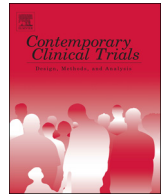




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# Advances and challenges in conducting ethical trials involving populations lacking capacity to consent: A decade in review

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## ABSTRACT

Informed consent is an essential requirement prior to clinical trial participation, however some ‘vulnerable’ groups, such as people with cognitive impairments and those in medical emergency situations, may lack decisional capacity to consent. This raises ethical and practical challenges when designing and conducting clinical trials involving these populations, who are frequently excluded as a result. Despite recent advances in improving informed consent processes, there has been far less attention paid to the enrolment of adults lacking capacity.

Exclusion criteria are an important determinant of the external validity of clinical trial results. The exclusion of these populations, and consent-based recruitment biases which arise from the challenges of identifying and involving surrogate decision-makers, leads to trials which are not representative of the clinical population.

This article discusses the involvement of adults who lack decisional capacity to consent in clinical trials and presents the advances over the previous decade and the remaining ethical challenges for the inclusion of this under-represented population in research.

## 1. Introduction

Despite the growing focus on improving informed consent processes for clinical trials over the previous decade [1], enrolment of participants who lack decisional capacity to provide informed consent has been the subject of much less attention. This is due, in part, to the challenging ethical issues that surround such trials, and uncertainty about how they should be addressed. However, this issue will become even more pressing in the coming decades with an increase in the prevalence of neurodegenerative and other conditions that can affect the ability to make informed decisions about participation in clinical trials [2]. In addition, the current coronavirus pandemic has resulted in a surge of critically ill patients and a corresponding explosion of clinical trials evaluating therapeutic agents for COVID-19 [3]. Patients admitted to critical care units are frequently unable to provide informed consent [4], and COVID-19 itself is associated with a number of psychiatric and neuropsychiatric effects, including delirium which is common in the acute stage [5]. Thus the need to conduct clinical trials to inform and transform evidence-based care for these growing populations is intensifying.

Over the previous decade there has also been a growing awareness of the issue of under-represented and underserved populations in research. This recognises that there is a considerable difference between trial and clinical populations, where participants in trials do not

represent the characteristics of patients who could benefit from the drugs in ‘real world’ clinical practice settings. This includes that trial populations are younger [6] less representative of women and minority groups [7] and have fewer health conditions [8] than those in the affected population. Approximately 58% of the total US population are typically excluded from research studies [9], and a third of randomized controlled trials are at high risk of bias, most commonly because the clinical population used is not appropriate for the trial [8]. Exclusions of people with cognitive impairment are seen in areas such as geriatrics research [10], rehabilitation interventions after hip fracture [11], learning disabilities [12], peri-operative medicine [13], trauma [14] and neurological research [15]. Clinical trials in other areas such as emergency research also encounter significant ethical challenges around informed consent which impacts on the populations included in trials [16]. Even in trials that are designed to include adults who lack capacity to consent, the proportion and numbers of participants lacking capacity actually recruited are worryingly small [17]. This recruitment bias leads to underpowered or abandoned studies [15] and trials which are not representative of the clinical population [14,16,18], resulting in evidence ‘biased’ medicine for these populations [19].

The prevalence of incapacity in different settings and populations can be hard to determine, in part due to the decision-specific nature of capacity, however a systematic review reported that the proportion of patients with incapacity in medical settings was 34% (95% CI 25–44%)

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and 45% (95% confidence interval (CI) 39–51%) in psychiatric settings [20]. Research conducted in UK care homes (long term care facilities) with older people found 71% of participants lacked capacity to consent [21], this proportion rises to over 90% in critical care settings [4]. Decisional capacity to consent to research is generally accepted to be the ability of a potential research subject to understand and process the information that is necessary to make an informed decision regarding study participation [22] and to communicate that decision [23]. Decisional capacity, however, is task-specific and not a static concept. People assessed as lacking capacity may have capacity to make some decisions but not others, may regain and lose capacity over time, or experience fluctuating capacity. Trials involving adults with cognitive impairment raises ethical issues, primarily because these groups are unable to provide adequate informed consent or protect their own interests [22]. National research regulations and ethical guidance require that investigators provide additional safeguards for vulnerable subjects who participate in research [24]. These regulations were originally designed to protect ‘vulnerable’ research participants. However this exclusionary ethics puts vulnerable populations at risk, while trying to protect them from exploitation [14]. More recent changes in the attitudes of research communities’ are starting to recognise that these groups should be protected *through* research, rather than *from* research [9]. This is echoed in international ethical guidance which states that adults who are not capable of giving informed consent must be included in health-related research unless a good scientific reason justifies their exclusion [25]. Incoming European regulations require that clinical trials participants should represent the population groups, for example gender and age groups, that are likely to use the medicinal product investigated in the clinical trial [26], although only if the trial cannot be conducted equally well with participants who are able to provide consent, and the research addresses health needs relevant to people with those particular conditions [25].

Eligibility criteria are intended to be used to recruit participants that are representative of the patient populations who will ultimately receive the medication or intervention in clinical practice [27]. Exclusion criteria are commonly used in trials to ensure the safety and protection of participants; however, some use a very restricted profile for patient eligibility [27]. Eligibility criteria which exclude groups without valid reasons can result in research samples that do not represent the diversity, symptom complexity, or daily challenges of the clinical population [15] which negatively affects the external validity of the trial [27]. Excluding patients with cognitive impairments is common but a robust rationale is rarely provided or discussed as a potential limitation [10,15]. Arbitrary use of this criterion excludes large numbers of the clinical population and so limits the pool of potential participants, and, as these excluded individuals are disproportionately from vulnerable populations, this exclusion also raises ethical concerns [15]. Current exclusion criteria, ethical barriers, and enrolment practices all impact on trial populations and so may reduce the clinical utility of research findings, leading to inequity in evidence-informed interventions for these populations [4,10,11,28]. While there have been calls for more active involvement of research funding organisations in the scrutiny of the justifications behind this exclusion, such as reviewing eligibility criteria [28], the clinical trials community can play a large role in designing more inclusive research, and identifying and addressing the ethical challenges that impact on the conduct of ethical trials with populations lacking capacity to consent. The start of a new decade presents an opportunity to pause and review the current issues encountered when conducting trials involving adults who lack decisional capacity to consent. This article discusses a number of the barriers and presents recent advances and remaining challenges for the inclusion of this under-represented population. Recommendations are made that seek to address these challenges for future clinical trials.

## 2. Challenges of surrogate consent

For adults who lack capacity to consent to participate in a trial, the consent or agreement of a family member or other person with a close personal relationship with the person concerned must be sought prior to their enrolment [25]. Surrogate or proxy decision-makers must evaluate to what extent trial participation is consistent with the person's wishes and values, and any previously stated preferences regarding the person's willingness to enrol in research should be respected [25]. In situations where a family member or friend is not available, in some jurisdictions researchers may obtain the permission of an alternative representative [25] who may be an independent member of the healthcare team or an individual appointed by the state. However, a number of challenges may be encountered, including problems with gaining ethical approvals, identifying surrogates, and the problems faced by surrogates making a decision about participation on behalf of another including determining the preferences and values of the person they represent.

### 2.1. Complexities of legislative frameworks and ethical review processes

The legal provisions for the involvement of adults who lack capacity to consent, and alternative arrangements for their inclusion in clinical trials, varies between different legal jurisdictions. One study which examined the ethical approval process for an intensive care observational study found substantial and persisting variations between EU member states in the organisation, structures, processes, efficiency, and decision-making of Research Ethics Committees (RECs) [29]. Within the US, there is considerable variability between Institutional Review Board (IRB) practices on surrogate consent [30]. However, most US states do not have laws regarding surrogate consent for research [31], and reliance on healthcare proxies is problematic because many people have no legally authorized representative for medical decision-making [32]. The authors of a recent study examining these practices argue that this variability may have adverse consequences for the much needed research involving adults who lack capacity, and call for guidance to help clarify current regulations [30]. A similar ‘patchwork of laws’ exist in many other countries, such as Australia [33]. These legislative complexities and accompanying heterogeneity in ethical approvals processes are challenging when conducting international clinical trials involving adults who lack capacity. The importance of international co-ordination of COVID-19 trials of candidate drugs and vaccines has been highlighted, including the need to ensure the representativeness of the trial population through the inclusion of vulnerable groups [34].

Research has identified the impact of the complex legislation governing research involving adults lacking capacity to consent in the UK [19]. This complexity leads to misunderstanding and misinterpretation of the legislation by researchers who design trials involving adults who lack capacity [35], RECs who review these trials [36] and healthcare professionals caring for these populations [37]. Current ethical guidelines fail to support the inclusion of participants unable to consent through the lack of specific and appropriate advice, which is in itself ethically problematic [14]. Further guidance is urgently needed for RECs/IRBs, the trials community, and healthcare professionals in order to improve confidence and reduce inconsistencies that act as barriers to conducting trials involving adults lacking capacity to consent.

### 2.2. Concerns about surrogate decision-making

Another issue that has been the focus of attention over the previous decades is surrogate decision-making. This includes aspects of the patient-surrogate relationship, concerns about ‘accuracy’ of the surrogate's decision, and how the risks and benefits of participation are balanced alongside respecting the preferences and values of the person who lacks capacity. Numerous studies have explored the accuracy of a surrogate's substituted judgement, often presenting a hypothetical

study to a patient and surrogate dyad and asking the surrogate to predict what the patient would decide about participating [38–43]. Across these studies, accuracy varied with a patient–surrogate discrepancy reported as between 32% and 42% depending on the hypothetical scenario in one study [40], and an accuracy rate of 76% reported in another study [39]. Newman and colleagues found that the overall percentage of discrepancy increased as the perceived risk associated with the hypothetical study rose [42]. However, it is important to note that such studies have important limitations and methodological flaws [44]. This includes that they are based on the assumption that decision-making in hypothetical and actual situations are the same [45], and that the patient's own 'decision' should be seen as the gold standard, although they too are expressing a prediction which may not be accurate [46]. In a number of studies, potential participants asked about future research participation in the event of incapacity reported that the choice of who acted as their proxy was important [47–49] which wasn't necessarily the family member accompanying them to clinic (as used in these dyad accuracy studies). Patients are willing to grant leeway to their surrogates when making decisions about research on their behalf on the basis that these are contextual decisions and many relevant factors won't be known in advance [50].

The discordance between patient and surrogate decisions may also be due to a difference in motivation for participation. Critical care patients' motives are primarily altruistic and centre on a desire to help others and advance science [4], and whilst this is also a consideration for their surrogates' [51], surrogates' motives focus on a belief that their loved one could benefit from participation [4]. Surrogates themselves describe how they balance a number of different factors during the decision-making process, including attempting to honour the wishes of the person they represent whilst assessing the risks and benefits of participation [52]. Despite concerns from some quarters about this lack of 'accuracy', many studies report that patients and the public want their surrogate to be involved in decisions about research participation [53–55] and that surrogates want to be involved [46,56].

### 2.3. Addressing the challenges of surrogate decision-making

One of the challenges in surrogate consent is identifying a surrogate who is willing and able to make a decision about trial participation. Previous studies have found that 40%–80% of eligible critical care patients who lacked decision-making capacity were not enrolled in a study because no family member was available to provide surrogate consent [57,58], with 15% having no visitors at any time during their stay [59]. Similar issues identifying, contacting, and receiving a reply from surrogates are encountered in trials in other setting such as care homes [60]. Additional challenges may be encountered during public health emergencies, such as COVID-19, where family members may not be permitted to visit patients or may themselves be unwell. Alternative arrangements are in place, such as conducting discussions with surrogates by phone or video conference and obtaining consent via electronic or other means [61], and may be useful to continue beyond the current pandemic.

One approach that may address this challenge is to encourage patients to prospectively appointment or nominate a surrogate for research, although it may not be helpful for those considered 'unbefriended' patients (those without any family member or friend who can act as a surrogate decisions-maker). When surveyed about who should be involved in decisions about their participation in research during periods of incapacity, most older people (88%) preferred the person they appointed as their surrogate decision-maker for healthcare matters [62], and 96% were willing to appoint a surrogate for research [63]. Generally in the US, a surrogate may be able to provide consent through their appointment as legally authorized representative, although the situation regarding treatment and research decisions across the different states is very complex [31]. In England and Wales, despite the growing focus on advance planning in the event of incapacity, there

is no legal mechanism to appoint a surrogate for research [64], although someone can be appointed to make decisions about health and welfare using Power of Attorney [23]. Further research is needed to explore whether expanding and harmonising legal provisions for prospectively appointing a surrogate for research does address the challenge of identifying a surrogate.

Even once identified, surrogates can find being involved in making decisions about research participation overwhelming [65], with nearly all proxies experiencing some degree of burden [66]. In one study of family members of critically ill patients, being asked to provide consent for research was associated with post-traumatic stress symptoms in 35% of family members interviewed, compared with less than 10% in those involved in 'everyday' decisions about clinical care [67]. However, despite the number of interventions developed to improve informed consent, very few interventions have been developed to improve surrogate decision-making for participating in trials. The interventions that have been developed either focus on elements of informedness, such as a computer-based education module to improve surrogates' understanding of the process of informed consent [68] or on enhancing surrogate decisions such as a decision aid to support surrogate decision-making [69]. Further research to explore patients and surrogates' views and experiences of surrogate decision-making about clinical trial participation is needed, alongside interventions to address the challenges and burdens experienced by surrogates.

Another approach to reducing the uncertainty for surrogates and protecting the autonomy of patients through ensuring surrogate decisions are more representative of their preferences and values, is by the use of advance research directives (ARD). An ARD can be used to document a person's wishes concerning research participation in the event of a loss of capacity, and also specify the general risk level that they are prepared to accept [70]. ARDs could be particularly useful for people who are living with a condition that may cause cognitive abilities to decline in the future, such as Parkinson's disease or dementia [70]. Although not necessarily legally binding, if participants have made advance directives for participation in research while fully capable of giving informed consent, the directives should be respected [25]. While many countries have recognized the importance and need for ARDs as a tool for research, particularly in dementia, clear legal regulations are still lacking in most countries [71]. Enabling the creation of ARDs may encourage discussion about future wishes between the patient and their surrogate and so enable surrogate decisions about research to be made that are in accordance with the person's preferences and wishes.

## 3. Informed consent in emergency research

It is widely accepted that it is impossible to obtain sufficiently informed consent in emergency and prehospital research, due in part to the physical and psychological effects of the medical emergency, but also the limited time frames for the initiation of the treatment or intervention being tested [72,73]. However, the requirement in some jurisdictions to obtain consent from either the patient or (if legislation permits) their surrogate prior to enrolment in a trial is a substantial barrier to emergency research [74]. Acute and critical care clinical trials have a four-fold higher risk of discontinuation due to recruitment issues [75].

### 3.1. Impact of requiring patient or surrogate consent

The consent mechanism used for an emergency trial has a profound effect on the ability to conduct the trial and the population enrolled [16]. It has been estimated that a trauma study requiring recruitment within a few hours of admission will see a 80% to 90% reduction in the number of potentially eligible patients if consent from either the patient or their legally authorized representative (LAR) is required [16]. In an observational study of 1734 trauma patients in the US, the requirement

for consent from either the patient or their LAR also led to recruitment bias as patients who were female, had blunt trauma, or were transported a shorter distance were significantly more likely to have LARs [74]. This consent-based recruitment bias was also seen in the CONTROL trial of factor VIIa in acute haemorrhagic shock, where the requirement for either individual or LAR consent meant that US participants bled more slowly, were randomized later, and represented a less injured population than those eligible but not enrolled [16]. The consent requirements also impacted on the numbers recruited as only 17% of all US eligible patients were enrolled, largely because of the delayed arrival of LARs with 63% arriving at the hospital > 12 h after the patient and so missing the inclusion criteria [16]. The requirement for these ‘consent rituals’ may also lead to harm through delaying potentially life-saving treatment when such delays would not be encountered in clinical practice, and potentially reduce or obscure any treatment effect [76].

### 3.2. Alternative models of consent in emergency research

In emergency situations, when prior consent of the patient is not possible, and the subject's legally acceptable representative is not available, enrolment of the patient should follow alternative procedures described in the protocol that has been reviewed and approved by the IRB/REC. In many jurisdictions, such as the US, EU, Canada, and Australia regulations allow research in emergency situations to be conducted without prospective informed consent and to use alternative models of consent provided certain conditions are met [77]. The subject or the patient's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested [78]. In the US, an Exception For Informed Consent (EFIC) may be allowed, provided certain conditions are met such as community consultation with members of the community in which the research will be conducted [79]. A waiver of informed consent (WIC) regulations apply to other types of research [80].

In the EU, the Clinical Trial Directive introduced in 2001 [81] appeared to overlook critical care and emergency research [82], which was subsequently covered by the introduction of national legislation in many EU member states including the UK [83]. Although a lack of harmonisation means that deferred consent (consent sought from either the patient and/or surrogate at a later timepoint) is accepted in acute emergency research in only half of the member states [84]. Amongst other reasons, this complexity has led to a reduction in clinical trial activity in Europe, particularly in academic trials [82]. Although it is hoped that the new incoming Clinical Trials Regulation [26] will facilitate and harmonise emergency research across the EU [85], the impact has yet to be seen, and the position in the UK once it leaves the EU remains unclear.

### 3.3. Addressing the challenges of deferred or waiver of consent

Gaining a favourable ethical opinion and regulatory approvals for conducting a trial using deferred consent or EFIC can be very challenging, particularly those in the ‘middle ground’ where a patient may be awake or coherent, yet extreme pain or a lack of time allows no possibility of prospective informed consent [86]. A review of US studies using EFIC/WIC over the past 20 years identified only 28 studies, with the authors suggesting that more studies using EFIC/WIC are needed and a greater description should be published of both the justification for the use of EFIC/WIC in these trials and the process followed to ensure transparency [80]. A useful approach has been suggested for those who design and review studies using deferred consent which proposes a practical framework of ‘questions and considerations’ that a researcher should be able to answer if planning to apply to a REC for waiver of consent in the context of emergency care research [87]. Further practical and evidence-based approaches are needed in order to

improve the design, review and regulation processes of trials in emergency settings, and to prevent and resolve slow patient recruitment in randomized clinical trials conducted in the critical and emergency care setting [75].

## 4. Conclusion

Trials involving adults who lack capacity to consent are methodologically and ethically challenging. These challenges impact on the ability of trials to recruit sufficient number of participants, and consent-based recruitment biases raise questions about the external validity of the results. With changing demographics which are predicted to increase the numbers of adults lacking decisional capacity, and the current global COVID-19 pandemic, further research and resources are needed to help address these challenges and to support the inclusion of people with impaired decision-making capacity.

Guidance is needed for those designing clinical trials which provides simple and accessible information and resources to help them understand and navigate the complex legal and ethical requirements of surrogate consent and deferred consent. Further research is needed to explore clarifying and extending frameworks for advance planning for research participation, such as prospectively appointing a surrogate for research decisions and creating Advance Research Directives to document preferences about future research participation.

These measures should be complemented by the development of evidence-based strategies and interventions to inform and support substitute decision-makers across different research settings. Greater transparency and reporting of the use of alternative models of consent such as deferred consent and EFIC/WIC should be encouraged, which in turn will support the development of practical and evidence-based approaches to improve the design, review, and regulation of trials in emergency settings. A wider review of the ethical barriers and a more active involvement of research funding organisations and RECs/IRBs to scrutinise the justifications behind the exclusion of adults lacking capacity might be also be warranted.

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