Published in final edited form as:

Am J Geriatr Psychiatry. 2010 December ; 18(12): 1124–1132. doi:10.1097/JGP.0b013e3181dd1c3b.

A memory and organizational aid improves AD research consent capacity: Results of a randomized, controlled trial

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Abstract

Objectives—AD patients' early and progressive cognitive impairments hinder their capacity to provide informed consent. Unfortunately, the limited research on techniques to improve capacity has shown mixed results. Therefore, we tested whether a memory and organizational aid improves AD patient performance on measures of capacity and competency to give informed consent.

Design, Setting, and Participants—AD patients randomly assigned to standard consent, or standard plus a memory and organizational aid.

Intervention—Memory and organizational aid summarized at a 6th grade reading level the content of information mandated under the Common Rule's informed consent disclosure requirements.

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Dr. Karlawish is the site principal investigator for a clinical trial sponsored by NIA and Pfizer. Other authors report no conflicts of interest.

Trial Registry: ClinicalTrials.gov #NCT00105612, <http://clinicaltrials.gov/show/NCT00105612>.

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Measurements—Three psychiatrists without access to patient data independently reviewed MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) interview transcripts to judge whether the patient was capable of providing informed consent. The agreement of at least two of three experts defined a participant as capable of providing informed consent. Secondary outcomes are MacCAT-CR measures of understanding, appreciation and reasoning, and comparison to cognitively normal older adult norms.

Results—AD intervention and control groups were similar in terms of age, education, and cognitive status. The intervention group was more likely to be judged competent than control group and had higher scores on MacCAT-CR measure of understanding. The intervention had no effect on measures of appreciation or reasoning.

Conclusions—A consent process that addresses an AD patients' deficits in memory and attention can improve capacity to give informed consent for early phase AD research. The results also validate the MacCAT-CR as an instrument to measure capacity, especially the understanding subscale.

Keywords

Alzheimer's disease; informed consent; capacity; research ethics

Alzheimer's disease (AD) is a common and chronic neurodegenerative dementia affecting up to 4.5 million people in the United States.(1) In the next 40 years, this number will likely triple.(1) Extensive research efforts are underway to improve symptomatic treatments(2,3) and to develop treatments that slow AD progression.(4) The success of these research efforts rests on the effective enrollment of AD patients as research participants. Yet, the very problems caused by AD that warrant research are also the cause of ethical challenges to that research. Patients' early and progressive cognitive impairments significantly hinder their ability to provide an informed consent to enroll in research.(5–9)

Common informed consent practice in AD research involves proxy informed consent with patient assent. Yet, questions arise whether this practice adequately protects subjects' rights and interests.(10–13) These questions are particularly significant for early phase research designed to test a drug's safety. This is often greater than minimal risk research such as double-blind, placebo-controlled dose escalation studies done in an inpatient acute care facility to assess a new drug's safety and maximum tolerated dose.(14–16)

Solutions to this problem include restricting enrollment to patients who are judged competent by a qualified independent capacity assessor and utilizing informational and educational techniques in the informed consent session.(17,18)(Recommendation #12) However, these proposals are problematic. Alterations to the method of disclosure (such as a story book, information sheet, audiovisuals, lower reading level of information, disclosure in parts, and larger type font) and in the assessment of capacity (quizzes and education sessions) have achieved “only limited success.”(19) But these studies have several limitations in their application to early phase AD research. Most of them measure understanding as delayed recall of up to three weeks using varying measures such as open or close ended questions, or true false questions; they do not measure the capacities to appreciate or reason. The previous alterations to consent disclosure have used limited amounts of theory to guide why the alteration would be expected to improve subject understanding. In addition, studies have not focused on the issue of informed consent for an early phase clinical trial that involves patients with AD. And no studies have tested methods that specifically address the cognitive deficits seen in persons with AD.

Data on the cognitive deficits of persons with AD may suggest an approach to this problem. Their neuropsychological deficits are typically associated with diminished performance on measures of decision making capacity, specifically their abilities to understand and appreciate information to make research decisions.(6,20,21) Much of the cause of this poor performance are the patients' impairments in short term memory and executive function. (22,23) In contrast, among persons with mild to early moderate AD, recognition memory is relatively preserved.(24,25)

Deficits in short term memory impair a person's ability to freely recall information. The term executive function refers to the ability to organize, plan, and focus on a task.(25) Taken together, impairments in both short term memory and executive function mean that the patient will have difficulty remaining focused on the task and sorting through complex information presented on a multi-page consent form.(22) In contrast, among persons with mild to early moderate AD, recognition memory is relatively well preserved.(26–28) This means that while a person may have notable troubles freely recalling information, when they are presented a prompt, they can recall it.

This mix of relative impairments and strengths in cognition in persons with mild to early moderate AD suggests that a memory and organizational aid might mitigate the functional consequences of impairments in executive dysfunction and short-term memory and instead utilize the residual abilities in recognition memory. Such an aid could function as a cognitive prosthetic because it will help these patients to stay focused with the consent session and find it less confusing. Such an intervention may improve performance on measures of decision making capacity. The ability to see the information presented on a single sheet may allow AD patients to recall it (supporting recognition memory) and having the information on a single sheet that is used throughout both the disclosure and capacity assessment processes may allow them to remain focused on the assessment (supporting executive function). In this way, a memory and organizational aid could function as a cognitive prosthetic to help these patients to stay focused on the consent session.

We performed a randomized and controlled trial to test whether a memory and organizational aid structured to support recognition memory and executive function can improve the capacity of a patient with very mild to early moderate AD to provide an informed consent to enroll in an early-phase clinical trial. We hypothesized that the intervention would improve patients' likelihood of being judged capable of providing their own informed consent. Additionally, we hypothesized that the intervention would improve capacity scores and move patients across criterion cutpoints established by cognitively normal older adults.

Methods

Study participants and eligibility criteria

Eighty patients with very mild to early moderate AD (MMSE 18 to 27) and 30 cognitively normal older adults (MMSE 28 to 30) were recruited from the participants in a NIA funded Alzheimer's Disease Center using the Center's patient database. The labels of AD and cognitively normal were based on the consensus of a geriatrician, neurologist, psychiatrist, and neuropsychologist applying National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria.(29) All participants spoke English, had at least a 6th grade education and a corrected visual acuity of at least 20/70 as defined by the ability to read from a handheld visual acuity card. All subjects received \$20 compensation for their time.

Description of the intervention

Patients with AD were randomized to one of two capacity assessment conditions: standard capacity assessment or the standard assessment plus a memory and organizational aid. Random assignment was produced by generating a list of block randomized binary assignments, varying block sizes from 4 to 8 to avoid bias in assignment.(30) Randomization assignments were produced by the study biostatistician (SX) who did not recruit or interview subjects.

Standard capacity assessment participants underwent the MacCAT-CR interview while retaining a copy of the informed consent form to consult at their discretion while answering the MacCAT-CR interview questions. The informed consent form described an early phase “bridging study” to test the safety of drug Z-298. It was written in the style and format of IRB approved informed consent forms that are routinely used at the PENN Alzheimer's Disease Center to include the content mandated under the requirements for informed consent described in the Common Rule.(31)

Standard capacity assessment plus a memory and organizational aid participants received, in addition to the informed consent form, a one-page memory and organizational aid. The aid was a summary of the key elements in the drug Z-298 informed consent form. It presented information in the same sequence and header titles as presented in the informed consent form. The text simplified important points from the consent form using language at a sixth grade reading level as calculated using the Flesch-Kincaid readability statistic in Microsoft Word. Table 1 shows an example of how the text was summarized.

All cognitively normal elderly underwent standard capacity assessment. Their scores on each of the ability measures were used to norm the AD patient capacity scores.

The disclosure session

The interviewer could not be blinded to intervention status. The interviewer had the participant read aloud each section of the informed consent form, and after each section, the interviewer asked the subject to say back what the section was about. If the subject was assigned to the memory and organizational aid, after the summary, the interviewer directed the subject to the relevant section of the aid and had the subject read it aloud as well. If a subject in either condition made an error while summarizing the section, the interviewer corrected the error and moved on to the next section.

The assessment of decision making capacity

We used the MacCAT-CR to assess capacity after the disclosure session.(32) The MacCAT-CR is the most widely used standardized assessment of capacity that measures the four decision making abilities: understanding, appreciation, reasoning, and expressing a choice. It has been shown to generate scores with evidence of reliability and validity in measuring the decisional capacities of persons with major depression(33), schizophrenia(34), and mild to early moderate AD(6) to enroll in a clinical trial.

The standard MacCAT-CR administration was modified to more accurately reflect the way informed consent is gathered in standard research practice. Instead of asking the relevant question after each section, the forms were reviewed in their entirety before asking the MacCAT-CR questions. At the start of asking those questions, the interviewer encouraged participants assigned to the standard informed consent condition to use the informed consent form and subjects assigned to the memory and organization aid to use the aid while they answered the MacCAT-CR questions. During the administration of the understanding subscale, subjects in both informed consent conditions received corrective feedback.

A research assistant who did not perform the capacity interview transcribed the capacity assessment interview. After initial transcription, statements indicating to which informed consent condition the participant was assigned were removed. This editing assured that the capacity scorer and the competency judges were blinded to whether the subject received the standard informed consent or the memory and organizational aid condition.

Subject competency

To assess patient competency, three blinded experts independently reviewed the AD patient's transcript and judged whether the patient was capable to provide his or her own informed consent. Experts were psychiatrists, members of the Academy of Psychosomatic Medicine, had experience in rendering competency judgments using the decisional capacity conceptual framework. None were at PENN, knew any of the patients, or had access to any patient information besides the study transcript. All had experience in directing informed consent in at least three AD clinical trials and at least five years of experience in the diagnosis and care of persons with AD. AD patients were determined to be capable of informed consent with agreement of at least two out of the three experts. Consensus of expert rater criteria has shown good overall agreement.(35–37)

Scoring the capacity interview

Scoring was completed by a researcher with 3 years of MacCAT-CR scoring experience who did not conduct any subject interviews, was blinded to subject assignment, and not located at PENN. Of particular importance, our scoring criteria did not credit a subject who simply parroted back information on either form. A subject who could not say the information in his or her own words even after prompting, did not know the answer, or made a factual error was not given credit. For example, in response to the question “What is the goal of this study?” a subject who responded by reading from the form “This research is trying to learn if Z-298 is safe and well tolerated” would receive no credit. In contrast, a subject who accurately transformed the relevant information into his or her own words would receive full credit.

Data analyses

All analyses were performed using STATA 8.2.(38) Sample size was calculated with Power Analysis and Sample Size (PASS) software(39) using pilot data to estimate sample needed to detect Cohen's d effect sizes of at least 0.3 between AD patient groups with 80% power and $\alpha=0.05$. Tests of significance were adjusted for multiple comparisons within each area by the use of Hochberg's modified Bonferroni procedure.(40)

We use descriptive statistics to describe the sample, and use Wilcoxon-Mann-Whitney tests to compare AD patient and cognitively normal older adults' age and education. We examine the main outcome measure of expert rater judgments of capacity to provide informed consent between AD standard informed consent and memory and organizational aid conditions using Pearson's chi-squared test.

To examine the secondary outcome measure for each domain of decision making capacity, we calculate the range, mean and standard deviation for the groups of patients in the standard informed consent and memory and organizational aid conditions, and the cognitively normal elderly. For each measure of decision making capacity on the MacCAT-CR, we compare persons who receive the memory and organizational aid to those who receive standard informed consent. We examine the intervention's efficacy by using Wilcoxon-Mann-Whitney tests to compare the median scores of understanding, reasoning, and appreciation of the standard informed consent versus memory and organizational aid conditions, and by calculating the effect size of the intervention.(41)

For the last outcome measure, we use the scores of the cognitively normal elderly to calculate norms for “adequate,” “marginal,” and “poor” subject performance on the measures of decision making capacity(42): adequate is a score that is ≥ -1 standard deviation of the cognitively normal mean score; marginal is a score < -1 standard deviation and ≥ -2 standard deviations; and poor is a score < -2 standard deviations. Thresholds based on normative values have been used as outcomes in previous studies of AD patient competency to provide informed consent.(43) We use standard binary logistic regression to calculate the odds ratio and its 95% confidence interval of the intervention's effect on the proportion of AD participants who have at least marginal capacity according to the norms established by the cognitively normal older adults. The outcome measure is dichotomous (1=adequate or marginal performance, 0=inadequate performance). We test whether the organizational aid increases the proportion of patients who are a “1” by comparing persons who receive the memory and organizational aid to those who receive standard informed consent and computing the odds ratio and its 95% confidence interval.

Human subjects protections

All participants provided written informed consent or in the case of those not capable, assent with the informed consent of their knowledgeable informant, to participate in this University of Pennsylvania Institutional Review Board approved study. The study is listed on the ClinicalTrials.Gov registry, #NCT00105612.

Results

Of the 112 eligible AD subjects approached to participate in this study, 80 (71%) agreed to participate and provided complete data from October 2004 to December 2006. Of 33 eligible cognitively normal elderly approached, 30 agreed (91%). All participants who began the study completed the study. Refusers were similar to completers in terms of gender ($\chi^2=1.3$, $df=1$, $p=0.25$) and race ($\chi^2=0.11$, $df=1$, $p=0.74$). Participant flow is outlined in Figure 1. Table 2 summarizes participants' self-reported characteristics. There was no difference between the AD standard informed consent and AD standard informed consent plus memory and organizational aid groups in terms of age, education, MMSE, sex or race.

Expert rater judgment of the capacity to provide informed consent showed that AD patients in the intervention group were more likely to be judged capable of giving their own informed consent than those in the control group (see Table 3). This result was also found when examining each individual rater's judgments: rater 1 ($\chi^2=8.5$, $df=1$, $p=0.004$), rater 2 ($\chi^2=6.0$, $df=1$, $p=0.015$), and rater 3 ($\chi^2=9.03$, $df=1$, $p=0.003$).

Table 4 shows the participants' scores on each of the MacCAT-CR measures of the decisional abilities. Patients who received the memory and organizational aid had higher understanding scores. This difference yields a Cohen's d effect size of 0.67. Between group differences in scores on the measure of appreciation were non-significant, though they were in the expected direction of higher appreciation scores for those assigned to the memory and organizational aid. There were no between group differences on the abilities to reason or to express a choice.

Table 4 also shows the scores of the cognitively normal older adults on the measures of the decisional abilities. We used these scores to define adequate (≥ -1 standard deviation below the cognitively normal mean score), marginal (< -1 standard deviation and ≥ -2 standard deviations below the cognitively normal mean score), and poor (< -2 standard deviations below the cognitively normal mean score) performance to examine whether the memory and organizational aid would affect the proportion of AD participants who have at least marginal

capacity according to a criterion variable. Confidence intervals of odds ratios for all MacCAT-CR capacity scores crossed 1.

Conclusions

This randomized and controlled trial shows that a memory and organizational aid tailored to the distinctive cognitive patterns of AD patients can improve the ability of patients with very mild to early moderate AD to provide their own informed consent to enroll in an early-phase clinical trial. A particular strength of the study is its use of a real world test of capacity; namely, the judgment of expert raters. Additionally, the raters who scored the capacity interviews and judged capacity to consent were blinded to AD assignment to the intervention or control condition.

The benefits of the memory and organizational aid were sufficiently large that experts in the field of capacity assessment, reviewing interview transcripts, were more likely to judge patients who received the intervention as capable of providing their own informed consent than those who did not. Additionally, the memory and organizational aid led to improvements in MacCAT-CR understanding scores. The magnitude of improvement in understanding scores was a medium to large effect as defined by a Cohen's *d* effect size of 0.67.(41) Despite the intervention, there were no differences between the two groups in the proportion of subjects who scored in the adequate, marginal, and poor ranges, and no differences on MacCAT-CR measures of appreciation or reasoning. Future research may address whether this lack of impact on subscales of appreciation and reasoning is due to a selective benefit of the intervention itself or to the comparatively restricted range of scores obtainable on these subscales.

Recommendations to protect the rights and welfare of participants in phase I research studies who have cognitive impairments that may affect their decisional capacity include restricting enrollment to patients who are judged competent by a qualified assessor and that the informed consent session should use informational and educational techniques. Restricting enrollment only to AD patients judged competent by an assessor would reduce the number of subjects available to join clinical trials. Reduction of subjects available for recruitment, as outlined in the first recommendation, would likely slow down the pace of research on AD. However, if such a rule were implemented, restrictive enrollment may be more palatable to clinical trial investigators if an aid such as the one studied here, which utilizes the techniques of the second recommendation, could improve decision-making capacity of potential research subjects. Improving capacity would be particularly useful for AD subjects with questionable or borderline capacity.

The results offer the first data available on the impact of a memory and organizational aid tailored to the distinct cognitive deficits caused by AD. Overall, the data suggest support for an informational and educational technique to improve consent capacity that can be used during an informed consent session. A consent process that addresses AD patients' deficits in memory and attention can improve capacity to give informed consent for early phase AD research. Additionally, this change in the informed consent process is inexpensive, simple to administer and not labor or technologically intensive.

The results also add to the on-going construct validation of the MacCAT-CR as an instrument to measure capacity when using the modified administration procedures used here, especially the measure of understanding. Specifically, the finding that the understanding subscale questions were sensitive to the intervention adds to existing validation of the questions' ability to capture the decision making abilities through a structured interview.

Previously available data has shown mixed or limited success for informed consent interventions to improve an elderly person's understanding. Yet, these previous studies have several limitations. Most of them measure understanding as delayed recall of up to three weeks using varying measures such as open, close ended, or true false questions; they do not measure the capacities to appreciate or reason. In addition, studies have not focused on the ethically charged issue of informed consent for an early phase clinical trial that involves patients with AD.

This study has addressed these issues in the ethically complex, greater than minimal risk early phase research in AD. Additionally, it used a randomized design with a well studied instrument measuring all of the decision making abilities. These results were also triangulated using the real world judgments of expert raters in the field of AD decisional capacity.

Limitations for this study include that the organizational aid was designed to address the specific cognitive constraints of AD patients. Thus, it is not known how such an aid would function on patients with a different pattern of cognitive impairments. Additionally, this study focused on a phase I clinical trial due to the specific risks and ethical issues associated with this type of research. Hence, our results may not generalize to informed consent sessions considering studies with different procedures and risk/benefit ratios. The sample, taken from an NIA funded Alzheimer's Disease Center, has a relatively high educational level and thus may not generalize to other populations. Finally, we used the performance of cognitively normal participants to calculate thresholds to examine whether the memory and organizational aid would alter the proportion of AD participants who have at least marginal capacity. These thresholds should not be taken to establish strict cut-off values for determining capacity judgments for persons with AD or in other populations.

Informed consent in AD research presents substantial challenges largely as a result of the impact of the patients' cognitive impairments on their capacity to provide an informed consent. These challenges are especially ethically problematic in the case of research that involves risks that are more than minimal or that does not present a reasonable prospect of benefit to the subjects. Our data support the value of a memory and organizational aid during a capacity assessment. More generally, they suggest that the cognitive disabilities seen in persons with very mild to early moderate AD are tractable to interventions designed to reduce those disabilities.

Acknowledgments

The authors wish to thank the participants and family members who participated in this research. They also thank James Beaver and Bryan James for their assistance in data gathering and analyses.

This research funded by NIH R01-AG020627, NIH P30-AG-10124, and the Marian S. Ware Alzheimer Program.

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Figure 1.
Flow diagram of participant progress through study phases.

Table 1

Comparison of text in standard informed consent form versus text in the memory and organizational aid: example of the purpose of the research.

Standard Informed Consent Form	Memory and Organizational Aid
<p>Drug Z-298 is an investigational drug. The purpose of this research is to learn if drug Z-298 is safe and tolerated in two kinds of people: people who have dementia such as Alzheimers disease and people who do not have dementia. Studies involving animals suggest that the drug may interrupt the inflammation that might cause the brain damage seen with Alzheimers Disease. The National Institute on Aging is developing Z-298. The Institute is the sponsor of this research project. This research is designed to compare the safety and tolerability of three different doses of Z-298 to placebo in persons with and without Alzheimers Disease. It will enroll 30 subjects: 15 with Alzheimers Disease and 15 without Alzheimers Disease.</p>	<p>Drug Z-298 is a new drug. This is the first use of Z-298 in humans. This research will involve two kinds of people:</p> <ol style="list-style-type: none"> 1 people who have dementia such as Alzheimers disease 2 people who do not have dementia. <p>This research is trying to learn if Z-298 is safe and well tolerated.</p>

Table 2

Participant characteristics.

	Cognitively normal older adults (n =30)	AD patients who received standard informed consent plus memory and organizational aid (n = 40)	AD patients who received standard consent (n = 40)	Comparison between AD groups
Sex				chi ² =1.80, df=1, p=0.18
Female	17 (57%)	17 (43%)	23 (58%)	
Male	13 (43%)	23 (58%)	17 (43%)	
Age	78.1 ± 6.2 (60–89)	74.4 ± 9.5 (45–92)	76.5 ± 6.6 (59–89)	Wilcoxon-Mann-Whitney z=0.593, p=0.55
Race				chi ² = 0.46, df=1, p=0.50
Caucasian	25 (83%)	34 (85%)	36 (90%)	
African-American	5 (17%)	6 (15%)	4 (10%)	
Education	16.0 ± 2.8 (11–20)	14.4 ± 3.3 (7–21)	15.3 ± 3.1 (10–22)	Wilcoxon-Mann-Whitney z=1.07, p=0.28
MMSE	29.5 ± .9 (27–30)	23.3 ± 2.7 (18–28)	23.6 ± 2.9 (18–28)	Wilcoxon-Mann-Whitney z=0.57, p=.057

Table 3

Expert judgment of ability to provide informed consent.

	AD patients who received standard informed consent	AD patients who received standard informed consent plus memory and organizational aid	Total
Incapable of providing own informed consent *	33	21	54
Capable of providing own informed consent	7	19	26
Total	40	40	80

Chi²=8.2, df=1, p=0.004.

* "Incapable of providing informed consent" was determined by agreement of at least two out of the three independent expert raters. See "Results" section for the results of analyses of each individual expert's judgments.

Table 4

Participant scores on the decision making abilities. Wilcoxon-Mann-Whitney tests used to compare Mac-CAT-CR subscale scores between AD standard informed consent plus memory and organizational aid and AD standard informed consent groups.

Decisional ability (range)	Cognitively normal older adults (n =30)	AD standard informed consent plus memory and organizational aid (n = 40)	AD standard informed consent (n = 40)	Wilcoxon-Mann-Whitney tests between AD groups
Understanding [†] (0 to 26)	24.9 ± 1.4 (21–26)	17.6 ± 5.6 (5–26)*	13.7 ± 6.1 (2–25)	z=2.86, p=0.004*
Appreciation [‡] (0 to 6)	5.5 ± 1.2 (2–6)	3.5 ± 1.8 (0–6)	2.8 ± 1.5 (0–6)	z=1.76, p=0.08
Reasoning [§] (0 to 8)	7.5 ± 0.8 (5–8)	6.3 ± 1.7 (2–8)	5.7 ± 2.5 (0–8)	z=0.82, p=0.41
Choice (0 to 2)	1.9 ± 0.3 (1–2)	1.8 ± 0.5 (0–2)	1.7 ± 0.6 (0–2)	z=0.11, p=0.91

[†] Kruskal-Wallis test corrected for tied ranks showed a significant effect of group on understanding subscale scores ($\chi^2=58.94$, $df=2$, $p=0.0001$): normal controls had higher scores than AD intervention ($z=6.14$, $p=0.0001$) and AD control groups ($z=6.86$, $p=0.0001$), and AD intervention group had higher scores than AD control group ($z=2.86$, $p=0.004$) (Wilcoxon-Mann-Whitney tests).

[‡] Group had a significant effect on appreciation subscale scores ($\chi^2=39.62$, $df=2$, $p=0.0001$): normal controls had higher scores than AD intervention ($z=4.84$, $p=0.0001$) and AD control groups ($z=6.08$, $p=0.0001$); AD intervention group not different from AD control group ($z=1.76$, $p=0.079$).

[§] Group had a significant effect on reasoning subscale scores ($\chi^2=17.03$, $df=2$, $p=0.0002$): normal controls had higher scores than AD intervention ($z=3.42$, $p=0.0006$) and AD control groups ($z=3.88$, $p=0.0001$); AD intervention group not different from AD control group ($z=0.82$, $p=0.41$).