Published in final edited form as:
Arch Gen Psychiatry. 2011 February ; 68(2): 214–220. doi:10.1001/archgenpsychiatry.2010.191.

Preservation of the Capacity to Appoint a Proxy Decision Maker: Implications for Dementia Research

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Abstract

Context—Research involving persons with impaired decision-making capacity, such as persons with Alzheimer's disease, remains ethically challenging, especially when the research involves significant risk. If subjects incapable of consenting to research studies were still 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 Alzheimer's disease retain their capacity to appoint a research proxy.

Design, Setting, and Participants—188 persons with Alzheimer's disease were interviewed for their capacity to appoint a proxy (CAP) for research and to provide consent to two 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 videotape reviews of capacity interviews by five 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.

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Financial Disclosure: All authors report institutional grant support from the National Institutes of Mental Health for work related to this manuscript. In addition to institutional support from NIMH, Jason Karlawish reports Board membership and stock/stock options from Senior Bridge Inc., Travel/accommodations expenses covered or reimbursed from the Alzheimer's Association for the International Conference on Alzheimer's Disease 2010, and institutional grant support from Pfizer Inc. for a clinical trial testing a drug in persons with Alzheimer's Disease. Paul Appelbaum reports royalties on sales of MacCAT-CR manual from Professional Resource Press, in addition to institutional support from NIMH. We report no other relationships/conditions/circumstances that present potential conflict of interest.

Results—37.7% (40/106) of those deemed incapable of consenting to the drug RCT and 54.4% (86/157) of those deemed incapable of consenting to the neurosurgical RCT were still found capable of appointing a research proxy. Very few subjects (7/186, 3.8%) were deemed capable of consenting to the neurosurgical RCT by all five psychiatrists.

Conclusion—A substantial proportion of AD subjects thought incapable of consenting to lower or to higher risk studies have preserved capacity for appointing a research proxy. Since so few subjects 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 very early stages of the illness, may help address key ethical challenges to AD research.

Alzheimer's disease (AD) is an incurable and devastating illness. The number of persons with AD worldwide is expected to reach 80.1 million by 2040.[1] Thus, clinical research with persons suffering from AD is a public health priority. Yet such research raises the ethical question of how best to enroll decisionally impaired adults in clinical research, i.e., who, if anyone, can provide consent on their behalf and under what conditions?[2] The response to this question varies widely among the states in the U.S.[3]; in the U.K., there are at least three sets of regulations that apply, depending on the location and on whether the research is a clinical trial.[4] Further, 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 subjects. An example of this stance comes from the Recombinant DNA Advisory Committee (RAC) of the U.S. National Institutes of Health, which limited recruitment for a sham surgery-controlled clinical trial of gene transfer for AD to subjects who were competent to provide their own consent.[5]

The impact 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 capacity 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 the threshold for capacity. In this study, we examined two potential implications of such a framework. First, as suggested by the National Bioethics Advisory Commission's (NBAC) report,[7] we examined to what extent a person with dementia who lacks the capacity to consent to a research study might still have the capacity to delegate the responsibility by appointing a proxy. This is important because surrogate consent may be more ethically acceptable if the decision maker is someone specifically designated by the subject rather than a de facto surrogate. Second, we examined the extent to which the risk level of a research study affects determinations of capacity for consenting to dementia research.

METHODS

Subjects

One hundred and eighty-eight subjects with possible or probable Alzheimer's disease by NINCDS criteria[8] were recruited from the University of Michigan (n=61), Michigan State University (n=23), and the University of Pennsylvania (n=104). Based on prior work [9, 10], the recruitment target was stratified by Mini-Mental State Examination (MMSE) [11] levels, with 50 subjects targeted for a MMSE score range of 12–17, 80 subjects with scores of 18–23, and 50 subjects with scores of 24 or higher. This stratification was designed to ensure that subjects with a sufficient range of abilities were recruited, with a greater proportion of subjects with MMSE scores in the mid-range where decision-making capacity status can be especially variable.[10]

The research protocol was reviewed and approved by the institutional review boards at the University of Michigan, Michigan State University, and the University of Pennsylvania. Given the minimal risk of this interview study, the subjects provided their own consent when determined to be capable by the interviewer; otherwise, a surrogate gave permission in addition to subject 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 capacity for giving informed consent to research according to the four-abilities model of decision-making capacity [14]: 1) *understanding* of the research protocol and activities required of subjects (13items); 2) *appreciation* of the potential effects of participating or not participating on the subject's own 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 0–2 with explicit scoring criteria. The MacCAT-CR has excellent test-retest and inter-rater reliability.[9, 15]

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

Capacity to Appoint a Proxy—The capacity to appoint a research proxy was assessed 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 a total 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 (mean age of 74.7 years [SD 8.1], 50% women, 11% African American, mean MMSE score of 22.5 [range 12 to 28]). The Cronbach's alpha 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, since there are other important factors in appointing a 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 a Spearman's correlation coefficient of 0.49 ($p = 0.04$) with the MMSE.

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

Procedures

To minimize subject interview burden, they were interviewed during two in-home visits separated by an average of 13.2 (SD 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 subject is impaired 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 subjects were administered the CAPA and the two versions of the MacCAT-CR. (Of the 188 subjects, 8 declined the second visit, one of whom also declined the first MacCAT-CR interview.)

Determination of Categorical Capacity Status by Expert Judges

Categorical judgments of the capacity status of the subjects were rendered by the expert judges who viewed digital videos of subjects undergoing the two MacCAT-CR and the CAPA interviews. We recruited five expert judges who were members of the Academy of Psychosomatic Medicine (APM), the primary professional society in the U.S. for consultation psychiatrists, a subgroup of psychiatrists highly experienced in 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 on average 29.4 (SD 8.3) years of clinical experience, represented different parts of the U.S. (West Coast, Southeast, Midwest, Northeast), and performed capacity evaluations with a range of frequencies, averaging an estimated 109.8 (SD 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 PowerPoint® presentations and 5 practice interviews, with two 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. On average, there were 8.2 months (SD 4.7) between the reviews of any two interviews of the same subject. In addition, the judges participated in conference calls at roughly 6-month intervals to jointly discuss three interviews from the monthly batch they had just rated.

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

Statistical Analyses

Means and standard deviations for continuous variables and proportions for categorical variables were calculated for participant characteristics. The reliability of determining final capacity status using the five expert judges' dichotomous decisions was measured using Cronbach's alpha.

To test whether the capacity to appoint a 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, McNemar's test was used with an odds ratio calculated as a measure of the strength of the relationship. Because the mean scores on the MacCAT-CR's Understanding and Appreciation subscales 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 two RCTs.

RESULTS

The characteristics of the participants are summarized in Table 1. We were successful in recruiting subjects with a wide range of cognitive impairment and, as intended, had the highest proportion (46%) of subjects in the range (MMSE 18–23) where capacities can be particularly difficult to assess.[9, 10]

The performance on the drug RCT MacCAT-CR and the neurosurgical RCT MacCAT-CR interviews are summarized in Table 2. Since the two MacCAT-CR interviews are adaptations of the same instrument, their subscale scores can be compared. The subjects performed significantly worse on the Understanding and Appreciation subscales of the neurosurgical RCT MacCAT-CR interview. On the CAPA, mean score for understanding was 14.8 (SD 5.2; possible score range 0–20), for appreciation 1.6 (SD 0.7; possible score range 0–2), for reasoning 3.6 (SD 0.9; possible range 0–4), and for choice 1.98 (SD 0.13; possible range 0–2).

The reliability of the 5-judge expert panel to determine the categorical capacity status of our subjects was high. The Cronbach's alpha for the panel was 0.80 for determination of 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 the three decision-making capacities based on 3 or more judges' agreement. 61.7% of the participants were determined to have capacity to appoint a proxy, 41.4% to have capacity to consent to the drug RCT, and 15.6% to have capacity to consent to the neurosurgical RCT. Unanimity among the 5 expert judges was most likely for determining the capacity to appoint a proxy when the subjects were judged to be capable (30% of cases), whereas for determining the capacity to consent to the two RCTs, unanimity was most likely for judgments of incapacity (31% for drug RCT and 56% for neurosurgical RCT). Of note, only 3.8% of cases were judged unanimously to have the capacity to consent to the neurosurgical RCT.

Table 4 shows the relationship between the capacity to appoint a proxy and the capacity to provide consent for the two clinical trials.

Subjects were more likely to be capable of appointing a proxy than of consenting to the drug RCT study. Of the 181 subjects assessed for both the capacity to appoint a proxy and the capacity to consent to the drug RCT, 106 were deemed incapable of consenting to the drug RCT study and of those, 40 (37.7%) retained the capacity to appoint a research proxy. Only 3 persons were deemed incapable of appointing a proxy yet capable of providing consent to a drug RCT. The odds of having the capacity to appoint a proxy was 13.3 times the odds of having the capacity to consent to the drug RCT (95% CI=4.3, 67.4). The pattern was more pronounced when comparing the capacity to appoint a proxy to the capacity to consent to the higher risk neurosurgical RCT. Of the 186 subjects who were assessed for both capacity to appoint a proxy and capacity to consent to the higher risk RCT, 157 were deemed incapable of consenting to the high-risk neurosurgical RCT; of these, 86 (54.8%) were still capable of appointing a proxy. No subjects who were found capable of consenting to the neurosurgical RCT were deemed incapable of appointing a proxy (OR not definable due to 0 denominator, 95% CI=22.8, ∞).

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

DISCUSSION

In this study, we compared the decision-making capacities to appoint a proxy and to consent to two different research studies of varying risks and potential benefits. We note four main findings. First, the capacity to appoint a research proxy was better preserved than the capacity to provide consent for a drug RCT study, 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 even early in the disease. However, in appointing a 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, since most proxies will be persons with whom subjects have had a close relationship for years.

Second, there was one unexpected finding, namely, that the subjects performed worse (i.e., received lower scores on the Understanding and Appreciation subscales) on the MacCAT-CR adapted for the neurosurgical RCT than on the one adapted for a drug RCT. This may be because the neurosurgical RCT, being less familiar to a layperson than a drug RCT, requires learning of new concepts and procedures (e.g., 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 subjects being deemed capable of consenting to the neurosurgical RCT compared to the drug RCT. Our results are therefore still consistent with previous experimental research showing that risk level mediates the capacity thresholds of experienced psychiatrists.[16]

Third, relatively few subjects (about 16%) were deemed capable of consenting to the higher risk RCT involving sham surgery, even if based on a relatively liberal method (i.e., the decision of a majority of the expert judges). Some may argue that if we are to rely *only* on the subject's consent to authorize the subject's 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 capacity to consent to the highly invasive neurosurgical RCT, then fewer than 4% of our AD subjects were capable of consenting to such research.

Fourth, although by using a 5-expert panel we were able to achieve a highly reliable categorization of capacity status for our subjects, a single clinician's assessment may not be very reliable, since there is considerable variability across judges. For judgments of capacity, this effect seems to increase as the risk consequences of the decision increases; whereas nearly 50% (57/116) of subjects found to be capable of appointing a proxy evoked unanimous agreement, this was true for only 24% (7/29) 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 subjects at the time when

they are being recruited for a research study. A person with AD who is being asked to enter a research study (or, if not a specific study, enter a research clinic's pool of potential subjects) 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 people at heightened risk for AD with favorable views of research are unlikely to complete an advance directive for research.[21] The NIH has long used a durable power of attorney for research decisions as AD patients join their research programs [22] and our results provide evidence for the appropriateness of such a practice. In our sample, 92% (55 of 60) of those who had a MMSE of 24 or higher were capable of appointing a proxy. Thus, 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 even 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 still recruit sufficient numbers for a small clinical trial--for example, involving sham neurosurgery to test a new intervention--it appears that recruiting unequivocally competent persons for such studies may prove difficult. At any rate, such subjects 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. Further, although for research purposes our approach to determining the capacity status of subjects is highly reliable when the entire 5-judge panel's opinion is used, a single judge's opinion may not be reliable enough for a high-stakes determination of capacity to consent to research (as opposed to 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 evaluators. Paradoxically, 2 subjects were deemed capable of consenting to the neurosurgical RCT but not the drug RCT and 3 subjects were deemed capable of consenting to drug RCT but not of appointing a 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 subject's home, it is possible that the scores are slightly inflated, since it would have been easier for our subjects to answer the orientation-to-place items than if they had been interviewed at a clinic. Second, our results regarding capacity to appoint a research proxy need to be interpreted cautiously because the concept is still in relatively early stages of legal and theoretical discussion, and thus may yet undergo further theoretical refinements. Third, our judges made their decisions under somewhat artificial conditions, since 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 even more variability in judgment.[23] Fourth, our sample is not a probability sample of those with AD and thus some may argue that, for example, our conclusion that less than 4% of the subjects are unequivocally (i.e., as represented by unanimous views of our five 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 subject pool persons with milder disease were highly represented, with 79% of our AD subjects having an MMSE of 18 or greater and 32% having scores of 24 or higher. We also note that although our group had a good representation of black subjects,

other minority groups were not well represented, and the average education level was higher and 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 AD research subjects.

The ethics of enrolling persons with dementia in clinical research, especially when the research involves considerable burden or risk, remain controversial. The results of our study provide important data for policymaking. Although limiting high-risk studies to competent persons is theoretically quite appealing, the realities of persons eligible to participate in such studies—the low prevalence of capacity and the difficulty of 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 highly vulnerable population while permitting important research to move forward.

Acknowledgments

Funding/Support: This work was supported by grant R01-MH075023 from the National Institute of Mental Health. Drs. Kim and Karlawish are also Greenwall Foundation Faculty Scholars in Bioethics. The funding source had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript. The corresponding author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

We thank James Bourgeois, Bernard Frankel, Kevin Hails, James Rundell, and Kathy Seibel for their work as expert judges in this study.

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Table 1

Participant characteristics, N=188

	N (%) or Mean±SD
Female	95 (50.5%)
White	162 (86.2%)
Black	25(13.3%)
Other	1 (.5%)
Age (years, mean±SD)	75.9±8.9
Education (years, mean±SD)	14.7±3.2
MMSE, (mean±SD)	20.8 ±5.0
<12	12 (6.4%)
12–17	27 (14.4%)
18–23	87 (46.3%)
24+	61 (32.4%)

Table 2

Performance on MacArthur Competence Assessment Tool-Clinical Research (MacCAT-CR) adapted for Drug RCT scenario and Neurosurgery RCT scenario, N=180.

	Understanding[a] (0–26)		Appreciation[b] (0–6)		Reasoning[c] (0–8)		Choice[d] (0–2)	
Version of MacCAT-CR	**Drug RCT**	**Neurosurgery RCT**	**Drug RCT**	**Neurosurgery RCT**	**Drug RCT**	**Neurosurgery RCT**	**Drug RCT**	**Neurosurgery RCT**
Mean score (SD)	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)

[a] Paired t-test: p<0.001, t=6.45, df179

[b] p<0.001, t=4.29, df179

[c] p=0.3, t=.37, df179

[d] p=.09, t=1.727, df179

Table 3

Categorical capacity status of AD subjects for the capacity to appoint a proxy and the capacity to consent to a drug RCT and to a neurosurgical RCT, as determined by 5 expert judges.

	Capacity to Appoint Proxy (n=188)*		Capacity to Consent to Drug RCT (n=181)*		Capacity to Consent to Neurosurgical RCT (n=186)*	
	N (%)	Mean MMSE (SD)	N (%)	Mean MMSE (SD)	N (%)	Mean MMSE (SD)
Capacity	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	27 (14.4)	22.2 (3.3)	30 (16.6)	23.0 (2.8)	14 (7.5)	25.1 (2.8)
5	57 (30.3)	23.8 (3.3)	25 (13.8)	25.3 (2.4)	7 (3.8)	26.0 (3.6)
No capacity	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	26 (13.8)	17.8 (4.3)	29 (16.0)	19.3 (4.2)	34 (18.3)	22.4 (3.1)
5	23 (12.2)	15.3 (5.7)	56 (30.9)	17.7 (5.2)	104 (55.9)	18.8 (5.1)

*The numbers are different because 188 completed the first interview, which included the CAPA and either the drug RCT or the neurosurgical RCT MacCAT-CR (randomly chosen), and 7 declined one of the MacCAT-CR interviews and one subject finished neither of the MacCAT-CR interviews.

Table 4

Relationships between capacity to appoint a research proxy and the capacity to consent to the two RCTs involving two different levels of risk-benefit.

		Capacity to Consent to Drug RCT		Capacity to Consent to Neurosurgical RCT	
		Yes	**No**	**Yes**	**No**
Capacity to Appoint Research Proxy	Yes	72 (39.8%)	40 (22.1%)	29 (15.6%)	86 (46.2%)
	No	3 (1.7%)	66 (36.5%)	0 (0%)	71 (45.2%)