


Informed consent practices in clinical research: present and future

Natasha A. Jawa ^{1,2,*}, J. Gordon Boyd^{1,3,4,5}, David M. Maslove^{4,5}, Stephen H. Scott⁶, Samuel A. Silver⁷

¹Centre for Neuroscience Studies, Faculty of Health Sciences, Queen's University, Kingston, Ontario K7L 3N6, Canada

²School of Medicine, Faculty of Health Sciences, Queen's University, Kingston, Ontario K7L 3L4, Canada

³Division of Neurology, Department of Medicine, Queen's University, Kingston, Ontario K7L 2V7, Canada

⁴Department of Critical Care Medicine, Queen's University, Kingston, Ontario K7L 2V7, Canada

⁵Department of Critical Care Medicine, Kingston Health Sciences Centre, Kingston, Ontario K7L 2V7, Canada

⁶Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario K7L 3N6, Canada

⁷Division of Nephrology, Department of Medicine, Queen's University, Kingston, Ontario K7L 2V7, Canada

*Corresponding author. Centre for Neuroscience Studies, Faculty of Health Sciences, Queen's University, Room 257, Botterell Hall, 18 Stuart Street, Kingston, Ontario K7L 3N6, Canada. E-mail: tasha.jawa@queensu.ca

Abstract

Clinical research must balance the need for ambitious recruitment with protecting participants' autonomy; a requirement of which is informed consent. Despite efforts to improve the informed consent process, participants are seldom provided sufficient information regarding research, hindering their ability to make informed decisions. These issues are particularly pervasive among patients experiencing acute illness or neurological impairment, both of which may impede their capacity to provide consent. There is a critical need to understand the components, requirements, and methods of obtaining true informed consent to achieve the vast numbers required for meaningful research. This paper provides a comprehensive review of the tenets underlying informed consent in research, including the assessment of capacity to consent, considerations for patients unable to consent, when to seek consent from substitute decision-makers, and consent under special circumstances. Various methods for obtaining informed consent are addressed, along with strategies for balancing recruitment and consent.

Keywords: intensive and critical care, neurological injury, neurology, ethics, medical ethics

What is already known on this topic:

- Clinical research must balance the need for ambitious recruitment with protecting participants' autonomy; a requirement of which is informed consent.
- Participants frequently report that they have not received sufficient information to be informed prior to providing consent to participate in research.

What this study adds:

- Patients with acute illness or neurological impairment have differing requirements for consent and may be unable to provide informed consent for themselves, necessitating the use of substitute decision makers.

How this study might affect research, practice, or policy:

- What are the components of informed consent as it pertains to participants' involvement in clinical research?
- How is capacity to consent determined, and what are the circumstances under which capacity may be impacted? How may the consent process be adapted under such circumstances to protect participant autonomy while preserving the ability of clinical research to progress?
- Are there novel consent paradigms that can be used to improve the balance of autonomy and recruitment in clinical research?

Introduction

Clinical research in critical care and neuroscience is pivotal for scientific discovery, translation, and ultimately improving patient care. Sound research relies on achieving sufficient sample sizes to draw meaningful scientific conclusions, rendering patient enrollment a critical component of clinical research. Equally important, however, is ensuring that participants' right to autonomy—i.e. to make their own decisions about whether or not to take part in the research—is upheld. Clinical research teams must therefore intricately balance the need for ambitious recruitment with protecting participants' autonomy, including for participants whose autonomy may be developing or impaired (termed respect for persons [1]). A requirement for respecting autonomy is informed consent: the process through which participants freely and voluntarily choose to enroll in a research study [2].

Despite great efforts to improve the process of informed consent, studies suggest that participants are seldom provided sufficient information regarding research, hindering their ability to make informed decisions. A recent meta-analysis on surgical clinical research revealed that only 54% of participants understood the aims of the study in which they were participating [3]. Additionally, less than half of participants understood the voluntary nature of their participation, ability to withdraw, and perceived risks [3]. These issues are even more pervasive among patients who experience critical illness or neurological impairments, as

Received: April 3, 2023. Accepted: May 6, 2023

© The Author(s) 2023. Published by Oxford University Press on behalf of Postgraduate Medical Journal. All rights reserved. For Permissions, please email: journals.permissions@oup.com

Table 1. Core principles of informed consent [1].

Principle	Description
Voluntary Informed	Consent should be given without (intentional or otherwise) undue influence, manipulation, coercion, or incentivization. Participants have the right to receive—in a way they can understand—all the relevant information required to make an informed decision. Participants must be allotted sufficient time and opportunity to consider the information provided and ask questions.
Ongoing	Active consent is required throughout the duration of participation. This includes obtaining consent after the presentation of new findings or information that may change a person's willingness to continue their participation. Consent must also be sought in cases where a person's capacity to consent has changed (e.g. if a formerly unconscious patient regains consciousness).
Precedes data collection	Research must only start after consent has been obtained from the participant, except in cases where deception, a waiver of consent, an exemption to seeking consent in advance of enrollment, or an exemption to seeking consent in the context of a medical emergency has been approved by the Research Ethics Board.

the nature of their illness may impede their capacity to engage in an informed discussion and provide consent. Therefore, there is a critical need within neuroscience and critical care research to understand the components, requirements, and methods of obtaining true informed consent in order to achieve the vast numbers required for meaningful research.

As a first step towards bridging this gap, this paper provides a comprehensive review of the tenets underlying informed consent in clinical research. This includes the assessment of capacity to consent, considerations for patients unable to consent, when to seek consent from substitute decision-makers (SDMs), and consent under special circumstances. Various methods for obtaining informed consent from the perspectives of participants and researchers are also addressed, along with strategies for balancing patient recruitment and the need for consent.

Informed consent

Informed consent is the process through which participants are enrolled into research studies [2], and is generally documented via a signed informed consent form. Notably, the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans states that four guiding principles define informed consent: consent must be voluntary, informed, ongoing, and precede data collection [1] (Table 1).

Elements of informed consent in clinical research

There are many elements of informed consent in clinical research that should be included in the conversation with the patient (summarized in Table 2). Critically, the language used to describe the study should be presented in lay terms such that anyone with no scientific or medical background can understand the consent documentation [4]. For this reason, Research Ethics Boards (REBs) dictate that information should be written at a Grade 6–8 comprehension level and be adjusted as required [4].

Exceptions to the consent process

Under certain circumstances (e.g. placebo effect trials, research with unconscious patients), the REB may grant exemptions to the standard processes for obtaining informed consent. Alterations to the consent process are possible if all the following are met: (i) there exists no more than a minimal risk to participants; (ii) participants' welfare will not be adversely affected; (iii) obtaining consent would render answering the research question impossible or impracticable; (iv) the nature and extent of the consent alteration are defined; and (v) participants may refuse consent or

withdraw data/biological specimens during a poststudy debriefing [1].

Use of deception and debriefing in clinical research

Certain research questions require participants to be unaware of some study details prior to engaging in the research, as knowledge of all aspects of the study may influence the phenomenon under investigation and impact study results (e.g. placebo effect studies) [5]. In these scenarios, temporary deception and withholding of information may be used to promote scientific validity, and participants should be debriefed once their study involvement has ended [5]. Beyond debriefing, additional approaches may also be used to promote participant autonomy in deceptive research. One such approach involves disclosing to participants up-front that deception will be used and that they will receive complete and accurate information following study completion, without providing the specifics of how deception will be employed. In this way, participants can provide their consent to be temporarily deceived and informed later—a process known as “authorized deception” [5]. However, the mere act of knowing that one is being observed through research can change the outcome of a study (termed the Hawthorne effect) [5]. Thus, the use of authorized deception may influence the participant's behavior, and special care should be taken in analyzing these results. The second approach involves allowing participants the opportunity to revoke their data/specimens from use at the time of debriefing [1, 5].

Exceptions to seeking consent prior to enrollment

Deferred consent may be suitable in situations where, at the time of experimental intervention, the patient is unable to provide informed consent. For example, for minimal risk observational studies where participants are unconscious, sedated, or have an altered level of consciousness and must be promptly enrolled while the patient's SDM is not able to be reached, it may be appropriate to proceed with enrollment and obtain consent at a later time (e.g. when decisional capacity is regained or when the SDM is able to be reached). If the patient or SDM does not ultimately provide their consent, then the REB may request that the research team remove and discard the participant's data or biological specimens from the study.

Waivers of consent

In some instances, the REB may waive the requirement to obtain informed consent altogether. Research teams request a waiver of

Table 3. Decision-making abilities [10, 52].

Ability	Description
Understanding	To provide an explanation of the meaning of pertinent details about the research.
Appreciation	To explain how the information about the research study may apply to the participant and their life.
Reasoning	To compare information provided about the study, infer the consequences of their decision to participate or not to participate in the study, and apply values and beliefs.
Choice	To clearly express a decision.

	Duration	Severity	Seriousness of decision
Description	How long is the impairment expected to last?	What is the extent of the impairment?	How influential or impactful is the decision to participate in the research on the participant or on the wider population?
Example	Temporary altered level of consciousness or delirium vs. permanent, progressive dementia	Mild vs. moderate vs. severe; Situational and infrequent vs. pervasive	Minor vs. moderate vs. high impact

Figure 1. Considerations for assessing capacity impairments.

evaluations of capacity are made on the basis of an interview with patients to gain an understanding of their decisional abilities [10]. These interview-based assessments are not only more time-efficient and less resource-intensive, but may also allow for a clear demonstration of capacity without the need to delve into more complex tools. Open-ended, nondirective questions are preferred over closed-ended questions to accurately assess participants' comprehension [12].

Importantly, capacity for consent is dynamic and decision-specific: a participant's capacity to make one decision does not imply that they have the capacity to make other (e.g. more complex) decisions [13]. Furthermore, for research involving children, there is no age limitation for capacity assessment. Hence, all children should be assessed for capacity and the opportunity to consent should first be given to the child to promote maximal autonomy [1].

According to the Ontario government's Health Care Consent Act, capacity to consent to participating in research can be assessed by any healthcare professional belonging to a regulated health profession [14]. If no regulated healthcare professional is part of the research team or available to make the assessment, research teams should consult with their REB for guidance on capacity assessments by non-healthcare professionals, including research staff and students.

Impaired capacity

Patients with neurocognitive impairment or neuropsychiatric illness may be unable to provide informed consent [15]. In such instances, factors such as duration and severity of impairment and the implications of study participation are vital to determine capacity (Fig. 1).

However, the first priority before attempting to consent a participant should be to try to treat the impairment (where the etiology of impairment permits), so long as consent is not urgent [12]. If the participant has mild to moderate cognitive impairment, they may benefit from more involved efforts to improve understanding, and reassessment of their capacity at a later time [12]. If the participant has more severe impairments, consent should be sought from the SDM [12].

Capacity is continually evolving and changing, and a participant's initial capacity assessment may not be indicative of their capacity later on. Therefore, assessing capacity on an ongoing basis throughout a participant's involvement in the study is imperative. This is particularly applicable for those with temporarily impaired decisional capacity (e.g. altered level of consciousness or delirium), and for children who may gain capacity as they develop, but it should not be excluded from those who seem to be without impairment [12, 16].

Participation in research for patients unable to provide self-consent

For patients who are incapable of consenting to participate in research, the decision should first be transferred to an SDM chosen in advance by the patient. If the patient has no chosen SDM (as in the case of an unforeseen emergency), then the order of priority outlined in Fig. 2 should be followed to determine the patient's proxy. SDMs must act in accordance with the participant's prior wishes [17]. If there are multiple individuals at the same priority level, consensus among those individuals is preferred.

Vulnerable populations

Some participant groups, referred to as vulnerable populations, require special considerations to ensure that their interests are protected throughout their research involvement. Notably, avoiding the inclusion of vulnerable populations in research simply because of the additional precautions required to protect their autonomy is unjust and precludes the study of critically important groups, limiting the generalizability of research findings. Vulnerability is generally the result of one of two factors: (i) diminished decision-making capacity, and/or (ii) reduced access to rights, powers, or opportunities [1]. For example, a critically ill patient in the intensive care unit (ICU) may not have the ability to make decisions surrounding their potential participation in research while delirious. Similarly, a trainee participating as a healthy control in a research study may have an inherent power imbalance with the study's principal investigator. In both examples, the participants are considered vulnerable due to



Figure 2. Order of proxy consent [10, 12].

their circumstance, and extra precautions must be taken to protect their interests in research. Furthermore, the inherent power balance between healthcare providers and potential research participants should be considered, and a third party (e.g. research team member who is not part of the circle of care of the patient) should be responsible for obtaining consent to avoid undue influence (intentional or otherwise) [18]. Children, elderly individuals, students/trainees, women with or without child [19], prisoners, institutionalized individuals, ethnocultural or visible minorities, and those with neurocognitive or psychiatric impairment are all vulnerable groups in research [1, 19].

Informed consent considerations for vulnerable populations

Although it is an important component of participating in research, some patients may not have the ability to exercise autonomy due to impaired cognitive, emotional, or decisional capacities. Researchers must therefore employ additional precautions to protect these patients [1].

Substitute decision-makers

Often, consent can be sought from a participant's SDM—an authorized third-party individual who is able to make decisions on behalf of the participant. If the participant's SDM changes throughout the course of their participation in a research study, the researcher must obtain consent from the new SDM [1]. This new consent encompasses both data or samples that have yet to be collected, as well as those previously collected. As such, if the new SDM refuses participation, previous data or samples may need to be discarded or excluded from the analysis [1].

Assent

Even in cases where consent is obtained from a third party, participants should be involved in decision-making to the extent that they are capable and informed about the research at a comprehension level that is suited to their individual needs. A common way that this can occur is through assent [1]. Participants who are incapable of providing full consent may still be able to understand more limited or superficial elements of the research, and thus may be able to agree (i.e. assent) or disagree (i.e. dissent) to being enrolled [20, 21]. Their assent should typically be sought first, and full consent from the SDM can be sought thereafter if assent is obtained. This is because assent is thought to supersede consent in cases where the research does not provide a direct benefit to the participant [21]. However, guidelines on the key components of an assent discussion, age, circumstances under which assent can be obtained from participants, and the relationship between assent and consent are disparate, and no consensus guidelines exist [22]. Of note, some participants do not have the capacity to provide consent or assent (e.g. infants, unconscious or sedated adults), and therefore consent should be sought directly from the SDM.

Considerations for vulnerable patient populations

The highest-risk vulnerable populations include those with neurodegenerative disease (e.g. Alzheimer's), psychiatric illness (e.g. schizophrenia, depression, substance use disorders), traumatic

brain injury, hospitalized adults, and participants at the end of their life [12].

Among participants with neurodegenerative disease, quick and efficient screening tools such as the Mini Mental State Exam (MMSE) [23] and the Montreal Cognitive Assessment (MoCA) [24] can be used to help differentiate individuals who are at higher risk of impaired capacity from those whose capacity may still be preserved [8, 12, 25, 26]. The MMSE is primarily useful for discriminating participants with severe vs. mild cognitive impairment, for whom MMSE scores are more highly correlated with decisional capacity [12]. In one study where MMSE scores were compared against a validated gold-standard decisional capacity assessment tool (MacCAT-CR), an MMSE cutoff score of 19 (out of a possible 30, with lower scores indicating greater impairment) was 85%–94% specific and 39%–54% sensitive for impaired capacity, whereas a cutoff of 26 was 91%–100% sensitive and 29%–36% specific [26]. The authors suggested that different MMSE threshold scores may be useful for different purposes, with more stringent thresholds used for higher-risk research studies [26]. Along these lines, another study examining the ability of participants with Parkinson's disease to consent to higher-risk research found that only scores ≤ 28 were able to identify participants incapable of providing consent [25]. Moderate cognitive impairment on the MMSE is less sensitive and specific in predicting decisional capacity [12, 26]; therefore, a decision-specific capacity assessment is warranted for these participants. The MoCA, on the other hand, may be more sensitive (>90% sensitivity at a threshold score of ≤ 22 out of a possible 30) in detecting impaired capacity than the MMSE, particularly for higher-risk clinical research trials [25].

Participants with psychiatric illness represent another vulnerable group within the field of cognition and neuroscience who may have an impaired capacity for consent. Up to 52% of participants with schizophrenia [27], 12%–17% of participants hospitalized with mood disorders [28], and 37% of participants with substance use disorders [29] may experience decisional incapacity. Participants with schizophrenia are at a higher risk of demonstrating impairments in decisional capacity if they are hospitalized, severely cognitively impaired, or experiencing negative symptoms [27]. Similarly, hospitalized patients with major depressive disorder are more likely to experience impaired decision-making than their outpatient counterparts [30].

Participants who have experienced a traumatic brain injury may experience decisional impairment that correlates with the severity of their brain injury. However, these impairments may improve over time [31, 32] and should therefore be assessed on an ongoing basis. While there are no consensus guidelines on the frequency of re-evaluating consent capacity, it may be most feasible to reassess the patient during each of their clinical follow-up visits.

Finally, impaired decisional capacity occurs in nearly one-third of hospitalized patients [33]. This is especially important for patients at the end of their life, for whom up to 70% may lack the capacity to make decisions [34]. Further complicating the issue of capacity assessment for hospitalized patients—particularly ICU patients—are barriers including intubation, sedation, delirium, or hearing impairment [13]. In these participants, other

communication tools (e.g. writing or nonverbal cues) should be used to determine capacity to consent to research [13].

Strategies for obtaining informed consent

The seven strategies to obtain informed consent from participants or their proxy, including both expressed consent and implied consent models as well as the advantages and disadvantages of each strategy, are outlined in Table 4. Crucially, the most feasible of the currently available consent frameworks in clinical research are those in which consent is not expressly given (implied), or is requested after a participant has been enrolled (deferred).

Perspectives of and consequences to participants

Recently, there has been a movement towards including patients and caregivers as integral members of the research team to provide input on study procedures, including the enrollment and consent process. This has led to a wide body of literature exploring patient and proxy perspectives on informed consent practices—particularly for pediatric, emergency, or critical illness research. Participants and consulted members of the public have also voiced the need for adaptations to the process of obtaining consent to improve research feasibility in these contexts [35].

The use of third-party consent is generally considered acceptable by most participants (85%) in acute care settings (e.g. ICU research) [35]. Patient and proxy support for deferred consent in research involving medical emergencies has also been widely reported [36, 37]. Patients often report being incapable of absorbing information provided to them when consented prospectively for research during stressful medical encounters (e.g. receiving a life-altering diagnosis) [38]. However, parental proxies reported temporary distress upon discovering that their child had been enrolled into a study without their prior consent, until the rationale for using a deferred consent model was explained by the research team [39]. Parents experienced the most profound alarm at the use of the word “trial” as a result of the experimental connotation of the term, as well as the fact that they assumed that the medical team was inexperienced in caring for their child if experimentation was needed [40]. In spite of these concerns, 94% of parents still ultimately agreed that they would want their child to be enrolled [40]. This points to the need for improved practices when using deferred consent paradigms, as opposed to negating their utility altogether, in order to decrease the potential stress experienced by the patients and their families. The majority (70%) of parent proxies also voiced that they wanted to be informed of their child’s inclusion in a study as soon as their child’s condition had stabilized [40]. Parents suggested that clear written materials at the time of deferred consent would aid in the conversation [41]. Even in cases where the child had ultimately died after inclusion into the research study, 66% of parents still wanted to be told that their child had been included, despite acknowledging the difficulty of processing and rationalizing with this information while coping with a concurrent bereavement [40].

Adult literature has also widely been in favor of using deferred consent models, particularly for low-risk observational research studies in the ICU (93%–96% of participants) [42]. For noninvasive studies (e.g. retrospective chart reviews), up to 86% of patients and 68% of relatives support the deferred consent model; but as the invasiveness of the study increases (e.g. to randomized trials), this reduces to 60% and 59% for patients and relatives, respectively [43]. Participants during a critical illness expressed mixed opinions regarding the use of prospective vs. deferred consent, some

citing that being asked to make research-related decisions while experiencing severe illness was unacceptable or even immoral [35]. Finally, although individuals generally agree that waivers of consent may be warranted in certain circumstances, most would prefer to be informed about research ongoing under a waiver of consent (e.g. via posters, flyers, information in clinical settings) [35], or would support the use of an alternative model of consent (e.g. verbal or deferred consent) over waiving the requirement for consent altogether [44].

Perspectives of and consequences to researchers

Clinical researchers generally support the need for deferred consent in research involving medical emergencies or critical illness [35, 36]. Verbal consent has also been shown to be preferred in principle by researchers over written consent as a method of reducing undue burden on prospective participants who are in high-acuity medical situations at the time of their consent, with subsequent use of written consent after the situation has resolved [36, 45]. However, in practice, the majority of research team members advocated for using written informed consent to avoid potential medicolegal ramifications should trial participation result in negative outcomes [36]. Notably, in cases where a verbal consent model is appropriately executed and approved by the local REB, these perceived concerns are not a true eventuality of using verbal consent.

Research staff also endorse the need for third-party consent to carry out research, particularly in the ICU. However, concerns were raised by 48%–61% of researchers regarding the capacity of the participant’s SDM to provide consent, as a result of their high level of distress [35]. Researchers also suggested that two independent physicians could be used in circumstances where an SDM was not available to make decisions surrounding participants’ research involvement [35], reflecting the need to balance timely and efficient participant recruitment with participant safety and research integrity [46, 47]. However, in busy clinical environments the feasibility of having two independent physicians available to make these decisions is limited. Additionally, this method goes against the designated order for selecting an SDM who would be most attuned to the participant’s wishes (Fig. 2).

Balancing patient recruitment and informed consent

Moving forward, clinical research should prioritize striking a balance between the need for ethical practices that protect research participants, while making efforts towards scientific advancement through efficient recruitment [41]. Surveys of clinical researchers have found that REBs and the strict consent guidelines imposed by these boards can be a barrier to conducting research [48]. Complicating this issue further, when given the opportunity to review consent documentation or participate in a consent conversation prior to enrolling in research in high-acuity scenarios, participants or proxies spend little time reviewing the documents and have limited interest in receiving such information [48]. For these situations, deferred consent provides a viable alternative to obtaining prospective consent during already difficult circumstances for both participants and researchers, as research can be discussed in a lower-stress setting. Waivers of consent can also aid in increasing recruitment rates, decreasing administrative burden on research teams, and increasing the timeliness of initiating participants on study interventions [6].

Although informed consent is the current gold standard for participant enrollment, its utility across all research contexts

Table 4. Comparison of consent methods [1, 40].

	Expressed			Implied		
	Written	Verbal	Telephone	Electronic	SDM	Deferred
Description	<ul style="list-style-type: none"> - A full description of the research is provided to the participant or proxy in writing and explained verbally. - Signed and dated by the person obtaining consent, with a copy given to the participant or proxy. - May be read to the participant or translated and signed by the translator. - Required for Health Canada studies. 	<ul style="list-style-type: none"> - Provides information to the participant or proxy via REB-approved verbal consent script. - The person obtaining consent records the participant or proxy's verbal consent on the verbal consent script and documents the consent process. - For use in minimal-risk studies. 	<ul style="list-style-type: none"> - A full description of the study is provided to the participant or proxy via telephone. - The participant or proxy is provided with a paper or electronic version of the written consent form to review, sign, and send back via mail, e-mail, or electronically. 	<ul style="list-style-type: none"> - A full description of the study is provided to the participant or their proxy via telephone or video conference. - The participant or proxy is provided with an electronic version of the written consent form to review and sign. - The consent form is then sent back by e-mail/electronically to the research team. 	<ul style="list-style-type: none"> - For incapacitated individuals, a third-party SDM may act as a proxy to make decisions regarding the potential participant's involvement in the research study. - Consent is obtained through written, verbal, telephone, or electronic means, and may be prospective or deferred. 	<ul style="list-style-type: none"> - Allows for the inclusion of participants in research without their (or a proxy's) prior consent. - Informed consent is required to be obtained as soon as possible following enrolment for participants to continue their participation in the study. - For use in minimal-risk studies.
Feasibility Additional considerations	<ul style="list-style-type: none"> Low - Language requirements (i.e. need for interpreter). 	<ul style="list-style-type: none"> Moderate - Should not be used when obtaining consent in person, unless there are cultural or other reasons why a participant or their proxy might prefer not to sign a written consent form. 	<ul style="list-style-type: none"> Moderate - Need to confirm identity of the participant or proxy. 	<ul style="list-style-type: none"> Moderate - Need to confirm identity of the participant or proxy. - Language requirements for informed consent form (e.g. need for interpreter). 	<ul style="list-style-type: none"> Low - If the participant regains capacity at any point during their participation in the study, consent should be sought from the participant. - In cases where there is a discrepancy between the choice of the participant and the prior indicated choice by the SDM, decision of the capable participant supersedes the decision of the SDM. 	<ul style="list-style-type: none"> High - If the participant has or regains capacity to consent at the time of deferred consent, the participant should be approached for consent rather than the SDM. - If the participant does not have capacity to consent at the time of deferred consent, the SDM should be approached.
Advantages	<ul style="list-style-type: none"> - Participant has written material for referral and decision-making. - Consent is documented directly by the participant. - Participant is readily accessible for discussion, as the conversation occurs in person. 	<ul style="list-style-type: none"> - Fast and efficient, allowing for timely enrolment of participants in research. 	<ul style="list-style-type: none"> - May be completed at a time that is convenient for both participants and researchers. 	<ul style="list-style-type: none"> - May be completed at a time that is convenient for both participants and researchers. 	<ul style="list-style-type: none"> - Enables efficient enrolment of participants even when participants are incapacitated. - Enables enrolment of participants in research when participants are incapacitated. 	<ul style="list-style-type: none"> - Enables efficient enrolment of participants. - Requires little to no resources, as consent is not individually sought by a member of the research team for each participant.
Disadvantages	<ul style="list-style-type: none"> - Time consuming both for the process of obtaining consent and for allowing participants sufficient time to consider the information presented and discuss it with others before arriving at a decision. - Patients and proxies often do not read these extensive documents. 	<ul style="list-style-type: none"> - May be difficult to reach a participant or SDM to obtain verbal consent (since they are not present in front of the research team in person). 	<ul style="list-style-type: none"> - May be difficult to reach a participant or SDM to obtain verbal consent. - Extra resources required to follow-up and ensure that the consent form is returned. 	<ul style="list-style-type: none"> - May be difficult to reach a participant or SDM to obtain verbal consent. - Extra resources required to follow-up to ensure that the consent form is returned. - May not be accessible to all participants. 	<ul style="list-style-type: none"> - Time consuming both for the process of obtaining consent and for allowing participants sufficient time to consider the information presented. - May not be truly reflective of the participant's wishes. 	<ul style="list-style-type: none"> - Eliminates participants' ability to decide whether or not to participate before they are enrolled in the study. - No formalized agreement to participate in the research is provided by the participant.

has been questioned. Studies have posited that it is unhelpful to consent participants when interventions occur at a departmental or institutional level [6] (e.g. cluster-randomized clinical trials [49]), since participation becomes integrated with clinical care, thereby rendering it impossible to avoid participation in the study. Additionally, individual participant- and study-specific consent does not enable those who are willing to provide consent in a broader context to do so [50]. This may be overly cumbersome and time-consuming for both participants and researchers when used for minimal risk studies, cluster-randomized trials, or those heavily intertwined with the clinical care that patients are already receiving.

Alternative consent models not currently in practice have been proposed, and include (i) broad/blanket consent, (ii) opt-out models, and (iii) meta-consent. In broad/blanket consent, participants are asked to provide overarching consent to the use of their health data for various research purposes without patients or researchers needing to engage in a consent conversation for each study for which a patient is eligible [50]. In opt-out models, participants are given the option to refuse participation on a study-by-study basis [50], while researchers are able to capture the majority of eligible participants in a timely and efficient manner. However, the caveat to this model is that studies must be widely publicized and information must be readily accessible in order for participants to make an informed decision when considering opting out. Meta-consent models have been proposed as an alternative to obtaining consent for individual research studies. Under the meta-consent framework, patients provide overarching input into how and when consent is requested from them, such that consent is not ultimately required to be obtained from every individual participant for every research study [50]. For example, a given patient could prefer a particular type of consent (specific consent for every research study, consent for broad categories of research, consent for all research, or refusal for all research), for a particular subset of data (electronic health record data, genetic/tissue data, all healthcare databases, or linkage with non-healthcare databases), in particular contexts (private vs. public, commercial vs. noncommercial, national vs. international) [50]. Although patients are generally agreeable to the use of such a hypothetical consent framework, clarity on issues of the commercial use of data, desire to know the future intended uses of data, and transparency (i.e. surrounding who would use the data, what data would be used, and for what purposes) is needed in order to realize the potential of this avenue for informed clinical research consent in the future [51].

Conclusion

Informed, ongoing, and voluntary consent is the pillar of autonomy in clinical research. Although a variety of strategies exist for obtaining informed consent in different research settings with both capable and incapacitated participants, they may limit participation in research by placing an undue burden on research teams and participants, particularly in the context of high-acuity medical situations where patients may be critically ill or have underlying neurological impairments. Although waivers of consent are appealing to improve study recruitment in these scenarios, they have received relatively poor feedback from patients and research staff. As an immediate solution, efforts should be made to use deferred consent models instead, with well-described written study materials for participants or proxies to aid in the consent conversation. Having patient partners as research team members may allow for improved written study materials to be

created for this purpose, with a patient-centered design. As a long-term solution, a movement towards more comprehensive and overarching models of consent such as meta-consent frameworks may ultimately help mitigate the logistical issues associated with obtaining informed consent on a study- and participant-specific basis, by targeting consent strategies based on participant preferences. Future studies should seek to further elucidate participant and researcher perspectives on novel consent models and explore the potential utility of alternative consent frameworks in hospital-based clinical research.

Key references

- 1) Bramstedt K. A guide to informed consent for clinician-investigators. *Cleve Clin J Med* 2004;**71**:907–10
- 2) Falagas ME, Korbila IP, Giannopoulou KP et al. Informed consent: how much and what do patients understand? *Am J Surg* 2009;**198**:420–35. <https://doi.org/10.1016/j.amjsurg.2009.02.010>
- 3) Hadden KB, Prince LY, Moore TD et al. Improving readability of informed consents for research at an academic medical institution. *J Clin Transl Sci* 2017;**1**:361–5. <https://doi.org/10.1017/cts.2017.312>
- 4) Appelbaum PS. Consent in impaired populations. *Curr Neurol Neurosci Rep* 2010;**10**:367–73. <https://doi.org/10.1007/s11910-010-0123-5>
- 5) Dunn LB, Nowrangi MA, Palmer BW et al. Assessing decisional capacity for clinical research or treatment: a review of instruments. *Am J Psychiatry* 2006;**163**:1323–34. <https://doi.org/10.1176/ajp.2006.163.8.1323>

Self-assessment questions

- (1) Alterations to the consent process are possible provided that any one of the following criteria is met: (i) there exists no more than a minimal risk to participants; (ii) participants' welfare will not be adversely affected; (iii) obtaining consent would render answering the research question impossible or impracticable; (iv) the nature and extent of the consent alteration are defined; and (v) participants may refuse consent or withdraw data/biological specimens during a poststudy debriefing.
- (2) Patients may be enrolled in research without consent if the study is minimal risk and the patient is unconscious, sedated, or has an altered level of consciousness and must be promptly enrolled.
- (3) Research teams may request a waiver of consent from the REB for any of the following reasons: (i) data validity and quality; (ii) practical issues; and (iii) participant unwillingness to participate.
- (4) A substitute decision maker (SDM) is an authorized third-party individual who is able to make decisions on behalf of the participant.
- (5) Alternative consent models that have been proposed to date include broad/blanket consent, opt-out models, and meta-consent.

Answers

- (1) False—all criteria must be met.
- (2) True

- (3) False—research teams may request a waiver of consent from the REB for three reasons: (i) data validity and quality; (ii) practical issues; and (iii) participant confusion or distress. Participant unwillingness to participate is not an acceptable reason for requesting a waiver of consent from an REB.
- (4) True
- (5) True

Acknowledgements

We would like to acknowledge and thank Brian Laight for his thoughtful feedback on this manuscript.

Conflict of interest statement: None declared.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. CIHR, SSHRC. *Tri-Council Policy Statement. Ethical Conduct for Research Involving Humans*. Ottawa, Canada: Canadian Institutes of Health Research (CIHR), 2018.
2. Bramstedt K. A guide to informed consent for clinician-investigators. *Cleve Clin J Med* 2004;**71**:907–10.
3. Falagas ME, Korbila IP, Giannopoulou KP et al. Informed consent: how much and what do patients understand? *Am J Surg* 2009;**198**:420–35. <https://doi.org/10.1016/j.amjsurg.2009.02.010>.
4. Hadden KB, Prince LY, Moore TD et al. Improving readability of informed consents for research at an academic medical institution. *J Clin Transl Sci* 2017;**1**:361–5. <https://doi.org/10.1017/cts.2017.312>.
5. Miller FG, Kaptchuk TJ. Deception of subjects in neuroscience: an ethical analysis. *J Neurosci* 2008;**28**:4841–3. <https://doi.org/10.1523/JNEUROSCI.1493-08.2008>.
6. Rebers S, Aaronson NK, van Leeuwen FE et al. Exceptions to the rule of informed consent for research with an intervention. *BMC Med Ethics* 2016;**17**:9. <https://doi.org/10.1186/s12910-016-0092-6>.
7. John S, Rowley J, Bartlett K. Assessing patients decision-making capacity in the hospital setting: a literature review. *Aust J Rural Health* 2020;**28**:141–8. <https://doi.org/10.1111/ajr.12592>.
8. Appelbaum PS. Consent in impaired populations. *Curr Neurol Neurosci Rep* 2010;**10**:367–73. <https://doi.org/10.1007/s11910-010-0123-5>.
9. Appelbaum PS, Grisso T. *MacCAT-CR: MacArthur Competence Assessment Tool for Clinical Research*. Sarasota, FL: Professional Resource Press, 2001.
10. Moyer J, Karel MJ, Azar AR et al. Capacity to consent to treatment: empirical comparison of three instruments in older adults with and without dementia. *Gerontologist* 2004;**44**:166–75. <https://doi.org/10.1093/geront/44.2.166>.
11. Dunn LB, Nowrangi MA, Palmer BW et al. Assessing decisional capacity for clinical research or treatment: a review of instruments. *Am J Psychiatry* 2006;**163**:1323–34. <https://doi.org/10.1176/ajp.2006.163.8.1323>.
12. Karlawish J. Assessment of decision-making capacity in adults. In: DeKosky ST, Mendez MF (eds.), *UpToDate*, Waltham, MA: UpToDate, 2021.
13. Isaac MLC, Randall J. Palliative care: issues in the intensive care unit in adults. In: Parsons PE, Silveira MJ (eds.), *UpToDate*, Waltham, MA: UpToDate, 2021.
14. Health Care Consent Act, 1996, SO 1996 c. 2, Sched. A.
15. Northoff G. Neuroscience of decision making and informed consent: an investigation in neuroethics. *J Med Ethics* 2006;**32**:70–3. <https://doi.org/10.1136/jme.2005.011858>.
16. Leibson T, Koren G. Informed consent in pediatric research. *Paediatr Drugs* 2015;**17**:5–11. <https://doi.org/10.1007/s40272-014-0108-y>.
17. CMPA. Mental incapacity / substitute decision-making. In: *Consent: a guide for Canadian physicians*. Ottawa, Canada: Canadian Medical Protective Association (CMPA), 2021.
18. Thomson CJ, Segrave RA, Carter A. Informed consent and voluntariness: balancing ethical demands during trial recruitment. *AJOB Neurosci* 2021;**12**:83–5. <https://doi.org/10.1080/21507740.2020.1867667>.
19. Shivayogi P. Vulnerable population and methods for their safeguard. *Perspect Clin Res* 2013;**4**:53–7. <https://doi.org/10.4103/2229-3485.106389>.
20. Grady C, Wiener L, Abdoler E et al. Assent in research: the voices of adolescents. *J Adolesc Health* 2014;**54**:515–20. <https://doi.org/10.1016/j.jadohealth.2014.02.005>.
21. Field MJ, Behrman RE (ed.) Institute of Medicine (US) Committee on Clinical Research Involving Children. *Ethical Conduct of Clinical Research Involving Children*. Washington (DC): National Academies Press (US), 2004.
22. Unguru Y, Coppes MJ, Kamani N. Rethinking pediatric assent: from requirement to ideal. *Pediatr Clin N Am* 2008;**55**:211–22. <https://doi.org/10.1016/j.pcl.2007.10.016>.
23. Folstein MF, Folstein SE, McHugh PR et al. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;**12**:189–98. [https://doi.org/10.1016/0022-3956\(75\)90026-6](https://doi.org/10.1016/0022-3956(75)90026-6).
24. Nasreddine ZS, Phillips NA, Bedirian V et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;**53**:695–9. <https://doi.org/10.1111/j.1532-5415.2005.53221.x>.
25. Jea K. Cognitive impairment and PD patients' capacity to consent to research. *Neurology* 2013;**81**:801–7. <https://doi.org/10.1212/WNL.0b013e3182a05ba5>.
26. Scott YK, Caine, ED. Utility and limits of the Mini Mental State Examination in evaluating consent capacity in Alzheimer's disease. *Psychiatr Serv* 2014;**53**:1322–4. doi: <https://doi.org/10.1176/appi.ps.53.10.1322>.
27. Jeste DV, Depp CA, Palmer BW. Magnitude of impairment in decisional capacity in people with schizophrenia compared to normal subjects: an overview. *Schizophr Bull* 2006;**32**:121–8. <https://doi.org/10.1093/schbul/sbj001>.
28. Grisso T, Appelbaum PS. The MacArthur Treatment Competence Study. III: Abilities of patients to consent to psychiatric and medical treatments. *Law Hum Behav* 1995;**19**:149–74. <https://doi.org/10.1007/BF01499323>.
29. Boettger S, Bergman M, Jenewein J et al. Assessment of decisional capacity: prevalence of medical illness and psychiatric comorbidities. *Palliat Support Care* 2015;**13**:1275–81. <https://doi.org/10.1017/S1478951514001266>.
30. Appelbaum PS, Grisso T, Frank E et al. Competence of depressed patients for consent to research. *Am J Psychiatry* 1999;**156**:1380–4. <https://doi.org/10.1176/ajp.156.9.1380>.
31. Triebel KL, Martin RC, Novack TA et al. Recovery over 6 months of medical decision-making capacity after traumatic brain injury.

- Arch Phys Med Rehabil 2014;**95**:2296–303. <https://doi.org/10.1016/j.apmr.2014.07.413>.
32. Steward KA, Gerstenecker A, Triebel KL et al. Twelve-month recovery of medical decision-making capacity following traumatic brain injury. *Neurology* 2016;**87**:1052–9. <https://doi.org/10.1212/WNL.0000000000003079>.
 33. Raymont V, Bingley W, Buchanan A et al. Prevalence of mental incapacity in medical inpatients and associated risk factors: cross-sectional study. *Lancet* 2004;**364**:1421–7. [https://doi.org/10.1016/S0140-6736\(04\)17224-3](https://doi.org/10.1016/S0140-6736(04)17224-3).
 34. Silveira MJ, Kim SY, Langa KM. Advance directives and outcomes of surrogate decision making before death. *N Engl J Med* 2010;**362**:1211–8. <https://doi.org/10.1056/NEJMsa0907901>.
 35. Gobat NH, Gal M, Francis NA et al. Key stakeholder perceptions about consent to participate in acute illness research: a rapid, systematic review to inform epi/pandemic research preparedness. *Trials* 2015;**16**:591. <https://doi.org/10.1186/s13063-015-1110-6>.
 36. Lawton J, Hallowell N, Snowdon C et al. Written versus verbal consent: a qualitative study of stakeholder views of consent procedures used at the time of recruitment into a peripartum trial conducted in an emergency setting. *BMC Med Ethics* 2017;**18**:36. <https://doi.org/10.1186/s12910-017-0196-7>.
 37. Molyneux S, Njue M, Boga M et al. ‘The words will pass with the blowing wind’: staff and parent views of the deferred consent process, with prior assent, used in an emergency fluids trial in two African hospitals. *PLoS One* 2013;**8**:e54894. <https://doi.org/10.1371/journal.pone.0054894>.
 38. Kenyon S, Dixon-Woods M, Jackson CJ et al. Participating in a trial in a critical situation: a qualitative study in pregnancy. *Qual Saf Health Care* 2006;**15**:98–101. <https://doi.org/10.1136/qshc.2005.015636>.
 39. Woolfall K, Frith L, Gamble C et al. How parents and practitioners experience research without prior consent (deferred consent) for emergency research involving children with life threatening conditions: a mixed method study. *BMJ Open* 2015;**5**:e008522. <https://doi.org/10.1136/bmjopen-2015-008522>.
 40. Gamble C, Nadel S, Snape D et al. What parents of children who have received emergency care think about deferring consent in randomised trials of emergency treatments: postal survey. *PLoS One* 2012;**7**:e35982. <https://doi.org/10.1371/journal.pone.0035982>.
 41. Woolfall K, Young B, Frith L et al. Doing challenging research studies in a patient-centred way: a qualitative study to inform a randomised controlled trial in the paediatric emergency care setting. *BMJ Open* 2014;**4**:e005045. <https://doi.org/10.1136/bmjopen-2014-005045>.
 42. Potter JE, McKinley S, Delaney A. Research participants’ opinions of delayed consent for a randomised controlled trial of glucose control in intensive care. *Intensive Care Med* 2013;**39**:472–80. <https://doi.org/10.1007/s00134-012-2732-8>.
 43. Gigon F, Merlani P, Chenaud C et al. ICU research: the impact of invasiveness on informed consent. *Intensive Care Med* 2013;**39**:1282–9. <https://doi.org/10.1007/s00134-013-2908-x>.
 44. Lecouturier J, Rodgers H, Ford GA et al. Clinical research without consent in adults in the emergency setting: a review of patient and public views. *BMC Med Ethics* 2008;**9**:9. <https://doi.org/10.1186/1472-6939-9-9>.
 45. Iwanowski P, Budaj A, Członkowska A et al. Informed consent for clinical trials in acute coronary syndromes and stroke following the European Clinical Trials Directive: investigators’ experiences and attitudes. *Trials* 2008;**9**:45. <https://doi.org/10.1186/1745-6215-9-45>.
 46. Duffett M, Burns KE, Kho ME et al. Consent in critical care trials: a survey of Canadian research ethics boards and critical care researchers. *J Crit Care* 2011;**26**:533.e11–22. <https://doi.org/10.1016/j.jcrc.2010.12.009>.
 47. Cook DJ, Blythe D, Rischbieth A et al. Enrollment of intensive care unit patients into clinical studies: a trinational survey of researchers’ experiences, beliefs, and practices. *Crit Care Med* 2008;**36**:2100–5. <https://doi.org/10.1097/CCM.0b013e31817c00b0>.
 48. Offerman SR, Nishijima DK, Ballard DW et al. The use of delayed telephone informed consent for observational emergency medicine research is ethical and effective. *Acad Emerg Med* 2013;**20**:403–7. <https://doi.org/10.1111/acem.12117>.
 49. Lin LY, Jochym N, Merz JF. Refusal rates and waivers of informed consent in pragmatic and comparative effectiveness RCTs: a systematic review. *Contemp Clin Trials* 2021;**104**:106361. <https://doi.org/10.1016/j.cct.2021.106361>.
 50. Ploug T, Holm S. Meta consent – a flexible solution to the problem of secondary use of health data. *Bioethics* 2016;**30**:721–32. <https://doi.org/10.1111/bioe.12286>.
 51. Cumyn A, Barton A, Dault R et al. Meta-consent for the secondary use of health data within a learning health system: a qualitative study of the public’s perspective. *BMC Med Ethics* 2021;**22**:81. <https://doi.org/10.1186/s12910-021-00647-x>.
 52. Grisso T, Appelbaum PS, Hill-Fotouhi C. The MacCAT-T: a clinical tool to assess patients’ capacities to make treatment decisions. *Psychiatr Serv* 1997;**48**:1415–9. <https://doi.org/10.1176/ps.48.11.1415>.