Informed consent practices in clinical research: present and future

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

<table>
<thead>
<tr>
<th>Principle</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voluntary</td>
<td>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.</td>
</tr>
<tr>
<td>Informed</td>
<td>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).</td>
</tr>
<tr>
<td>Ongoing</td>
<td>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.</td>
</tr>
</tbody>
</table>

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 2. Information to be included in informed consent [1].

<table>
<thead>
<tr>
<th>Element</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invitation</td>
<td>An invitation to participate in the research project.</td>
</tr>
<tr>
<td>Purpose</td>
<td>The purpose and specific goals of the study.</td>
</tr>
<tr>
<td>Risk-benefit profile</td>
<td>Description of the risks, harms, discomforts, and potential benefits to the participant and to the greater society that may result from their participation.</td>
</tr>
<tr>
<td>Identifying details</td>
<td>The identity of the researcher, funder, and sponsor.</td>
</tr>
<tr>
<td>Conflicts of interest</td>
<td>Conflict of interest disclosures to inform the participant if there is a potential benefit to the investigators or other members of the research study team or their immediate family members, which goes beyond the professional benefit and future benefit to patients for their participation in the study.</td>
</tr>
<tr>
<td>Time</td>
<td>Duration of participation in study-related activities and entire study duration.</td>
</tr>
<tr>
<td>Responsibilities</td>
<td>Requirements for participation and their responsibilities as a participant in the study.</td>
</tr>
<tr>
<td>Procedures</td>
<td>Research procedures, visits, and/or interventions (e.g. biological specimen collection and analysis, imaging, medical chart review).</td>
</tr>
<tr>
<td>Voluntary nature and</td>
<td>Voluntary nature of the research and ability to withdraw their participation at any time during the study, including the conditions of withdrawal of data and/or biological specimens.</td>
</tr>
<tr>
<td>withdrawal procedures</td>
<td></td>
</tr>
<tr>
<td>New information</td>
<td>Notice that participants will be provided with any new information relevant to their decision to participate as it arises.</td>
</tr>
<tr>
<td>Commercialization</td>
<td>Information regarding the commercialization of findings.</td>
</tr>
<tr>
<td>Knowledge translation</td>
<td>How research results will be disseminated, and how participants will be identified in presentations/publications.</td>
</tr>
<tr>
<td>Research contacts</td>
<td>Contact information for a research team member in case any questions arise.</td>
</tr>
<tr>
<td>Ethics contacts</td>
<td>Contact information in case of ethical questions.</td>
</tr>
<tr>
<td>Data collection</td>
<td>Data to be collected from participants and purpose of collecting this information.</td>
</tr>
<tr>
<td>Confidentiality</td>
<td>Confidentiality of data and biological specimens to be collected.</td>
</tr>
<tr>
<td>Costs/compensation</td>
<td>Expenses, compensation, or reimbursements the participant will have/receive.</td>
</tr>
<tr>
<td>Legal rights</td>
<td>A statement that participants do not waive their legal rights in the event of research-related harm.</td>
</tr>
</tbody>
</table>

consent from the REB for three primary reasons: (i) data validity and quality; (ii) practical issues; and (iii) participant confusion or distress [6]. Waivers of consent are also appropriate for studies making secondary use of nonidentifiable information (e.g. retrospective chart-review studies that do not collect identifiable patient information) [1]. Arguments related to data validity and quality are rationalized via the Hawthorne effect [6]. Furthermore, the requirement for informed consent may lead to lower recruitment rates as the time to obtain consent may exceed the allowable enrollment window, leading to poorly powered studies and reduced data quality [6]. Consent also creates a selection bias, as there may be inherent differences between participants who consent to a study and those who do not [6]. For example, unconscious patients in acute care settings may not be able to consent; thus, enrollment would be weighted towards favoring those with lower illness severity and potentially underestimate results.

In terms of practical concerns, incapacitated, unconscious, or sedated patients present notable challenges, as they are unable to provide informed consent [6]. As these patients are commonly seen in emergency or critical care settings, research in these fields often demands alternative consent models (e.g. waivers or deferrals). However, deferred consent becomes impossible for the many patients who do not survive their illness [6], thus prompting the use of consent waivers. The time-sensitive nature of administering interventions also hinders the ability to gather informed consent in high-acuity settings [6], further encouraging the use of waivers.

Finally, critical illnesses and medical emergencies are inherently stressful, and research is not often top-of-mind for patients and families in these scenarios. Discussing research in these instances may therefore serve to increase their level of distress [6]. Patients and families may also be distressed that their clinician does not know which treatment option is more efficacious, or the treatment to which they will be randomized in a clinical trial [6]. Consequently, research teams often elect to use a waiver of consent model to ease the stress on patients.

Exceptions to consent in the context of a medical emergency

Research can occur without consent during a medical emergency if all of the following criteria are met: (i) immediate intervention is needed; (ii) no standard efficacious care options exist, or the research study will realistically provide a direct benefit to the participant over the standard of care (e.g. if the standard of care consists solely of supportive measures); (iii) the risk of participating in research is not greater than that of the standard of care, or is justified by the direct benefit to the participant; (iv) the participant is unconscious or lacks capacity to provide consent; (v) consent from an SDM cannot be obtained within sufficient time, in spite of documented efforts; and (vi) no prior directive by the participant regarding research exists [1].

Capacity assessment

Participants are considered to have the capacity to consent only when the four primary decision-making abilities described in Table 3 are present [7].

It is widely accepted that the absence of one or more of these decision-making abilities constitutes decisional impairment and, therefore, insufficient capacity [8]. The importance of accurate capacity assessment has led to the development of standardized tools (e.g. MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) [9]); however, there is currently no gold-standard assessment tool. Furthermore, these tools are time-consuming, cumbersome, and require training to be administered, reducing the feasibility of their use in practice [10, 11]. Electronic formats may improve their utility, as they are more accessible and often abbreviated. However, abbreviated formats may reduce the validity of the assessment [11]. More commonly,
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 clearer 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 or 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
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].

<table>
<thead>
<tr>
<th>Imagined</th>
<th>Deferred</th>
<th>SDM</th>
<th>Electronic</th>
<th>Telephone</th>
<th>Verbal</th>
<th>Written</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>- 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.</td>
<td>- Allows for the inclusion of participants in research without their (or a proxy’s) prior consent.</td>
<td>- If the participant has or regains capacity at any point during their participation in the study, consent should be sought from the participant.</td>
<td>- Enables enrollment of participants in research even when participants are incapacitated.</td>
<td>- May be completed at a time that is convenient for both participants and researchers.</td>
<td>- A full description of the study is provided to the participant or proxy via telephone.</td>
</tr>
<tr>
<td><strong>Feasibility</strong></td>
<td>High</td>
<td>- 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.</td>
<td>High</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Additional considerations</strong></td>
<td>- May not be accessible to all participants.</td>
<td>- Enables efficient and timely enrollment of participants and may be particularly of benefit in emergency or critical care contexts.</td>
<td>- If the participant does not have capacity to consent at the time of deferred consent, the SDM should be approached.</td>
<td>- Language requirements for informed consent form (e.g. need for interpreter).</td>
<td>- Need to confirm identity of the participant or proxy.</td>
<td>- Language requirements (i.e. need for interpreter).</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>- Enables efficient and timely enrollment of participants and may be particularly of benefit in emergency or critical care contexts.</td>
<td>- Enables efficient enrollment of participants.</td>
<td>- Enables efficient enrollment of participants.</td>
<td>- May be completed at a time that is convenient for both participants and researchers.</td>
<td>- Fast and efficient, allowing for timely enrollment of participants in research.</td>
<td>- A full description of the study is provided to the participant or proxy via telephone.</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>- No formalized agreement to participate in the research is provided by the researcher.</td>
<td>- Requires little to no resources, as consent is not individually sought by a member of the research team for each participant.</td>
<td>- Requires little to no resources, as consent is not individually sought by a member of the research team for each participant.</td>
<td>- Extra resources required to follow-up and ensure that the consent form is returned.</td>
<td>- 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).</td>
<td>- The person obtaining consent records the participant or proxy’s verbal consent on the verbal consent script and documents the consent process.</td>
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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 researchers and participants 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 participati and researcher perspectives on novel consent models and explore the potential utility of alternative consent frameworks in hospital-based clinical research.

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### Key references


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### 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.

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### 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

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