10.5 (9)</td>
<td>75.6 (65)</td>
</tr>
<tr>
<td>Provides information on probabilities for all adv/disadv</td>
<td>1.2 (1)</td>
<td>15.1 (13)</td>
<td>32.6 (28)</td>
<td>51.2 (44)</td>
</tr>
<tr>
<td>Specifies population(s) that yielded the probabilities</td>
<td>1.2 (1)</td>
<td>5.8 (5)</td>
<td>19.8 (17)</td>
<td>73.3 (63)</td>
</tr>
<tr>
<td>Specifies probabilities in natural frequencies</td>
<td>3.5 (3)</td>
<td>2.3 (2)</td>
<td>1.2 (1)</td>
<td>93 (80)</td>
</tr>
<tr>
<td>Specifies time period over which probabilities apply</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.2 (1)</td>
<td>98.8 (85)</td>
</tr>
<tr>
<td>Comparison of probabilities using same denominator</td>
<td>8.1 (7)</td>
<td>2.3 (2)</td>
<td>7 (6)</td>
<td>82.6 (71)</td>
</tr>
<tr>
<td>Provides information about levels of uncertainty around probabilities</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>75.6 (65)</td>
<td>24.4 (21)</td>
</tr>
<tr>
<td>Provides more than one way of viewing probabilities</td>
<td>4.7 (4)</td>
<td>5.8 (5)</td>
<td>10.5 (9)</td>
<td>79.1 (68)</td>
</tr>
<tr>
<td>Describes probabilities in multiple frames to limit framing biases</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>100 (86)</td>
</tr>
<tr>
<td>Describes adv/disadv. with enough detail to help imagine impact on life</td>
<td>1.2 (1)</td>
<td>17.4 (15)</td>
<td>22.1 (19)</td>
<td>59.3 (51)</td>
</tr>
<tr>
<td>Asks PPs to think about which adv and/or disadv matter most to them</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>100 (86)</td>
</tr>
<tr>
<td>Provides a step-by-step way to decide whether or not to participate</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>100 (86)</td>
</tr>
<tr>
<td>Includes a tool designed to facilitate further discussion</td>
<td>1.2 (1)</td>
<td>0 (0)</td>
<td>3.5 (3)</td>
<td>95.3 (82)</td>
</tr>
<tr>
<td>Provides citations to scientific evidence referenced</td>
<td>1.2 (1)</td>
<td>0 (0)</td>
<td>1.2 (1)</td>
<td>97.7 (84)</td>
</tr>
<tr>
<td>Provides a production date</td>
<td>81.4 (70)</td>
<td>8.1 (7)</td>
<td>4.7 (4)</td>
<td>5.8 (5)</td>
</tr>
<tr>
<td>Describes that there are different levels of quality of evidence</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.2 (1)</td>
<td>98.8 (85)</td>
</tr>
<tr>
<td>Describes quality of research evidence used</td>
<td>1.2 (1)</td>
<td>3.5 (3)</td>
<td>15.1 (13)</td>
<td>80.2 (69)</td>
</tr>
<tr>
<td>Provides info. about funding sources for the study</td>
<td>48.8 (42)</td>
<td>18.6 (16)</td>
<td>5.8 (5)</td>
<td>26.7 (23)</td>
</tr>
<tr>
<td>Name, credentials &amp; contact info. of the PI(s)</td>
<td>25.6 (22)</td>
<td>65.1 (56)</td>
<td>9.3 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Name &amp; contact info. of someone to whom questions can be asked</td>
<td>73.3 (63)</td>
<td>18.6 (16)</td>
<td>4.7 (4)</td>
<td>3.5 (3)</td>
</tr>
<tr>
<td>Name of the Research Ethics Board that approved the study</td>
<td>46.5 (40)</td>
<td>36 (31)</td>
<td>12.8 (11)</td>
<td>4.7 (4)</td>
</tr>
</tbody>
</table>
ICU-Specific Items

Overall conformity with ICU-specific item (Figure 5, Table 9) ranged from 2.3% for 1 item (acknowledge that the decision may be stressful) to 96.5% for 1 item (non-participation will not affect quality of care received). There was much variation within this range. Conformity to six items (asks proxy to consider Participants research participation wishes, indicates time within which to make a decision, addresses personal/financial interest of PI(s), explains criteria for proxy’s participation decision, explains that non standard of care study components may not be tailored to individual needs, states whether intervention influences survival/risk of death) was below 30%. Conformity to three items (explains how to withdraw consent, indicates consent would be obtained from PP if/when possible, indicates whether a proxy can make decisions for a patient) was under 50%. Conformity to 2 items (avoids treatment terminology for investigational components, indicates that non-participation will not affect quality of care received) was over 90%. Only 2 of the 86 consent documents acknowledged that trial participation decisions were being made under stressful conditions.
Figure 5: ICU-Specific consent Guideline Items- Percent of ICDs rated as Strongly Agree, Agree, Disagree or Strongly Disagree
Table 9: Percent (n) of ICDs rated as Strongly Agree, Agree, Disagree or Strongly Disagree on Set 3 - 18 ICU-specific Informed Consent Guidelines

<table>
<thead>
<tr>
<th>Item Description</th>
<th>Percent Strongly Agree (n)</th>
<th>Percent Agree (n)</th>
<th>Percent Disagree (n)</th>
<th>Percent Strongly Disagree (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicates time within which to make a decision</td>
<td>2.3 (2)</td>
<td>5.8 (5)</td>
<td>8.1 (7)</td>
<td>83.7 (72)</td>
</tr>
<tr>
<td>Avoids treatment terminology for investigational components</td>
<td>17.4 (15)</td>
<td>75.6 (65)</td>
<td>7 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Distinguishes between therapeutic and non-therapeutic interventions</td>
<td>32.6 (28)</td>
<td>47.7 (41)</td>
<td>9.3 (8)</td>
<td>10.5 (9)</td>
</tr>
<tr>
<td>Explains that non standard of care study components may not be tailored to individual needs</td>
<td>5.8 (5)</td>
<td>11.6 (10)</td>
<td>25.6 (22)</td>
<td>57 (49)</td>
</tr>
<tr>
<td>Describes standard of care</td>
<td>43 (37)</td>
<td>31.4 (27)</td>
<td>17.4 (15)</td>
<td>8.1 (7)</td>
</tr>
<tr>
<td>Describes how each arm differs from Standard of care ¹</td>
<td>39 (32)</td>
<td>41.5 (34)</td>
<td>9.8 (8)</td>
<td>9.8 (8)</td>
</tr>
<tr>
<td>Indicates that non-participation will not affect quality of care received</td>
<td>89.5 (77)</td>
<td>7 (6)</td>
<td>1.2 (1)</td>
<td>2.3 (2)</td>
</tr>
<tr>
<td>Indicates whether or not the intervention has regulatory approval</td>
<td>47.7 (41)</td>
<td>25.6 (22)</td>
<td>11.6 (10)</td>
<td>15.1 (13)</td>
</tr>
<tr>
<td>States whether intervention influences survival/risk of death</td>
<td>9.3 (8)</td>
<td>11.6 (10)</td>
<td>9.3 (8)</td>
<td>69.8 (60)</td>
</tr>
<tr>
<td>Indicates whether a proxy can make decisions for a patient ²</td>
<td>37.6 (32)</td>
<td>11.8 (10)</td>
<td>22.4 (19)</td>
<td>28.2 (24)</td>
</tr>
<tr>
<td>States who has been identified as proxy</td>
<td>61.3 (46)</td>
<td>20 (15)</td>
<td>14.7 (11)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Acknowledges the decision may be stressful</td>
<td>1.2 (1)</td>
<td>1.2 (1)</td>
<td>1.2 (1)</td>
<td>96.5 (83)</td>
</tr>
<tr>
<td>Asks proxy to consider PP research participation wishes ²</td>
<td>4 (3)</td>
<td>4 (3)</td>
<td>0 (0)</td>
<td>92 (69)</td>
</tr>
<tr>
<td>Explains criteria for proxy's participation decision ²</td>
<td>5.3 (4)</td>
<td>12 (9)</td>
<td>2.7 (2)</td>
<td>80 (60)</td>
</tr>
<tr>
<td>Indicates proxy can withdraw consent ²</td>
<td>54.7 (41)</td>
<td>13.3 (10)</td>
<td>9.3 (7)</td>
<td>22.7 (17)</td>
</tr>
<tr>
<td>Indicates consent would be obtained from PP if/when possible ²</td>
<td>27.6 (21)</td>
<td>7.9 (6)</td>
<td>21.1 (16)</td>
<td>43.4 (33)</td>
</tr>
<tr>
<td>Explains how to withdraw consent</td>
<td>4.7 (4)</td>
<td>26.7 (23)</td>
<td>14 (12)</td>
<td>54.7 (47)</td>
</tr>
<tr>
<td>Addresses personal/financial interest of PI(s)</td>
<td>7 (6)</td>
<td>3.5 (3)</td>
<td>3.5 (3)</td>
<td>86 (74)</td>
</tr>
</tbody>
</table>

1. For trials in which participants were not randomized to an intervention, n was less than 86
2. For surrogate specific items and surrogate only ICDs, n was less than 86
DISCUSSION

The overall goal for this work was to evaluate the extent to which existing consent documents used in critical care trials adhere to standards and recommendations for high quality informed consent and decision making. A systematic search to identify core sources for guidelines and recommendations for research investigators and ethics boards dealing with protocols that involve vulnerable populations, including critically ill patients, was conducted. Ten such sources were identified. A search through these for recommendations specific to the informed consent process of studies conducted in the critical/intensive care unit (ICU) yielded 40 recommendations. These recommendations were then operationalized as 18 items that could be evaluated against individual informed consent documents (ICDs). The items were then piloted on a series of local critical care trial ICDs. Finally, from the Clinical Trials.gov database a sample of 86 ICDs used in critical care trials was obtained and evaluated against all 77 items in our evaluation tool, including the 18 new ICU-specific items.

Eighteen ICU-specific items were gleaned from the 10 sources with recommendations around consent in ICU research. In the clinical trials database, 412 trials met inclusion criteria and 137 investigators responded to our request with a consent document, 86 of which were evaluated on how they addressed standards and recommendations for high quality informed consent. Percentage scores of strongly agree and agree was variable for each of the three sets of items that the consent documents were rated against.
As with other samples of trial consent documents, our evaluated informed consent documents conformed well on most informed consent guideline items and not very well on a lot of decision aid standard items; 21 out of the 27 general informed consent recommendations scored over 60% and only 10 out of the 32 IPDAS items scored over 60%. Item scores were variable in the 18 ICU specific items, with 8 out of the 18 items scoring over 60%. These suggest that implementation of these guidelines is incomplete.

The following discussion looks at the differences and similarities between this work and the previous one by Brehaut and colleagues, discusses our sample frame and response from study investigators, and explores how the obtained consent documents performed against the general informed consent standards, International Patient Decision Aid Standards- (IPDAS), and the recommended ICU- specific standards. Implications and limitations of this work are highlighted, and recommendations for future research are suggested.

**Comparison to Previous Works by Brehaut and Resnik**

A few similarities and differences with the works of Brehaut 54, 105 and Resnik 104, 115 bear mentioning. The previous studies, like this work, rated consent documents obtained from a sample of trial investigators listed in the clinicaltrials.gov database against informed consent document guidelines. Both had similar inclusion/exclusion criteria in selecting studies with respect to study phase (2 and 3) and population (excluded children). This project and that of Brehaut excluded solely industry funded studies.
While the previous works excluded all but English speaking countries to ensure that consent documents received were in English, this work included and rated both English and French informed consent documents. Considerable important work on critically ill patients is being done in French speaking countries (Dr. L McIntyre, personal communication), which motivated our desire to include French studies. For example, one of the largest trials looking at low dose corticosteroid use in patients with septic shock came from France. Including French ICDs was important to obtaining a good balance and a wider range of ICU conditions, as well as obtaining an appropriate sample size.

Resnik and colleagues focused on consent documents used in oncology trials. Brehaut’s work looked at consent documents from a wide range of trials, and explicitly excluded trials that involved surrogate decision makers. This work focused specifically on consent documents used in ICU trials. The concept of informed consent was developed with the assumption that research participants were competent to make decisions about trial participation. This is often not the case in the ICU environment. Surrogate decision makers are known to play a role in the care of ICU patients, and we wanted to explore how issues of consent and protecting vulnerable research participants play out in this environment. This work extends the discussion about how to improve the informed consent process to include the special issues specific to the critically ill.

Our response rate of 34% was comparable to similar studies (34%, 45%). Common reasons given for not providing a consent document included the investigator not having access to the document and the final version of the document awaiting ethics approval. About 40 of the ICDs received were not on conditions usually encountered in the ICU. The ICDs were used with patients who (though very sick, and could potentially
end up in the ICU) did not face the same degree of trial challenges, especially with respect to time constraints and surrogate issues (Dr. McIntyre, personal communication). This resulted in a lower number of consent documents being rated than originally anticipated (86 instead of 100 ICDs).

Information on respondents and non-respondents was examined and compared to ascertain if the low response rate might have introduced a bias in our sample and hence our item rating score estimates. This information was limited to what was available in the clinicaltrials.gov database. Studies funded solely by industry were excluded, but studies with any industry involvement were less likely to respond to our request. Response from these investigators was significantly lower than that from studies funded by other sources. As well, investigators working on drugs, most of which are funded by industry were less likely to provide us with the consent document used in their trial. It is known that generally, industry funded trials are less likely to respond to request for their data. This might be because industry owns the data, and are protecting their intellectual property, or that investigators might have limited access to them, thus unable to honour the request. Growing calls for sharing of pharmaceutical data may help consent documents used in industry funded trials to be more readily available in future.

**Inter-rater Agreement**

Inter-rater agreement overall was quite high (92%), and compared well with previous work, demonstrating an overall ‘substantial’ (Kappa between 0.61-0.8) agreement. Despite the complexity of some of the items, this relatively high level of agreement was achieved because clear anchors for each of the items that were in the
evaluation instrument were developed (through piloting). During piloting, specific examples from previously evaluated ICDs were drawn on for clarification. Where possible, text and associated anchors were revised for clarity. Coders trained in how to use this instrument should be able to obtain similar agreement to our results.

**Item ratings**

**General Informed Consent guidelines Ratings**

Competent prospective research participants (or their surrogates, when necessary) are presented with information about a research activity and what participation entails so that they can make decision about participation. Our data shows variability in conformity (strongly agree and agree) to general informed consent guideline items, suggesting that participants are not all receiving the same level of details in informed consent documents.

Items on **formatting and style** were presented well in our sample. Over 90% of our sample had readable font sizes, clearly labelled graphics (n=3), no spelling or grammatical errors, defined any acronyms used, and did not unnecessarily repeat any text. Previous work evaluating formatting and style had scores over 85%. Presenting needed information in a clear, readable and concise manner may be particularly important for surrogates and patients in this setting, who may not always have enough time within which to read documents, assimilate their content, and make decisions.

Conformity to items on the **key regulatory elements** (for example, participation is voluntary) was variable, between 51% and 100%. Only 2 of the 10 items scored below 65%. This is similar to previous work, where conformity ranged between 39% and
98%, with 2 items under 65%. That these are well laid out may be a testament to the validity of the trial and the oversight provided by the REB tasked with ensuring that the basis for a trial are ethically, scientifically and legally sound for adequate protection of participants. It is of great importance for participants and surrogates in this setting to know that the participant population was thoughtfully and fairly selected; that the condition could not be studied in any other patient population and that their well-being is being considered and monitored.

There was variability (17%-97%) in how our sample described items related to study design. Items about duration of participant’s participation, number of participants, explaining randomization and different groups to which participant can be assigned, scored more than 79% (strongly agree and agree). However, information about the duration of the entire study scored poorly (17.4% strongly agree and agree). This is comparable to previous work, \(^{105}\) where conformity ranged between 6% and 93%, and study duration score was 6%. Duration of a study could potentially determine when an intervention becomes widely available outside the clinical trial environment, and, to that end, how soon a patient can receive it for a condition that exists after discharge from ICU. Work needs to be done to determine whether this omission is of particular importance to trial participation decisions.

We examined a series of items focused on general ethical issues- potential risk(s) to embryos, foetus, that participation may benefit society, how personal information will be protected, organizations/individuals with access to personal information, whether PI/organization receive compensation for participant enrolment. Conformity to these was variable, from 7% to 84% (strongly agree and agree). Very few
ICDs provided information about compensation for participant enrolment (7%), or described potential risk(s) to foetus (28.6%). This is comparable with other studies that have looked at how risks are presented in consent documents.\textsuperscript{54, 132, 133, 105} For example, in Brehaut and colleagues work evaluating these items, conformity ranged between 6\% and 89\%. Risks and how they are presented influences decision making, which will be discussed in the following sections. Admissions of pregnant women to the ICU are not common. Pregnancy changes the body’s physiology, so pregnant women are usually excluded from ICU trials.\textsuperscript{134} It is possible that our sample reflects this uncommon admission of pregnant individuals to the ICU, and might explain why little attention is paid to foetal protection in our sample of ICDs.

**IPDAS Items Rating**

Decision aids are decision support tools designed to allow a user to work through a specific decision in a careful and deliberate way. There were substantial variations in how our sample of ICDs performed on the 32 decision aid standards items, and thus, how these documents incorporated components known to facilitate deliberative decision making. Conformity to these items was generally poor, with 21 of the 32 items scoring below 20\%.

Disclosure and transparency in consent documents has increased over the years,\textsuperscript{135} and this was reflected in our sample of ICDs. Items on disclosure and transparency (for example, name and contact information of the REB that approved the study) performed well, none scoring under 65\%. This is comparable to the scores obtained by Brehaut and colleagues\textsuperscript{54}, which ranged between 65\% and 98\%. Disclosing information
helps patients and surrogates determine the integrity of the research, which can influence their trial participation decisions. Such information can also potentially help allay fears of surrogates who might have misgivings about enrolling an incapacitated loved one.

Conformity to 2 items evaluating whether the choice made about participation matches the decision maker’s stated preference (s) was low. These are known to help decision makers make decisions in line with their personal treatment goals, and could potentially reduce the stress inherent in making decisions for loved ones. None of our sample of ICDs asked participants to consider what outcomes mattered most to them in their trial participation decisions, like in previous study. Items specific to values are very poorly conformed to, suggesting that these ICDs are not serving a key function of decision aids. Outcomes in ICU patients are numerous, including mortality (and conversely, survival), organ dysfunction, time to discharge (hospitalization), economic outcomes, functional outcomes (such as ability to walk, sit or breath without ventilator assistance), and quality of life measures. Mortality is a frequently used outcome measure in ICU trials because it is considered less prone to biases and is relatively easy to measure. Surveyed participants who had as yet to suffer a critical illness (and could be potential surrogates making decisions for critically loved ones), did not consider mortality a key outcome measure, placing more value on quality of life measures instead. This may be especially important given the prognosis in the ICU and the added complexity of a proxy making participation decisions. Canada’s Strategy for Patient Oriented Research (SPOR) aims to actively engage patients and caregivers/surrogates in the conduct of research activities so as to improve health practices and treatments, as well as improve the uptake of new practices. Future work needs to focus on key trial
outcomes that are important to patients and surrogates. Facilitating such a process to know what outcomes patients and surrogates deem essential, could help investigators as they incorporate patient views in their research designs, and might help a proxy to be more confident in their participation decisions, improve the quality of their decision, and reduce the stress associated with such decisions.

Our sample of ICDs performed poorly on the 2 IPDAS items about providing guidance, items known to help decision aid users avoid decision pitfalls and improve the quality of their decision. Conformity to these items was under 20%, as in previous work. The decision aid standards suggest guidance approaches that may be particularly important for surrogates, who may not know the preferences of their loved ones, and are making decisions based on their best interest. They also suggest ways of improving the consent process by incorporating both in-person and documentation components of consent. Work is underway in this direction. A grant (Title: Improving informed consent for research participation: Developing and evaluating a new model based on patient decision aids. Lead Investigator J Brehaut) has been submitted that looks to understand and evaluate how potential participants are being guided in their trial participation decisions.

It is known that the way information and options are presented can affect the choices and decisions that are made about them. For informed consent documents, this would mean presenting as much information about non-participation as for participation. It would also mean presenting information about probabilities in a manner that makes sense to patients and surrogates.
However, conformity to all 8 IPDAS items on **presenting probability information** (or lack thereof) in ICDs was under 20% (0%-16%), as in the previous work (0%-19%). It is possible that such information is unavailable, and the rational for the study being conducted in the first place. The ICD could explicitly state that such information was lacking, if that was the case. Information about probabilities is known to help users understanding of risk estimates\textsuperscript{145} a participant’s chance of being randomized to a particular study arm, experiencing side effects, long term effects and even the possibility of death, is important for patients and especially surrogates, to know in deciding to enrol a loved one. Including such information (known to help people understand risk estimates\textsuperscript{54, 146, 147} in the ICD may be important in helping surrogates and patients make trial participation decisions. Future work could focus on whether such information improves the quality of trial participation decisions made in the ICU.

There were also variations in how our sample of ICDs provided **information about options** (for example, advantages and disadvantages of non-participation and describing them in a consistent manner). Conformity to the 12 items on information about options ranged between 0% and 89%. This variation is consistent with previous work, where conformity was between 0% and 96%.\textsuperscript{54} Including information about participation and non-participation in equal measure in a consent documents may be especially important in the ICU where complex protocols are employed, outcomes are rather uncertain in the face of rapidly changing health conditions, and proxies need to make decisions on participants’ behalf. Providing as much information about other options in a clear and consistent manner in these circumstances may be essential to reassuring and
helping surrogates make a good decision about involving their loved one in a study when they do not know what their preferences might be.

On the other hand, our sample of ICDs did well in providing information about participation compared to previous work. Conformity to this item was 79%, compared to 35% in the other study. Descriptions of the health condition, intervention, advantages and disadvantages of participation were well addressed. The ICDs did not merely mention the name of a condition (for example septic shock), but explicitly explained what the condition entailed (‘Septic shock is a life-threatening medical condition whereby a person suffers from severe infection and/or inflammation which causes the blood pressure to drop and may decrease oxygen delivered to vital organs such as the brain, heart and kidneys …’). More than 80% of consent documents evaluated were directed at surrogates, probably because patients in the ICU may not necessarily know their health condition, conditions can change, and surrogates are usually relied on to make decisions. This might explain why so much information about the condition is provided in the consent document of ICU trials compared to that of general trials; participants outside the ICU usually make decisions for themselves, may already know their condition, and it might be perceived as repetitive to include such in the consent document. Future work should focus on how much patients and surrogates understand the information presented, as has been done in other participant populations, and how this understanding affects trial participation decisions of patients and surrogates.

Participants and especially surrogates need to know the kind of scientific evidence (“empirical observations about the options and their consequences”–148) driving the research being undertaken. Such evidence is known to help users have confidence in the
risk and benefit estimates presented in the consent document\textsuperscript{149}. Aside from the item on providing a production date (89% conformity), our sample of ICDs lacked conformity to items on \textit{using evidence} (conformity less than 5%), rarely providing evidence on which the research is based, or the strength of that evidence. This is comparable to that obtained in previous studies, where conformity, again, was under 5% for all but the item on providing a production date (76%). Poor conformity may be due to the complexity of conducting trials in the ICU. Some ICU management strategies are not based on strong scientific evidence, but rely mainly on body physiological principles to improve outcomes.\textsuperscript{150-152} Thus evidence may not be available, and can therefore not be included in the ICD. It is this lag in evidence and management strategies that the trials are seeking to address.

\textbf{ICU Recommendations Rating}

The fact that 18 new items were identified underscores the unique challenges for the consent process in the ICU. These items speak to additional safeguards needed to protect vulnerable trial participants. Conformity to ICU specific recommendations was highly variable in our sample, ranging between 2\% and 96.5\%.

The majority of ICDs obtained were targeted either at the surrogate, or designed for both surrogate and patient. This is important because ICU trial investigators recognize that surrogates are needed for trial participation decisions when a prospective participant is incapacitated, and have taken steps to identify surrogates as a way to further protect vulnerable participants involved in research activities. However, less than 12\% of our sample of ICDs was targeted solely at surrogates. This suggests that as much as possible,
patients are involved in trial participation decisions. It also suggests that the consent document developers are using patient specific templates for surrogates. Surrogate consent documents were not different from the patient version, containing the same information, except addressed to a surrogate by changing ‘you’ to ‘your’ (mentioned as family member, a loved one, next of kin, a legally authorized representative). Future work should investigate whether surrogate-specific ICDs would be more effective in communicating information that helps surrogates make good decisions about involving their loved ones in a trial.

Respect and acknowledgement of patient autonomy was evident in our sample of consent documents. Conformity to item about identifying surrogates for incapacitated patients was high (81%) as was the item looking at patients ability to re-consent for themselves should they be able to (64.5%). In the same vein, 68% of ICDs conformed to the item on whether surrogates can withdraw their consent if they so desire.

Our sample of ICDs identified surrogates for incapacitated patients, but did not explicitly provide them with any guidance (criteria for a decision or considering patients’ wishes was under 20%) around making a participation decision in these circumstances. This is an important safeguard for critically ill patients if surrogates are coached on how to make these decisions. Surrogates can be assured that that their loved one has the condition under study, which cannot be researched in any other patient population, and that their loved ones are not unnecessarily enrolled (by surrogates or investigators) in or taken advantage of in the name of altruism or scientific research. Given that real and hypothetical decisions about choices (delivering electric shocks to another person in different scenarios) can differ, future work should investigate how well surrogates
know about their loved ones preference in actual studies being conducted in the ICU, as has been done for hypothetical ICU scenarios in subsets of the ICU patient population.\textsuperscript{93}

More than 95\% of our sample of ICDs assured participants and surrogates that non-participation would not influence the quality of care they would be provided with. Given that emotions can affect decision making,\textsuperscript{155, 156} this may be assuring to surrogates, who may be too overwhelmed by the environment and situation to make any meaningful decisions. It is also reassuring for surrogates and patients to know that despite their dependence on their care team, they can refuse participation without any consequences to them.

It has been noted that severely ill research participants are very prone to therapeutic misconception, equating trial participation with therapeutic intent\textsuperscript{157-159}. Research participants sometimes fail to distinguish between research, and usual clinical treatment/care, believing them to be the same, especially when the study investigator is also their regular clinician. That these documents use explicit non-treatment vocabulary are steps in the right direction. The documents could further add that non-standard of care study components may not be tailored to individual needs (17.4\% conformity) and provide information on how to withdraw consent (31.4\% conformity). Interventions in a study are administered based on a restrictive protocol. Doses, time to take medication, other medications that can be taken (or not) during participation, are all pre-determined for enrolled patients based on random assignment, and not on individual preferences, as is the case in regular care\textsuperscript{159, 160}. Explicitly stating these in the informed consent
document could improve comprehension, help dispel misunderstandings, and reduce decisional conflict.

ICU trials are implemented within time constraints and under stressful circumstances. Conformity to items about indicating time within which to make a decision and acknowledging that the decision may be stressful was less than 10%. Low conformity may be due to investigators using standardised consent forms for their institution. It is also possible that investigators are so used to the pace and nature of the work, they perceive it as any other unit of the hospital. Yet for patients and surrogates, this setting can be quite terrifying and disturbing, and making important decisions in the space of a few minutes or hours can add to this stress. Recognizing these in the consent document can reassure surrogates and participants of the integrity of the research and that their wellbeing is critical to the investigators.

Not only was conformity to the item on disclosing compensation for enrolment low, our sample of ICDs also did not disclose any conflicts of interest that the investigators might have (10.5% strongly agree and agree). In reviewing the impact of financial disclosure on clinical practice and research, Licurse and colleagues noted that patients and participants believed health professionals should disclose any outside financial interests, be it for enrolling patients into a trial, drug samples, devices or any such. Such disclosure influenced research participation decisions. Like the previous study, relatively few consent documents provided information about compensation received by investigators/institution for any aspect of their study. It is important that investigators provide information and disclose funding sources, and any ties (financial or other interests) that the investigators/institution have with the funding agency to allow patients
and surrogates to gauge the extent that such ties may influence investigators and the integrity of the trial. How such disclosures will affect their decision to enrol their incapacitated loved ones in the ICU need to be explored.

**Strengths of Project**

To our knowledge, this is the first project to access a large set of ICDs used in critical care trials on a wide range of standards, namely general informed consent guidelines, ICU-specific recommendations and IPDAS standards. We believe that together, this is the most comprehensive set of standards that make recommendations about how one might improve the informed consent process for critical care trials.

This work is also the first to apply decision aid standards to ICDs used in critical care trials. While consent documents used in many clinical areas have been assessed against general consent guidelines, this work is the first to focus on and assess the consent documents of critical care trials on this set of guidelines. The notion that informed consent documents can do better at improving decision making for people in the highly stressful environment of the ICU is a new and important one.

A systematic search for literature on specific recommendations for the informed consent documents used in ICU research was performed. While guidelines for consent documents are fairly well established, our work focused on how critical care practitioners translate and incorporate these in their research.

Our sample frame included all relevant ICU trials in the clinicaltrials.gov database. Consent documents used in a variety of critical care trials and not any specific
condition or intervention were therefore evaluated. Other works have focused on consent
documents used in a variety of clinical areas\textsuperscript{54} or other sub populations\textsuperscript{104}.

While previous work has been limited to English only, this work evaluated ICDs
written in both English and French. The similar finding with previous work lends
evidence of the validity of our knowledge of this area.

**Limitations**

Some limitations of this work warrant consideration. While we sought to contact
all eligible critical care trialists, only one critical care trials database was consulted in
searching for ICU researchers. The WHO trials registry portal puts together trials from
many different registries and countries (e.g. German Clinical Trials Register,
ClinicalTrials.gov, Australian New Zealand Clinical Trials Registry, International
Standard Randomised Controlled Trial (ISRCTN), European Union Clinical Trials
Register), and around 80\% of listed studies are from clinicaltrials.gov\textsuperscript{166}. A comparison
of this database to the next largest four registries (Australian New Zealand Clinical Trials
Registry, EU Clinical Trials Registry, ISRCTN, and Japan Primary Registries Network)
on April 7\textsuperscript{th} 2015 showed that clinicaltrials.gov had 30\% more entries than the other 4
combined (187856 compared to 55620 total for the others). This work also included trials
from around the globe in both English and French, defining distinct inclusion criteria.
Since most academic journals require trials to be registered before they can be published
in their journals and clinicaltrials.gov is considered one of the largest registries of clinical
trials\textsuperscript{167}, we believe our sample of ICDs is representative of non-industry trials
undertaken in critical care in this time.
Non response is a recognised problem with survey methods that reduces generalizability of study results. Our response rate was 34.1%, consistent with similar work. We had a carefully written introductory letter, answered any concerns raised by investigators, sent a reminder two weeks after the initial email, and contact was made not only with principal investigators, but also with others knowledgeable about and involved in the trial. Our request went out at the tail end of the academic year, which might have contributed to the response received. Future work could also look at increasing the number of reminders set to investigators to understand how that affects response rates.

Studies that responded with an ICD were more likely to be conducted in an ICU facility and funded by non-industry sources. We sought, with our inclusion/exclusion criteria, to capture only ICU studies that were not funded solely by industry. This proved more challenging than expected. In an effort at standardization, it is recommended that conditions submitted to clinicaltrials.gov be mapped to MeSH terminology, but this is not always done. This might account for why some of our sample was on diseases that are not typically observed in the ICU, why fewer of these investigators responded to our request, and why a third of the ICDs received were excluded from evaluation. It is also possible that our approach to the database accounted for non ICU results and subsequent ICD exclusions. Future work focused on the ICU would need to take this into account when designing a sample size, or perhaps limit to specific conditions in the ICU.

Trials known to be funded solely by industry were excluded in our search on clinical trials.gov due to concerns about not being able to obtain documents from industry
within the time frame of this project. Our results might therefore not be applicable to industry funded trials.

We worked hard to identify all relevant recommendations for consent documents used in critical care research, conducting a systematic search of Medline, hand searching reference section of relevant articles, and consulting websites of relevant organizations. Still, some relevant papers (in the grey literature or in languages other than English) may have been excluded in this work, so it is possible that not all recommendations on consent for critical care research were explored. However, Medline returns precise and valid results to queries, is updated daily, and allows for use of more keywords per search compared to other similar databases\textsuperscript{169,170}. Major ICU journals were also searched for recommendations, and are confident that most ICU- specific issues in the literature were identified.

This work did not consider the verbal/conversational aspects of the consent process. It is difficult to ascertain the extent to which the issues that are not addressed in the consent document are explored in the more informal discourse with trial participants and surrogates. This work is ongoing; in the meantime, we maintain that many of the recommendations will need to be reflected in the informed consent document, given its central role in the larger informed consent process.

**Future Research Suggestions**

This work represents a fraction of the work that needs to be done on informed consent documents as we help ICU patients and surrogates through trial participation decisions. Below is an outline of some issues that need to be addressed going forward.
The ICU-specific items were developed from recommendations from the literature. Some of them were not recommended specifically for inclusion in the ICD per se. We do not know whether conformity to these issues would have any beneficial effects on research conducted in the ICU. More work needs to be done to demonstrate any positive benefits of these recommendations in the ICD to patient and surrogate understanding and subsequent participation decisions.

ICU specific issues need to be addressed in the consent document. Future research could focus on particular information (from the 18 ICU-specific set of items) to include in the consent document that is of uttermost importance to helping patients and surrogates make participation decision. This could potentially reduce the length of ICDs that prevent some from reading them at all.

Rigorous development of the 77 items using psychometric methods (e.g. validity, reliability analyses, and inter-item correlation) could be performed to help turn the 77 raw items into a smaller set that function as a scale measuring quality of the informed consent process specific to the ICU.

The evaluation tool could be used to collect evidence of learning after workshops on designing better ICDs for ICU trials (rate ICDs before and after workshop and compare average ratings of items)

Consent documents written in both English and French were evaluated. Future work could compare particular strengths of English documents to those of French documents with respect to their conformity to these standards and guidelines. With the consent document being a major tool for knowledge translation, this could help us target
particular areas to direct education and training efforts for patients, surrogates and critical care researchers.

Future work could focus on designing a decision-aid type informed consent documents, and evaluating it against typical consent documents as well as critical care specific consent documents. Such work could also explore whether area/disease specific consent documents or a more general template is important to participant understanding of the documents.

A decision aid approach to consent may address the pitfalls in understanding of informed consent documents. Given the time constrains and stresses within which consent is sought in the ICU, it would be interesting to explore the type of tool most effective in facilitating further consent discussions.

Durand and Colleagues (2015)\textsuperscript{171} rated a sample of existing patient decision aids on decision aid standards (IPDASi). Such an approach could be used to compare decision aids to consent documents on IPDAS items. This could help with identifying similarities and differences of these documents on decision quality standards as well as identifying items that are not routinely discussed in these documents. Further exploration of how the absence of such items impact understanding of information and subsequent decisions made could also be done.

Results from this study could be used to organize workshops for REBs and researchers, to reiterate the challenges of consent in the ICU, encourage re-examination of consent document templates and ascertain areas where some recommendations might have been overlooked for amendments to their ICD templates for critical care trials.
These workshops could also be used as a way to introducing REB and researchers to the idea of using decision aid –consent documents and illicit potential barriers to their use to help researchers as they embark on developing such consent document templates.

Collaboration among researchers, patients, surrogates, REB members and research centre administrators could identify priorities from among the items that are not addressed in consent documents for immediate and future actions.

**Conclusion**

This work set out to investigate how informed consent documents used in critical care research help patients and surrogates make trial participation decisions. This was done by obtaining 86 informed consent documents from critical care trial investigators listed on clinicaltrials.gov, and evaluating these documents against standards and recommendations for informed consent documents. The ICU presents an area with special issues related to informed consent for trial participation, and there are specific recommendations targeted at these issues. With the majority of critical care patients aged 65 or more \(^{72}\), it is expected that the baby boomer population would have a huge impact on the healthcare systems, including ICU resources, of many countries in the coming years. That the recommendations for consent in the ICU span various disciplines demonstrate the growing concern and preparation from various entities to continually ensure that prospective research participants are always respected and protected in human research endeavours.

Overall, our sample of consent documents conformed to standards for the consent document used in human research, suggesting key informed consent and regulatory
information is usually being provided to research participants and their surrogates. They did not conform well to decision aid standards, suggesting that more could be done to help people with the process of making trial participation decisions. They did not do well at conforming to ICU-specific standards, suggesting that ICU-specific issues need to be represented more completely in informed consent documents used in critical care trials. Current and future consent documents used in these trials need to be improved to optimize the help they provide to patients and surrogates as they make trial participation decisions.

Research in the ICU is essential, patients and surrogates in this environment need help to work through tough and stressful decisions about trial participation, and this work is a start in this direction.
APPENDICES

Appendix I - The Nuremberg Code

1. The voluntary consent of the human subject is absolutely essential.
   This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision. This latter element requires that, before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person, which may possibly come from his participation in the experiment.

   The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study, that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted, where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment, the human subject should be at liberty to bring the experiment to an end, if he has reached the physical or mental state, where continuation of the experiment seemed to him to be impossible.

10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgement required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Appendix II- Search strategy for articles with recommendations for consent in ICU

Search terms used: December 11/2013; Rerun on March 12, 2014

informed consent
documentation
ethics
proxy
third-party consent
consent forms
(informed adj 3 consent).twr.
Informed consent OR documentation OR ethics OR proxy OR third-party consent OR consent forms OR (informed adj 3 consent).twr.
clinical trials as topic
controlled clinical trial
human experimentation
biomedical research
clinical trials as topic OR controlled clinical trial OR human experimentation OR biomedical research
vulnerable populations
mental competency
critical illness
intensive care
cognition disorders
critical care
vulnerable populations OR mental competency OR critical illness OR intensive care OR cognition disorders OR critical care
Informed consent OR documentation OR ethics OR proxy OR third-party consent OR consent forms OR (informed adj 3 consent).twr. AND clinical trials as topic OR controlled clinical trial OR human experimentation OR biomedical research AND vulnerable populations OR mental competency OR critical illness OR intensive care OR cognition disorders OR critical care
Remove duplicates from 21 (above)
Limit 22 (above) to English
Appendix III- Request to PIs for consent documents

A French message follows/La version française suit l’anglais dans ce courriel.

Dear Dr. _________.

Our team is hoping to obtain your help with a research project. As you know, it can be challenging to ensure that research participants are fully and properly informed when being recruited for clinical trials. In the case of research conducted in critical care settings, these challenges can be even greater, often involving surrogate decision making, time pressures, emotional situations, etc. We are conducting a study to examine the informed consent documents of critical care trials, to examine how these challenges are addressed.

We are hoping you will be able to provide us with the informed consent documents (consent forms, patient information sheets) used in your study. Your trial ________- NCT____ was selected from a sample of critical care trials registered with clinicaltrials.gov.

We are gathering informed consent documents which we will evaluate in an effort to shed light on how informed consent materials may be improved. This project is an extension of a previous work funded by the Canadian Institutes of Health Research that we have previously published: https://www.ncbi.nlm.nih.gov/pubmed/22537428

If there is someone else who can more easily provide us with these materials, we would greatly appreciate you passing this letter on to them. If there are multiple versions of the informed consent documents for this study, please send the most current, non-template version that is conveniently available to you.

Any identifying information (e.g. investigator names, institutions, proprietary drug names) will be redacted by our study coordinator before any assessments are performed. Our results will only be described in aggregate, identifying no individual investigator, institution, or intervention. This study is being run out of the University of Ottawa and the Ottawa Hospital Research Institute (OHRI), and has been reviewed by the Ottawa Health Science Network Research Ethics Board (OHSN-REB). By e-mailing us your informed consent form(s), consent is implied. This will not have any effect on you and your relationship with the database Clinicaltrials.gov.

We greatly appreciate your consideration of this request. Documents can be sent as email attachments or faxed, at your convenience. Please feel free to contact me by email if you have any further questions.

Sincerely,

Dr. Jamie Brehaut, PhD.
Senior Scientist-Clinical Epidemiology Program, OHRI.
Associate Professor-Department of Epidemiology and Community Medicine, University of Ottawa.
Email: icuinformedconsent@toh.on.ca
Fax: (613) 739-6938

For the team

Dr. Lauralyn McIntyre, MD, MSc, FRCPC.
Scientist, Clinical Epidemiology, OHRI.
Physician, Critical Care, The Ottawa Hospital.
Assistant Professor-Department of Medicine, University of Ottawa.

Dr. Ray Saginur, MD.
Clinical Investigator, OHRI.
Chief, Division of Infectious Diseases, The Ottawa Hospital.
Chair, OHSN-REB

Pearl Atwere, M.Sc. (Candidate)
Department of Epidemiology and Community Medicine, University of Ottawa.
Cher docteur ______,

Notre équipe souhaite obtenir votre assistance dans le cadre d’un projet de recherche. Comme vous le savez déjà, il peut être difficile de s’assurer que l’ensemble des participants de recherche soit informé de manière complète et appropriée au moment d’être recrutées dans le cadre d’essais cliniques. Dans le cadre de recherches effectuées en soins intensifs, ces défis peuvent s’avérer d’autant plus importants, comportant souvent la prise de décisions d’un représentant légal, des contraintes relatives au temps, des situations émotionnelles, etc. Nous entreprenons une étude dans le but d’examiner les documents de consentement éclairé relatifs aux essais en soins intensifs, afin d’examiner comment on procède lorsque vient le temps de relever ces défis.

Nous espérons que vous serez en mesure de nous fournir les documents de consentement éclairé (formulaires de consentement, feuilles renseignements à l’intention des patients) employés dans le cadre de votre étude. Votre étude – NCT_____ a été sélectionnée à partir d’un échantillon d’essais cliniques enregistrée sur clinicaltrials.gov.

Nous recueillerons les documents de consentement éclairé que nous évaluerons en vue de faire la lumière sur les possibilités d’améliorer les documents de consentement éclairé. Ce projet se veut une prolongation de travaux antérieurement financés par les Instituts de recherche en santé du Canada, et publiés précédemment : https://www.ncbi.nlm.nih.gov/pubmed/22537428

Si vous connaissez une autre personne qui serait en mesure de nous fournir ces documents plus aisément, nous apprécierions grandement si vous pouviez leur transmettre cette lettre. Si vous avez en votre possession plusieurs versions des documents de consentement éclairé liées à cette étude, veuillez nous faire parvenir la version la plus récente à laquelle vous pouvez facilement accéder.

Nos coordinateurs de l’étude retireront toute information qui pourrait servir à vous identifier (ex., noms des chercheurs, des établissements ou des spécialités pharmaceutiques) avant de procéder aux évaluations. Nos résultats seront décrits uniquement sous forme d’agrégat, n’identifiant aucun chercheur, aucun établissement, ni aucune intervention. Cette étude est effectuée conjointement par l’Université d’Ottawa et Institut de Recherche de l’Hôpital d’Ottawa (IRHO), et a été révisé par le Conseil d’éthique de recherche du Réseau de science de la santé d’Ottawa (CER-RSSO). En nous faisant parvenir vos formulaires de consentement éclairé par courriel, votre consentement à la participation devient implicite. Ceci n’aura aucun effet sur vous ou votre relation avec la base de données de Clinicaltrials.gov.

Nous vous remercions de l’attention que vous porterez à cette demande. Vous pourrez nous faire parvenir les documents par courriel ou par télécopieur, à un moment qui vous conviendra. N’hésitez pas à communiquer avec moi par courriel si vous avez d’autres questions.

Je vous prie d’agréer de mes salutations les plus sincères,

D’ Jamie Breault, Ph.D.
Senior Scientist-Clinical Epidemiology Program, Ottawa Hospital Research Institute (OHRI).
Associate Professor-Department of Epidemiology and Community Medicine, University of Ottawa.
Courriel : icuinformedconsent@toh.on.ca
Télécopieur : (613) 739-6938

Au nom de l’équipe :

D’ Lauralyn McIntyre, MD, MSc, FRCPC
Scientist, Clinical Epidemiology, OHRI.
Physician, Critical Care, The Ottawa Hospital.
Assistant Professor-Department of Medicine, University of Ottawa.

D’ Ray. Saginur, MD
Clinical Investigator, OHRI.
Chief, Division of Infectious Diseases, The Ottawa Hospital.
Chair, Ottawa Health Science Network Research Ethics Board.

Pearl Atwere, MSc. (Candidate)
Department of Epidemiology and Community Medicine, University of Ottawa
Appendix IV- Follow-up letter to PIs for consent documents

A French message follows/La version française suit l’anglais dans ce courriel.

Dear Dr. ___,

A few weeks ago, we sent you an email asking if you would provide us with the informed consent documents that were used in your study (___-NCT___) registered with ClinicalTrials.gov. As we have not yet received your response, we would like to reach out to you once again. Your help with this would be very much appreciated. The original email request follows.

Our team is hoping to obtain your help with a research project. As you know, it can be challenging to ensure that research participants are fully and properly informed when being recruited for clinical trials. In the case of research conducted in critical care settings, these challenges can be even greater, often involving surrogate decision making, time pressures, emotional situations, etc. We are conducting a study to examine the informed consent documents of critical care trials, to examine how these challenges are addressed.

We are hoping you will be able to provide us with the informed consent documents (consent forms, patient information sheets) used in your study. Your trial ___ - NCT___ was selected from a sample of critical care trials registered with clinicaltrials.gov.

We are gathering informed consent documents which we will evaluate in an effort to shed light on how informed consent materials may be improved. This project is an extension of a previous work funded by the Canadian Institutes of Health Research that we have previously published: https://www.ncbi.nlm.nih.gov/pubmed/22537428

If there is someone else who can more easily provide us with these materials, we would greatly appreciate you passing this letter on to them. If there are multiple versions of the informed consent documents for this study, please send the most current, non-template version that is conveniently available to you.

Any identifying information (e.g. investigator names, institutions, proprietary drug names) will be redacted by our study coordinator before any assessments are performed. Our results will only be described in aggregate, identifying no individual investigator, institution, or intervention. This study is being run out of the University of Ottawa and the Ottawa Hospital Research Institute (OHRI), and has been reviewed by the Ottawa Health Science Network Research Ethics Board (OHSN-REB). By e-mailing us your informed consent form(s), consent is implied. This will not have any effect on you and your relationship with the database Clinicaltrials.gov.

We greatly appreciate your consideration of this request. Documents can be sent as email attachments or faxed, at your convenience. Please feel free to contact me by email if you have any further questions.

Sincerely,

Dr. Jamie Brehaut, PhD.
Senior Scientist-Clinical Epidemiology Program, Ottawa Hospital Research Institute (OHRI).
Associate Professor-Department of Epidemiology and Community Medicine, University of Ottawa.
Email: icuinformedconsent@toh.on.ca
Fax: (613) 739-6938

For the team
Dr. Lauralyn McIntyre, MD, MSc, FRCPC.
Scientist, Clinical Epidemiology, OHRI.
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Clinical Investigator, OHRI.
Chief, Division of Infectious Diseases, The Ottawa Hospital.
Chair, OHSN-REB

Pearl Atwere, M.Sc. (Candidate)
Department of Epidemiology and Community Medicine, University of Ottawa.
Cher docteur _____,

Il y a quelques semaines, nous vous avons envoyé un e-mail vous demandant si vous pouviez nous fournir les documents relatifs au consentement éclairé qui ont été utilisés dans votre étude (_____ - NCT____) inscrite sur ClinicalTrials.gov. Vu que nous n’avons pas encore reçu cette documentation, nous aimerions vous présenter notre demande à nouveau. Votre aide serait très appréciée. L’e-mail de la demande originale est ci-dessous.

Notre équipe souhaite obtenir votre assistance dans le cadre d’un projet de recherche. Comme vous le savez déjà, il peut être difficile de s’assurer que l’ensemble des participants de recherche soit informé de manière complète et appropriée au moment d’être recrutées dans le cadre d’essais cliniques. Dans le cadre de recherches effectuées en soins intensifs, ces défis peuvent s’avérer d’autant plus importants, comportant souvent la prise de décisions d’un représentant légal, des contraintes relatives au temps, des situations émotionnelles, etc. Nous entreprenons une étude dans le but d’examiner les documents de consentement éclairé relatifs aux essais en soins intensifs, afin d’examiner comment on procède lorsque vient le temps de relever ces défis.

Nous espérons que vous serez en mesure de nous fournir les documents de consentement éclairé (formulaires de consentement, feuilles renseignements à l’intention des patients) employés dans le cadre de votre étude. Votre étude ______-NCT__ à été sélectionnée à partir d’un échantillon d’essais cliniques enregistrée sur clinicaltrials.gov. Nous recueillerons les documents de consentement éclairé que nous évaluerons en vue de faire la lumière sur les possibilités d’améliorer les documents de consentement éclairé. Ce projet se veut une prolongation de travaux antérieurement financés par les Instituts de recherche en santé du Canada, et publiés précédemment :

Si vous connaissez une autre personne qui serait en mesure de nous fournir ces documents plus aisément, nous apprécierions grandement si vous pouviez leur transmettre cette lettre. Si vous avez en votre possession plusieurs versions des documents de consentement éclairé liées à cette étude, veuillez nous faire parvenir la version la plus récente à laquelle vous pouvez facilement accéder.

Nos coordonnateurs de l’étude retireront toute information qui pourrait servir à vous identifier (ex., noms des chercheurs, des établissements ou des spécialités pharmaceutiques) avant de procéder aux évaluations. Nos résultats seront décrits uniquement sous forme d’agrégat, n’identifiant aucun chercheur, aucun établissement, ni aucune intervention. Cette étude est effectuée conjointement par l’Université d’Ottawa et Institut de Recherche de l’Hôpital d’Ottawa (IRHO), et à été révisé par le Conseil d’éthique de recherche du Réseau de science de la santé d’Ottawa (CÉR-RSSO). En nous faisant parvenir vos formulaires de consentement éclairé par courriel, votre consentement à la participation devient implicite. Ceci n’aura aucun effet sur vous ou votre relation avec la base de données de Clinicaltrials.gov.

Nous vous remercions de l’attention que vous porterez à cette demande. Vous pourrez nous faire parvenir les documents par courriel ou par télécopieur, à un moment qui vous conviendra. N’hésitez pas à communiquer avec moi par courriel si vous avez d’autres questions.

Je vous prie d’agréer de mes salutations les plus sincères,

Dre Jamie Brehaut, Ph.D.
Senior Scientist-Clinical Epidemiology Program, Institut de Recherche de l’Hôpital d’Ottawa (IRHO).
Associate Professor-Department of Epidemiology and Community Medicine, University of Ottawa.

Courriel : icuinformedconsent@toh.on.ca
Télécopieur : (613) 739-6938

Au nom de l’équipe :
Dre Lauralyn McIntyre, MD, MSc, FRCPC
Scientist, Clinical Epidemiology, IRHO.
Physician, Critical Care, The Ottawa Hospital.
Assistant Professor-Department of Medicine, University of Ottawa.

Dre Ray. Saginur, MD
Clinical Investigator, IRHO.
Chief, Division of Infectious Diseases, The Ottawa Hospital.
Chair, Ottawa Health Science Network Research Ethics Board.

Pearl Atwere, MSc. (Candidate)
Department of Epidemiology and Community Medicine, University of Ottawa.
Appendix V- Documents with guidelines/recommendations for consent in the critically ill

Medline search on March 12, 2014

Titles identified = 927

Excluded = 164
- Non-English = 23
- Duplicates = 78
- Paediatric, Adolescent/Children = 63

Abstracts Reviewed = 763

Exclude = 742
- [Commentaries/Reviews/Recommendations for specific group/disease] = 81
- Disease/Group specific (e.g. HIV/AIDS, Prisoners) = 661

Full text reviewed = 21

Exclude = 14
- No recommendations for consent in the critically ill/ICU

Eligible articles from Medline = 7

Hand searched references of eligible articles (3)

Articles meeting inclusion n=10
Appendix VI- Items extracted from articles with recommendations for consent in the critically ill

1. Does the ICD clearly indicate the time period over which the decision must be made?\textsuperscript{71, 76, 122} \textit{Item 1}

2. Do the ICDs define in the first page (sentence) what is meant by research?\textsuperscript{80} 
OVERLAP WITH \textit{Item 1} on general consent guidelines

3. Do the ICDs clearly explain clinical equipoise?\textsuperscript{80, 80} \textit{Addressed by REB/FEASIBILITY}

4. Do the ICDs avoid the use of terms like ‘treatment’, ‘medication’, ‘therapy’ to describe investigational interventions? \textsuperscript{80, 106} 
COMBINED WITH NEXT FOR Section C, \textit{item 2}

5. Do the ICDs avoid the use of the terms ‘doctor’ in favour of ‘study doctor’, ‘investigator’, etc. to refer to study personnel? \textsuperscript{80} 
COMBINED WITH ABOVE FOR Section C, \textit{item 2}

6. Do the ICDs explain the difference between medical care and research care? (The different arms of the trial are clearly spelt out in the ICD) \textsuperscript{106} 
OVERLAP WITH Item 5, and \textit{Item 20} on general consent guidelines

7. Do the ICDs make a distinction between therapeutic and non-therapeutic interventions? \textsuperscript{71, 94, 106, 122, 123} \textit{Item 3}

8. Do the ICDs explicitly indicate that randomization means that those components of treatment may not be optimized for the individual patient? \textsuperscript{71, 108} \textit{Item 4}

9. Do the ICDs clearly describe the control arm in terms of usual care, best practice, or other similar? \textsuperscript{71, 122} 
SPLIT INTO \textit{Item 5} AND \textit{Item 6}: The ICD clearly describes what standard of care is for the health condition AND The ICD clearly describes how each arm of the trial differs from standard of care for the condition

10. Do the ICDs indicate that no non-therapeutic procedures involve greater than minimal risk? \textsuperscript{122} 
COMBINED WITH NEXT and considered to be addressed by REB

11. Do the ICDs categorize risks as minimal (physical exam), minor increase over minimal (blood draws), greater risk but possible personal benefit (surgery)? \textsuperscript{71} 
COMBINED WITH ABOVE FOR REB

12. Do the ICDs indicate that the decision not to participate will not affect the quality of care? \textsuperscript{980, 107} \textit{Item 7}

13. Do the ICDs clearly indicate that the intervention is legally approved (or unproven) for the condition under investigation? The ICD indicates that the
<table>
<thead>
<tr>
<th>Item</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>Do the ICDs indicate that the reader should read the entire document carefully?</td>
</tr>
<tr>
<td>80</td>
<td>NOT SPECIFIC TO ICU</td>
</tr>
<tr>
<td>80</td>
<td>If appropriate, does the ICD specifically and clearly refer to death as one of the risks of the research? COMBINED WITH NEXT TWO AND REWORD FOR</td>
</tr>
<tr>
<td>80</td>
<td>Item 9</td>
</tr>
<tr>
<td>106</td>
<td>Risk(s) to participant has been explained (referred to), including mortality where applicable. The ICD lists/explains all foreseeable risks of intervention to participants. The ICD mentions death as a possible risk</td>
</tr>
<tr>
<td>80</td>
<td>If death is an endpoint, do the ICDs clearly state that one of the purposes of the research is to determine if there is an effect on survival?</td>
</tr>
<tr>
<td>94</td>
<td>Do the ICDs specify that patients in the ICU require special ethical protections due to their vulnerability? COMBINED WITH NEXT FOR REB consideration</td>
</tr>
<tr>
<td>71</td>
<td>Do the ICDs specify that because ICU patients cannot make decisions for themselves, they need special protections in the context of enrolling them for research?</td>
</tr>
<tr>
<td>76</td>
<td>Does the ICD address the fact that when a patient is too sick, a proxy must make decisions for them? Item 10</td>
</tr>
<tr>
<td>76</td>
<td>Do the ICDs mention that the decision needs to be made by the legal representative? COMBINED WITH NEXT 2 FOR Item 11</td>
</tr>
<tr>
<td>71</td>
<td>Do the ICDs clearly state that the proxy has been identified as the for the patient?</td>
</tr>
<tr>
<td>76</td>
<td>Do the ICDs clearly state /explain why you can be a surrogate.</td>
</tr>
<tr>
<td>76</td>
<td>Do the ICDs acknowledge that this is an emotional time for the family? COMBINE WITH NEXT 2 FOR Item 12</td>
</tr>
<tr>
<td>76</td>
<td>Do the ICDs acknowledge that this decision may be stressful for the proxy?</td>
</tr>
<tr>
<td>76</td>
<td>Do the ICDs acknowledge that despite best efforts, it is known that proxy decisions can be different than patient decisions?</td>
</tr>
<tr>
<td>93</td>
<td>Do the ICDs ask surrogates to consider whether they have discussed with the patient their wishes with respect to participation in research? Item 13</td>
</tr>
<tr>
<td>94</td>
<td>Do the ICDs make it clear a surrogate should make the decision not based on their own opinion but based on the wishes of the patient? COMBINE WITH NEXT 2 FOR Item 14</td>
</tr>
<tr>
<td>Number</td>
<td>Question</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>29</td>
<td>Do the ICDs explain what the surrogate should base a decision on (substituted judgement/ best interest judgement)</td>
</tr>
<tr>
<td>30</td>
<td>Do the ICDs indicate that the proxy is supposed to make the decision that, to the best of their knowledge, the patient would make if there were able? (Lauralyn, Is this the standard, persons’ best interests, compatible with wishes?)</td>
</tr>
<tr>
<td>31</td>
<td>Do the ICDs indicate that a decisional capacity assessment has/will been made of the patient?</td>
</tr>
<tr>
<td>32</td>
<td>Do the ICDS clearly say that the patient is very sick?</td>
</tr>
<tr>
<td>33</td>
<td>Do the ICDS indicate that the SDM can refuse to consider the decision? (not sure about this, but it does seem different than clearly saying that the patient wouldn’t want to be part of the trial)</td>
</tr>
<tr>
<td>34</td>
<td>Do the ICDs explain that surrogate can withdraw their consent (if patient regains capacity, if surrogate changes his mind, if patient’s condition changes, information on risks changes,)</td>
</tr>
<tr>
<td>35</td>
<td>Do the ICDs indicate that informed consent may be revisited throughout the trial?</td>
</tr>
<tr>
<td>36</td>
<td>Do the ICDs indicate that involvement in the study will cease if/when patient decides they do not wish to participate?</td>
</tr>
<tr>
<td>37</td>
<td>It has been explained that no direct benefit to the patient may be gained from enrolling patient</td>
</tr>
<tr>
<td>38</td>
<td>Do the ICDS indicate that informed consent will also be obtained from the patient when they are well enough to do so?</td>
</tr>
<tr>
<td>39</td>
<td>How to withdraw consent has been explained. The steps to go through to withdraw (contact information, room # etc) are indicated on the ICD.</td>
</tr>
<tr>
<td>40</td>
<td>Do the ICDs specify that wherever possible, someone other than the treating physician should explain the study to potential participants/proxies?</td>
</tr>
</tbody>
</table>
Appendix VII: Informed Consent Evaluation Instrument (ICEi)

Section A

Informed Consent Document: # __________
Date: __________
Rater: __________

Key
- ICDs = Informed Consent Documents
- PP = Potential Participant
- Advantages = positive health outcomes, any other positive features
- Disadvantages = harms, risks, side effects, inconveniences, any other negative outcomes or features

Providing Information about Options in Sufficient Detail to Make a Decision.

1. On the first page of the ICDs there is a description that PPs need to make a decision about whether or not to participate in the trial.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = Early in the ICDs there is a clear description that a decision must be made. (e.g. “Take time to decide whether or not you wish to take part”).
A = Use this rating if you think the ICDs fulfill the criterion, but there is room for improvement. (e.g. “Consider the information carefully before making your decision”)
D = Use this rating if you do NOT think the decision is clearly described, or if unclear. (e.g. “before you decide to participate”; “should you agree to join the study”)
SD = The decision is NOT explicitly described at all, or participation is assumed.

2. The ICDs describe the health condition or problem.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
<th>N/A</th>
</tr>
</thead>
</table>

SA = There is a clear description of the condition or problem
A = Use this rating if you think the ICDs fulfill the criterion, but there is room for improvement.
D = Use this if you do NOT think the ICDs fulfill the criterion, or if unclear.
SD = There is NO description of the condition or problem.

3. The ICDs describe the intervention.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>
SA = There is a clear description of the intervention
A = Use this rating if you think the ICDs fulfill the criterion, but there is room for improvement.
D = Use this if you do NOT think the ICDs fulfill the criterion, or if unclear.
SD = There is NO description of the intervention.

4. The ICDs describe the advantages of participation in the study.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = All advantages are clearly presented.
A = Use this if you think the ICDs fulfill the criterion, but there is room for improvement.
D = Some advantages are NOT clearly described.
SD = There is NO description of the advantages of participation in the study.

5. The ICDs describe the disadvantages of participation in the study.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = All disadvantages are clearly presented.
A = Use this if you think the ICDs fulfill the criterion, but there is room for improvement.
D = Some disadvantages are NOT clearly described.
SD = There is NO description of the disadvantages of participation in the study.

6. The ICDs describe the advantages of NOT participating in the study.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = All advantages are clearly presented.
A = Use this if you think the ICDs fulfill the criterion, but there is room for improvement.
D = Some advantages are NOT clearly described.
SD = There is NO description of the advantages of NOT participating in the study.

7. The ICDs describe the disadvantages of NOT participating in the study.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = All disadvantages are clearly presented.
A = Use this if you think the ICDs fulfill the criterion, but there is room for improvement.
D = Some disadvantages are NOT clearly described.
SD = There is NO description of the disadvantages of NOT participating in the study.

8. The ICDs describe the disadvantages of participation in a consistent order (e.g. rarity, severity).
SA = Disadvantages of participation are clearly presented in a consistent order.
A = Use this if you think the ICDs fulfill the criterion, but room for improvement.
D = Only some disadvantages are presented in a consistent order.
SD = Disadvantages of participation are NOT presented, or NOT presented in a consistent order.

9. The ICDs describe the disadvantages of NON-participation in a consistent order (e.g. rarity, severity).

SA = Disadvantages of non-participation are clearly presented in a consistent order.
A = Use this if you think the ICDs fulfill the criterion, but room for improvement.
D = Only some disadvantages are presented in a consistent order.
SD = Disadvantages of NON-participation are NOT presented, or NOT presented in a consistent order.

10. The ICDs make it possible to compare, head to head*, the advantages and disadvantages of both participation and non-participation.

SA = Potential advantages and disadvantages are presented in a head to head comparison.
A = Use this rating if you think the ICDs fulfill the criterion, but there is room for improvement.
D = Some, but not all advantages and disadvantages are presented head to head, or only disadvantages are presented head to head.
SD = Advantages and disadvantages are scattered throughout the text; direct comparison of advantages and disadvantages are difficult or impossible.

• *‘Head to head’ refers to presentation on the same page, in text, table, figure, or other manner that encourages direct comparison between features.

11. The ICDs describe the reversibility of any potential disadvantages of participation (e.g., likely reversible; likely permanent).

SA = The reversibility of all potential side effects are clearly presented.
A = Use this if you think the ICDs fulfill the criterion, but room for improvement.
D = Reversibility information is provided for only some of the potential side effects, or only general statements of reversibility (e.g., “most side effects should be temporary”) are provided.
SD = No information is provided about the reversibility of potential side effects.

12. The ICDs describe the likely time of onset of any potential side effects of participation (e.g., immediate, delayed, late).
### Presenting Probabilities.

13. The ICDs provide information on the probabilities* (or describe a lack of probability information) for all advantages/disadvantages stemming from the intervention.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
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</table>

SA = The ICDs clearly present probabilities (or clearly describe a lack of data) for all intervention advantages and disadvantages.
A = Probabilities for most intervention advantages/disadvantages are clearly outlined
D = Probabilities for intervention advantages/disadvantages are missing or unclear (i.e. descriptors provided, but NO explanation of what they mean) in many cases.
SD = Probabilities for intervention advantages/disadvantages are NOT provided at all.

* ‘Probabilities’: The likelihood associated with an outcome/advantage/disadvantage, which can be expressed as %, proportion, or in the absence of more detailed numbers, standardized descriptors (e.g.: very rare = < 1/1000), with descriptors explained.

14. The ICDs specify the population(s) that yielded the probabilities associated with intervention advantages/disadvantages.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
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</table>

SA = The ICDs provide a clear definition of the population to which the probabilities apply.
A = The population is presented for most, but not all probabilities.
D = Use this if you do NOT think that the ICDs fulfill the criterion, or if unclear.
SD = There is NO definition at all of the population to which the probabilities apply, or no probabilities are provided.

15. The ICDs specify probabilities in natural frequencies; (e.g.: “If 1000 patients are treated with NSAIDs, our best guess is 800 patients will improve”).

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
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<tbody>
<tr>
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</tbody>
</table>

SA = The ICDs clearly present probabilities in natural frequencies.
A = Some natural frequencies are provided, but not for all probabilities.
D = Use this if you do NOT think that the ICDs fulfill the criterion, or if unclear.
SD = There is NO reference to natural frequencies for probabilities, or there are NO probabilities.
16. The ICDs specify the time period over which the probabilities apply (e.g.: 9/1000 over the next year will have a heart attack; N.B. this does NOT refer to duration of symptoms).

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
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</thead>
</table>

SA = The ICDs clearly present the time period for the stated probabilities.
A = Time periods are provided for most, but not all probabilities.
D = Use this if you do NOT think that the ICDs fulfill the criterion, or if unclear.
SD = There is NO description of the time period for the given event rates of the stated probabilities, or there are NO probabilities.

17. The ICDs allow the user to compare probabilities using the same denominator.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = The ICDs use constant denominators.
A = Use this if you think the ICDs fulfill the criterion, but there is room for improvement.
D = Use this if you do NOT think the ICDs fulfill the criterion, or if unclear.
SD = The denominators vary considerably across the ICDs, or there are NO outcome probabilities.

18. The ICDs provide information about the levels of uncertainty around probabilities.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = The uncertainty around the probabilities are conveyed explicitly through ranges, 95% confidence intervals, etc.
A = Uncertainty around probabilities is conveyed for some, but not all, probabilities.
D = Vague descriptors of uncertainty are used, i.e., phrases such as ‘roughly’ or ‘approximately’, ‘you may experience X’, etc.
SD = There is NO acknowledgement of uncertainty in the probabilities, or there are NO probabilities.

19. The ICDs provide more than one way of viewing probabilities (e.g., words, numbers, and diagrams).

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
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</thead>
</table>

SA = More than one method is used to present all probabilities.
A = More than one method is used for some, but not all, probabilities.
D = Use this if you do NOT think that the ICDs fulfill the criterion, or if unclear.
SD = Multiple methods to view the probabilities are NOT included, or there are NO probabilities.

20. The ICDs describe probabilities in multiple frames to limit framing biases

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>
Clarifying and Expressing Values.

21. The ICDs describe important intervention advantages and/or disadvantages with a level of detail that helps PPs imagine the impact on their life (e.g., “Drug X may cause low blood pressure. People with low blood pressure may feel weak or tired”).

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
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</thead>
</table>

SA = The ICDs provide clear additional detail about how all important intervention advantages and/or disadvantages might impact someone’s life.
A = Some additional detail of intervention advantages and/or disadvantages is provided.
D = Very little additional detail on intervention advantages and/or disadvantages is provided
SD = The discussion of advantages and/or disadvantages does not include reference to the personal importance of advantages and/or disadvantages (at most only providing the chances of the outcomes happening).

22. The ICDs ask PPs to think about which intervention advantages and/or disadvantages matter most to them.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
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</thead>
</table>

Structured Guidance in Deliberation and Communication.

23. The ICDs provide guidance on a step-by-step way to decide whether or not to participate in the trial.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = The ICDs provide clear guidance, e.g. by providing worksheets, describing specific decision-making steps, or specifying a detailed action plan for progressing with the decision.
A = Use this if you think the ICDs fulfill the criterion, but there is room for improvement.
D = Use this if you do NOT think the ICDs fulfill the criterion, or if unclear.
SD = The ICDs do NOT provide any features of structured guidance.

24. The ICDs include a tool (e.g. worksheet, list of questions) designed to facilitate further discussion with recruiter / study nurse / others involved in the decision.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = The ICDs provide a tool that is clearly intended to facilitate discussion with others involved in the decision.
A = Use this if you think the ICDs fulfill the criterion, but there is room for improvement.
D = The ICDs include a sentence asking people to write down any questions they may have, or to use the document for consultation with others.
SD = The ICDs do NOT provide any means to facilitate communication with others involved in the decision.

Using Evidence

25. The ICDs provide citations to the scientific evidence referenced.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = The ICDs provide clear citations to the scientific evidence used.
A = Only some citations are presented, or not all citations clear.
D = Use this if you do NOT think that the ICDs fulfill the criterion, or if unclear.
SD = The ICDs do NOT provide any information on the scientific references.

26. The ICDs provide a production date.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = The ICDs provide a clear, explicit and easily accessible date when the ICD was developed.
A = Use this if you think the ICDs fulfill the criterion, but there is room for improvement.
D = Use this if you do NOT think that the ICDs fulfill the criterion, or if unclear (e.g., a date is provided, but it’s not clear what it refers to).
SD = The ICDs do NOT provide a production date.

27. The ICDs describe that there are different levels of quality of evidence.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = The ICDs explicitly describe the hierarchy of evidence quality (e.g. evidence can come from systematic review, RCT, observational study etc.).
A = Use this if you think the ICDs fulfill the criterion, but there is room for improvement.
D = Use this if you do NOT think that the ICDs fulfill the criterion, or if unclear.
SD = The ICDs do NOT provide any description of the hierarchy of evidence quality.
28. The ICDs describe the quality of the research evidence used.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = The ICDs provide a clear, explicit, and easily accessible description of the quality of the scientific evidence supporting all probabilities.
A = The quality of evidence supporting probabilities (e.g. “results of a randomized controlled trial show...”) are provided for some, but not all probabilities.
D = Use this if you do NOT think that the ICDs fulfill the criterion, or if unclear.
SD = The ICDs do NOT provide any description of the quality of the scientific evidence.

Disclosure and Transparency

29. The ICDs provide information about the funding sources for the study.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = The ICDs clearly and explicitly state sources of funding for the study.
A = Use this if you think the ICDs fulfill the criterion, but there is room for improvement.
D = Use this if you do NOT think that the ICDs fulfill the criterion, or if unclear.
SD = The ICDs do NOT provide any information about sources of funding.

30. The ICDs include the name, credentials and contact information of the principal study investigator(s).

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = The names, credentials and contact information of the study investigators are clearly given.
A = Use this if you think the ICDs fulfill the criterion, but there is room for improvement (e.g., no credentials, but everything else).
D = Use this if you do NOT think that the ICDs fulfill the criterion (2 of 3 of the above are missing).
SD = The ICDs documents do NOT provide any information about the study investigators.

31. The ICDs include the name and contact information of someone to whom questions can be asked.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = The ICDs clearly provide this information.
A = Use this if you think the ICDs fulfill the criterion, but there is room for improvement.
D = Use this if you do NOT think that the ICDs fulfill the criterion, or if unclear.
SD = The ICDs documents do NOT provide this information.

32. The ICDs include the name of the Research Ethics Board that approved the study.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>
SA = The ICDs clearly provide this information.
A = Use this if you think the ICDs fulfill the criterion, but there is room for improvement.
D = Use this if you do NOT think that the ICDs fulfill the criterion, or if unclear.
SD = The ICDs documents do NOT provide this information.
Consent Form Guidelines
Section B

Key Elements

1. There is a statement at the start of the ICD that the study involves research

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations (e.g., you are being asked to take part in this research study….”)
A = fulfills the criterion, but room for improvement (e.g., the statement could be clearer)
D = considerable room for improvement (e.g., the statement is buried in the text)
SD = completely lacking

2. The rationale for the research is explained

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations
A = fulfills the criterion, but room for improvement
D = considerable room for improvement
SD = completely lacking

3. There is a statement at the start of the ICD about why the PP is being asked to participate in the study (e.g., you are being asked to participate in this study because…)

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations
A = fulfills the criterion, but room for improvement
D = considerable room for improvement
SD = completely lacking

4. All procedures* to be carried out are explained

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations
A = fulfills the criterion, but room for improvement
D = considerable room for improvement
SD = completely lacking

*Procedures: any clinical activity carried out on a patient (e.g. examination, screening, test, imaging, blood draw, surgery, etc.)
5. The ICDs describe which procedures are solely for research purposes.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = There is a clear statement which procedures are solely for research purposes
A = fulfills the criterion, but some room for improvement
D = considerable room for improvement
SD = There is no effort to distinguish study procedures from those that are standard of care.

* If only healthy participants are involved, a statement should be provided indicating that all procedures are additional.

6. The ICDs describe the other options available if the PP declines participation (e.g., standard of care, different treatment drug X, another trial, etc).

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations
A = fulfills the criterion, but some room for improvement
D = considerable room for improvement
SD = completely lacking

7. There is a statement that the PPs’ participation is voluntary

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations
A = fulfills the criterion, but room for improvement
D = considerable room for improvement
SD = completely lacking

8. There is a statement that the PP can withdraw from the study at any time

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations
A = fulfills the criterion, but room for improvement
D = considerable room for improvement
SD = completely lacking

9. Reasons under which the PPs’ participation may be terminated are described

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = There is a clear statement indicating the reasons under which a PPs’ participation may be terminated.
A = fulfills the criterion, but room for improvement
D = considerable room for improvement
SD = completely lacking
10. There is a statement that if new evidence relevant to the study becomes available, the PPs will be informed

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations  
A = fulfills the criterion, but room for improvement  
D = considerable room for improvement  
SD = completely lacking

**Ethical Issues**

11. Potential risks to an embryo, fetus, or nursing infant are described

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
<th>N/A</th>
</tr>
</thead>
</table>

SA = no reservations  
A = fulfills the criterion, but room for improvement  
D = considerable room for improvement  
SD = completely lacking

12. There is a statement that participation in research may benefit others/society

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations  
A = fulfills the criterion, but room for improvement  
D = considerable room for improvement  
SD = completely lacking

13. It is indicated how personal health information will be protected (e.g., locked cabinets, password protected, etc.)

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations  
A = fulfills the criterion, but room for improvement  
D = considerable room for improvement  
SD = completely lacking

14. It is indicated which organizations and individuals will have access to personal health information.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations
A = fulfills the criterion, but room for improvement  
D = considerable room for improvement  
SD = completely lacking  

15. There is a statement about whether study investigators or institutions receive compensation for patient enrolment (if not, there should be a statement that they don’t).

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations  
A = fulfills the criterion, but room for improvement (e.g. there is a statement, but it’s unclear)  
D = considerable room for improvement  
SD = completely lacking  

Study Design  

16. The expected duration of the study as a whole is described

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations  
A = fulfills the criterion, but room for improvement  
D = considerable room for improvement  
SD = completely lacking  

17. The expected duration of the PPs’ participation in the study is described

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations  
A = fulfills the criterion, but room for improvement  
D = considerable room for improvement  
SD = completely lacking  

18. The expected number of participants in the study is described

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations  
A = fulfills the criterion, but room for improvement  
D = considerable room for improvement  
SD = completely lacking  

19. The term ‘randomization’ is explained

| | | | | |
SA = no reservations (e.g., randomization means that your are put into a group by chance; is similar to “flipping a coin”; like “pulling a number out of a hat”)
A = fulfills the criterion, but room for improvement (e.g., uses “flipping a coin” when there are more than 2 groups).
D = considerable room for improvement
SD = completely lacking
N/A = Not applicable- no randomization involved

20. The different groups to which the PPs can be assigned are explicitly described.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
<th>N/A</th>
</tr>
</thead>
</table>

SA = no reservations
A = fulfills the criterion, but room for improvement
D = considerable room for improvement
SD = completely lacking

Formatting

21. The spelling is error-free

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations
A = fulfills the criterion, but room for improvement (e.g., very few errors)
D = considerable room for improvement (e.g., some errors)
SD = not at all appropriate (e.g., multiple errors that impede understanding)

22. The grammar is error-free

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations
A = fulfills the criterion, but room for improvement (e.g., very few errors)
D = considerable room for improvement (e.g., some errors)
SD = not at all appropriate (e.g., multiple errors that impede understanding)

23. Abbreviations and acronyms are minimally used and well-defined

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>
SA = no reservations
A = fulfills the criterion, but room for improvement (1 or 2 acronyms not well-defined)
D = considerable room for improvement (several acronyms not well-defined)
SD = not at all appropriate

24. All font sizes are 11 point or greater (e.g., this is 11 point Times New Roman font)

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SA = no reservations
A = fulfills the criterion, but room for improvement
D = considerable room for improvement
SD = not at all appropriate

25. Graphical elements are clear and clearly labeled

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SA = no reservations
A = fulfills the criterion, but room for improvement
D = considerable room for improvement
SD = not at all appropriate
N/A = Not applicable

26. The language used is as non-technical as is feasible.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SA = no reservations (all technical terms are explained)
A = fulfills the criterion, but room for improvement
D = considerable room for improvement
SD = not at all appropriate

**Style**

27. There is no need to remove repetition from this document

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SA = no reservations
A = only minimal/trivial repetition could be removed
D = some repetition could be removed
SD = substantial repetition could be removed or removal of repetition would substantially improve comprehensibility.
ICU-Specific Consent Guidelines  
Section C

1. The ICD clearly indicates the time period within which the decision must be made.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = A clear/definite time period over which a decision must be made is provided  
A = fulfils the criterion, but room for improvement (e.g. ‘time is of the essence’)  
D = considerable room for improvement/unclear (time period implied)  
SD = No time period for the decision is provided  

2. The ICD avoids the use of treatment terminology to describe investigational components of the study.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = Avoids using words like ‘doctor’, ‘therapy’ ‘medication’ and ‘treatment’ to describe study components (‘study doctor’ is okay for describing study investigators)  
A = fulfils the criterion, but room for improvement  
D = considerable room for improvement/unclear  
SD = uses words like ‘doctor’, ‘therapy’ and ‘treatment’ to describe study components  

3. The ICD makes a clear distinction between therapeutic and non-therapeutic interventions.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = procedures for the study only are distinguished from those that may benefit the patient or standard treatment options (e.g. ‘this is in addition to…’ OR interventions are standard practice)  
A = fulfils the criterion, but room for improvement  
D = considerable room for improvement/unclear  
SD = No distinction is made between therapeutic and non-therapeutic interventions  

4. The ICD makes explicit that non standard of care study components may not be tailored to the individual patient’s specific needs.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = the ICD clearly indicates that non-standard of care is dictated by study protocol and not individual need(s) (E.g. “the decision on what intervention you receive is not made by your doctor, or based on your medical needs)  
A = fulfils the criterion, but room for improvement  
D = considerable room for improvement/unclear  
SD = no indication
5. The ICD clearly describes what standard of care is for the health condition

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = there is a clear description of usual care/best practice (clear description of procedure/drug/device that constitutes standard of care is provided)
A = fulfils the criterion, but room for improvement (defines standard of care, no specifics)
D = considerable room for improvement/ unclear (mentions standard of care without explanation)
SD = no description or mention of what current practice/standards are

6. The ICD clearly describes how each arm of the trial differs from standard of care for the condition. (if N/A, or no arms, consider exclusion from sample)

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = there is a clear description of how the different arms relate to current practice/standards (i.e. standard of care VS other arm(s))
A = fulfils the criterion, but room for improvement
D = considerable room for improvement/ unclear
SD = relationship among different arms of trial and current practice/standards not described

7. The ICD indicates that the decision not to participate will not affect the quality of care.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = there is a clear statement that non-participation will not affect quality of care
A = fulfils the criterion, but room for improvement
D = considerable room for improvement/ unclear
SD = no effort to address care received for non-participation

8. The ICD clearly indicates whether or not the intervention has or needs regulatory approval in the context of the health condition/problem.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = there is a clear statement that intervention has/needs regulatory approval for this use
A = fulfils the criterion, but room for improvement (mentions approval but not the condition under study. E.g. “Drug X is approved for use in humans”, “Drug X is standard of care”)
D = considerable room for improvement/ unclear (blanket statement of approval with no explanations.)
SD = completely lacking
9. The ICD includes a statement about whether or not the intervention is expected to change/influence risk of death/survival.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = effect of intervention on survival/death is clearly addressed  
A = fulfils the criterion, but room for improvement  
D = considerable room for improvement/ unclear  
SD = no effort to address outcome of survival/death

10. The ICD addresses the fact that when a patient is too sick or unable to make a decision, a proxy can make decisions for them.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = there is a clear statement that when the patient cannot make decisions, a proxy can make decisions for them.  
A = fulfils criterion, but room for improvement  
D = considerable room for improvement/ unclear/ implicit/ found on signature page only  
SD = completely lacking

11. The ICD clearly states who has been identified as the proxy for the patient.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
<th>N/A</th>
</tr>
</thead>
</table>

SA = the ICD mentions legal relationship between proxy and patient (identified as a family member/ next of kin/ legally authorized representative).  
A = fulfils the criterion, but room for improvement  
D = considerable room for improvement/ unclear/ found on signature page only  
SD = completely lacking  
NA = ICD is targeted for patient only

12. The ICDs clearly acknowledge that the decision/situation may be stressful

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservation  
A = fulfils criterion, but room for improvement  
D = considerable room for improvement/ unclear  
SD = completely lacking
13. The ICD asks the proxy to consider whether they have discussed with the patient their wishes with respect to participation in research.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
<th>N/A</th>
</tr>
</thead>
</table>

SA = no reservations  
A = fulfils the criterion, but room for improvement  
D = considerable room for improvement/unclear  
SD = completely lacking  
NA = ICD is targeted for patient only

14. The ICD explains the criteria the proxy should base their participation decision on.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
<th>N/A</th>
</tr>
</thead>
</table>

SA = no reservations (asks proxies to use “substituted judgment”, “best interest”, own opinion)  
A = fulfils the criterion, but room for improvement  
D = considerable room for improvement/ unclear  
SD = item not addressed  
NA = ICD is targeted for patient only

15. The ICD specifically indicates that the proxy can revisit or withdraw informed consent at anytime throughout the trial.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
<th>N/A</th>
</tr>
</thead>
</table>

SA = no reservations  
A = fulfils the criterion, but room for improvement  
D = considerable room for improvement  
SD = completely lacking  
NA = ICD is targeted for patient only
16. The ICD indicates that informed consent will also be obtained from the patient if/when they are well enough to do so.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
<th>N/A</th>
</tr>
</thead>
</table>

SA = no reservations  
A = fulfils the criterion, but room for improvement  
D = considerable room for improvement/ found on signature page only  
SD = completely lacking  
N/A = ICD is targeted for patient only

17. The ICD explains HOW to withdraw consent.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations (clear steps on how to withdraw)  
A = fulfils the criterion, but room for improvement (‘discuss with/talk to study personnel’, ‘in writing’, discusses how to withdraw data but not from study)  
D = considerable room for improvement (e.g. withdraw consent for information but not from study)  
SD = completely lacking

18. The ICD addresses any personal/financial interests of study investigators (conflict of interest).

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

SA = no reservations  
A = fulfils the criterion, but room for improvement  
D = considerable room for improvement  
SD = completely lacking.
# Appendix VIII: Matched ratings of items by section

General Informed Consent Guidelines Items - Section Kappa = 0.8227(0.7969-0.8485)

<table>
<thead>
<tr>
<th>Item Description</th>
<th>Matched pairs</th>
<th>Percent Matched</th>
<th>Kappa</th>
<th>Kappa Limit Lower</th>
<th>Kappa Limit Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>States why the PP is being asked to participate in the study</td>
<td>63</td>
<td>73.3</td>
<td>0.3393</td>
<td>0.1578</td>
<td>0.5209</td>
</tr>
<tr>
<td>Explains randomization</td>
<td>66</td>
<td>76.7</td>
<td>0.7961</td>
<td>0.6439</td>
<td>0.9392</td>
</tr>
<tr>
<td>Describes procedures that are solely for research purposes</td>
<td>74</td>
<td>86.0</td>
<td>0.543</td>
<td>0.3183</td>
<td>0.7676</td>
</tr>
<tr>
<td>Describes duration of PP’s participation</td>
<td>75</td>
<td>87.2</td>
<td>0.6291</td>
<td>0.4149</td>
<td>0.8242</td>
</tr>
<tr>
<td>Describes reasons for which PP’s participation may be terminated</td>
<td>76</td>
<td>88.4</td>
<td>0.7681</td>
<td>0.6342</td>
<td>0.9019</td>
</tr>
<tr>
<td>Describes other options aside from participation</td>
<td>77</td>
<td>89.5</td>
<td>0.7856</td>
<td>0.6549</td>
<td>0.9163</td>
</tr>
<tr>
<td>Indicates which organizations/individuals have access to personal information</td>
<td>77</td>
<td>89.5</td>
<td>0.5816</td>
<td>0.3392</td>
<td>0.824</td>
</tr>
<tr>
<td>Describes potential risk(s) to embryos, fetus or nursing infants</td>
<td>78</td>
<td>90.7</td>
<td>0.5573</td>
<td>0.2597</td>
<td>0.8549</td>
</tr>
<tr>
<td>States whether PI/organization receive compensation for PP enrollment</td>
<td>78</td>
<td>90.7</td>
<td>0.2848</td>
<td>-0.0736</td>
<td>0.6433</td>
</tr>
<tr>
<td>State that new information will be conveyed to PP</td>
<td>79</td>
<td>91.9</td>
<td>0.8253</td>
<td>0.7023</td>
<td>0.9483</td>
</tr>
<tr>
<td>Indicates how personal information will be protected</td>
<td>79</td>
<td>91.9</td>
<td>0.8356</td>
<td>0.7192</td>
<td>0.952</td>
</tr>
<tr>
<td>Explains all procedures to be carried out</td>
<td>80</td>
<td>93.0</td>
<td>0.3645</td>
<td>-0.0321</td>
<td>0.7611</td>
</tr>
<tr>
<td>Non-repetitive text</td>
<td>81</td>
<td>94.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State that study involves research</td>
<td>82</td>
<td>95.3</td>
<td>-0.0178</td>
<td>-0.0445</td>
<td>0.009</td>
</tr>
<tr>
<td>Describes duration of the study</td>
<td>82</td>
<td>95.3</td>
<td>0.8391</td>
<td>0.6871</td>
<td>0.9911</td>
</tr>
<tr>
<td>Non-technical Language</td>
<td>82</td>
<td>95.3</td>
<td>0.5795</td>
<td>0.2144</td>
<td>0.9446</td>
</tr>
<tr>
<td>States that participation is voluntary</td>
<td>83</td>
<td>96.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>States that participation may benefit society</td>
<td>83</td>
<td>96.5</td>
<td>0.9249</td>
<td>0.8414</td>
<td>1</td>
</tr>
<tr>
<td>Describes the different groups to which PP can be assigned</td>
<td>83</td>
<td>96.5</td>
<td>0.8845</td>
<td>0.7046</td>
<td>1</td>
</tr>
<tr>
<td>Clearly labelled graphics</td>
<td>83</td>
<td>96.5</td>
<td>0.3828</td>
<td>-0.1689</td>
<td>0.9345</td>
</tr>
<tr>
<td>States that participant can withdraw at any time</td>
<td>84</td>
<td>97.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Describes the number of participants</td>
<td>84</td>
<td>97.7</td>
<td>0.9325</td>
<td>0.8402</td>
<td>1</td>
</tr>
<tr>
<td>No grammatical errors</td>
<td>84</td>
<td>97.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explains rationale for the research</td>
<td>85</td>
<td>98.8</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No Spelling errors</td>
<td>85</td>
<td>98.8</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Minimally used and well defined acronyms</td>
<td>86</td>
<td>100.0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Readerable font sizes</td>
<td>86</td>
<td>100.0</td>
<td>1</td>
<td>1</td>
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</tr>
</tbody>
</table>
### IPDAS Items—Section  
**Kappa 0.8376 (0.8046-0.8706)**

<table>
<thead>
<tr>
<th>Item Description</th>
<th>Matched Pairs</th>
<th>Percent Matched</th>
<th>Kappa</th>
<th>Kappa Limits Lower</th>
<th>Kappa Limits Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Describes adv/disadv. with enough detail to help imagine impact on life</td>
<td>73</td>
<td>84.9</td>
<td>0.4914</td>
<td>0.2556</td>
<td>0.7271</td>
</tr>
<tr>
<td>Describes that a participation decision needs to be made</td>
<td>75</td>
<td>87.2</td>
<td>0.7422</td>
<td>0.601</td>
<td>0.8835</td>
</tr>
<tr>
<td>Describes time of onset of side effects of participation</td>
<td>77</td>
<td>89.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name of the Research Ethics Board that approved the study</td>
<td>77</td>
<td>89.5</td>
<td>0.6772</td>
<td>0.4819</td>
<td>0.8726</td>
</tr>
<tr>
<td>Describes quality of research evidence used</td>
<td>78</td>
<td>90.7</td>
<td>0.3065</td>
<td>-0.0233</td>
<td>0.6362</td>
</tr>
<tr>
<td>Describes disadvantages of participation</td>
<td>79</td>
<td>91.8</td>
<td>0.4941</td>
<td>0.1775</td>
<td>0.8107</td>
</tr>
<tr>
<td>Provides more than one way of viewing probabilities</td>
<td>79</td>
<td>91.8</td>
<td>0.586</td>
<td>0.3093</td>
<td>0.8626</td>
</tr>
<tr>
<td>Provides info. about funding sources for the study</td>
<td>79</td>
<td>91.8</td>
<td>0.817</td>
<td>0.6883</td>
<td>0.9457</td>
</tr>
<tr>
<td>Name, credentials &amp; contact info. of the PI(s)</td>
<td>79</td>
<td>91.8</td>
<td>0.431</td>
<td>0.0988</td>
<td>0.7632</td>
</tr>
<tr>
<td>Describes advantages of participation</td>
<td>80</td>
<td>93</td>
<td>0.6623</td>
<td>0.4138</td>
<td>0.9108</td>
</tr>
<tr>
<td>Specifies population(s) that yielded the probabilities</td>
<td>80</td>
<td>93</td>
<td>0.5346</td>
<td>0.2067</td>
<td>0.8619</td>
</tr>
<tr>
<td>Describes health condition or problem</td>
<td>81</td>
<td>94.2</td>
<td>0.8126</td>
<td>0.6543</td>
<td>0.9701</td>
</tr>
<tr>
<td>Describes disadvantages of NOT participating</td>
<td>81</td>
<td>94.2</td>
<td>-0.0287</td>
<td>-0.056</td>
<td>-0.0015</td>
</tr>
<tr>
<td>Comparison of adv. &amp; disadv. for participation &amp; non-participation</td>
<td>81</td>
<td>94.2</td>
<td>-0.0287</td>
<td>-0.056</td>
<td>-0.0015</td>
</tr>
<tr>
<td>Describes reversibility of side effects of participation</td>
<td>82</td>
<td>95.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provides information on probabilities for all adv/disadv</td>
<td>82</td>
<td>95.3</td>
<td>0.8189</td>
<td>0.6475</td>
<td>0.9904</td>
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<tr>
<td>Includes a tool designed to facilitate further discussion</td>
<td>82</td>
<td>95.3</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Provides a production date</td>
<td>82</td>
<td>95.3</td>
<td>0.7261</td>
<td>0.474</td>
<td>0.9782</td>
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<tr>
<td>Describes intervention</td>
<td>83</td>
<td>96.5</td>
<td>0.8682</td>
<td>0.7224</td>
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</tr>
<tr>
<td>Comparison of probabilities using same denominator</td>
<td>83</td>
<td>96.5</td>
<td>0.8042</td>
<td>0.5896</td>
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<tr>
<td>Specifies probabilities in natural frequencies</td>
<td>84</td>
<td>97.7</td>
<td>0.7386</td>
<td>0.393</td>
<td>1</td>
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<tr>
<td>Describes that there are different levels of quality of evidence</td>
<td>84</td>
<td>97.7</td>
<td>-0.0118</td>
<td>-0.0281</td>
<td>0.0045</td>
</tr>
<tr>
<td>Name &amp; contact info. of someone to whom questions can be asked</td>
<td>84</td>
<td>97.7</td>
<td>0.8448</td>
<td>0.6347</td>
<td>1</td>
</tr>
<tr>
<td>Describes disadvantages of NOT participating</td>
<td>85</td>
<td>98.8</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Describes disadvantages of participation in a consistent order</td>
<td>86</td>
<td>100</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Describes disadvantages of NON-participation in a consistent order</td>
<td>86</td>
<td>100</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Specifies time period over which probabilities apply</td>
<td>86</td>
<td>100</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Provides information about levels of uncertainty around probabilities</td>
<td>86</td>
<td>100</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Describes probabilities in multiple frames to limit framing biases</td>
<td>86</td>
<td>100</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asks PPs to think about which adv and/or disadv matter most to them</td>
<td>86</td>
<td>100</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Provides a step-by-step way to decide whether or not to participate</td>
<td>86</td>
<td>100</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Provides citations to scientific evidence referenced</td>
<td>86</td>
<td>100</td>
<td>1</td>
<td>1</td>
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</tbody>
</table>
### ICU-specific Informed Consent Guidelines Items - Section Kappa = 0.7128 (0.6793-0.7463)

<table>
<thead>
<tr>
<th>Item Description</th>
<th>Marched Pair</th>
<th>Percent Matched</th>
<th>Kappa</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>distinguishes between therapeutic and no-therapeutic interventions</td>
<td>64</td>
<td>74.42</td>
<td>0.312</td>
<td>0.088</td>
<td>0.535</td>
</tr>
<tr>
<td>indicates consent would be obtained from PP if/when possible</td>
<td>64</td>
<td>74.42</td>
<td>0.564</td>
<td>0.334</td>
<td>0.795</td>
</tr>
<tr>
<td>states who has been identified as proxy</td>
<td>65</td>
<td>75.58</td>
<td>0.437</td>
<td>0.179</td>
<td>0.695</td>
</tr>
<tr>
<td>indicates whether or not the intervention has regulatory approval</td>
<td>66</td>
<td>76.74</td>
<td>0.513</td>
<td>0.342</td>
<td>0.685</td>
</tr>
<tr>
<td>indicates proxy can withdraw consent</td>
<td>66</td>
<td>76.74</td>
<td>0.53</td>
<td>0.292</td>
<td>0.768</td>
</tr>
<tr>
<td>describes how each arm differs from standard of care</td>
<td>71</td>
<td>82.56</td>
<td>0.513</td>
<td>0.198</td>
<td>0.828</td>
</tr>
<tr>
<td>explains that non standard of care study components may not be tailored to individual needs</td>
<td>72</td>
<td>83.72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>indicates whether a proxy can make decisions for a patient</td>
<td>72</td>
<td>83.72</td>
<td>0.755</td>
<td>0.589</td>
<td>0.922</td>
</tr>
<tr>
<td>asks proxy to consider PP research participation wishes</td>
<td>72</td>
<td>83.72</td>
<td>0.462</td>
<td>0.182</td>
<td>0.742</td>
</tr>
<tr>
<td>explains criteria for proxy's participation decision</td>
<td>72</td>
<td>83.72</td>
<td>0.484</td>
<td>0.217</td>
<td>0.75</td>
</tr>
<tr>
<td>describes standard of care</td>
<td>75</td>
<td>87.21</td>
<td>0.67</td>
<td>0.49</td>
<td>0.849</td>
</tr>
<tr>
<td>states whether intervention influences survival/risk of death</td>
<td>75</td>
<td>87.21</td>
<td>0.568</td>
<td>0.341</td>
<td>0.795</td>
</tr>
<tr>
<td>explains how to withdraw consent</td>
<td>76</td>
<td>88.37</td>
<td>0.712</td>
<td>0.546</td>
<td>0.877</td>
</tr>
<tr>
<td>avoids treatment terminology for investigational components</td>
<td>79</td>
<td>91.86</td>
<td>0.418</td>
<td>0.064</td>
<td>0.772</td>
</tr>
<tr>
<td>indicates that non-participation will not affect quality of care received</td>
<td>79</td>
<td>91.86</td>
<td>0.324</td>
<td>-0.05</td>
<td>0.698</td>
</tr>
<tr>
<td>addresses personal/financial interest of PI(s)</td>
<td>79</td>
<td>91.86</td>
<td>0.489</td>
<td>0.163</td>
<td>0.815</td>
</tr>
<tr>
<td>indicates time within which to make a decision</td>
<td>82</td>
<td>95.35</td>
<td>0.516</td>
<td>0.204</td>
<td>0.949</td>
</tr>
<tr>
<td>acknowledges the decision may be stressful</td>
<td>85</td>
<td>98.84</td>
<td>0.661</td>
<td>0.041</td>
<td>1</td>
</tr>
</tbody>
</table>
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Ref Type: Online Source

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Ref Type: Online Source

Ref Type: Online Source


Ref Type: Online Source

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