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Research Ethics Issues in Geriatric Psychiatry

Laura B. Dunn, M.D.¹ and Sahana Misra, M.D.²

¹ Department of Psychiatry, University of California, San Francisco, California

² Mental Health Division, Portland VA Medical Center; Department of Psychiatry, Oregon Health & Science University, Portland, Oregon

Synopsis

With an aging population, and the prevalence of psychiatric illness in the older population expected to rise dramatically in coming decades, advances in geriatric psychiatry research are urgently needed. Ethical issues in the design, conduct, and monitoring of research involving older adults parallel these same issues related to human subjects research generally. Yet a number of special issues relevant to geriatric psychiatry research merit further discussion. These special issues include the assessment of capacity in populations where cognitive disorders are more prevalent, the role of surrogate decision makers, the legal status of surrogate consent, the use of advanced directives for research participation, and research involving suicidal individuals.

Introduction

Geriatric psychiatry research seeks to elucidate the etiology, course, and modifying factors of mental disorders affecting older people and to develop treatment options with greater safety, tolerability and effectiveness than those currently available. Despite many advances, further research is urgently needed on mood, anxiety, psychotic, and cognitive disorders, and disorders commonly seen in older medically ill patients, such as delirium. Alzheimer's Disease (AD) is a looming public health crisis; in the U.S. alone, the prevalence is estimated to rise to 13 million people by the year 2050 [1]. A host of other neurologic and medical conditions that are often accompanied by behavioral sequelae and/or psychiatric comorbidity, including other forms of dementia, Parkinson's Disease and stroke, will also increase in prevalence as the population ages. Given these predictions and the need for improved treatment options for older adults suffering from these illnesses, much work toward the development of improved treatment options remains to be done [2].

Clinical research relies on the participation of volunteers with (or at risk for) the disorder being studied. Ethical issues in the design, conduct, and monitoring of research involving older adults overlap substantially with those relevant to human subjects research in general (for an excellent summary, see [3]). There are, however, issues unique to research involving older adults that warrant further discussion. This paper reviews pressing ethical issues in geriatric psychiatric

Corresponding author for proofs and reprints: Laura B. Dunn, M.D., Associate Professor of Psychiatry, Director of Psycho-Oncology, Department of Psychiatry, University of California, San Francisco, 401 Parnassus Avenue, Box GPP-0984, San Francisco, CA 94143-0984, Phone: 415-476-7518, Fax: 415-476-7320, Email: E-mail: laura.dunn@ucsf.edu.

Co-author address: Sahana Misra, M.D., Staff Psychiatrist, Portland VA Medical Center, Assistant Professor of Psychiatry, Oregon Health & Science University, 3710 SW U.S. Veterans Hospital Road, Portland, OR 97239, Phone: 503-220-8262, Fax: 503-721-1085, Email: sahana.misra@va.gov

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research, including capacity and cognition, the role of surrogates, and research involving suicidal individuals.

Informed Consent and Capacity Assessment

Conceptual issues

Three principles--respect for persons, beneficence and justice—guide the ethical conduct of human subject research [4]. The principle of “respect for persons” articulates that researchers endeavor to support individual autonomy and the right to self-determination, while protecting those with diminished autonomy. “Beneficence” ensures that researchers maximize benefits, minimize risks and do not harm individuals. “Justice” requires that researchers equitably distribute the benefits and burdens of research. For example, subject selection consists of an appropriate sampling of participants based on the problem being studied rather than individuals that are readily accessible or easily manipulated.

“Respect for persons” provides the foundation for the doctrine of informed consent. The informed consent process is comprised of three unique components: (1) disclosure of pertinent information including risks, benefits and alternatives; (2) decision-making capacity; and (3) voluntariness (a free and genuine choice made without of coercion) [5].

Decision-making capacity is most commonly conceptualized as involving four decisional abilities (often equated with legal standards of competence, but actually legal standards vary according to jurisdiction). These four abilities or domains are to: (1) understand relevant information (re: research, the specific research protocol and the research enterprise, including risks and benefits) (2) appreciate the information by applying it to one’s personal situation, (3) reason through the information in a rational manner (the “reasoning” standard), and; (4) communicate a clear and consistent choice (re: research, whether or not to participate) [6]. A second, similar model incorporates a fifth legal standard of “reasonableness of choice” [7]. In clinical and legal contexts, the stringency with which each of these decisional abilities (or some combination) is demonstrated should vary according to the risk-to-benefit ratio of the decision in question. This sliding-scale concept sees the threshold for sufficient capacity as resting on a continuum based on the risk to benefit ratio of the specific decision: a lower threshold for capacity is adequate for decisions with minimal risks, while decisions that involve greater risk necessitate a greater level of capacity. Of interest, some legal jurisdictions do not require demonstration of all four legal standards for an individual to be judged competent, thus having a lower threshold of sufficient demonstration of competence compared to other states.

The research setting is inherently different than clinical or legal settings, as participation is voluntary and the risk-to-benefit ratio is typically skewed toward more direct risk with less direct benefit. Nevertheless, the sliding scale concept of decisional capacity is the most useful guide for investigators in determining how stringent to be when evaluating capacity for research participation [8].

Capacity assessments begin with the informed consent process, ideally occurring as an information sharing process. For potential research participants, full disclosure of relevant information pertaining to a study is required in order to make knowledgeable decisions that reflect personal values. A capacity assessment should be performed only after relevant information, including the purpose of the study, risks and benefits of participation, the alternatives to study participation, is disclosed and questions are elicited and answered. Capacity assessments are focused on the specific decision in question (e.g. whether to undergo a surgical procedure, a desire to leave the hospital against medical advice, or whether to participate in research participation). Through the examination the four decisional abilities mentioned above, the process of how someone ultimately arrives at their choice becomes clear.

Whether the final decision or choice is considered ideal or preferred by the examiner is not a focus of the examination. In the clinical setting, if an individual demonstrates diminished capacity for a pressing medical decision, consent is generally sought from an appropriate proxy or surrogate decision maker—typically a close family member [6]. The use of proxies for research decisions is discussed later in this paper.

Methods of assessing research consent capacity

In recent years, various instruments have been developed to assist clinicians and researchers in conducting decision-making capacity assessments. These tools are designed to allow the interviewer to systematically evaluate the decisional abilities outlined above. Yet, variation exists among these instruments, so, when selecting an instrument, it is important to understand the purpose of the evaluation and the specific characteristics of the tool chosen. In a review of studies published from 1980 to 2004 that included 23 instruments designed to assess decisional capacity in both research and treatment contexts, substantial variation in format, degree of standardization, flexibility of content, and scoring, as well as widely varying reliability and validity was found [9].

Of the instruments identified, the MacArthur Competence Assessment Tools for Clinical Research (MacCAT-CR) [10] and Treatment (MacCAT-T) [11] were considered the most well-studied and well-validated [12]. They were developed from substantially lengthier instruments used in a landmark study of competence, the MacArthur Treatment Competence Study, that included psychiatric and medical patients, as well as healthy controls [12]. The MacCAT-T and MacCAT-CR take between 15 and 20 minutes to administer and, given the content-specific nature of capacity assessments, must be adapted to the treatment or research protocol in question. The Competency to Consent to Treatment Inventory (CCTI) is another tool that has been validated in patients with dementia for treatment decisions [7]. In this tool, two hypothetical treatment vignettes are presented and followed by standardized questions to evaluate decision-making capacity based on five legal standards (including the “reasonableness of choice” standard described above).

One of the limitations of existing instruments, including the MacCAT-T and MacCAT-CR, is the lack of a final determination of whether someone has or lacks sufficient capacity to provide informed consent [9]. In the MacCAT-CR, for example, subscores for each decisional ability are obtained, but there is no pre-determined cutpoint above which sufficient capacity can be said to exist. The rationale for this aspect of the instrument lies in the previously mentioned notion that the desired threshold for “adequate capacity” should be considered a continuum, or sliding scale, depending on the risk:benefit ratio of the decision at hand. As a result, there continues to be an element of subjectivity in capacity assessment. Nevertheless, using a systematic and structured method for assessing decisional abilities can enable researchers to gain a more complete picture of individuals’ decision-making abilities, as well as to highlight where there may be common and specific difficulties with understanding the specific protocol (which can lead, in turn, to adjustment of the consent process to facilitate better understanding).

Cognitive tests or screens, such as the Mini-Mental State Examination (MMSE) [13] —while not substituting for a systematic assessment of decisional abilities—can provide useful complementary information for decision-making capacity assessments. The MMSE has been shown in several studies to correlate with performance on measures of decision-making capacity [14–17], however, it does not have adequate predictive validity to be used as a stand-alone or surrogate marker for decisional impairment [15,17]. Also some screens, such as the MMSE, may be less sensitive to higher order executive deficits seen in patients with frontal-focused neuropathology [18]. Thus, if specific cognitive test or tests are used as an adjunct to a capacity assessment, they should be selected with the target population and a clear rationale for the cognitive test in mind.

To underscore a main point of this review, when deficits in understanding (or other domains of capacity) are detected, these do not necessarily justify excluding that participant from research participation. Rather, such deficits in performance indicate the need for enhanced methods of consent to provide the consent information in an iterative and interactive format that facilitates information sharing and assessment of understanding [19].

Decision-making capacity and the older research participant

Although age has been demonstrated to be associated with lower scores on assessments of capacity in a number of studies [15,20,21], these findings have sometimes been confounded by other factors (education, verbal reasoning, reading skills) that also affect performance on decision-making assessments. It is clear, however, that cognitive impairment seen in disorders associated with aging places patients at risk for impaired decision-making capacity.

AD, the most common form of dementia, affects the very cognitive abilities—e.g., memory, language, judgment, abstraction, conceptualization—necessary for informed decision making [7,14,16,22,23]. Although a diagnosis of AD is not equivalent to impaired capacity to consent, a number of studies conducted over the last decade indicate that AD patients inevitably lose decisional capacity—some patients in the mild stages, most patients probably somewhere in the transition from mild to moderate disease [7,16,17,24,25]. Moreover, as shown by several research groups, executive functioning and verbal recall are closely associated with clinical assessments of decision-making abilities [26–28]. These types of impairments are not always readily apparent to the medical professional, researcher, or research staff. For instance, among medical inpatients—tested for treatment-related decisional capacity by Raymont and colleagues [15]—nearly one-third were found to lack capacity, based on a consensus among the researchers who used the MacCAT-T. Yet few of these patients had been identified by their treating physicians, or their relatives, as having impaired capacity, and cognitive impairment and age were the only independent predictors of incapacity. Such findings suggest that older individuals who are medically ill or who have cognitive impairment are at increased risk for impaired capacity, but cannot be assumed to lack capacity without assessment.

While psychiatric diagnoses have been a focus of intense scrutiny with respect to capacity to consent to research, capacity studies specifically focusing on older adults with specific psychiatric diagnoses are relatively few. Studies of decision-making capacity in depressed patients, either for treatment or research decisions, have overall reported good performance on measures of capacity, and little to no association with depression severity. Among the depressed inpatients studied in the original MacArthur Treatment Competence Study (who scored primarily in the high moderate to low severe range on the Beck Depression Inventory) [29,30], treatment-related capacity performance was lower than that of controls, but the majority of the depressed patients were not impaired. Studies of decisional capacity in patients with schizophrenia, including older patients, have demonstrated mean scores worse than control or depressed comparison populations. Factors associated with poor performance include cognitive symptoms, conceptual disorganization, negative symptoms and acute psychosis. Of importance, significant heterogeneity in performance was apparent with a substantial proportion of subjects (in some studies a majority of subjects) meeting thresholds for adequate capacity, stressing that the diagnosis of schizophrenia itself is not sufficient to establish lack of capacity [31].

Studies of consent capacity in patients with bipolar disorder are sparse. Misra et al. examined research consent capacity in manic (n=26) and euthymic subjects (n=25). Compared to euthymic subjects, those with mania demonstrated poorer understanding of relevant research information [32]. Palmer and colleagues similarly assessed research consent capacity in patients with bipolar disorder and compared them to patients with schizophrenia and normal

controls [33]. The patients with bipolar disorder had worse understanding than the healthy controls and did not differ from the patients with schizophrenia. For the entire sample, poor performance on the MacCAT-CR was associated with neurocognitive deficits and negative symptoms. Importantly, in both studies, patients with bipolar disorder, including manic patients, demonstrated improvement in understanding when relevant research information was re-reviewed.

To summarize, consent capacity studies have not found an association between decision-making capacity and specific diagnoses. Certain diagnoses may have higher rates of diminished capacity than others, but on an individual basis, many patients with psychiatric illnesses are able to provide informed consent. Impairments in cognitive abilities, on the other hand, particularly memory and frontal lobe-mediated executive functioning, do seem to affect decisional abilities.

Methods of enhancing the research consent process

Intrapersonal factors, the sociocultural context, and factors related to the study itself all influence the consent and decision-making process [34]. Clearly, some intrapersonal factors (e.g., level of arousal, anxiety, distraction, pain) may be transitory and are potentially modifiable. Other intrapersonal factors may be more stable and thus difficult to modify (e.g., prior experience with research, educational level, vocabulary/reading abilities). These factors nevertheless must be taken into account in tailoring the enrollment, consent, and overall research experience for individual participants, to ensure that the process is respectful of these individual differences and enhances autonomy whenever possible. External to the individual, factors including complexity of the information presented and the quality of the consent discussion will directly impact the decision-making process. Researchers and their staff should also endeavor to assess whether potential subjects are alert, attentive, and comfortable during the informed consent process and that relevant information is discussed in a quiet environment.

Growing concerns about capacity to consent, particularly in people with psychiatric illnesses, have led to increased interest in identifying educational interventions that will improve the overall decision-making process and consent-related abilities in people at risk for decisional impairments. Although the inherent complexity of pertinent research information may not be easily modified, the nature in which the information is communicated by the researcher can be improved. To this end, educational interventions ('enhanced consent' procedures) have been increasingly examined.

Tested interventions have ranged from multiple repetitions of consent information (reiterative review) to using different modalities of providing information (e.g., presentation software, DVDs, group discussions) [35–37]. Iterative review of pertinent information has been demonstrated to improve patients' understanding of relevant information in multiple populations, including populations with cognitive, affective and psychotic disorders [31,36–38].

Special issues in geriatric psychiatry research

Surrogate consent for research: current context and ethical issues

Informed consent raises ethical challenges in geriatric research protocols (particularly in studies of AD or other cognitive disorders) because many potential participants will have impaired decision-making capacity [16,23,24,39]. Investigators most commonly address the consent dilemma through "double consent"—i.e., obtaining consent from the proxy, as well as assent from the subject [39], making proxy consent central to the ethical integrity of clinical AD research [40]. Reliance on proxy consent for research on adults who lack capacity is done either formally or informally, depending on specific state law and IRB requirements [41,42].

In part, this is because there is no unified accepted approach, and no federal regulations that speak directly to this issue. Ethics codes, organizational and governmental guidelines, legislative efforts, and commentators' proposals vary widely in their approach to proxy consent (see Table 1), representing what Appelbaum called a "gray zone of law and ethics" [41]. For instance, although California and Virginia have laws specifically allowing proxy consent for research, the two laws differ in degree of detail regarding protocols to which proxies can consent [43]. It is unclear how differences would be reconciled, for instance, in a multisite protocol. In the absence of clear guidance, individual IRBs may adopt more restrictive or cautious stances. In addition, although a great deal of discussion of proxy consent centers on risks and benefits, some believe that further definition of levels and types of risks and benefits is needed [44].

Proxy consent also raises ethical questions, because proxies must decide on behalf of another person, which may involve accepting potential risks and unknown benefits for someone whose research-related preferences are unknown [45,46]. Karlawish and colleagues studied the views of competent older adults (n=538, all 65 years or older) toward delegating decisions about AD research to proxies [47]. Interview questions included items about how much power subjects would grant their proxy to enroll them (even against their wishes) in studies that presented more than minimal risk (i.e., a study involving a lumbar puncture) but no potential for direct benefit. Two hypothetical research scenarios were utilized to explore these attitudes. Presumably these scenarios were provided in less detail (i.e., shorter vignettes) than typical, lengthy consent forms given for actual research studies. However, only those participants who demonstrated sufficient understanding of core research concepts relevant to proxy consent were interviewed regarding the hypothetical research protocols. The majority of subjects endorsed willingness to be enrolled by their proxy, even *against* their advance consent, in the blood draw study (81% willing) and the blood draw plus lumbar puncture study (70%). Interview items also examined subject views on providing advanced consent for future studies. Advanced research directives have been proposed as another strategy to complement surrogate decision making for conditions anticipated to result in lack of research consent capacity in the future. Most adults (83%) said they would be willing, in advance, to consent to a study involving a blood draw, while approximately half (48%) would be willing to give consent in advance to a blood draw plus a lumbar puncture. Challenges to advanced directives include being able to discuss in detail key elements about specific studies to be conducted in the future as well as the genuineness of desire to participate for a situation that is yet to happen. Overall, general positive attitudes toward biomedical research predicted willingness to be enrolled, although, for the greater than minimal risk vignette, ethnic minorities were less willing to be enrolled

Kim and colleagues, using 10 briefly described research studies, varying in objectively-defined (by expert consultants) level of risk, looked at views of people at risk for AD regarding the acceptability of surrogate consent for research either for themselves or for their loved ones [48]. Overall, subjects viewed surrogate consent for themselves favorably yet were more cautious when considering decisions for others vs. themselves. The results suggested greater acceptability of lower risk/lower benefit studies and lower acceptability of higher risk/higher benefit studies.

While proxy consent seems to be viewed favorably by patients with dementia, evidence suggests this cannot be assumed to be true for other populations. Misra *et al.* demonstrated that patients with bipolar disorder rejected a role for family in decision-making about research participation [49] Roberts and colleagues similarly reported in patients with schizophrenia that family have a weak influence on patients' decisions whether to participate in research [50]. These results raise concern about the acceptability of proxy consent for research in these populations and populations yet to be studied.

Influences on proxies' willingness to enroll relatives in research

A number of studies suggest that proxies cite motivations for participation similar to those reported in the broader literature on research participation: altruism, trust in researchers and institutions, desperation, and hope for direct benefit [14,51,52]. The roles of perceived risk and benefit have received moderate attention in the literature on proxy decision making in the research context [53,54]. Several studies suggest that proxies' willingness to enroll their relative decreases in relation to increased risk, and that proxies cite both risk and benefit in their considerations about whether to participate [14,51]. Sugarman and colleagues found that, though informed of risks, proxies seldom seemed to weigh these risks; they seemed to assume that if the institution was doing the study, it must be safe [54]. In several studies, many proxies hoped for direct benefits, even from non-direct benefit research or those with very low probabilities of benefit [52,54]—even when explicitly told the study did not carry potential for direct benefit [14].

Decision-making abilities and processes of proxies

The importance of studying proxies' own decisional abilities is two-fold. First, in any research involving vulnerable populations, ensuring protection of those with diminished autonomy is paramount. Second, if some proportion of proxies (even if relatively small) has poor understanding of key aspects of research, it would be important for IRBs, investigators, and safety monitoring boards to be aware of this possibility and to enact appropriate safeguards. It is also worth noting that some proportion of AD caregivers may themselves be suffering from cognitive impairment [55].

One study found that some proxies did not adequately understand research-specific procedures [56]; another found that proxies described understanding the methods and risks as relatively unimportant to them [54]. In two studies of proxy decision making for AD research, gaps in understanding of research were identified [14,57]. Such findings should not come as a surprise, given literature documenting suboptimal understanding of informed consent in numerous study populations [21,56]. Other factors potentially relevant to proxy consent include the role of caregiver burden or depression [52] on decision making, as well as the possibility of proxies feeling burdened by the research decision itself [54]. Such findings are relevant not only for ensuring that recruitment, consent, monitoring, and debriefing procedures are sensitive to these possibilities, but also for the generalizability of AD trials' findings. Patient illness severity, proxies' perception of patient quality of life, and the nature/quality of the relationship may also affect proxy decision making. For example, Sugarman *et al.* reported that severe illness was associated with less decision burden experienced by proxies than mild or moderate illness [54]. In another study, adult children were more likely than spouses to decline enrollment in a placebo-controlled medication trial [57].

Two models of proxy decision-making include the "best interests" standard and the "substituted judgment" standard. Several researchers have examined the modes proxy decision makers use in the research setting to make decisions for their relative. Muncie *et al.* [58] and Sachs *et al.* [51] found that proxies' decisions more closely reflected wishes for themselves than what patients reported as their wishes, suggesting a dominance of a "best interests" vs. "substituted judgment" mode of decision making [52]. Karlawish and colleagues reported that disagreement between proxy and patient about whether to enroll was more common among those who declined enrollment in a trial [57]. Taken together, these findings highlight how difficult it is to generalize regarding how proxies actually use the "best interests" vs. "substituted judgment" standards when asked to decide about research for their relative.

Depression and suicide research

In 2004, the U.S. adults 65 years of age or older comprised 12% of the population yet accounted for 16% of suicide deaths. In addition, 14.3 of every 100,000 adults that were 65 and older died by suicide compared to 11 of every 100,000 in the general population [59]. Older U.S. adults, white males in particular, are at increased risk for completed suicide compared to other age groups [60]. Research on suicide in older adults is clearly an area in need of further study, including identifying those at greatest risk and developing effective interventions. Suicide research, however, has been challenging to conduct, in part because of real, as well as perceived, ethical issues. In most mental health research, as a result, an endorsement of suicidality frequently results in exclusion or, if detected during the study, withdrawal. Moreover, institutional review boards and grant reviewers will ask for detailed plans on how researchers will handle potentially suicidal individuals.

Because of these challenges, an NIH and American Foundation for Suicide Prevention sponsored meeting was convened in 2001, entitled “Ethical Issues in Including Suicidal Individuals in Clinical Research.” An outgrowth of this meeting, a discussion by Fisher *et al.* [61] of these issues should be required reading for investigators (and reviewers) involved in any depression or suicide research. One question central to designing an ethical research design is whether suicide research is analogous to research enrolling people with terminal illnesses. As argued by these experienced researchers and ethicists, IRBs have not “assessed equitably” the risk-to-benefit ratio of research involving suicidal individuals. The authors argue, “for scientifically sound research on suicide prevention to move forward, and eventually benefit those at risk, death by suicide needs to be understood as an expectable event.”

In addition, the authors challenge widely held assumptions (by researchers, institutional review boards and the public) that attribute responsibility for suicide to the individual and/or the health care provider, and that oversimplify the liability. In contrast, again using the authors’ own words, “...preliminary evidence would suggest that psychosocial, pharmacologic, and community-based efforts require systematic, multipronged, and sustained efforts to provide real protection against suicide.” A second question that remains unclear is whether suicidal patients have diminished capacity to consent to research, given that this is the same population who clinically may meet criteria for involuntary hospitalization. This is an area in need of systematic research. Finally, there are challenges around determining the presence of sufficient clinical equipoise with existing treatments for suicide prevention to justify randomized clinical trials and, if equipoise is thought to be present, there are many difficulties in designing an adequate control arm, such as the ‘treatment as usual’ (TAU) model. [61].

Reynolds [one of the lead investigators for the multisite NIMH-funded PROSPECT study (Prevention of Suicide in Primary Care Elderly)] and colleagues further elaborated on the tensions between research design and ethics that occur when using TAU designs in suicide research, using the PROSPECT study as an example [62]. The PROSPECT study sought to determine whether depression health specialists, placed in primary care clinics (intervention arm), would prevent or reduce suicidal ideation, hopelessness and depressive symptoms in elderly primary patients. In order to determine the effectiveness of the intervention, the design included a TAU comparison arm. “Treatment as usual,” however, when incorporated into a study design becomes altered for both research design and ethical reasons. In PROSPECT, all subjects including the TAU control group needed to be initially screened for depression (eligibility criteria), and the control group also needed to be monitored over time for any adverse effects of study participation (in this case worsening depression or suicidal ideation). The authors noted that this ‘enhanced’ TAU design, while confounding their ability to detect the true effect of the addition of depression health specialists in the primary care clinics, was a necessary and important part of meeting the ethical standard of beneficence [62]. Despite

limitations, PROSPECT demonstrates that, careful research can be conducted—and should be conducted— in populations potentially at risk for suicidal ideation or suicide to provide the critical information needed on how best to identify and address their unmet needs.

Conclusions

Progress in geriatric psychiatry research may be impeded by lack of attention to collecting evidence relevant to ethical issues. As has been noted for some time, unless proactive work is done to identify, clarify, and remediate ethical challenges (see Table 2 for research directions), deleterious effects on research can result—including research bans, unduly overprotective stances, or inaccurate weighing of risks and benefits of research by review boards [41,63–67]. With regard to proxy consent, a number of issues require further study. These include: how state laws address (or fail to address) research involving cognitively impaired individuals—and what effects this has on research conduct [41–43]; how institutional review boards (IRBs) define and weigh risks and benefits in considering research involving proxy consent [68]; how various stakeholders, including the general public, people with disorders that may impair decision-making capacity, and proxies themselves view proxy consent for research [47,48]; and to what degree proxies' research decisions reflect what patients themselves would decide. The use of advanced directives as a stand alone method for future consent is fraught with difficulties around adequate informed consent for a particular study however future study may clarify if such directives provide surrogates with improved understanding of their relative's overall views of the research enterprise and possibly the types of studies they would be willing to participate in even if they are no longer able to provide their own consent. In depression and suicide research, further work is needed to develop standard procedures for meeting the ethical demands of research while conducting rigorous, crucial research.

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Table 1
Codes, statements, and proposed guidelines relevant to research with cognitively impaired

Organization/Author	Proxy consent allowable	Proxy consent not allowable	Gaps remaining
A) ETHICS CODES, FEDERAL REGULATIONS, AND STATE LAWS			
Nuremberg Code [69]	<ul style="list-style-type: none"> • Never 		<ul style="list-style-type: none"> • Does not address issue of proxy consent for research in cognitively impaired (and was not intended to)
Declaration of Helsinki [70] (most recent amendment 2000; two clarifications in 2002 & 2004)	<ul style="list-style-type: none"> • When condition impairing capacity is focus of research; consent from legally authorized representative; research with some risk if has potential to benefit population from which incompetent subjects are drawn 	<ul style="list-style-type: none"> • If research could be performed on competent persons 	<ul style="list-style-type: none"> • Lack of clarity regarding levels of risk and benefit; refers to legally authorized representative but definition is left to legal bodies (which have failed to address this for the most part)
Belmont Report [4]	<ul style="list-style-type: none"> • Possible, but unclear under what circumstances. • Subject's wishes should be taken into account when possible 	<ul style="list-style-type: none"> • Unclear 	<ul style="list-style-type: none"> • Numerous gaps, e.g., who can serve, for what types of research; unclear course when subject's wishes unknown
The Common Rule (Code of Federal Regulations 45CFR46) [71]	<ul style="list-style-type: none"> • Legally authorized representative (LAR) 	<ul style="list-style-type: none"> • Unclear: if no "LAR"? 	<ul style="list-style-type: none"> • "Exceedingly vague" [44]: LARs not clearly defined (left up to the states), making research vulnerable to inconsistencies
California Amendment [72]	<ul style="list-style-type: none"> • Research related to cognitive impairment, lack of capacity, or serious or life threatening diseases and conditions; hierarchical list of surrogates; 	<ul style="list-style-type: none"> • Research participant is inpatient on a psychiatric unit or in mental health facility or on psychiatric hold 	<ul style="list-style-type: none"> • Unclear status of research unrelated to cognitive impairment but important to quality of life • Does not distinguish among protocols of different levels of risk or potential for direct benefit
Virginia Code [73]	<ul style="list-style-type: none"> • Minimal risk research • Minor increase over minimal risk research (as determined by human research committee), regardless of potential for therapeutic effect 	<ul style="list-style-type: none"> • Major increase over minimal risk research if no potential for therapeutic effect 	<ul style="list-style-type: none"> • How are risk levels operationalized? (variation in how IRBs evaluate risks and benefits).
B) ORGANIZATIONAL POSITION STATEMENTS/PROPOSED GUIDELINES (EXAMPLES)			
American College of Physicians [74]	<ul style="list-style-type: none"> • Legally authorized surrogate consent permissible if no advance consent document, and if in subject's best interests 		<ul style="list-style-type: none"> • Proxies should use mixed substituted judgment/best interests standard—but how is this operationalized?

Organization/Author	Proxy consent allowable	Proxy consent not allowable	Gaps remaining
			<ul style="list-style-type: none"> IRBs should establish “special protections” (consisting of what?)
Alzheimer’s Association [75]	<ul style="list-style-type: none"> Minimal risk research Research with potential therapeutic effect No more than minor increase over minimal risk research if no potential for therapeutic effect 	<ul style="list-style-type: none"> Greater than minor increase over minimal risk research if no potential for therapeutic effect (with two exceptions: condition causing cognitive impairment is object of the study; or individual has given a research advance directive) 	<ul style="list-style-type: none"> Variation in how IRBs assess risk and benefit is not addressed. Suggests that proxies be instructed to use a substituted judgment standard when possible; if impossible, then best interests standard—suggesting need for study of actual practices
NIH (“Points to Consider”) [76]	<ul style="list-style-type: none"> “Where permitted by law” 	<ul style="list-style-type: none"> Subject indicates a wish to withdraw from study 	<ul style="list-style-type: none"> Safeguards should be commensurate with severity of capacity impairment or magnitude of experimental risk—but how to operationalize risk levels?
C) ETHICIST POSITIONS (selected examples)			
“Proposed Guidelines” for consent with cognitively impaired research subjects (Berg) [77]	<ul style="list-style-type: none"> Minimal risk research Research with potential therapeutic effect Additional protections as risks increase 	<ul style="list-style-type: none"> Most restrictions in studies with high degree of risk with no potential for therapeutic benefit 	<ul style="list-style-type: none"> Proposes hierarchy of protections with increasing level of risk, e.g., surrogate consent monitor—operationalization and stakeholders’ views of such protections in need of study
“Full Spectrum Proxy Consent” (Post, 2003) [44]	<ul style="list-style-type: none"> Research at or below maximum potential risk, regardless of potential for therapeutic effect 	<ul style="list-style-type: none"> Research above maximum potential 20 risk 	<ul style="list-style-type: none"> Argues need for consensus regarding risk threshold for dementia research, e.g., through a consensus conference—yet, empirical work should also inform such discussions

Table 2

Special Issues in Geriatric Psychiatry Research

Concept	Ethical and Practical Challenges	Future Research Directions
Decision Making Capacity	<ul style="list-style-type: none"> Impairment in cognitive abilities, such as memory and executive function, are associated with decision-making capacity deficits, including ability to consent to research participation 	<p>Further examination of interventions aimed at improving decision-making capacity</p> <ul style="list-style-type: none"> Enhance the informed consent process (different modalities of presenting pertinent information, improving intra and extra personal factors that influence the decision-making process)
Surrogate/Proxy Consent	<ul style="list-style-type: none"> Variations in patients' desire for surrogate consent Variations in extent of knowledge about impaired relative's wishes Different models of proxy making – "best interest" (what I would do) vs "substituted judgment" (what my relative would want) Lack of uniform federal regulations – different states vary regarding types of studies that qualify for surrogate consent (problematic for multi-site studies) 	<ul style="list-style-type: none"> Examination of state laws on research in cognitively impaired individuals and the impact on conduct of research Examination of how various stakeholders (public, patients, IRBs) define and weigh risks and benefits in research involving proxy consent Examination of factors associated with patients' desire for or against surrogate consent, i.e. demographics, primary illness, risk:benefit ratio of study in question Interventions aimed at improving concordance rates between patients and potential surrogates
Advanced Directives for Research Participation	<ul style="list-style-type: none"> Inability to address specific information about a future study that is required for an informed consent process Questions about the genuineness of consent for future studies –based on hypothetical considerations 	<ul style="list-style-type: none"> Design of an advanced directive for research participation and examination of its utility, feasibility and applicability Usefulness of an advanced directive for research participation for a surrogate when faced with consenting for a study for their loved one
Suicide Research	<ul style="list-style-type: none"> Inclusion of suicidal subjects in studies Can suicide be viewed as an expected event in a study including suicidal subjects Do suicidal patients have diminished capacity to consent to research Strong scientific design plus clinical equipoise for all arms including control arms 	<ul style="list-style-type: none"> Examination of how various stakeholders (public, patients, researchers, IRBs) define and weigh risks and benefits in research involving suicidal patients Development of procedures for conduct of research that maintain the highest ethical and scientifically sound standards.