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Featured Article

Measuring informed consent capacity in an Alzheimer's disease clinical trial

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Abstract

Introduction: Accurately and efficiently determining a participant's capacity to consent to research is critically important to protect the rights of patients with Alzheimer's disease (AD).

Methods: Understanding of the informed consent document was assessed in 613 community-dwelling patients with mild-to-moderate AD enrolled in a randomized, placebo-controlled trial. Associations were examined between clinically determined capacity to consent and (1) patient demographics and clinical characteristics and (2) the Informed Consent Questionnaire (ICQ), an objective measurement of a participant's factual understanding and perceived understanding.

Results: A total of 453 (74%) participants were determined to have capacity to consent by clinical judgment. ICQ perceived understanding, race, measures of cognitive function, and caregiver time were all significantly associated with the determination of capacity in multivariate analyses.

Discussion: We found a significant association between capacity and disease severity level, caregiver time, race, and ICQ perceived understanding.

Keywords: Informed consent; Alzheimer's disease; Consent forms; Comprehension; Mental competency; Third-Party consent; Clinical trials as topic

1. Introduction

Obtaining informed consent is considered by researchers and the general public as a critical element for ethical human research [1–4]. Nevertheless, current informed consent practices are often inadequate, particularly among vulnerable individuals, such as persons with Alzheimer's disease (AD) [5,6]. In addition, the strength of the relationship between

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cognitive decline and loss of capacity in mild-to-moderate AD remains ill-defined [6–9].

One of the ethical principles of informed consent is *respect for persons*, which includes two requirements: first, individuals should be treated as autonomous agents, and second, those with diminished autonomy are entitled to extra protection [10]. Because the ability of AD patients to make informed decisions is often questionable, it is essential to determine whether patients have adequate capacity to consent [11–13]. Despite this, there is no consensus on how to reliably assess decision-making capacity in AD research subjects [14–16]. In addition, there are no consistent or clear policies for researchers or institutional review boards (IRBs) regarding the involvement of adults with dementia or their surrogates in clinical research trials [14,17].

We developed a capacity assessment instrument that focused on understanding of factual information about an AD clinical trial and the patient's perceived understanding (participant's subjective beliefs about understanding). The instrument was designed to provide an objective measure to assist researchers and oversight committees in balancing the need to (1) protect the right of individuals to decide for themselves whether to participate and (2) protect the collective rights of vulnerable individuals for ethical and regulatory imperatives. The assessment was not designed to address other important components of capacity such as appreciation of the significance of the decision, reasoning, or expression of choice. These elements were components of the investigator's judgment of capacity that were separate from our capacity assessment.

2. Methods

2.1. Objectives

The objectives of this study were to (1) assess the associations between capacity to consent as determined by site investigators and an objective measure of a participant's understanding of the study, demographics, and cognitive and functioning assessments at the time of consent; and (2) examine the relationship between capacity to consent as determined by the site investigator and a participant's perceived understanding of the study.

2.2. Study design

This informed consent study was incorporated in the Department of Veterans Affairs (VA) Cooperative Studies Program placebo-controlled, randomized clinical trial to assess the effectiveness of alpha-tocopherol, memantine, and the combination vs. placebo on clinical progression in patients with AD (CSP#546). Details regarding the CSP#546 design and study results have been published [18,19]. Briefly, mild-to-moderate AD patients were randomized to receive one of the four treatments. The mean (SD) follow-up time was 2.3 (1.2) years with treatment duration ranging from 6 to 48 months. The study was approved by the IRB at each of the 14 participating VA medical centers.

2.3. Patients

Veterans with possible or probable AD of mild-to-moderate severity (Mini-Mental State Examination [MMSE] total score between 12 and 26 inclusive) were recruited from 14 VA medical centers between August 2007 and March 2012 [18,19]. All participants or their surrogates provided written informed consent.

2.4. Informed consent

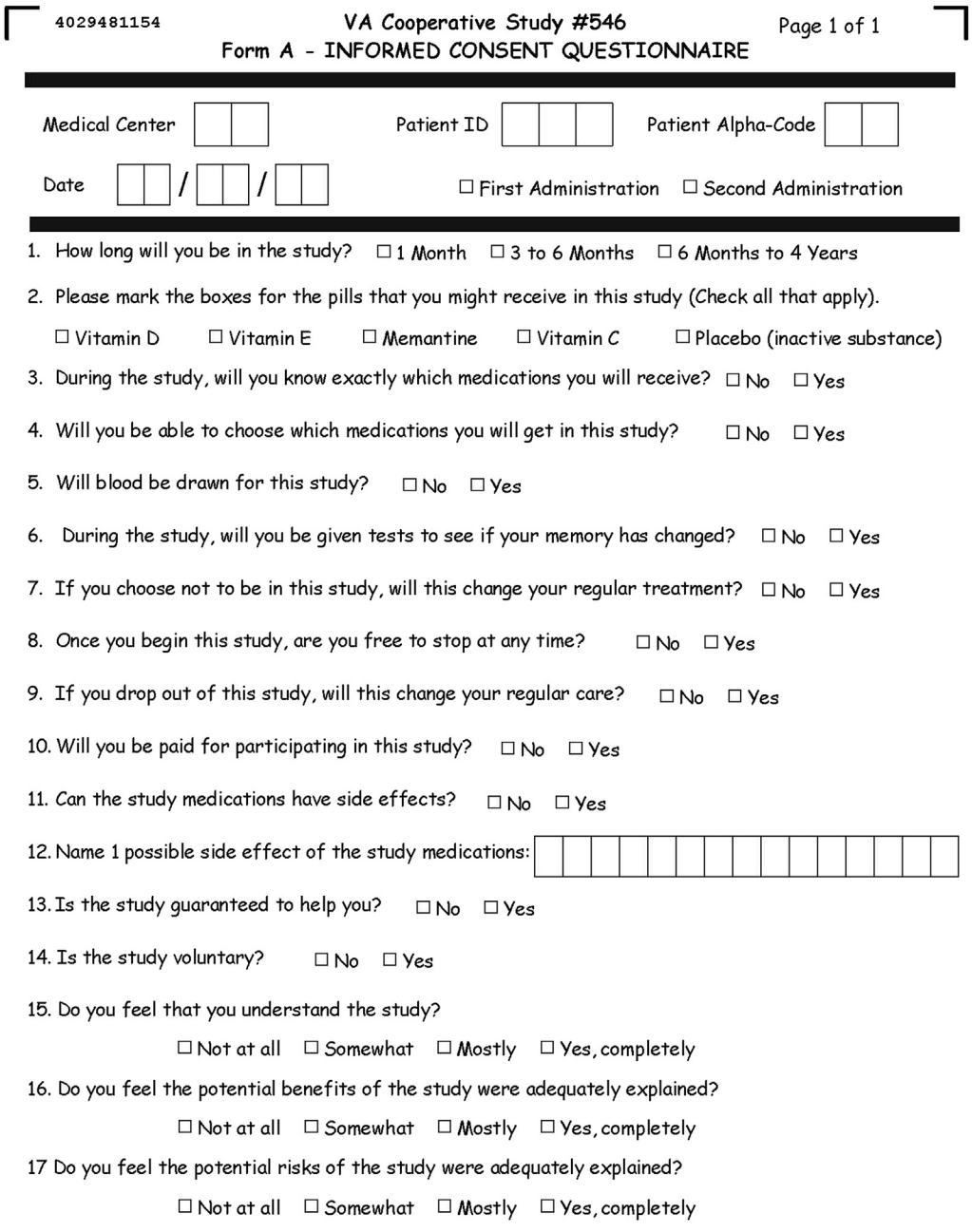
Before initiating the study, study coordinators and clinical investigators were trained to assess capacity using a 17-item Informed Consent Questionnaire (ICQ) aimed at clarifying a participant's understanding of the study and his/her rights as a research subject (Fig. 1). This study-specific tool was developed to provide a simple, consistent, and objective measure of both understanding and perceived understanding to assist investigators in their assessment of capacity.

During the informed consent process, study coordinators and/or site investigators described the CSP#546 study, its purpose and procedures, and the risks and benefits of participation. Patients and caregivers were given an opportunity to read and take home the informed consent document and ask questions. Before completing the consent process, patients were asked to complete the ICQ without assistance from their caregivers. Questionnaire responses were reviewed with the patient, and all items answered incorrectly were clarified. After the discussion, the ICQ was readministered. If the participant was able to adequately understand the study on the first or second administration and/or the investigator believed that the participant had adequate decisional capacity and was making a voluntary decision, the participant was judged to have capacity to consent. If it was determined that the participant lacked capacity, the investigator requested assent from the patient and proxy consent from a surrogate. While the ICQ was used by investigators as a tool to help determine capacity, the final decision was ultimately based on the primary site investigator's clinical judgment. The decision about capacity was also carried out according to (1) local VA policy, which typically requires consultation with an independent clinician if it is determined that an individual may not have capacity, and (2) state laws, which vary and typically only address court-appointed legally authorized representatives and surrogate decision makers.

If a participant with adequate decisional capacity at enrollment appeared to have lost capacity during follow-up, or his/her cognitive function declined to a severe level (defined as MMSE <15), the site investigator repeated the informed consent process and sought surrogate consent if needed.

2.5. Outcome measures

The primary outcome measures were (1) the clinical investigator's determination of a patient's capacity to consent and (2) the ICQ measurement of a patients' knowledge and understanding of the information in the consent form as



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VA Cooperative Study #546
Form A - INFORMED CONSENT QUESTIONNAIRE

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Medical Center ☐☐ Patient ID ☐☐☐ Patient Alpha-Code ☐☐

Date ☐☐/☐☐/☐☐ ☐ First Administration ☐ Second Administration

1. How long will you be in the study? ☐ 1 Month ☐ 3 to 6 Months ☐ 6 Months to 4 Years
2. Please mark the boxes for the pills that you might receive in this study (Check all that apply).
   ☐ Vitamin D ☐ Vitamin E ☐ Memantine ☐ Vitamin C ☐ Placebo (inactive substance)
3. During the study, will you know exactly which medications you will receive? ☐ No ☐ Yes
4. Will you be able to choose which medications you will get in this study? ☐ No ☐ Yes
5. Will blood be drawn for this study? ☐ No ☐ Yes
6. During the study, will you be given tests to see if your memory has changed? ☐ No ☐ Yes
7. If you choose not to be in this study, will this change your regular treatment? ☐ No ☐ Yes
8. Once you begin this study, are you free to stop at any time? ☐ No ☐ Yes
9. If you drop out of this study, will this change your regular care? ☐ No ☐ Yes
10. Will you be paid for participating in this study? ☐ No ☐ Yes
11. Can the study medications have side effects? ☐ No ☐ Yes
12. Name 1 possible side effect of the study medications: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
13. Is the study guaranteed to help you? ☐ No ☐ Yes
14. Is the study voluntary? ☐ No ☐ Yes
15. Do you feel that you understand the study?
    ☐ Not at all ☐ Somewhat ☐ Mostly ☐ Yes, completely
16. Do you feel the potential benefits of the study were adequately explained?
    ☐ Not at all ☐ Somewhat ☐ Mostly ☐ Yes, completely
17 Do you feel the potential risks of the study were adequately explained?
    ☐ Not at all ☐ Somewhat ☐ Mostly ☐ Yes, completely

Fig. 1. Informed Consent Questionnaire.

well as his/her subjective beliefs about understanding. The first 14 questions of the ICQ tested understanding of the important elements of the study including potential benefits and risks. To be judged to have capacity as measured by the ICQ, the participant had to answer 70% of questions 1 to 10 and 100% of questions 11 to 14 correctly on the first or second administration. With input from the human rights committee at the coordinating center, the questions and the scoring algorithm were developed by the study's planning committee based solely on face validity. The ICQ and its scoring were also reviewed and approved by the IRBs at each participating site.

The ICQ included the assessment of participants' perceived understanding, that is, participants' beliefs about their understanding, and whether they felt the benefits and risks were adequately explained. Perceived understanding was assessed with ICQ items 15 to 17 derived from the validated ICQ-4 [20]. The score for each of these questions ranged from 0 to 3 (total score range: 0–9).

The primary outcome measure of the CSP#546 study was the AD Cooperative Study/Activities of Daily Living (ADCS/ADL) inventory to assess functional abilities [21]. Secondary clinical outcome measures included the MMSE [22] and the AD Assessment Scale—Cognitive Subscale (ADAS-cog)

[23] to assess cognitive function; the 12-item Neuropsychiatric Inventory [24] to assess psychological and behavioral problems; and the Caregiver Activity Survey (CAS) [25] to measure caregivers' time required to care for the patient.

2.6. Statistical analysis

A κ coefficient was calculated to assess the agreement between the ICQ and the clinical investigators' assessment of capacity [26]. Sensitivity analyses examining different criteria for determining a "passing" ICQ score on the level of agreement were also conducted. The associations between capacity, demographics, ICQ perceived understanding scores, and the AD cognitive and functioning measures were analyzed by univariate and multivariate logistic regression. All tests of significance were conducted at the 5% level without correction for multiplicity. Analyses were performed using SAS, version 9.1 (SAS Institute, Inc., Cary, NC).

3. Results

Between August 7, 2007, and March 31, 2012, 613 veterans with mild-to-moderate AD were randomized. A total of 453 (74%) had capacity and 160 (26%) lacked capacity to consent at enrollment as determined by the site investigator. Eighty-three (18%) participants who had capacity at enrollment were reassessed and determined to have lost capacity during study follow-up. Significant associations with capacity were found for race, education, the ADCS/ADL Inventory, the MMSE, the ADAS-cog, and the CAS (Table 1).

Determination of capacity by site investigators and the ICQ was in agreement on 502 (82%) participants (Table 2; κ 0.60; 95% CI, 0.54–0.66). We examined whether there were any differences in population where investigators and the ICQ were in agreement compared to when they disagreed. We found that the mean perceived understanding score was significantly lower (6.7 vs. 7.4; $P = .006$) and time spent by caregivers was borderline higher (7.0 vs. 4.8 hours: $P = .05$) for patients the investigators determined had capacity when the ICQ did not (n = 99) compared to those where both the investigator and the ICQ agreed on capacity (n = 354). For those patients whom the investigators had determined lacked capacity when the ICQ rated them as having capacity (n = 12), the mean perceived understanding score was significantly higher (6.6 vs. 4.8; $P = .004$) compared to those when both the investigator and the ICQ agreed on lack of capacity (n = 148).

The sensitivity analyses examining different cut points for a "passing grade" revealed that the highest level of agreement (κ 0.71; 95% CI, 0.64–0.78) was achieved by keeping the requirement of 70% correct for questions 1 to 10 but reducing the requirement to at least 3 out of 4 answers to be correct on questions 11 to 14.

There were significantly more correct responses for those with investigator-determined capacity versus those without capacity on all ICQ questions ($P < .001$) except for #10: "Will you be paid for participating in this study?" (Table 3). Correct responses on question 1 through 14 ranged from 68% to 99% for participants with capacity and from 11% to 69% for those without capacity. Questions that were answered incorrectly most frequently were #2 (identification of the medications used in the study [11%]) and #12 (identification of a possible side effect of treatment [18%]).

Perceived understanding scores were also significantly different by investigator-determined capacity. The mean

Table 1
Baseline characteristics of the study participants according to site investigator's determination of capacity at enrollment

Characteristic	No capacity (N = 160)	Capacity (N = 453)	*P* value
Age (y)			.35
Mean ± SD	79.2 ± 7.0	78.6 ± 7.1	
Sex, n (%)			.98
Male	155 (97)	439 (97)	
Female	5 (3)	14 (3)	
Race, n (%)*			**.02**
White	129 (81)	400 (88)	
Black + other	31 (19)	53 (12)	
Ethnic group, n (%)			.60
Hispanic	19 (12)	47 (10)	
Education, n (%)			**.04**
Less than high school graduation	46 (29)	91 (20)	
High school graduation	58 (36)	149 (33)	
Some college	29 (18)	106 (23)	
College graduation or advanced degree	27 (17)	107 (24)	
Alzheimer's disease assessments, mean ± SD			
ADCS-ADL†	49.1 ± 14.5	59.5 ± 13.1	**<.001**
CAS‡	11.1 ± 16.0	5.3 ± 7.9	**<.001**
NPI§	13.6 ± 14.6	12.1 ± 13.0	.24
ADAS-Cog‖	24.9 ± 9.4	16.6 ± 6.8	**<.001**
MMSE¶	18.4 ± 3.8	22.0 ± 3.0	**<.001**
Alzheimer's disease severity			**<.001**
Mild Alzheimer's disease, n (%), MMSE score 20–26,	62 (15)	348 (85)	
Moderate Alzheimer's disease, n (%), MMSE score 12–19	98 (48)	105 (52)	

NOTE. Values in bold indicate statistical significance at the .05 level.

Abbreviations: SD, standard deviation; ADCS-ADL, Alzheimer's Disease Cooperative Study/ Activities of Daily Living; CAS, Caregiver Activity Survey; NPI, Neuropsychiatric Inventory; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive portion; MMSE, Mini-Mental State Examination.

*Race and ethnicity were self-identified by participants; other race included American Indian or Alaska Native (2), Asian (1), and Native Hawaiian or Other Pacific Islander (1).

†Range, 0 to 78; higher scores = better functioning.

‡Measures caregiver time in caring for patients with dementia, summing total hours spent in a day on 6 caregiving tasks; range, 0 to 144 hours; higher scores = more time spent on caregiving.

§Assesses frequency and severity of psychological and behavioral problems in patients with dementia; range, 0 to 144; higher scores = more frequent and/or severe behavioral problems.

‖Assesses cognitive function in the areas of memory, language, and praxis functions; range, 0 to 70; higher scores = worse functioning.

¶Range, 0 to 30; higher scores = better functioning.

Table 2
Association between capacity as measured by the Informed Consent Questionnaire and capacity as determined by the site investigator

Informed Consent Questionnaire determination of capacity, n (%)	Site investigator–determined capacity, n (%)		
	No capacity	Capacity	Total
No capacity	148 (93)	99 (22)	247 (40)
Capacity	12 (7)	354 (78)	366 (60)
Total	160 (26)	453 (74)	613

NOTE. Number of observed agreements: 502 (81.9% of the observations); Number of agreements expected by chance: 335 (54.6% of the observations): κ (standard error) = 0.60 (0.03); 95% CI, 0.54 to 0.66.

(SD) total score for the perceived understanding for those with capacity was 7.2 (1.9) and 4.9 (3.2) for those without capacity ($P < .001$). On average, participants with capacity believed that they understood the trial and that the risks and benefits were adequately explained (Table 3). The Pearson correlation coefficient for perceived understanding and number of correct responses for questions 1 to 10 was 0.24 for those with capacity, 0.67 for those without capacity, and 0.60 overall. For questions 11 to 14, it was 0.29 for those with capacity, 0.58 for those without capacity, and 0.58 overall (all P values$<.001$).

Perceived understanding score, race, MMSE, ADAS-cog, and CAS were all significantly associated with investigator-determined capacity after adjustment in multivariate analysis (Table 4). The mean (SD) MMSE score for those with capacity was 22.0 (3.0) and 18.4 (3.8) for those without capacity. The odds of a participant lacking capacity to consent increased by 26% for every 1-point decrease on the MMSE in a univariate analysis and by 13% after adjustment in the multivariate analysis ($P < .001$). When the MMSE total score was divided into ranges that define mild (20–26) versus moderate (12–19) AD, the odds for lacking capacity decreased by 81% for the milder group. Of the 203 participants with moderate AD, 48% (n=98) lacked capacity; of the 410 with mild AD, only 15% (n=62) lacked capacity.

The mean (SD) ADAS-cog score for those with capacity was 16.6 (6.8) and 24.9 (9.4) for those without capacity. For every 1-point increase on the ADAS-cog, the odds of lacking capacity increased by 7% in the adjusted multivariate analysis ($P = .001$). The mean (SD) hours on the CAS for those with capacity was 5.3 (7.9), and for those without capacity, it was 11.1 (16.0). In the adjusted analysis, the odds of lacking capacity increased by 3% for every hour increase in caregiver time ($P = .01$). White race was also associated with a greater likelihood of being determined to have capacity.

4. Discussion

We assessed the relationships between clinically determined capacity to consent and (1) patient demographics, (2) an objective measurement of understanding and perceived knowledge about the study, and (3) standard AD assessment measures. We found that the strength of the agreement between the ICQ score and the clinical investigator's determination of capacity was "good" (κ 0.60) [26]. A stronger agreement was expected because all investigators reviewed the ICQ as part of their determination of capacity. When examining differences between investigators' and the ICQs' determinations of capacity, we found significant differences in perceived understanding scores, which may indicate that investigators gave less weight to participants' perceptions about their understanding when determining

Table 3
Informed Consent Questionnaire: Participant correct responses by site investigator–determined capacity at enrollment

	Correct response, n (%)*	
	No capacity (N = 160)	Capacity (N = 453)
1. How long will you be in the study?	81 (51)	427 (94)
2. Please mark the boxes for the pills that you might receive in this study.	17 (11)	308 (68)
3. During the study, will you know exactly which medications you will receive?	83 (52)	398 (88)
4. Will you be able to choose which medications you will get in this study?	86 (54)	434 (96)
5. Will blood be drawn for this study?	104 (65)	442 (98)
6. During the study, will you be given tests to see if your memory has changed?	103 (64)	445 (99)
7. If you choose not to be in this study, will this change your regular treatment?	94 (59)	442 (98)
8. Once you begin this study, are you free to stop at any time?	110 (69)	436 (97)
9. If you drop out of this study, will this change your regular care?	97 (61)	436 (97)
10. Will you be paid for participating in this study?†	91 (57)	339 (75)
Number of correct responses for questions 1–10, mean (SD)	5.6 (2.9)	9.1 (1.2)
11. Can the study medications have side effects?	93 (58)	441 (98)
12. Name 1 possible side effect of the study medications:	29 (18)	375 (85)
13. Is the study guaranteed to help you?	86 (54)	423 (94)
14. Is the study voluntary?	111 (69)	447 (99)
Number of correct responses for questions 11–14, mean (SD)	2.0 (1.3)	3.7 (0.6)
Perceived understanding, mean (SD)‡		
15. Do you feel that you understand the study?	2.0 (0.8)	2.3 (0.7)
16. Do you feel the potential benefits of the study were adequately explained?	2.1 (0.8)	2.5 (0.7)
17. Do you feel the potential risks of the study were adequately explained?	2.1 (0.8)	2.5 (0.7)
Total perceived understanding score	4.9 (3.2)	7.2 (1.9)

Abbreviation: SD, standard deviation.

*Missing responses on questions ranged for 20 to 39 participants without capacity and 0 to 6 for those with capacity.

†$P = .42$ for question 10; all other P values $< .0001$.

‡Perceived understanding (ICQ items 15, 16, and 17) responses are scored as follows: not at all = 0; somewhat = 1; mostly = 2; yes, completely = 3. Total perceived understanding score = total of items 15, 16, and 17; range = 0 to 9.

Table 4
Association between capacity as determined by the site investigator and demographic, ICQ perceived understanding scores, and Alzheimer's disease cognitive and functioning measures

	Univariate analyses: odds ratio estimates for no capacity		Multivariate analysis:* odds ratio estimates for no capacity	
Baseline measure	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Education level	0.78 (0.66–0.93)	.005	0.97 (0.78–1.20)	.75
Race (white vs. black + other)	1.84 (1.12–2.95)	.02	2.22 (1.23–4.01)	.008
Perceived understanding total score	0.69 (0.64–0.75)	<.001	0.77 (0.70–0.84)	<.001
Alzheimer's disease severity: MMSE mild (20–26) vs. MMSE moderate (12–19)	0.19 (0.13–0.28)	<.001	—	—
MMSE	0.74 (0.70–0.79)	<.001	0.87 (0.80–0.94)	<.001
ADAS-Cog	1.14 (1.11–1.17)	<.001	1.07 (1.03–1.10)	<.001
ADCS-ADL	0.95 (0.94–0.96)	<.001	0.99 (0.97–1.01)	.39
CAS	1.05 (1.03–1.07)	<.001	1.03 (1.01–1.05)	.02
NPI	1.01 (0.99–1.02)	.24	0.98 (0.97–1.00)	.06

Abbreviations: ICQ, Informed Consent Questionnaire; CI, confidence interval; MMSE, Mini-Mental State Examination; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive portion; ADCS-ADL, Alzheimer's Disease Cooperative Study/ Activities of Daily Living; CAS, Caregiver Activity Survey; NPI, Neuropsychiatric Inventory.

*Full multivariate analyses excluded severity level because it was derived from the MMSE score and was highly correlated with it (correlation coefficient = 0.84).

capacity. Nevertheless, the ICQ was widely accepted and many investigators reported that it was very helpful, particularly in patients with milder impairments. Several of the IRBs involved in the study expressed their support for using the ICQ noting the need for more objective measures to assess capacity.

Significant associations were found between the investigators' determination of capacity and perceived understanding, educational level, race, and AD assessments. The association between race and capacity remained significant after controlling for severity level, education, and ICQ scores. It is unclear whether there was any racial bias in the assessment of capacity or whether race was a proxy for another important unmeasured variable related to capacity or the need for surrogate consent, such as socioeconomic status, social support, or social networks [27]. It is also possible that racial differences in capacity were related to racial differences in literacy, quality of education, comorbidities, or specific aspects of AD progression that are not fully controlled for by the study's cognitive or functional assessments [28–30].

Cognitive impairment measured by the MMSE and the ADAS-cog were both significantly related to capacity in univariate and multivariate analysis. This finding is similar to a study that found that the level of cognitive functioning measured by the MMSE was the best predictor of decisional capacity [31]. There is also some evidence that clinicians' assessment of capacity in AD is partially related to particular aspects of a patients' cognitive function such as conceptualization and memory functioning [32]. In our study, although the MMSE was significantly related to capacity, it did not fully differentiate participants' capacity to consent. Of the participants with moderate AD (MMSE 12–19), 52% were determined to still have capacity, whereas 15% of those with mild AD (MMSE 20–26) were determined to lack capacity. This is similar to other studies that have shown that individuals with cognitive impairment may still have sufficient capacity to give informed consent [33–35]. In a study of 176 individuals with mild-to-moderate dementia in the United Kingdom, 24% were unable to give informed consent according to the country's legal criteria and the MMSE was not a significant predictor of capacity in multivariate analyses [35]. It is unknown whether the use of the ICQ in this study was causally related to the somewhat unusual findings of 52% of moderate cases being assessed as having capacity or if cognitive measures are insufficient by themselves to determine AD patients' capacity and that more individualized considerations of capacity are warranted [16,35].

The time caregivers spend aiding AD patients with their day-to-day activities was also significantly related to capacity in multivariate-adjusted analyses. The ADCS/ADL functional assessment, however, was only significantly associated with capacity in the unadjusted analysis, indicating the measure did not independently add to the prediction in the adjusted analyses. Caregiver time, a proxy measure of the independence of the patient, may better capture the relationship between a patient's functioning level and his/her capacity to consent. The severity of psychological and behavioral problems was not significantly related to capacity in any of the analyses.

The ICQ was developed to test understanding of the CSP#546 study, specifically, and research participants' rights in general. The "passing grade" of 70% correct for questions 1 to 10 and 100% correct for 11 to 14 was based on the planning committee's and IRBs' assessments of what constituted a reasonable level of comprehension of the study and the necessity to fully understand information related to a participant's rights and the risks of participation. The sensitivity analyses on the cut point for an ICQ passing grade showed that lowering the requirement slightly increased the level of agreement between the ICQ and the investigators. We did not require a passing ICQ score because there is often a need to include a subjective assessment of capacity to take into account the unique circumstances and social support of individuals as well as their cognitive, communication, and insight abilities [35].

We allowed two attempts to "pass" the ICQ to provide an opportunity to correct any misunderstandings and to more fully protect participants' autonomy. We believed that a third assessment or a repeated teach-to-goal strategy would have

been inefficient and potentially frustrating for AD patients. In a study in nondemented patients who repeated the consent process and comprehension test until full understanding was achieved, only 28% of patients answered all comprehension questions correctly on the first administration [36]. This increased to 80% on the second administration, suggesting that a second administration is beneficial and that the majority of individuals achieve understanding by the second test.

In addition to measuring actual understanding of the consent document, the ICQ included an assessment of participants' perceived understanding. Perceived understanding was significantly related to capacity in adjusted and unadjusted analyses. There was also a significant correlation between perceived and actual understanding on the ICQ, indicating that participants' perception of their understanding was related to their ability to correctly answer questions about the study; however, the correlation was not strong with only 33% to 36% of the overall variance in the number of correct answers explained by perceived understanding. This correlation was particularly weak in the group with capacity where only 6% to 8% of the variance was explained. A similar finding was seen in a non–cognitively impaired population where no significant relationship was found between knowledge and perceptions of being well-informed [37]. One factor that may contribute to this discordance in understanding is a possible disagreement between researchers and patients on what is the most important information to convey and understand [38,39]. Another possible factor is that AD patients often have diminished insight into their cognitive deficits; however, it is not known how impaired insight relates to performance on cognitive measures or measures of capacity [16,40]. Nevertheless, diminished insight is likely to impact a measure of perceived understanding and may make the measure less valuable in AD patients. Ideally, measures of actual and perceived understanding would not differ, but when they do, it is not clear which construct is more important or whether a participant should be entered into a study when they do differ. More research is needed on what should be done in these situations and whether assessing both perceived and actual understanding should be considered to fully respect a participant's autonomy while also protecting vulnerable individuals.

While there are some published instruments for assessing the informed consent process or understanding of consent documents, none are widely used in research [15,41–45]. The MacArthur Competency Assessment Tool for Clinical Research (MacCAT-CR), however, has the most empirical data supporting its use in the clinical setting [15,46,47]. Results from a recent clinical trial of mild-to-moderate AD suggest that the use of the MacCAT-CR understanding subscale can help guide judgments about patient's capacity to consent in AD research [48]. In another study in mild-to-moderate AD, however, the authors concluded that standardized assessment tools may not be that helpful [49]. One reason for the lack of a widely accepted instrument is that research questions, study procedures, and other details of disclosure can vary widely among studies, and most published measures were either tailored to a specific trial or were for more general use. We felt that developing an instrument that measured patient's specific understanding of the CSP#546 study would better assist investigators in their determination of capacity and could be used to identify specific areas that were not understood so that education in those areas could be reinforced. Ideally, to better understand the ICQ's utility, a general measure such as the MacCAT-CR could also have been used in the study, and the investigator's assessment of capacity could have been done independently of the ICQ. However, due to practicality and the need for efficiency, a decision was made to use one simple questionnaire only to aid investigators in capacity assessment.

A limitation of this study was a nearly all-male population that may reduce generalizability to women. In addition, the ICQ and its cutoff score were based solely on face validity. Finally, although there were guidelines and training for administering the ICQ, a script was not provided for its administration or for introduction of the informed consent itself, which may have led to increased variability in the ICQ scores and in the determination of capacity to consent.

4.1. Conclusions

In this study of informed consent capacity in an AD clinical trial, we found that the strength of agreement between the ICQ score and the clinical investigator's determination of capacity was "good." We also found that there were significant associations between clinical assessment of capacity and cognitive impairment, caregiver time, race, and perceived understanding; however, these did not fully differentiate participants' capacity to consent. The results indicate that the use of a study-specific informed consent questionnaire and assessment of perceived understanding can be a valuable tool to aid investigators in determining capacity to consent in AD.

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TEAM-AD study staff and committee membership have been previously published [17].

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RESEARCH IN CONTEXT

1. Systematic review: The authors searched the literature using PubMed for specific studies for determining capacity to give informed consent in clinical trials with dementia patients and for objective tools for assessment of capacity.
2. Interpretation: We assessed the associations between (1) investigator-determined capacity to consent, (2) study participants' characteristics, and (3) a study-specific measurement of participants' understanding of the informed consent document in an Alzheimer's disease clinical trial. We found significant associations between capacity and disease severity, caregiver time, race, and perceived understanding. These results suggest that an objective measure of understanding at study entry can be a valuable tool to help determine capacity to consent.
3. Future directions: More research is needed in Alzheimer's disease and in other vulnerable patient populations to (1) establish the reliability and validity of objective tools such as the ICQ and (2) explore the relationship between perceived and actual understanding.

References

[1] Beauchamp TL, Childress JF. Principles of biomedical ethics. 4th ed. New York: Oxford University Press; 1996.
[2] Faden RR, Beauchamp TL. A history and theory of informed consent. New York: Oxford University Press; 1986.
[3] Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA 2000;283:2701–11.
[4] Kim SYH. Evaluation of capacity to consent to treatment and research. Oxford; New York: Oxford University Press; 2010.
[5] Falagas ME, Korbila IP, Giannopoulou KP, Kondilis BK, Peppas G. Informed consent: how much and what do patients understand? Am J Surg 2009;14:420–35.
[6] Marson DC, Chatterjee A, Ingram KK, Harrell LE. Toward a neurologic model of competency: cognitive predictors of capacity to consent in Alzheimer's disease using three different legal standards. Neurology 1996;46:666–72.
[7] Marson DC, Hawkins L, McInturff B, Harrell LE. Cognitive models that predict physician judgments of capacity to consent in mild Alzheimer's disease. J Am Geriatr Soc 1997;45:458–64.
[8] Earnst KS, Marson DC, Harrell LE. Cognitive models of physicians' legal standard and personal judgments of competency in patients with Alzheimer's disease. J Am Geriatr Soc 2000;48:919–27.
[9] Dymek MP, Marson DC, Harrell L. Factor structure of capacity to consent to medical treatment in patients with Alzheimer's disease: an exploratory study. J Forensic Neuropsychol 1999;1:27–48.
[10] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont report: ethical principles and guidelines for the protection of human subjects of research. 3 Volumes. DHEW Publication no. (OS) 78–0012/G. 1978. Washington, DC.
[11] Meisel A, Roth L, Lidz C. Toward a model of the legal doctrine of informed consent. Am J Psychiatry 1977;134:285–9.
[12] Kapp M. Geriatrics and the law: patient rights and professional responsibilities. New York: Springer; 1992.
[13] Drickamer MA, Lai JM. Assessment of decisional capacity and competencies. Chapter 13. In: Halter JB, Ouslander JG, Tinetti ME, Studenski S, High KP, Asthana S, eds. Hazzard's geriatric medicine and gerontology. 6th ed. New York, NY: McGraw-Hill; 2009.
[14] Howe E. Informed consent, participation in research, and the Alzheimer's patient. Innov Clin Neurosci 2012;95:47–51.
[15] Dunn LB, Nowrangi MA, Palmer BW, Jeste DV, Saks ER. Assessing decisional capacity for clinical research or treatment: a review of instruments. Am J Psychiatry 2006;163:1323–34.
[16] Karlawish J. Measuring decision-making capacity in cognitively impaired individuals. Neurosignals 2008;16:91–8.
[17] Kim SY. The ethics of informed consent in Alzheimer disease research. Nat Rev Neurol 2011;7:410–4.
[18] Dysken MW, Sano M, Asthana S, Vertrees J, Pallaki M, Llorente M, et al. Effect of vitamin E and memantine on functional decline in Alzheimer's disease: The TEAM-AD VA cooperative randomized trial. JAMA 2014;311:33–44.
[19] Dysken MW, Guarino PD, Vertrees JE, Asthana S, Sano M, Llorente M, et al. Vitamin E and memantine in Alzheimer's disease: clinical trial methods and baseline data. Alzheimers Dement 2014;10:36–44.
[20] Guarino P, Lamping DL, Elbourne D, Carpenter J, Peduzzi P. A brief measure of perceived understanding of informed consent in a clinical trial was validated. J Clin Epidemiol 2006;59:608–14.
[21] Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease: the Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997;11:S33–9.
[22] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
[23] Mohs RC, Rosen WG, Davis KL. The Alzheimer's disease assessment scale: an instrument for assessing treatment efficacy. Psychopharmacol Bull 1983;19:448–50.
[24] Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–14.
[25] Davis KL, Marin DB, Kane R, Patrick D, Peskind ER, Raskind MA, et al. The Caregiver Activity Survey (CAS): development and validation of a new measure for caregivers of persons with Alzheimer's disease. Int J Geriatr Psychiatry 1997;12:978–88.
[26] Cohen J. A coefficient of agreement for nominal scales. Educ Psychol Meas 1960;20:37–46.

[27] Barnes LL, Mendes de Leon CF, Bienias JL, Evans DA. Social resources and cognitive decline in a population of older African Americans and whites. Neurology 2004;63:2322–6.
[28] Barnes LL, Wilson RS, Li Y, Gilley DW, Bennett DA, Evans DA. Change in cognitive function in Alzheimer's disease in African-American and white persons. Neuroepidemiology 2006;26:16–22.
[29] Chin AL, Negash S, Xie S, Arnold SE, Hamilton R. Quality, and not just quantity, of education accounts for differences in psychometric performance between African Americans and white non-Hispanics with Alzheimer's disease. J Int Neuropsychol Soc 2012; 18:277–85.
[30] Sachs-Ericsson N, Blazer DG. Racial differences in cognitive decline in a sample of community-dwelling older adults: the mediating role of education and literacy. Am J Geriatr Psychiatry 2005; 13:968–75.
[31] Palmer BW, Dunn LB, Appelbaum PS, Mudaliar S, Thal L, Henry R, et al. Assessment of capacity to consent to research among older persons with schizophrenia, Alzheimer disease, or diabetes mellitus: comparison of a 3-item questionnaire with a comprehensive standardized capacity instrument. Arch Gen Psychiatry 2005;62:726–33.
[32] Palmer BW, Ryan KA, Kim HM, Karlawish JH, Appelbaum PS, Kim SY. Neuropsychological correlates of capacity determinations in Alzheimer disease: implications for assessment. Am J Geriatr Psychiatry 2013;21:373–81.
[33] Hougham GW. Waste not, want not: cognitive impairment should not preclude research participation. Am J Bioeth 2005;5:36–7.
[34] Eth S, Leong GB. Toward revising the ethical boundaries of research with noncompetent subjects. Am J Psychiatry 2009;166:131–3.
[35] Warner J, McCarney R, Griffin M, Hill K, Fisher P. Participation in dementia research: rates and correlates of capacity to give informed consent. J Med Ethics 2008;34:167–70.
[36] Sudore RL, Landefeld CS, Williams BA, Barnes DE, Lindquist K, Schillinger D. Use of a modified informed consent process among vulnerable patients: a descriptive study. J Gen Intern Med 2006; 21:867–73.
[37] Sepucha KR, Fagerlin A, Couper MP, Levin CA, Singer E, Zikmund-Fisher BJ. How does feeling informed relate to being informed? The DECISIONS survey. Med Decis Making 2010;30:77S–84.
[38] Edwards SJ, Lilford RJ, Hewison J. The ethics of randomised controlled trials from the perspectives of patients, the public, and healthcare professionals. BMJ 1998;317:1209–12.
[39] Tait AR, Voepel-Lewis T, Robinson A, Malviya S. Priorities for disclosure of the elements of informed consent for research: a comparison between parents and investigators. Paediatr Anaesth 2002;12:336.
[40] Starkstein SE, Sabe L, Chemerinski E, Jason L, Leiguarda R. Two domains of anosognosia in Alzheimer's disease. J Neurol Neurosurg Psychiatry 1996;61:485–90.
[41] Wirshing DA, Wirshing WC, Marder SR, Liberman RP, Mintz J. Informed consent: assessment of comprehension. Am J Psychiatry 1998;155:1508–11.
[42] Miller CK, O'Donnell DC, Searight HR, Barbarash RA. The Deaconess Informed Consent Comprehension Test: an assessment tool for clinical research subjects. Pharmacotherapy 1996;16:872–8.
[43] Joffe S, Cook EF, Cleary PD, Clark JW, Weeks JC. Quality of informed consent: a new measure of understanding among research subjects. J Natl Cancer Inst 2001;93:139–47.
[44] Sugarman J, Lavori PW, Boeger M, Cain C, Edsond R, Morrison V, et al. Evaluating the quality of informed consent. Clin Trials 2005; 2:34–41.
[45] Karlawish J, Cary M, Moelter ST, Siderowf A, Sullo E, Xie S, et al. Cognitive impairment and PD patients' capacity to consent to research. Neurology 2013;81:801–7.
[46] Appelbaum PS, Grisso T. MacCATCR, MacArthur Competence Assessment Tool for Clinical Research. Sarasota, FL: Professional Resource Press; 2001.
[47] Grisso T, Applebaum PS, Hill-Fotouhi C. The MacCAT-T: a clinical tool to assess patients' capacities to make treatment decisions. Psychiatr Serv 1997;48:1415–9.
[48] Karlawish J, Kim SY, Knopman D, van Dyck CH, James BD, Marson D. Interpreting the clinical significance of capacity scores for informed consent in Alzheimer disease clinical trials. Am J Geriatr Psychiatry 2008;16:568–74.
[49] Kim SY, Caine ED, Currie GW, Leibovici A, Ryan JM. Assessing the competence of persons with Alzheimer's disease in providing informed consent for participation in research. Am J Psychiatry 2001;158:712–7.