RESEARCH ARTICLE

Ethical considerations within pragmatic randomized controlled trials in dementia: Results from a literature survey

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Abstract

Introduction: This review aims to describe the landscape of pragmatic randomized controlled trials (RCTs) in the context of Alzheimer’s disease (AD) and related dementias with respect to ethical considerations.

Methods: Searches of MEDLINE were performed from January 2014 until April 2019. Extracted information included: trial setting, interventions, data collection, study population, and ethical protections (including ethics approvals, capacity assessment, and informed consent).

Results: We identified 62 eligible reports. More than two-thirds (69%) included caregivers or health-care professionals as research participants. Fifty-eight (94%) explicitly identified at least one vulnerable group. Two studies did not report ethics approval. Of 57 studies in which patients were participants, 55 (96%) reported that consent was obtained but in 37 studies (67%) no mention was made regarding assessment of the patients’ capacity to consent to research participation.

Discussion: Few studies reported protections implemented when vulnerable participants were included. Shortcomings remain when reporting consent approaches and capacity assessment.

KEYWORDS
capacity, consent, ethics, research participant
1  INTRODUCTION

The aging population has led to an increase in the number of patients with Alzheimer’s disease (AD) and AD-related dementias (ADRD).1,2 According to the World Health Organization, an estimated 50 million people have dementia worldwide, with up to 10 million new cases per year.3 While randomized controlled trials (RCTs) continue to search for efficacious drug treatments to mitigate the progression of the disease, much research pertains to non-pharmacological interventions to improve the health care delivered to people living with dementia (PLWD) and their caregivers.

An ongoing challenge has been the lack of evidence regarding effectiveness of interventions when implemented under real-world conditions. As such, there have been calls for high-quality RCTs to evaluate the effectiveness of interventions as they would be used in practice.4,5 The hope is that these trials, often referred to as pragmatic RCTs, would generate results that could directly inform real-life clinical decisions.

Despite the opportunities offered by more pragmatic RCT designs, unique challenges remain in their application to dementia research. For example, beyond the very early stages of dementia, many PLWD may lack the decisional capacity to provide individual consent to participate in the study, often requiring surrogate decision-makers to be identified.5 Such consent approaches, while consistent with long-established research ethics guidance, may require reconsideration in the context of low-risk pragmatic RCTs where researchers have advocated for increased use of waivers of consent.6,7 Moreover, several groups affected by AD/ADRD research may constitute vulnerable populations—defined as those who “may have an increased likelihood of being wronged or of incurring additional harm”—including those individuals with limited capacity to consent or decline to consent to research participation, and individuals living in nursing homes.8 The inclusion of such vulnerable populations in trials brings with it an additional array of ethical and regulatory challenges, such as the need for increased protections. These ethical protections may run counter to more pragmatic RCT designs. Finally, many studies may actively involve caregivers as the target of an intervention, to deliver an intervention to PLWD, or for data collection on behalf of the PWLD. The involvement of caregivers in these varied roles raises important questions about when to consider caregivers as research participants, particularly from a regulatory standpoint.9

To better understand the scale of the challenge posed by the above ethical concerns, we undertook a review and descriptive analysis of a sample of pragmatic RCTs relevant to AD/ADRD. Our main objectives were to describe:

1. Trial characteristics, including the range of settings, types of interventions, and data collection procedures;
2. Study populations, including the types and combinations of research participants and whether their vulnerability was acknowledged and accounted for;
3. The prevalence of reporting of ethical protections, including research ethics review, informed consent, and capacity assessment.

2  METHODS

2.1  Identification of trials

The current cohort of trials is a subsample from a larger database of reports generated for a previous cross sectional analysis of pragmatic RCTs.10 Briefly, the larger database was generated using a validated electronic search filter11 from January 1, 2014 to April 3, 2019. Studies were included in the larger cohort if they were the primary report of an RCT of a health or health-care intervention with a target accrual of at least 100 individuals. Full details of the inclusion and exclusion criteria and process of screening have been published previously together with results of the larger review of 4337 pragmatic RCTs.10

For the present analysis we identified the subset of trials that (1) specifically focused on PLWD or their caregivers, or (2) focused on a broader cohort of older adults but include a subgroup of PLWD or their caregivers and conducted some sort of stratified or subgroup analyses on that cohort. For present purposes, dementia was considered an umbrella term for many conditions (such as AD, Lewy body disease, multi-infarct dementia, and senility). To identify the subset of trials relevant to these criteria, we applied two algorithms: First, we applied a search filter from the Cochrane Dementia and Cognitive Improvement Group12 to identify trials that focus on AD/ADRD. Second, we used a generic search using Medical Subject Heading (MeSH) terms to identify trials in the elderly (aged 65 and over). This was done to identify additional trials that may not be specifically focused on people living with AD/ADRD but may include them as a subgroup. The supporting information provides full details of our search. For the subset of trials identified as potentially relevant to AD/ADRD a calibration exercise was conducted among five reviewers (BQ, CC, LZ, MT, and FL) in which 15 potentially eligible trials were reviewed by all reviewers and discussed. Discrepancies were reviewed until consensus was achieved. After this training period three reviewers (BQ, CC, LZ) reviewed all remaining trial reports, with each trial report reviewed independently by one reviewer. An analysis of methodological and statistical considerations in these trials has been published elsewhere.13

2.2  Data elements and extraction

Data elements for extraction were identified within three domains: trial characteristics, research participants including vulnerability considerations, and ethical protections (the data extraction form is available as supporting information).

2.2.1  Trial characteristics

Trial characteristics were: trial design, nature of the intervention, and setting. These items were extracted as part of a previous statistical review.13 Trial design was categorized as an individually randomized, cluster randomized, or an individually randomized group treatment...
trial (i.e., an individually randomized trial but with an intervention delivered in a group setting). Trial setting was coded as primary care, hospital or specialist care, nursing home or long-term care, community-based or residential, adult day centers, or other. In addition, the nature of the interventions was characterized as an educational intervention targeting health professionals; health service delivery intervention targeting the organization or health-care system, pharmacological intervention targeting the patient, non-pharmacological intervention targeting the patient only, any intervention targeting the patient-caregiver dyad, or any intervention targeting the caregiver only. For each trial, multiple selections could be made reflecting the possibility for complex interventions.

2.2.2 Research participants and vulnerability

For the study population we extracted information regarding the types and combinations of research participants, whether participants were explicitly identified as vulnerable, and if so whether any special protections were reported in the article as being provided. Research participants were identified as per the “Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials,” which specifies that an individual should be deemed a research participant if that individual is the intended recipient of an experimental (or control) intervention, is the direct target of an experimental (or control) manipulation of his/her environment, interacts with an investigator for the purpose of collecting data about them, or if an investigator obtains identifiable private information about that individual for the purpose of collecting data about them. Using these criteria, we assessed whether the research participants included PLWD, informal caregivers (e.g., family members), health-care professionals, another group (e.g., other professional groups such as social workers), or any combination of the above.

To address the question regarding the extent to which vulnerability is considered within pragmatic RCTs in AD/ADRD, we examined the eligibility criteria for any explicit mention of vulnerable participants. Participant groups were adapted from an aggregate list created by Bracken-Roche et al. based on international guidance documents, namely: participants with dementia, cognitive impairment, or deterioration; patients in the emergency setting; subordinate members of hierarchies or relationships (e.g., nursing home staff, medical and nursing students, subordinate hospital and laboratory personnel); homeless persons; institutionalized persons or those with mental health problems beyond dementia; persons in nursing homes; refugees or displaced persons; economically or disadvantaged persons; patients in terminal care or who have life-threatening diseases; elderly persons (defined here as ≥ 65 years); pregnant or breastfeeding women; specific ethnic, racial minority, linguistic, or ethnocultural groups; or any other reference to participants identified as vulnerable. We did not review the demographic results to identify if potentially vulnerable participants were potentially included in the trial as we wished to focus on whether the inclusion or exclusion of vulnerable participants had been recognized by the study authors. Whenever vulnerable participants were identified, we examined the article text for any explicit mention of special protections that were used within the trial, for example, additional training given to trial staff in relation to the identified vulnerabilities. We did not count capacity assessments and use of substitute decision-maker consent in this category of “special protections.”

2.2.3 Ethical protections

With respect to ethical protections, we extracted whether each study was submitted for ethics review, deemed exempt from ethics review, or approved by a research ethics committee. If the authors reported that the study had not been reviewed by a research ethics committee, we extracted any justification(s) provided. In addition, we extracted information about the reported approaches to obtaining consent. Details of ethics review and consent approach were in part extracted
as part of a previous review but were supplemented for this analysis with specific information regarding details of the consent process. We further evaluated whether capacity to consent was an explicit eligibility criterion and whether any capacity assessment was reported in relation to participant consent.

The extraction form for the additional ethics items was pilot tested and applied to a random sample of trials by three reviewers (SGN, KC, HPN) with input from MT. Upon completion of the pilot testing each trial was extracted in triplicate by the same reviewers with discussion and consensus. Any trials that raised difficulties for interpretation were reviewed by MT whenever necessary.

3 RESULTS

From the initial 4337 pragmatic trials identified in our review, 488 were deemed to be potentially relevant to AD/ADRD after application of the two additional dementia-related search filters. From these, a total of 62 trials were identified as being eligible for data extraction by virtue of the trial being specifically focused on PLWD or their caregivers, or focused on a broader cohort of older adults but including a subgroup or stratified analysis of PLWD or their caregivers.

3.1 Trial characteristics

Table 1 provides an overview of the trial characteristics. Approximately one-quarter (15, 24%) were individually randomized, while almost two-thirds (38, 61%) were cluster randomized trials. The remainder (9, 15%) were individually randomized group treatment trials. All trials included both men and women.

More than half of the included trials (32, 51%) were conducted in the UK or Europe, and almost one-quarter (15, 24%) in North America. A total of 28 trials (44%) took place in nursing homes, while 11 (18%) took place in community or residential settings, and 8 (13%) were conducted through primary care. Only 4 trials (6%) were conducted within hospitals or a specialist care setting.

Twenty-nine studies (47%) evaluated non-pharmacological interventions, 3 (5%) pharmacological interventions targeting solely the PLWD, 19 (31%) studied an educational intervention targeting a health-care professional, and a similar number (20, 32%) included an intervention that targeted either the caregiver alone or the caregiver–patient dyad.

Table 1 | General characteristics of trials included in the review (N = 62)

| Item                                      | N (%) |
|-------------------------------------------|-------|
| **Country of trial conduct**              |       |
| Canada                                    | 2 (3%)|
| USA                                       | 13 (21%)|
| UK                                        | 14 (22%)|
| Other European Union Country              | 18 (29%)|
| Australia or New Zealand                  | 5 (8%) |
| Low- or middle-income country             | 4 (6%) |
| Other                                     | 9 (14%)|
| **Participant sex**                       |       |
| Female only                               | 0     |
| Male only                                 | 0     |
| Both male and female                      | 62 (100%)|
| **Trial design**                          |       |
| Individually randomized trial             | 15 (24.2%)|
| Cluster randomized trial                  | 38 (61.3%)|
| Individually randomized group treatment trial | 9 (14.5%)|
| **Trial setting**                         |       |
| Primary care                              | 8 (13%)|
| Hospital, specialist care                 | 4 (6%) |
| Nursing homes, long-term care             | 28 (44%)|
| Communities, residential areas            | 11 (18%)|
| Adult day care centers                    | 2 (3%) |
| Other                                     | 10 (16%)|
| **Type of interventions**                 |       |
| Educational intervention targeting health professionals | 19 (30.6%)|
| Health service delivery intervention targeting organization/health-care system | 17 (27.4%)|
| Patient non-pharmacological intervention  | 29 (46.8%)|
| Patient pharmacological intervention       | 3 (4.8%)|
| Any intervention targeting caregiver only | 12 (19.4%)|
| Any intervention targeting patient–caregiver dyad | 8 (12.9%)|
| **Data collection methods**               |       |
| Review of medical records                 | 21 (33.9%)|
| Routinely collected health administrative data | 2 (3.2%)|
| Mental or physical examination not required for normal care | 33 (53.2%)|
| Patient-focused questionnaires completed by patient and/or caregiver | 45 (72.6%)|
| Caregiver-focused questionnaires          | 21 (33.9%)|
| Health professional questionnaires        | 4 (6.5%)|
| Direct observation                         | 4 (6.5%)|

4 A trial can belong to multiple categories; thus, numbers do not sum to 100%.
5 A trial could be conducted in multiple countries; thus, percentages do not sum to 100%.

3.2 Study populations

In approximately one-third of studies (19, 31%) patients alone were research participants; 18 (29%) included both patients and their care-
givers; 14 (23%) involved the patient and the health-care professional; and in 6 (10%) the patient, caregiver, and the health-care professional were all research participants (Table 2).

Fifty-eight studies (94%) explicitly identified at least one vulnerable group. Forty-seven (76%) included patients who were potentially vulnerable in ways other than dementia. Most common among these were: people in nursing homes (29, 47%), elderly persons (27, 44%), and subordinate members of hierarchies or relationship (6, 10%). However, only nine of these studies (16%) reported specific safeguards or adaptations to protect the identified vulnerable groups (aside from capacity assessments and substitute decision-makers). Examples of safeguards reported included a risk assessment protocol for participants, additional training provided to those delivering the intervention with respect to detecting patient anxiety, protocols if patient abuse was suspected, and procedures regarding how to deal with a participant who was judged to lose capacity to give ongoing consent to participate in the trial.

Thirty-nine studies (63%) reported the explicit exclusion of a potentially vulnerable group: PLWD who had certain levels of cognitive impairment (21, 54%); institutionalized persons, or those with mental health problems beyond dementia (18, 46%); patients in terminal care or who have life-threatening diseases (14, 36%); and persons in nursing homes (5, 13%; see Table 2).

### 3.3 | Ethical protections

One study reported that it was deemed exempt from ethics review, noting that “The committee stated that, in accordance with Dutch legislation, the study can be performed without a review procedure by the committee because in the study, only observational data gathered by nursing staff as part of the daily work were used.” One study did not provide a statement regarding ethics review.

Table 3 presents details of the reported approach to consent and capacity assessment. Almost all studies (59, 95%) included a statement that participant consent (or substitute decision-maker consent for the participant) was obtained for at least one component of the trial, and from at least one group. Of 57 studies in which patients were participants, 55 (96%) reported that consent was obtained: 25 (46%) indicated that consent related to trial participation, 24 (46%) that consent was obtained for data collection, and 25 (46%) did not specify what the consent was for. In 41/58 studies (75%) written consent was reported, 6 studies (11%) allowed verbal consent, while 9 studies (16%) obtained consent was for. In 41/55 studies (75%) written consent was reported, and 28 (51%) did not specify what the capacity assessment was made. In 13 of the 16 studies reporting a capacity assessment (81%), no formal assessment measure was mentioned, or

| Item | N (%) |
|------|-------|
| Who were the research subjects? | |
| Patients with dementia only | 19 (31%) |
| Caregiver of patient with dementia only | 3 (5%) |
| Health-care professional only | 1 (2%) |
| Patient with dementia and caregiver | 18 (29%) |
| Patient with dementia and health-care professional | 14 (23%) |
| Caregiver and health-care professional | 1 (2%) |
| Patient, caregiver, and health-care professional | 6 (10%) |

Were any of the following groups explicitly mentioned in the inclusion criteria or identified as part of the trial population?

| Item | N (%) |
|------|-------|
| Those with dementia, a cognitive impairment, or determined not to have capacity | 54 (87%) |
| Patients in emergency setting | 1 (2%) |
| Subordinate members of hierarchies or relationships | 6 (10%) |
| Institutionalized persons, or those with mental health problems beyond dementia (e.g., psychosis, learning disabilities, etc.) | 3 (5%) |
| Persons in nursing homes | 29 (47%) |
| Economically disadvantaged persons | 1 (2%) |
| Patients in terminal care or who have life-threatening diseases | 1 (2%) |
| Elderly persons (here defined as ≥ 65 years) | 27 (44%) |
| Specific ethnic, racial minority, linguistic, or ethnocultural groups | 1 (2%) |
| None of the above groups identified | 4 (6%) |

If any of the above were included, were any specific safeguards or adaptations reported to protect identified vulnerable groups (N = 58)?

| Item | N (%) |
|------|-------|
| Yes | 9 (16%) |
| No | 49 (79%) |
| Unclear | 0 |

a Analyses could consider multiple characteristics, so responses do not sum to 100%.
b Empty categories not shown for brevity. Full list of options is listed in the Methods.

For example, nursing home staff or “medical and nursing students, subordinate hospital and laboratory personnel, employees of pharmaceutical companies, and members of the armed forces or police.”
The assessment approach was unclear. One study used the “Evaluation to Sign Consent” tool developed by Resnick et al.23 and two UK studies referred to assessments being made in accordance with the Mental Capacity Act 2005 criteria.

### TABLE 3 Reporting on consent and capacity assessment

| Challenge | N (%) |
|-----------|-------|
| Was there a statement about individual level consent? (N = 62) | |
| Yes—statement that individual level consent was obtained | 59 (95%) |
| Yes—statement indicated no consent (or waiver) was obtained | 0 |
| No statement about consent | 3 (5%) |
| Was capacity to consent to participation (as a whole, to the intervention, or to data collection) explicitly stated either as a requirement within the inclusion criteria or through the explicit exclusion of participants without capacity to consent? | |
| Yes | 3 (4.8%) |
| No | 59 (95.2%) |

If consent was sought, for which aspects of the trial was consent sought? (N = 55)²

| Challenge | N (%) |
|-----------|-------|
| Trial participation (e.g., “trial enrolment,” “to participate in the study”) | 25 (45.5%) |
| Data collection (e.g., completion of questionnaires, review of medical records) | 2 (3.6%) |
| Study interventions (e.g., receiving the treatment) | 0 |
| Other (specify) | 1 (1.8%) |
| Not specified | 28 (50.9%) |

For studies with individual consent, were any of the following details about the consent process explicitly reported? (N = 55)³

| Challenge | N (%) |
|-----------|-------|
| Written informed consent | 41 (74.5%) |
| Substitute decision-maker consent | 41 (74.5%) |
| Verbal or oral informed consent | 6 (10.9%) |
| Assent | 9 (16.4%) |
| Professional consent | 4 (7.3%) |
| Gatekeeper consent | 3 (5.5%) |
| Simple opt out | 2 (3.6%) |
| Other (specify) | 4 (12%) |

For studies where the requirement for consent was not waived, was an assessment of capacity conducted with patients? (N = 55)

| Challenge | N (%) |
|-----------|-------|
| Yes—a statement of capacity was conducted | 16 (29%) |
| No—a statement of capacity was not conducted | 2 (3.6%) |
| Not stated, no mention of capacity assessment was made | 37 (67.3%) |

²May not sum to 100% as multiple selections could be made.

### 4 | DISCUSSION

While pragmatic RCTs present opportunities to facilitate research with PLWD and to enhance the evidence base for effective interventions in AD/ADRD, they raise ethical challenges. Questions of consent and research protections for PLWD are particularly important given the potentially vulnerable status of PLWD and possibility for dependent relationships with those who care for them. In the present study we analyzed these issues in a sample of published pragmatic RCTs conducted in AD/ADRD. This analysis revealed that while most articles reported obtaining approval from a research ethics committee and obtaining participant informed consent, there was a lack of information provided as to how the consent process was implemented and specifically how decision-making capacity was assessed. Moreover, the majority of studies indicated inclusion of participants who may be vulnerable in multiple ways, yet few studies noted any special protections being implemented. While this does not imply that there were no special protections in place for the trial, it does point to a gap in reporting these important ethical safeguards, and consequently, a missed opportunity to advance generalizable knowledge about the state of human research protections.

To our knowledge this is the first review to critically assess the reporting of identified ethical issues in the context of pragmatic RCTs conducted in AD/ADRD. The use of a validated search is a major strength to this review. However, no reporting guidelines require authors to explicitly state the pragmatic intent of their trial, meaning that this must be inferred in many cases, and we did not conduct a formal scoring of the design of each included RCT (using tools such as PRECIS-235), due to noted concerns about the retrospective scoring of trials using such tools.36,37 Further, despite comprehensive work to develop and validate the search filter, the present analysis should not be considered to be a review of the totality of pragmatic RCTs in AD/ADRD. Finally, our extractions were based on the primary trial report, and we did not access protocols, nor did we contact authors for further details.

In most studies, patients or caregivers were research participants by virtue of them being the target of the intervention or data collection procedures. However, many studies involved patient–caregiver dyads, potentially challenging notions of who the research participant is, and consequently from whom consent is required. Caregivers completing study questionnaires about the health of the patient with dementia may not, under current guidelines,14 be deemed to be a research participant. We suggest that existing guidance be broadened, such that an individual would be considered a research participant if an investigator interacts with that individual for the purpose of collecting data about that individual or an individual for whom that individual serves as a caregiver.

While PLWD are considered potentially vulnerable²⁴ our results also indicate other sources of potential vulnerability, most notably, due to the choice of the nursing home as a common setting for these trials. While nursing homes may be an efficient setting for the conduct of pragmatic trials due to the higher prevalence of dementia compared to community settings,²⁵-²⁷ nursing home residents have been
identified as a potentially vulnerable population within international ethics guidelines.\textsuperscript{15} The most recent Council for International Organizations of Medical Sciences (CIOMS) guidance states, for example, that residents of nursing homes may be considered vulnerable due to them being denied certain freedoms and the potential for them to form dependent relationships with their carers.\textsuperscript{8}

Additionally, nursing home staff may be vulnerable if they are research participants, as was the case in a number of studies within our analysis. Nursing home staff may be vulnerable given their position as employees, especially if the research team includes supervisors or nursing home leadership. Finally, there is also a need to consider how the conduct of a study might impact the care provided to non-research participants residing in the home. In the context of pragmatic RCTs in AD/ADRD, clinical care staff may be delivering research interventions in addition to clinical care requirements, which could place non-participants at risk due to extra effort and limited resources. While there has been much discussion of the research protections owed to participants, and increased discussion with respect to the responsibilities of researchers to bystanders affected by research,\textsuperscript{28,29} this is a nascent area in the context of pragmatic RCTs in AD/ADRD and we suggest an area for further ethics guidance.

While the majority of RCTs obtained written consent from either the patient or a surrogate decision-maker, a minority of studies specified what the consent was for. In the context of pragmatic cluster RCTs, participants may not be able to avoid the intervention but may be contacted directly for data collection. As such, participants may feasibly provide consent to data collection and details of what consent was for should be noted. Further, few studies provided details about how the determination regarding individual capacity to provide research consent was made. This compares poorly to work by Karlawish et al., who found that 46\% of studies of research conducted in nursing homes reported a method for determining the individual’s decision-making capacity or that capacity was assessed as part of the inclusion/exclusion criteria.\textsuperscript{30} Furthermore, two studies presumed incapacity to provide consent—in both cases a surrogate decision-maker was approached. Such presumed incapacity to consent to research fails to consider the decision-specific nature of capacity.\textsuperscript{31} At the same time, the large-scale failure to report on capacity assessment processes means that it is unclear what standards are applied and whether patients with dementia are being denied the opportunity to make autonomous decisions.

However, we found a greater proportion of studies reported a capacity assessment than a recent analysis of cluster randomized trials conducted in residential facilities, which found that only 16\% of trials reporting individual consent described the process used to assess capacity to consent. Further, and similar to our findings, 72\% of trials reported in that study used surrogate decision-maker consent,\textsuperscript{32} implying that an assessment or assumption was made regarding whether the individual patient was incapable of providing informed consent. Our results and those of previous studies point to the poor reporting of consent processes, and particularly the processes regarding individual participant consent and/or the use of a substitute decision-maker. While we cannot say whether our results reflect solely on reporting or the actual conduct of research and use of capacity assessment, we advocate for better reporting of consent processes, including capacity assessment.

Finally, our finding that few pragmatic RCTs reported using a waiver of consent is in contrast to recent academic writing, and research funding in AD/ADRD, which have emphasized the use of waivers of consent.\textsuperscript{6,7,33} Waivers of consent may be granted when risks to study participants are minimal, when the research has important social value, and where requiring consent would make it infeasible or not practicable to conduct the study.\textsuperscript{8,34} While it may be argued that the application of a waiver of consent in minimal risk research is a way to facilitate socially important research which would be impractical to conduct if individual consent were required,\textsuperscript{6} we do not have data regarding studies that potentially sought a waiver of consent but were refused so by a research ethics committee: our cohort consists of published trials, which potentially skews our sample toward studies that could be feasibly completed with consent. Moreover, we did not seek to examine which trials potentially could have applied for a waiver of consent. In addition, we do not know the extent to which trials requiring consent were terminated due to feasibility concerns. Gaining a better understanding of the role of waivers of consent in AD/ADRD research, the perceptions of research ethics committees regarding this, and application of waivers of consent in the context of research with vulnerable participants will be important as practice develops.

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CONFLICTS OF INTEREST

Charles Weijer receives consulting income from Cardialen, Eli Lilly & Company, and Research Triangle Institute International. The other authors declare no conflicting interests.

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.