ORIGINAL ARTICLE

Preservation of the Capacity to Appoint a Proxy Decision Maker

Implications for Dementia Research

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Context: Research involving persons with impaired decision-making capacity (such as persons with Alzheimer disease [AD]) remains ethically challenging, especially when the research involves significant risk. If individuals incapable of consenting to research studies were able to appoint a research proxy, it would allow for an appointed surrogate (rather than a de facto surrogate) to represent the subject.

Objective: To assess the extent to which persons with AD retain their capacity to appoint a research proxy.

Design: Interview study.

Setting: Academic research.

Participants: One hundred eighty-eight persons with AD were interviewed for their capacity to appoint a proxy for research and to provide consent to 2 hypothetical research scenarios, a lower-risk randomized clinical trial testing a new drug (drug RCT) and a higher-risk randomized clinical trial testing neurosurgical cell implants using a sham control condition (neurosurgical RCT). Categorical capacity status for each subject was determined by independent videotaped reviews of capacity interviews by 5 experienced psychiatrists.

Main Outcome Measures: Categorical capacity determinations for the capacity to appoint a research proxy, capacity to consent to a drug RCT, and capacity to consent to a neurosurgical RCT.

Results: Data showed that 37.7% (40 of 106) of those deemed incapable of consenting to the drug RCT and 54.8% (86 of 157) of those deemed incapable of consenting to the neurosurgical RCT were found capable of appointing a research proxy. Only 7 of 186 (3.8%) were deemed capable of consenting to the neurosurgical RCT by all 5 psychiatrists.

Conclusions: A substantial proportion of persons with AD who were thought incapable of consenting to lower-risk or higher-risk studies have preserved capacity for appointing a research proxy. Because few persons are found to be unequivocally capable of providing independent consent to higher-risk AD research, providing for an appointed surrogate even after the onset of AD, which might best be done in the early stages of the illness, may help address key ethical challenges to AD research.

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Alzheimer disease (AD) is an incurable and devastating illness. By 2040, the number of persons with AD worldwide is expected to reach 80.1 million.[1] Therefore, clinical research with persons with AD is a public health priority. However, such research raises the ethical question of how best to enroll decisionally impaired adults in clinical research (ie, who, if anyone, can provide consent on their behalf and under what conditions).[2] The response to this question varies widely among states in the United States.[3] In the United Kingdom, there are at least 3 sets of regulations that apply, depending on where the study is located and whether the research is a clinical trial.[4] Furthermore, when AD research involves invasive or potentially risky procedures, regulatory bodies may be reluctant to allow family members to provide surrogate consent on behalf of potential participants. An example of this is a sham surgery controlled clinical trial of gene transfer for AD in which the investigators and the Recombinant DNA Advisory Committee of the National Institutes of Health decided to limit recruitment to persons who were competent to provide consent.[5]

The effect of such policies will depend on the actual decision-making capacities of persons with AD. In this regard, the current theory of decisional capacity may have important implications. The modern view of capacity is that it is a domain-specific and risk-sensitive concept.[6,7] A person's ca-

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pacity to perform one function cannot be presumed to be equivalent to his or her capacity to perform other functions. Also, the threshold for capacity should be adjusted to the risk-benefit profile of the decision so that, the higher the net risk, the stricter is the threshold for capacity. In this study, we examined 2 potential implications of such a framework. First, as suggested in a report from the National Bioethics Advisory Commission,[7] we examined to what extent a person with dementia who lacks the capacity to consent to a research study might have the capacity to delegate the responsibility by appointing a research proxy. This is important because surrogate consent may be more ethically acceptable if the decision maker is someone specifically designated by the participant rather than a de facto surrogate. Second, we examined the extent to which the risk level of a research study influences determinations of capacity for consenting to dementia research.

METHODS

PARTICIPANTS

One hundred eighty-eight participants with possible or probable AD determined by National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association criteria[8] were recruited from the University of Michigan, Ann Arbor (n=61), Michigan State University, Lansing (n=23), and University of Pennsylvania, Philadelphia (n=104). Based on prior work,[9,10] the recruitment target was stratified by Mini-Mental State Examination (MMSE)[11] scores, with 50 participants targeted for an MMSE score range of 12 to 17, 80 participants targeted for scores of 18 to 23, and 50 participants targeted for scores of 24 or higher. This stratification was designed to ensure that participants with a sufficient range of abilities were recruited, with a greater proportion of participants having MMSE scores in the midrange, where decision-making capacity status can be especially variable.[10]

The research protocol was reviewed and approved by the institutional review boards at the 3 participating universities. Given the minimal risk of this interview study, participants provided consent when determined to be capable by the interviewer; otherwise, a surrogate gave permission in addition to participant assent.

MEASURES

Capacity to Consent to Research

The MacArthur Competence Assessment Tool–Clinical Research (MacCAT-CR) is the most widely used instrument for assessing the capacity to consent to research and has been adapted and validated for use in persons with depression, schizophrenia, and dementia, among other disorders.[9,12,13] It has excellent content validity and assesses the range of abilities relevant to the capacity for giving informed consent to research according to the following 4 abilities model of decision-making capacity[14]: (1) understanding of the research protocol and activities required of participants (13 items), (2) appreciation of the potential effects of participating or not participating on the participant's situation (3 items), (3) reasoning through a decision to participate or not participate in the research (4 items), and (4) evidencing a choice to participate or not (1 item). Each item is scored from 0 to 2 using explicit scoring criteria. The MacCAT-CR has excellent test-retest and interrater reliability.[9,15]

The MacCAT-CR must be adapted for each research scenario, in keeping with the decision-specific nature of capacity. Based on different research scenarios, the 2 versions herein have been used in previous research.[16] One scenario describes a lower-risk randomized clinical trial testing a new medication for AD (drug RCT), and the other describes a higher-risk randomized placebo-controlled (sham surgery) neurosurgical clinical trial of cell transplantation for AD (neurosurgical RCT).

Capacity to Appoint a Research Proxy

The capacity to appoint a research proxy was evaluated by the Capacity to Appoint a Proxy Assessment (CAPA), an instrument specifically developed as part of this study. A prototype CAPA instrument was developed based on a detailed theoretical and empirical framework (published elsewhere[17]) and on written feedback solicited from 7 experts in the fields of mental health law, psychiatry, and psychology.

The CAPA follows the 4-abilities model of capacity[18] and consists of 14 items, with 10 items for understanding and 4 items for appreciation, choice, and reasoning. A prototype CAPA was pilot tested in 18 subjects with possible or probable AD (50% female and 11% African American), with a mean (SD) age of 74.7 (8.1) years and a mean MMSE score of 22.5 (range, 12-28). Cronbach α for the 14 CAPA interview items was 0.87, indicating strong internal consistency for the instrument. In terms of construct validity, we anticipated some convergence with measures of cognitive impairment but not a perfect one, as there are other important factors in appointing a research proxy (such as a person's sense of trust and ability to use that sense of trust in making decisions).[19] This expectation was supported by the Spearman rank correlation coefficient of 0.49 (P=.04) with the MMSE.

The prototype CAPA instrument was modified in minor ways based on the experience of administering it in the pilot study. Interrater reliability of the final CAPA instrument used in this study was measured using intraclass correlation coefficient (among pairs of research staff who scored the interviews independently). During the 30-month course of recruitment, there were 4 research staff who performed and scored CAPA interviews. For any given pair, intraclass correlation coefficients for total CAPA scores ranged from 0.93 to 0.99, confirming excellent interrater reliability of the final CAPA instrument. A copy of the CAPA is available online (available at: http://www.cbssm.org/downloads/CAPA_Instrument_Final.pdf).

PROCEDURES

To minimize participant interview burden, they were interviewed during 2 in-home visits separated by a mean (SD) of 13.2 (8.2) days. During the first visit, the CAPA and one of the MacCAT-CR interviews (randomly chosen) were conducted; the second MacCAT-CR was administered during the second visit. The CAPA and MacCAT-CR interviews typically take about 20 minutes each, although when the participant has impairment and requires repeated disclosures and probes, they can take as long as 45 minutes. They were administered by trained bachelor's-level research assistants. With few exceptions, all participants were administered the CAPA and the 2 versions of the MacCAT-CR. (Of 188 participants, 8 declined the second visit, 1 of whom also declined the first MacCAT-CR interview.)

DETERMINATION OF CATEGORICAL CAPACITY STATUS BY EXPERT JUDGES

Categorical judgments regarding the capacity status of participants were rendered by expert judges who viewed digital vid-

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Table 1. Characteristics of Participants

Characteristic	Value (n=188)
Female sex, No. (%)	95 (50.5)
Race/ethnicity, No. (%)	
White	162 (86.2)
Black	25 (13.3)
Other	1 (0.5)
Age, mean (SD), y	75.9 (8.9)
Education, mean (SD), y	14.7 (3.2)
MMSE score[a]	
Mean (SD)	20.8 (5.0)
<12, No. (%)	12 (6.4)
12-17, No. (%)	27 (14.4)
18-23, No. (%)	87 (46.3)
≥24, No. (%)	61 (32.4)

Abbreviation: MMSE, Mini-Mental State Examination.
[a]Values total 187 because 1 person finished only the first part of the first interview and did not complete the MMSE.

eos of participants undergoing the 2 MacCAT-CR and the CAPA interviews. We recruited 5 expert judges who were members of the Academy of Psychosomatic Medicine, the primary professional society in the United States for consultation psychiatrists, a subgroup of psychiatrists experienced with capacity determinations in the clinical setting. The theoretical and statistical rationale for the use of 5 judges is extensively discussed elsewhere.[20] Our judges had a mean (SD) of 29.4 (8.3) years of clinical experience, represented different parts of the United States (West Coast, Southeast, Midwest, and Northeast), and performed capacity evaluations at a range of frequencies, with an estimated mean (SD) of 109.8 (139.3) clinical capacity evaluations per year. (One judge was nearing retirement, with a current yearly rate of 9 evaluations.)

The expert judges were trained using slide (PowerPoint; Microsoft, Seattle, Washington) presentations and 5 practice interviews, with 2 one-hour conference calls to explain their task, review their experience, and answer questions regarding the practice interviews. They were not told of the goals or hypotheses of the study and rendered their capacity judgments independently based solely on each videotaped capacity interview. The judges rated 555 interviews over 36 months, in batches of approximately 16 interviews (5-6 of each interview type) per month. To minimize rater bias, we constructed a review schedule that used a stratified random sample to evenly distribute the interviews by subjects' MMSE scores in the monthly batches. There was a mean (SD) of 8.2 (4.7) months between the reviews of any 2 interviews of the same participant. In addition, the judges participated in conference calls at roughly 6-month intervals to jointly discuss 3 interviews from the monthly batch they had just rated.

Each judge's capacity judgment was made on a 4-point scale regarding the participant's possession of decisional capacity (definitely, probably, probably not, or definitely not). The criterion standard for the final categorical capacity rating for each participant was based on the decision of 3 or more judges, dichotomized as capable or incapable.[20]

STATISTICAL ANALYSIS

Means (SDs) for continuous variables and proportions for categorical variables were calculated for participant characteristics. Reliability of determining final capacity status using the 5 expert judges' dichotomous decisions was measured using Cronbach α.

To test whether the capacity to appoint a research proxy is better preserved than the capacity to give informed consent, as well as whether the capacity to give consent to a lower-risk study is better preserved than the capacity to give consent to a higher-risk study, the McNemar test was used, with an odds ratio (OR) calculated as a measure of the strength of the relationship. Because the mean scores on the understanding and appreciation subscales of the MacCAT-CR for the neurosurgical RCT scenario were lower than those for the drug RCT scenario, we adjusted for those subscales of MacCAT-CR scores using a conditional logistic regression model with capacity status as the dependent variable in comparing the proportions of subjects with the capacity to consent to the 2 RCTs.

RESULTS

Characteristics of the participants are summarized in **Table 1**. We were successful in recruiting participants with a wide range of cognitive impairment and, as intended, had the highest proportion (46.3%) of participants in the MMSE score range of 18 to 23, at which capacities can be particularly difficult to assess.[9,10]

Performances on the drug RCT and neurosurgical RCT MacCAT-CR interviews are summarized in **Table 2**. Because the 2 MacCAT-CR interviews are adaptations of the same instrument, their subscale scores can be compared. Participants performed significantly worse on the understanding and appreciation subscales of the neurosurgical RCT MacCAT-CR interview. On the CAPA, the mean (SD) scores were 14.8 (5.2) for understanding (possible score range, 0-20), 1.6 (0.7) for appreciation (possible score range, 0-2), 3.6 (0.9) for reasoning (possible score range, 0-4), and 1.98 (0.13) for choice (possible score range, 0-2).

Reliability of the 5-judge expert panel to determine the categorical capacity status of our subjects was high. Cronbach α for the panel was 0.80 for determination of the capacity to appoint a research proxy, 0.85 for determination of the capacity to consent to the drug RCT, and 0.81 for determination of the capacity to consent to the neurosurgical RCT.

Table 3 summarizes the capacity status for each of 3 decision-making capacities based on 3 or more judges' agreement. Results showed that 61.7% of participants were determined to have the capacity to appoint a research proxy, 41.4% to have the capacity to consent to the drug RCT, and 15.6% to have the capacity to consent to the neurosurgical RCT. Unanimity among the 5 expert judges was most likely for determining the capacity to appoint a research proxy when subjects were judged to be capable (30.3% of subjects), whereas for determining the capacity to consent to the 2 RCTs, unanimity was most likely for judgments of incapacity (30.9% for the drug RCT and 55.9% for the neurosurgical RCT). Only 3.8% of participants were judged unanimously to have the capacity to consent to the neurosurgical RCT.

Table 4 summarizes the relationship between the capacity to appoint a research proxy and the capacity to provide consent for the 2 clinical trials. Participants were more likely to be capable of appointing a research proxy than of consenting to the drug RCT. Of 181 participants assessed for both the capacity to appoint a research proxy

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Table 2. Performance Among 180 Participants on the MacArthur Competence Assessment Tool–Clinical Research Adapted for the Drug Randomized Clinical Trial (RCT) Scenario and the Neurosurgical RCT Scenario

	Understanding[a]		Appreciation[b]		Reasoning[c]		Choice[d]	
Variable	Drug RCT	Neurosurgical RCT	Drug RCT	Neurosurgical RCT	Drug RCT	Neurosurgical RCT	Drug RCT	Neurosurgical RCT
Mean (SD) score	15.3 (7.6)	12.6 (7.3)	4.4 (1.9)	3.9 (1.9)	6.2 (1.6)	6.1 (1.8)	1.95 (.26)	1.89 (.40)
t Statistic[e]	t_{179}=6.45, $P < .001$		t_{179}=4.29, $P < .001$		t_{179}=.0.37, P=.3		t_{179}=1.73, P=.09	

[a] Score range, 0 to 26.
[b] Score range, 0 to 6.
[c] Score range, 0 to 8.
[d] Score range, 0 to 2.
[e] By paired *t* test.

Table 3. Categorical Capacity Status of Participants as Determined by 5 Expert Judges[a]

	Capacity to Appoint Research Proxy (n=188)		Capacity to Consent to Drug RCT (n=181)		Capacity to Consent to Neurosurgical RCT (n=186)	
Determination	No. (%)	Mean (SD) MMSE Score	No. (%)	Mean (SD) MMSE Score	No. (%)	Mean (SD) MMSE Score
Capable	**116** (61.7)	22.9 (3.3)	**75** (41.4)	23.7 (3.1)	**29** (15.6)	25.0 (2.8)
3 Judges agree	32 (17.0)	21.8 (3.0)	20 (11.0)	22.7 (3.6)	8 (4.3)	24.0 (1.9)
4 Judges agree	27 (14.4)	22.2 (3.3)	30 (16.6)	23.0 (2.8)	14 (7.5)	25.1 (2.8)
5 Judges agree	57 (30.3)	23.8 (3.3)	25 (13.8)	25.3 (2.4)	7 (3.8)	26.0 (3.6)
Incapable	**72** (38.3)	17.3 (5.3)	**106** (58.6)	18.9 (4.9)	**157** (84.4)	20.1 (4.8)
3 Judges agree	23 (12.2)	18.8 (5.4)	21 (11.6)	21.2 (4.3)	19 (10.2)	23.0 (2.6)
4 Judges agree	26 (13.8)	17.8 (4.3)	29 (16.0)	19.3 (4.2)	34 (18.3)	22.4 (3.1)
5 Judges agree	23 (12.2)	15.3 (5.7)	56 (30.9)	17.7 (5.2)	104 (55.9)	18.8 (5.1)

Abbreviations: MMSE, Mini-Mental State Examination; RCT, randomized clinical trial.
[a] A total of 188 participants completed the first interview, which included the Capacity to Appoint a Proxy Assessment (CAPA) and either the drug RCT or the neurosurgical RCT MacArthur Competence Assessment Tool–Clinical Research (MacCAT-CR)(decided randomly) as well as the Mini-Mental State Examination (MMSE). One person finished CAPA during the first interview but did not finish MMSE or MacCAT-CR; and this person declined the second interview as well. This person is 1 of 8 who declined the second interview. The remaining 7 of 8 persons who declined the second interview did finish the CAPA, MMSE, and 1 of 2 MacCAT-CRs, but are missing the second MacCAT-CR.

Table 4. Relationship Between Capacity to Appoint a Research Proxy and Capacity to Consent to the 2 Randomized Clinical Trials (RCT)[a]

	No. (%)			
	Capacity to Consent to Drug RCT (n=181)		Capacity to Consent to Neurosurgical RCT (n=186)	
Capacity to Appoint Research Proxy	Yes	No	Yes	No
Yes	72 (39.8)	40 (22.1)	29 (15.6)	86 (46.2)
No	3 (1.7)	66 (36.5)	0	71 (38.2)

[a] A total of 188 participants completed the first interview, which included the Capacity to Appoint a Proxy Assessment (CAPA) and either the drug RCT or the neurosurgical RCT MacArthur Competence Assessment Tool–Clinical Research (MacCAT-CR)(decided randomly) as well as the Mini-Mental State Examination (MMSE). One person finished CAPA during the first interview but did not finish MMSE or MacCAT-CR; and this person declined the second interview as well. This person is 1 of 8 who declined the second interview. The remaining 7 of 8 persons who declined the second interview did finish the CAPA, MMSE, and 1 of 2 MacCAT-CRs, but are missing the second MacCAT-CR.

and the capacity to consent to the drug RCT, 106 were deemed incapable of consenting to the drug RCT, and 40 of them (37.7%) retained the capacity to appoint a research proxy. Only 3 persons were deemed incapable of appointing a research proxy yet capable of providing consent to a drug RCT. The odds of having the capacity to appoint a research proxy was 13.3 (95% confidence interval [CI], 4.3-67.4) times the odds of having the capacity to consent to the drug RCT. The pattern was more pronounced when comparing the capacity to appoint a research proxy with the capacity to consent to the higher-risk neurosurgical RCT. Of 186 participants who were assessed for both the capacity to appoint a research proxy and the capacity to consent to the higher-risk RCT, 157 were deemed incapable of consenting to the higher-risk neurosurgical RCT; of these, 86 (54.8%) were capable of appointing a research proxy. No participants who were found capable of consenting to the neurosurgical RCT

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were deemed incapable of appointing a research proxy (OR not definable because of 0 denominator; 95% CI, 22.8 to ∞).

For the capacity to consent to the 2 RCT studies, of 180 participants who were assessed for both capacities, 151 were incapable of consenting to the higher-risk neurosurgical RCT, but 48 of them were capable of consenting to the lower-risk drug RCT (OR, 24.0; 95% CI, 6.3-203.9), whereas only 2 were capable of consenting to the higher-risk study but not to the lower-risk study. A conditional logistic regression model showed that the difference in competency status for the drug RCT scenario and neurosurgical RCT scenario remained significant, with an OR of 20.4 (95% CI, 4.35-95.8) after adjusting for MacCAT-CR scores on the understanding and appreciation subscales.

COMMENT

In this study, we compared the decision-making capacities to appoint a research proxy and to consent to 2 different research studies of varying risks and potential benefits. We note 4 main findings. First, the capacity to appoint a research proxy was better preserved than the capacity to provide consent for a drug RCT, which was, in turn, better preserved than the capacity to consent to a higher-risk neurosurgical RCT. The relative preservation of the capacity to appoint a proxy may be because providing valid informed consent for research requires subjects to learn new and sometimes technical information about research design, a particularly difficult task for persons with AD, whose memory for new information is affected early in the disease. However, in appointing a research proxy, the most salient ethical issues have to do with trusting someone else to make a decision, a concept that is already familiar to many and is relationship based, as most proxies will be persons with whom subjects have had a close relationship for years.

Second, there was an unexpected finding, namely, that participants performed worse (ie, received lower scores on the understanding and appreciation subscales) on the MacCAT-CR adapted for the neurosurgical RCT than on that adapted for a drug RCT. This may be because the neurosurgical RCT, being less familiar than a drug RCT to a layperson, requires learning new concepts and procedures (eg, the idea of a sham surgery RCT is novel to most people), something that is particularly difficult for persons with AD. Still, this poorer performance did not fully account for far fewer participants being deemed capable of consenting to the neurosurgical RCT compared with the drug RCT. Therefore, our results are consistent with previous experimental research showing that risk level mediates the capacity thresholds of experienced psychiatrists.[16]

Third, few participants (about 16%) were deemed capable of consenting to the higher-risk RCT involving sham surgery even if based on a liberal method (ie, the decision by a majority of the expert judges). Some may argue that, if we are to rely only on the participant's consent to authorize his or her involvement in such a high-risk study, a more conservative approach should be used. Following this logic, if unanimity among our experts is used as the criterion for the capacity to consent to the highly invasive neurosurgical RCT, then less than 4% of our participants with AD were capable of consenting to such research.

Fourth, although by using a 5-expert panel we were able to achieve a reliable categorization of capacity status for our participants, a single clinician's assessment may not be reliable because there is considerable variability across judges. For judgments of capacity, this effect seems to increase as the risk consequences of the decision increases; while 49.1% (57 of 116) of subjects found to be capable of appointing a research proxy evoked unanimous agreement, this was true for 24.1% (7 of 29) of subjects found to be capable of consenting to the neurosurgical RCT.

What are the policy and practice implications of these findings? First, the results support the legitimacy of obtaining a concurrent proxy directive from many persons at the time of recruitment for a research study. A person with AD who is being asked to enroll in a research study (or, if not a specific study, to enroll in a research clinic's pool of potential participants) may be able to appoint a proxy at the time of that request even if he or she lacks the capacity to give independent consent for research. This is a critical concept because even persons at heightened risk for AD with favorable views of research are unlikely to complete an advance directive for research.[21] The National Institutes of Health has long used a durable power of attorney for research decisions when persons with AD join their research programs,[22] and our results provide evidence for the appropriateness of such a practice. In our sample, 91.7% (55 of 60) of those who had an MMSE score of 24 or higher were capable of appointing a research proxy. Therefore, persons in the early stages of AD are excellent candidates for appointing a research proxy, and at the earliest stage of the disease, a presumption of capacity to appoint a proxy may be appropriate. At later stages, given the risk-benefit profile of the decision, a single evaluator's assessment may be sufficient.

Second, the results raise some difficult questions for a policy that requires enrollment of only those determined to be competent to provide informed consent. Although it is possible that, given the high prevalence of AD, one could recruit sufficient numbers for a small clinical trial (eg, involving sham neurosurgery to test a new intervention), it seems that recruiting unequivocally competent persons for such studies may prove difficult. At any rate, such persons will represent a small higher-functioning subgroup of those who have AD, raising important issues concerning external validity; such subjects also have the most to lose from an adverse event given their higher level of functioning. Furthermore, although for research purposes our approach to determining the capacity status of participants is reliable when the opinion of the entire 5-judge panel is used, a single judge's opinion may not be reliable enough for a high-stakes determination of the capacity to consent to research (as opposed to the capacity to appoint a proxy) in practice. This may well remain the case until the practice of capacity assessment in the research context becomes more widespread, with greater consensus achieved by the evalua-

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tors. Paradoxically, 2 participants were deemed capable of consenting to the neurosurgical RCT but not to the drug RCT, and 3 participants were deemed capable of consenting to the drug RCT but not of appointing a research proxy. Although the numbers are small, this reflects the imprecise nature of clinician judgments of capacity. Research ethics policies that rely heavily on the capacity determination process may be assuming more precision and reliability than is currently warranted.

There are several caveats and limitations to our results. First, because the MMSE was performed at each participant's home, it is possible that the scores are slightly inflated because it would have been easier for our participants to answer the orientation-to-place items than if they had been interviewed at a clinic. Second, our results regarding the capacity to appoint a research proxy need to be interpreted cautiously because the concept is in early stages of legal and theoretical discussion and may undergo further theoretical refinements. Third, our judges made their decisions under somewhat artificial conditions because they did not follow the usual procedure of capacity determination, which would have involved actual interviews with individualized probing of unclear areas (rather than just viewing a video) and the availability of more background clinical information. However, it is also possible that more individualized styles of interviewing with less standardization could lead to more variability in judgment.[23] Fourth, our sample is not a probability sample of persons with AD, and some may argue that, for example, our conclusion that less than 4% of participants are unequivocally (ie, as represented by unanimous views of our 5 judges) capable of consenting to a neurosurgical RCT is overly pessimistic. However, although it is true that our sample is not representative, it is likely the 4% estimate is actually optimistic given that in our participant pool persons with milder disease were highly represented, with 79.7% of our participants with AD having an MMSE score of 18 or higher and 32.4% having a score of 24 or higher. We also note that, although our group had good representation of black individuals, other minority groups were not well represented, and the mean educational level was higher and the proportion of women lower than might be expected among persons with AD in general. However, because this is a common limitation in AD research,[24] our study may in fact be generalizable to the likely population of research participants with AD.

The ethics of enrolling persons with dementia in clinical research, especially when the research involves considerable burden or risk, remains controversial. The results of our study provide important data for policy making. Although limiting high-risk studies to competent persons is theoretically appealing, the realities of persons eligible to participate in such studies—the low prevalence of capacity and the difficulty in achieving clear consensus on judgments of capacity—pose challenges to such a policy. On the other hand, the fact that many persons who lack the capacity to provide informed consent to research may yet retain the important capacity to appoint a research proxy may provide ethical alternatives in the quest to effectively protect a vulnerable population, while permitting important research to move forward.

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