

Informed Consent for the Human Research Subject with a Neurologic Disorder

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Abstract

The doctrine of informed consent sits at the intersection of law, ethics, and neuroscience, posing unique challenges for human subject research involving neurological patients. These challenges are compounded by the variegated nature of both neurological injury and the law governing research consent. This article provides a framework for investigators likely to encounter subjects with some degree of neurological impairment, whose capacity to consent requires scrupulous assessment prior to enrollment in research trials. We consider several researches and disease contexts—from emergency epilepsy research to long-term dementia research—and clarify the ethical and legal principles governing consent for participation in each. We additionally explore empirical research on consent capacity and survey several areas of emerging ethical import that will require the attention of investigators in decades to come.

Keywords

- ▶ consent
- ▶ capacity
- ▶ law
- ▶ ethics
- ▶ neurologic

Informed consent to research in neurological patients presents unique challenges, as many neurological diseases interfere directly with cognitive functions necessary for consent. Chronic neurological conditions such as neurodegenerative illnesses may slowly erode the capacity for meaningful decision making, while acute neurological injury frequently presents with impairments in consciousness or language that prevent the exchange of information that informed consent presumes. Even when patients' capacity to consent is not compromised by disease, the legal framework that purports to guide consent to research remains in need of greater development and coherence. This article describes some of the problems facing clinicians conducting human subject research on neurological diseases, and reviews ethical and legal principles governing consent for research participation.

Decisional Capacity

Informed consent is conventionally grounded in the ethical principle of autonomy.¹ The principle of autonomy stems

both from particulars of U.S. law, which entitles adults to authority and freedom from interference over their persons and property, and from ethical recognition of the central importance of patients' values and preferences.² Autonomy presumes intact capacity to make meaningful decisions. U.S. law strongly presumes that decisions made by adults concerning their own medical care and body are autonomous and must therefore be recognized. At the same time, the law also grants clinicians substantial authority to determine when patients lack capacity within the clinical setting.³

Early legal and clinical approaches tended to treat neurological and psychiatric disabilities in an all-or-none fashion. In this setting, a finding of patient "incompetence" typically reflected a global determination that the patient was unable to manage his or her affairs, resulting in a virtually complete loss of civil rights.⁴ However, over time it has become clear that many patients with compromised neurological function have sufficient ability to make some decisions (such as appointing a proxy or taking medication), even if they are unable to make others (such as in checkbook management).⁵ Thus, in both clinical and legal settings,

global determinations of incompetence have become disfavored. In contemporary approaches, decision-making ability cannot be determined on the basis of a diagnosis but must be functionally assessed on a case-by-case basis.⁶ Two patients at different stages of Alzheimer's disease, for instance, may retain disparate degrees of capacity depending on the decision to be made. One patient may clearly display capacity to consent to research or a complex medical treatment, whereas the second patient may not. The second patient, however, may still retain capacity to consent to low-risk procedures or other proposed therapeutic interventions consistent with values he or she is still able to express.

The problem of assessing capacity for consent, however, is compounded by the absence of federal legal standards for making such an assessment.¹ The legal standards for capacity have, instead, been left to states, predictably resulting in wide variation. States disagree, for instance, as to whether the degree of capacity required for consenting to a proposed treatment (conventionally understood as a health care decision) is the same as the standard for appointing a *proxy* to make health care decisions.⁷ To address this legal variation while simultaneously recognizing the widespread adoption of the ethical principles undergirding the capacity requirement, clinicians have abstracted standards from existing statutes for consent to medical *treatment* and applied them to consent to research. These standards identify four abilities necessary for capacity to consent to treatment: understanding, appreciation, reasoning, and the expression of choice.^{1,6} Though these are standards for treatment, rather than research, they have largely been imported into the research context and, in most cases, can be used to guide the conduct of investigators.³

"Understanding" refers to a patient's ability to grasp the basic facts surrounding a medical decision—such as the nature of the condition, the proposed treatment, and possible risks and benefits. "Appreciation" refers to the patient's ability to apply these basic facts to her own case. For instance, does the patient recognize that her physicians have diagnosed her with a condition that is fatal, if untreated, but then insist that she is not ill? That patient may possess understanding without appreciation. Anosognosia following neurological injury is a common source of such a discrepancy between understanding and appreciation. The "reasoning" requirement addresses the patient's ability to logically manipulate information, such as comparing the possible likely outcomes of various treatment options. Lastly, the patient must be able to "express a choice," which requires not only articulation of a treatment preference but also relative stability of that preference in the absence of new information. A locked-in patient might be able to understand, appreciate, and reason, yet still could lack capacity if unable to reliably articulate treatment preferences. Similarly, patients with fluctuating delirium who can articulate choice but cannot maintain a treatment preference would lack capacity under this criterion.^{1,4,6}

Importantly, there is no requirement embedded in any of the four elements of consent that patients' preferences be "reasonable" or match any existing medical consensus.

Courts ask only whether patients followed a rational process—whether their conclusions follow from their stated premises—in reaching decisions that may be deemed unsound by clinicians or researchers. *In re Milton*, a 1987 Ohio Supreme Court case provides a striking example.⁸ In *Milton*, a 53-year-old woman with a history of psychiatric symptoms refused treatment for her uterine cancer on the grounds that a local faith healer, whom she incorrectly believed to be her husband, would cure her. The patient demonstrated both understanding and appreciation of her physician's conclusion that without medical treatment she would likely die. The court reasoned that the patient's religious belief in faith healing stood apart from her apparent delusions regarding her marriage. Additionally, because her conduct was consistent with her religious convictions, the court could not compel her to undergo medical treatment, no matter how "unwise, foolish, or ridiculous" legal or medical experts considered her beliefs to be. Clinicians who find themselves in similar situations should therefore recognize that the prevailing legal standard errs on the side of preserving autonomy in cases of unconventional decision making. Expression of unusual preferences are broadly considered reflections of patients' subjective preferences, even though such unorthodoxy might be a subtle manifestation of underlying frontal lobe dysfunction or other neurological disorder.³

It bears emphasizing that there is no clear legal standard specifically tailored to determining capacity to consent to research. While the underlying principles guiding consent for treatment—autonomy and the right to physical integrity—remain foundational in the research realm and are enshrined in the federal Common Rule, current regulations are silent on the boundary between capacity and incapacity in research subjects.⁹ It therefore remains uncertain precisely when proxy consent may be appropriate, though 2017 Revisions to the Common Rule have at least clarified who may provide that consent for cognitively impaired subjects (discussed in more detail below).¹⁰

Several advisory commissions without power to make law have proposed guidelines tailored to determining capacity for research consent, though these have not achieved broad consensus. The National Bioethics Advisory Commission (NBAC), for example, has proposed that capacity to consent to research requires the ability to "understand the purpose, risks, and possible benefits" of a study.¹¹ This standard is notable for requiring research subjects to understand the purpose of a study in which their enrollment is sought. The NBAC proposal illustrates that meaningful consent to research may require elements that are not shared with consent to clinical treatment.

Empirical Research on Capacity to Consent and Standardized Instruments

A long-standing challenge for research consent has been the consistent interpretation of decision-making abilities across clinicians under the four-pronged test for consent described earlier. Early empirical work on the topic found that

clinicians rendered consistent capacity judgments on normal older controls ($\kappa = 1.0$) but highly inconsistent judgments for patients with mild Alzheimer's disease ($\kappa = 0.14$).¹² A 1994 study that surveyed 823 Massachusetts internists, surgeons, and psychiatrists similarly found that while 89% of respondents knew the correct standard for competence, most incorrectly believed that diagnoses of dementia or psychosis were sufficient to establish incompetence.¹³ Such inconsistency is problematic, as it may lead to biased and unwarranted deprivation of patient decision-making authority. Early investigators also assessed whether commonly used cognitive batteries such as the Mini-Mental State Examination (MMSE) could be used to standardize capacity assessments. Though MMSE scores correlate with expert assessments of capacity at the extremes, the results provide little information when the scores occupy the middle range, where assessment instruments would be most useful. For instance, MMSE scores below 19 are highly likely to be associated with incapacity, but studies disagree over how to interpret scores above 23.^{14–16}

Following these early studies, several validated instruments, used primarily as research tools, have been developed for assessing capacity. These instruments are based on the clinical framework for capacity described earlier but cannot by themselves render judgment as to whether a patient has capacity to consent to treatment or research. Instead, these instruments purport to measure the cognitive functions—understanding, appreciation, reasoning, stable expression of a choice—on which a clinical judgment of capacity is based. The clinician must then assess the results in the context of other data available about the patient to make a final determination as to the patient's capacity. Despite the element of subjectivity inherent in incorporating instrument data into clinical judgment, instrument-aided assessment is associated with a higher degree of interrater agreement than unaided assessment.¹⁷ Among the most widely adopted and studied instruments are the MacArthur Competence Assessment Tools for Treatment (MacCAT-T), the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR), and the Capacity to Consent to Treatment Instrument (CCTI).^{18–20} The CCTI describes two hypothetical scenarios, whereas the two MacCAT instruments require providing information about the immediate medical intervention or study to which the patient must consent. The CCTI therefore allows greater comparison across raters or institutions, while the MacCAT instruments are more applicable to actual clinical cases. All three instruments use a standard series of questions to measure each of the four decisional abilities that together constitute capacity.

Informed Consent for Research Subjects without Capacity

If a patient has capacity to consent to research participation, the following elements of informed consent must be satisfied: the patient must (1) voluntarily authorize a plan, based on (2) a recommendation by the clinician or researcher, (3) the nature of which plan has been described, for which (4)

risks, benefits, and alternatives have been disclosed and for which (5) the patient has demonstrated understanding.²¹ When encountering patients who lack capacity, priority should first be given to their explicit wishes (including through the explicit designation of a surrogate decision maker whom the patient authorizes to decide on his or her behalf) and, second, to their beliefs and values, which a default surrogate may assist in articulating.²² In the treatment setting, after failure to discern patient beliefs and values, clinical decisions sometimes must be made based on a judgment of their best interests, though this standard is usually inapplicable for the research context where interventions are not strictly intended to promote participant's health or welfare.

If a patient's prior wishes (e.g., to enroll in clinical trials for treatments of late-stage Alzheimer's disease) can in fact be ascertained, they should be followed. Such wishes may be found in the patients' written advance directives. Advance directives may take two forms: living wills ("instruction directives"), which outline the treatments a patient would or would not want to receive in a given situation, and durable powers of attorney ("proxy directives"), which designate a surrogate decision maker to act on the patient's behalf and in a manner consistent with the patient's own values and goals. The degree to which advance directives empower surrogates to make research decisions will likely vary across jurisdictions, though the National Institutes of Health (NIH) has endorsed their use for dementia research.²³ Both forms of advance directives have notable limitations. Living wills frequently fail to anticipate the precise clinical situation in which a decision is to be made and therefore require extrapolation from the patient's known values. Though proxy directives allow for greater flexibility by delegating decision making to a surrogate, research on decisions made by common surrogates—spouses and children—finds that they anticipate patient preferences at lower than expected rates.²⁴ Where recommendations are possible, proxy directives are considered preferable to living wills, as the mismatch between surrogate and patient values can often be resolved through discussion, whereas the narrow language of most living wills precludes the kind of extrapolation that clinical situations frequently require.²²

Where the patient's wishes are not available, priority must be given to the patient's beliefs and values. This priority is sometimes grounded in the principle of autonomy (i.e., the patient's self-determination as articulated when the patient had capacity) or, as Kim has argued, in the principle of authenticity (the congruence between a person's known values and a decision where the patient's exercise of self-determination is impossible).²⁵ In the research setting, it is important to gauge whether participation in a given study is concordant with a patient's values. Was the patient known to have reservations about the use of gene therapies to treat disease or general privacy concerns that would be incompatible with a study protocol? Conversely, was the patient broadly enthusiastic about engaging in the research enterprise if it meant generating new knowledge about his or her disease?

Patient values regarding research-relevant questions may have been expressed to treating physicians prior to incapacity or, more commonly, be inferred by a surrogate once capacity is lost. The most important ethical obligations for a surrogate are knowledge of the patient's goals and values as well as a commitment to use the patient's values (rather than the surrogate's) as a basis for making decisions. In other words, the surrogate should attempt to make the decision that the patient would make if he or she were able to do so—a standard known as substituted judgment. In the absence of proxy directives, the 2017 Revised Common Rule Code of Federal Regulations clarifies that, where state law is silent on research consent, individuals identified as appropriate for surrogate decision making in the clinical context can also serve as decision makers in the research context.²⁶ In states with law governing clinical consent but not research consent, rules for clinical surrogate priority are presumed to apply to research. In jurisdictions without specific law, existing institutional practice for identifying clinical surrogates may be imported wholesale into the research setting. As the majority of states have codified rules for default surrogacy in the clinical but not in the research setting, the 2017 revision filled a gap in the earlier rule, which left the priority of surrogate decision makers in the research context undefined. In four states—California, Kansas, New Jersey, and Oklahoma—the law governing default surrogacy is applicable only to the research context. These states give priority to spouses or domestic partners, followed by adult children, parents, and siblings—a pattern that largely holds in those states that have drafted rules only for the treatment context. The precise scope of decision-making authority also varies by state, even among those few states that have adopted research-specific rules. In California, for instance, the ability of default surrogates to provide consent is “restricted to medical experiments that relate to the cognitive impairment, lack of capacity, or serious, or life-threatening diseases and conditions,” whereas the other three states permit surrogate consent to protocols approved by institutional review boards to which patients did not previously object.^{27–30} California does not limit the allowable level of risk for nontherapeutic research, whereas New Jersey requires the application of specific risk/benefit criteria to decisions. The American Bar Association's Commission on Law and Aging provides state-by-state legislative summaries and other resources for researchers seeking additional information.³¹ While researchers should be aware of laws in their jurisdiction applicable to the research enterprise, as those laws supersede institutional practice, their ethical obligation is primarily to identify those individuals best able to represent the patient's values and goals.

Neurological Conditions in which Consent Issues Often Arise

While the broad principles described earlier provide foundations for approaching problems of consent, several neurological conditions pose unique ethical and legal challenges for researchers. Illustrative conditions include chronic diseases

such as Alzheimer's disease, as well as more emergently presenting conditions, such as epilepsy and stroke.

Exception from Informed Consent Requirements for Status Epilepticus Trials

Several recent neurological trials in the United States—including the pivotal Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART)—have been conducted under the Food and Drug Administration's (FDA) Exception from Informed Consent (EFIC) Requirements for Emergency Research.³² The EFIC regulations apply only in the United States and were first promulgated in 1996 to permit research involving human subjects in need of emergency medical interventions but whose ability to consent was impaired due to life-threatening conditions.³³ EFIC, moreover, applies only where there is no reasonable way to identify prospectively those individuals who would be eligible for participation in the study. EFIC sought to balance the need for research on life-threatening conditions for which existing treatments were unproven or unsatisfactory against the traditional principles of autonomy and the right to physical integrity. The EFIC regulations sought to effect this balance by imposing several safeguards, including a requirement that the EFIC plan be incorporated into an Investigational New Drug (IND) application to the FDA; the ongoing concurrence of a licensed physician, not participating in the research, with the IRB; oversight of an independent data monitoring committee; and, most distinctively, a requirement for public disclosure and community consultation prior to study approval and initiation.

Though the EFIC requirements have been embraced by the emergency research community, they have not been clearly defined by regulatory agencies or other lawmaking bodies. Particularly challenging have been the requirements for public disclosure and community consultation. In recent nonbinding recommendations, the FDA defines community consultation as an activity “providing the opportunity for discussing with, and soliciting opinions from, the community in which the study will take place and the community from which the study subjects will be drawn.”³⁴ The community to be consulted, therefore, is defined with respect to geography and individuals affected by the investigated condition. Where those communities do not overlap, the FDA recommends consulting both groups. Notably, the FDA recommendations acknowledge that community consultation is not a substitute for the mechanism of individual consent. However, community consultation attempts to serve the principle of respect for autonomy that underlies individual consent by seeking input from those expected to be similar to the study subjects—such as those who have or are at risk for the condition under study.

EFIC regulations require investigators to seek out family members of study participants within the therapeutic window to give them an opportunity to object to study inclusion. Regulations do not require that the study protocol include opt-out mechanisms for individuals who are likely to be enrolled, though the FDA encourages their inclusion where feasible. If opt-out mechanisms are included in the study

protocol, they should be described during community consultations. Examples of opt-out mechanisms employed in EFIC studies include medical jewelry, wallet cards, and driver's license annotations.

While the community consultation requirement envisions two-way communication between community members and investigators, the public disclosure requirement is a one-way dissemination of information about the study to the affected community or communities. Public disclosure must take place both before and after the study, with differing goals. Prestudy disclosure must provide sufficient information "to allow a reasonable assumption that the broader community is aware of the plans for the investigation, its risks and expected benefits ... and the fact that the study will be conducted without obtaining informed consent from most study subjects."³⁴ Poststudy disclosure must ensure that affected communities are aware of the study results, particularly so that future studies can account for the experiences of vulnerable subjects who were not able to consent.

Despite the FDA recommendations, there remains controversy concerning the most effective way to meet EFIC standards. The resulting uncertainty has elicited a rich literature on trial designs attempting to comply with regulatory requirements as well as empirical investigation into participant and surrogate perspectives on EFIC enrollment.

The RAMPART trial, a multicenter study that compared intravenous to intramuscular benzodiazepines for prehospital treatment of status epilepticus, represents one attempt to satisfy regulatory requirements in a manner that allowed innovation and refinement of EFIC processes. RAMPART investigators developed central resources, such as informed consent forms; a template EFIC plan for FDA and IRB approval; videos, brochures, and slides for use in public disclosure and community consultation activities; a menu of methods for disclosure and consultation along with advantages and disadvantages of each; and a full-time human subjects protection coordinator (HSPC) who leveraged experience across the trial network to address issues unique to each trial site.³⁵ These centralized resources largely served as starting points for individual site investigators, who could then tailor the resources to their respective communities. Progress toward EFIC approval was centrally tracked with a set of milestones and allowed documentation of site-to-site variation. RAMPART investigators catalogued the types of community consultation activities conducted as well as the number of individuals reached by each type of activity. Activities included setting up booths or exhibits, random digit dialing, focus groups, internet surveys, and calling into local radio shows. Public disclosure was achieved through newspapers, radio, and television.

The RAMPART investigators described this approach as a "federated" model that provides strong central guidance while allowing local flexibility, thereby allowing identification and development of best practices. Additionally, the initial trial was followed by empirical research on the perspectives of study participants and their families. In one study, researchers found that 82% of patients or surrogates were glad that they or their family member had been

included in the study, and 95% felt that research on emergency seizures was important.³⁶ However, 17% of participants felt that their inclusion in the study was unacceptable. There was a trend toward lower acceptance of EFIC among non-white participants and those who had previously participated in research. Additionally, multiple individuals raised concerns about being approached for consent to follow-up and data collection while still critically ill, suggesting that attention to communication may affect study perception.

In another study, 90% of patients and surrogates perceived community consultation to be important, largely as a method of obtaining feedback from the community for improving the study and also as a means of facilitating trust and respecting the community's right to be informed.³⁷ Participants also cited healthcare professionals (43%) and individuals with a connection to the study condition, such as patients or family members (41%), as the relevant "community" for consultation efforts. Given the ambiguity of the FDA guidelines, these results may suggest that the goals of community consultation and public disclosure may be achieved by a more targeted approach, seeking those likely to be involved in the study, rather than the geographic area in which the study will take place.

Consent in Acute Stroke Trials

As with status epilepticus, stroke patients often present emergently and may lack decision-making capacity due to cognitive impairments. Moreover, the therapeutic window treating ischemic stroke, either with thrombolysis or endovascular thrombectomy, is limited, requiring a rapid determination as to whether the patients are eligible to receive treatment. Confirmation that they are within the therapeutic window may be provided by someone appropriate for surrogacy or who can provide contact information of someone who can serve as a surrogate. At the same time, available surrogate decision makers are often less willing to enroll patients in clinical research than the patients themselves would be if they retained capacity. The upshot of this latter situation has been slow recruitment and therefore delayed progress in the development of novel therapies.³⁸

This mismatch between patient wishes and surrogate behavior has encouraged experts to propose waiving the requirement of written informed consent in acute stroke trials. In the United States, studies may be eligible for waivers of consent where (1) they present no more than minimal risk to patients; (2) the waiver or alteration will not adversely affect the rights and welfare of the participants; (3) the research could not practicably be performed without the waiver or alteration; and (4) whenever appropriate, the participants will be provided with additional pertinent information after participation.³⁹ Recent empirical investigation into the effect of waivers on recruitment in trials of stroke treatments has found that waivers generally had no effect on recruitment rates for trials comparing the effects of different therapeutic interventions.⁴⁰ However, based on a limited sample, waivers did appear to facilitate studies of systems-level interventions, for example, of delivery of

thrombolysis in a mobile stroke unit with on-board imaging and point-of-care laboratory testing instead of an emergency department. It has been observed that the greatest reductions in stroke morbidity and mortality in the near term may come from improving these systems-level interventions, suggesting a significant possible benefit for waivers of consent in such contexts.

Perhaps unsurprisingly, empirical research has discovered differences in the baseline characteristics of patients enrolled via self versus proxy consent. Participants enrolled by surrogate consent tend to be older, present with more severe strokes, and are more frequently aphasic, suggesting that an inflexible approach to informed consent may create the potential for bias.⁴¹ While, in the United States, surrogate enrollment may account for up to 70% of study participants, significant variation exists across countries. In Germany, for instance, only 33% of participants in acute stroke trials are enrolled via proxy consent. In Denmark, the percentage falls to 1%. This presents a particular concern for investigators participating in multinational trials, who should consider this variation and the bias it may introduce.

Declining Capacity in Alzheimer's Disease

Unlike the emergency conditions described earlier, Alzheimer's disease is marked by cognitive impairments that progress over the course of disease, rendering capacity judgments both crucial and challenging, and highlighting many of the ethical considerations described earlier. As even mild disease can impair some aspects of decision making, subjects may lose the ability to consent to complex research trials in the early stages of disease. Empirical research has found that even small declines in neuropsychological measures have been associated with decreased decisional capacity.⁴² In a study of 40 individuals with mean MMSE scores of 28, 40% of patients were judged by experienced evaluators to lack capacity to consent to participation in a clinical trial.⁴³ Such results suggest that mild impairments can have substantial effects on capacity and also that significant variation in retained capacity exists among patients at the same stage of illness, making functional case-by-case assessments a necessity.

As disease progresses, obtaining valid informed consent to research proves even more difficult. For instance, in a 2011 study of patients judged to have mild to moderate Alzheimer's disease, less than 4% were judged to have the capacity to participate in a neurosurgical trial.⁴⁴ Attempting to ensure that all subjects in such a trial who possess capacity to consent would likely be logistically impractical or produce ungeneralizable results.

A bright spot in Alzheimer's disease research on consent has been the substantial preservation of capacity to appoint a surrogate for consent to research. Recent research has found that more than 90% of patients with early-stage Alzheimer's disease demonstrate capacity to appoint a research proxy.⁴⁴ Additionally, the majority (55%) of those without capacity to consent to a neurosurgical trial were found to have capacity to appoint a surrogate. Importantly, some investigators have

observed that surrogates for patients with Alzheimer's disease may show greater fidelity in representing patient views than surrogates for other conditions, as these patients retain the ability to communicate about values and preferences long into the disease course and remain in conversation with the surrogates about those values and preferences.^{45,46} Additional research has complemented this view, finding that patients with Alzheimer's disease are able to distinguish between complex research decisions, which they prefer to delegate to a proxy, and simpler decisions over which they choose to retain control, citing a desire for autonomy.⁴⁷

One proposed solution to the problem of declining capacity in this context is the use of an iterative consent process that involves reevaluating consent capacity at multiple predetermined time points in the study.⁴⁸ This may prove particularly relevant in longitudinal trials that focus on presymptomatic patients with known risk factors or biomarkers for the disease. The NIH has also recommended that patients appoint legally authorized representatives at the outset of a study, as many patients can be expected to lose capacity before study termination.⁴⁹

Emerging Ethical Issues

Several emerging ethical issues that may complicate or extend the principles mentioned above also warrant discussion, as they are likely to be encountered in future research contexts and will need to be addressed before seeking consent from study participants.

1. Adaptive trials:

Adaptive trials allow for modification of a study as data become available, so that changes in sample size, dosage, or the number of treatment groups might occur before study termination. The goals of such studies are to increase the speed and lower the cost of trials, while reducing the number of patients who receive placebos or ineffective treatments.⁵⁰ To provide informed consent, researchers will need to inform their patients that assignment is not based purely on chance but on accumulating data, that likelihood of benefit may be associated with the time of enrollment, and that they may be randomized to a therapy for which evidence of inferiority has been produced even before the trial ends. As a result, researchers will need to be aware of two extreme possibilities. First, some very knowledgeable research participants may attempt to "game the system" by postponing enrollment to increase the likelihood of receiving an effective treatment, which distorts the element of fairness captured by traditional randomization.⁴⁸ Alternatively, as Saxman has argued, given that traditional randomization has proven difficult for participants to comprehend, even with both oral and written explanations, it is possible that comprehension of adaptive randomization will be minimal, threatening autonomous decision making.^{50,51}

2. Cluster-randomized trials:

Cluster randomization occurs at the group level (e.g., clinic, nursing home) rather than at the individual level

typical of randomized controlled trials. Cluster-randomized trials (CRTs) are particularly useful for community-level interventions, those that otherwise cannot be targeted to specific individuals, or studies in which “contamination” of the intervention across individuals will occur. For instance, a study on the use of education materials to reduce anxiety in early-stage Alzheimer’s patients may be compromised by the tendency of regular patients in the same clinic to interact with one another and share information.

Ethical challenges posed by CRTs largely arise for two reasons: (1) determining the locus of consent for groups remains difficult (see related discussion concerning EFIC, earlier) and (2) the group that serves as the target of intervention may not be the same as the group from which data are collected.⁵² In many CRTs, clinicians themselves may be the target of intervention (e.g., by training in a new safety protocol), while the outcome is measured by the effect on patients. It is unclear whether patients must consent to data collection, the intervention, or both, and the response of ethical and regulatory bodies to CRTs has been inconsistent across jurisdictions. A recent CRT investigating stroke prevention after transient ischemic attacks measured the effect of a decision support tool used by general practitioners in New Zealand on 90-day stroke risk in their patients. While patients were not blinded to the study, individual patient consent was not required by the ethics committee, “because the unit of intervention was general practices and individual patient data were completely de-identified.”⁵³

In contrast, the Michigan Health and Hospital Association Keystone ICU study—though not formally a CRT—also targeted health professionals with educational and other quality-improvement interventions designed to reduce rates of catheter-associated infections. The approving ethics committee concluded that the study merely involved the analysis of de-identified information and therefore did not require patient or provider consent. Shortly after the study’s publication, however, the U.S. Office for Human Research Protections found that the ethics committee’s conclusion had been incorrect and that informed consent should have been obtained from both healthcare professionals and patients or their proxies.⁵⁴

A more recent controversy over the application of cluster consent emerged in the HeadPoST trial, which examined whether head position after acute stroke was associated with outcomes at 90 days. In HeadPoST, hospital executives sought institutional consent prospectively and individual patient consent only after intervention for data collection and follow-up, even though an intervention—head position—was targeted directly toward patients. This method of consent was approved by ethics committees in 114 hospitals on grounds that it minimized recruitment, selection, and responder bias; facilitated rapid implementation in the chaotic emergency setting; and was low risk. Responses to the arguments proffered by the study authors observed that minimizing bias could serve as a basis for forgoing consent in any clinical trial, that interventions were initiated a median of 7 hours after hospital arrival, and the intervention did not unambiguously pose minimal risk.⁵⁵

As the aforementioned examples demonstrate, there exist no clear federal requirements or regulatory guidelines on the appropriate manner of obtaining consent in CRTs. Weijer et al and McRae et al have proposed applying existing waiver of consent regulations (described earlier) to CRTs, so that cluster randomization and de-identification do not per se permit investigators to avoid seeking patient consent.^{52,56} Instead, investigators would be required to evaluate the proposed intervention’s risks to patients and the practicability of acquiring consent without compromising the intervention before determining whether and what kind of consent may be necessary. The Ottawa Statement on the ethical design of CRTs, a consensus statement issued in 2012, proposes that all CRT “research participants” should be consented before randomization whenever feasible or as soon as practicable after randomization.^{57,58} The term “research participant” is defined to include those directly intervened upon, those interacting with investigators for data collection, and those about whom identifiable information is used to generate data. The Statement authors concede that waivers of consent may often be required in cluster-designed trials but should be reserved for situations in which the study would not otherwise be feasible and the risks to participants are minimal. Additionally, the Ottawa Statement emphasizes that special care should be taken to identify and acquire the consent of subjects with impaired decisional capacity, particularly those whose presence within a cluster may not be obvious.

3. Biomarkers for Alzheimer’s disease:

Asymptomatic patients may increasingly request amyloid biomarker testing to gauge their susceptibility for Alzheimer’s disease. Informed consent for such testing requires full disclosure of the associated risks, which may be primarily legal and financial.⁵⁹ Currently, there are no legal protections in place for patients who test positive for amyloid biomarkers. Biomarker data are not protected under the Genetic Information Nondiscrimination Act (GINA), as biomarkers are not genetic information. Nor are they protected under nondiscrimination provisions in the Affordable Care Act, as biomarkers do not necessarily indicate the presence of a preexisting condition. Additionally, there are no federal legal prohibitions against long-term care or employment discrimination on the basis of biomarker information. Researchers conducting studies in which the risk of biomarker disclosure is high should therefore counsel patients on the attendant legal risk such information may pose.

Conclusion

Neurological patients constitute a uniquely vulnerable population in the research setting. Neurological conditions often compromise capacity to consent, and individual variation in deficits calls for case-by-case functional assessment of capacity. At the same time, the limited availability of treatments for these conditions can be remedied only by further research with neurological patients. Additionally, the canonical ethical principles of justice and autonomy suggest that

individuals who lack the full range of decisional capacities should not be excluded from the research enterprise without due consideration of their retained abilities and their preferences. The aforementioned discussion should provide researchers guidance in making those considerations, while also pointing toward issues that may shape the emerging ethical landscape.

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