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Committee on High-Quality Alzheimer's Disease Studies (CHADS) Consensus Report

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FEATURED ARTICLE

Committee on High-quality Alzheimer's Disease Studies (CHADS) consensus report

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Abstract

Background: Consensus guidance for the development and identification of high-quality Alzheimer's disease clinical trials is needed for protocol development and conduct of clinical trials.

Methods: An ad hoc consensus committee was convened in conjunction with the Alzheimer's Association to develop consensus recommendations.

Results: Consensus was readily reached for the need to provide scientific justification, registration of trials, institutional review board oversight, conflict of interest disclosure, funding source disclosure, defined trial population, recruitment resources, definition of the intervention, specification of trial duration, appropriate payment for participant engagement, risk-benefit disclosure as part of the consent process, and the requirement to disseminate and/or publish trial results even if the study is negative.

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Conclusions: This consensus guidance should prove useful for the protocol development and conduct of clinical trials, and may further provide a platform for the development of education materials that may help guide appropriate clinical trial participation decisions for potential trial participants and the general public.

KEYWORDS

Alzheimer's disease, clinical trial, consensus, Delphi, dementia

1 | INTRODUCTION

Over the last decade, there has been a steady increase in the number of high-quality clinical trials focused on cognitive decline and dementia.¹ These trials have targeted the prevention, treatment, and/or disease modification of neurodegenerative, medical, and psychosocial conditions that are associated with and presumed to be causes of cognitive decline and dementia in the aging population.^{1,2} Although these studies hold much promise, few therapies have been approved for these indications internationally, despite the wealth of resources invested and the breadth of possible therapeutic targets identified through basic laboratory and clinical research discoveries.² The relative lack of new, scientifically justified, and approved therapies for Alzheimer's disease and related disorders (ADRD), combined with the devastating progression of the disease, has created an urgency for many persons and their caregivers to find new ways to treat ADRD. Although such social pressure has spurred engagement in high-quality clinical trials, there has also been an increasing number of lesser quality studies over the last decade. These trials often do not meet best practices for clinical trial conduct, regulatory approval, trial registration, and participant engagement.³

Clinical trial conduct is regulated through international directives, national laws, institutional review boards (IRBs), research ethics committees (RECs), and trial registration services (such as ClinicalTrials.gov in the United States and the EU Trial registration platform in Europe, <https://www.clinicaltrialsregister.eu>). Trial conduct is further monitored through national agencies and international consensus groups, such as Consolidated Standards of Reporting Trials (CONSORT), that provide guidance for publication of clinical trial results and which have been widely adopted by leading scientific and medical journals and enforced by the editorial staff.⁴⁻⁶ Such efforts have been successful in enhancing clinical trial participant protections, trial registration, reporting of results, and incentivizing researchers to ensure quality in their research protocols and procedures.⁴⁻⁶

Due to the lack of approved therapies for ADRD, there is widespread off-label use of medicines and interventions that remain untested and unproven.^{3,5} The use of such approaches in lieu of evidence-based treatment may fall under the auspices of the "Right to Try" Act, but may also be offered to desperate patients solely for the purpose of financial gain.^{5,7} Such "fee-for-treatment" schemes are sometimes presented as clinical trials to legitimize the use of the treatment in the view of patients, while simultaneously circumvent-

ing the other regulatory controls required for legitimate clinical trial conduct.³

Many health professionals and health-care consumers, including patients and their caregivers, have difficulty navigating the landscape of unproven alternative and experimental therapies. In particular, there is often a lack of clarity and available guidance related to the characteristics of a legitimate clinical trial compared to approaches that may be offered largely to enrich its proponents.^{3,5} As such, consensus guidance for the development and identification of high-quality AD clinical trials need to be established to assist health-care providers and consumers as they assess the appropriateness of studies on unproven treatments. Such a need was envisioned by the Alzheimer's Association in 2018, leading to the development of a Committee on High-quality Alzheimer's Disease Studies (CHADS), comprising scientific experts, clinical trialists from both academia and private practice (including a trialist outside the field of aging and dementia), industry representatives, ethics consultants, government scientific officers, and public advocacy representatives. It is hoped that such guidance may serve as a foundation for the future development of both health-care provider and public education materials to inform decisions in the face of the complex landscape of unapproved treatments for ADRD.

2 | METHODS

2.1 | Overview

There are few objective reports or studies that have addressed the question of criteria for high-quality clinical trials in ADRD. As such, consensus was sought based on the opinions of experts. Many consensus strategies are available and in the simplest case, a formal majority vote using Robert's Rules of Order can establish consensus.⁸ More nuanced approaches such as the Delphi or modified Delphi approach (PubMed search for Delphi consensus retrieved 5041 citations) are also available.^{8,9} We used a modified Delphi method to reach consensus.

2.2 | Modified Delphi method

A modified Delphi approach including anonymous reiterative questionnaires followed by re-survey was repeated until consensus was achieved. It was designed to limit "group think."⁸

RESEARCH IN CONTEXT

- Systematic Review:** The authors developed consensus recommendations using a modified Delphi approach to establish best practices for clinical trial conduct, regulatory approval, trial registration, and participant engagement. No similar recommendations for Alzheimer's disease studies are available.
- Interpretation:** Final consensus recommendations for high-quality clinical trials in aging and dementia research were reached using the modified Delphi approach. These recommendations are consistent with CONSORT (Consolidated Standards of Reporting Trials) recommendations and general human subjects research protections.
- Future Directions:** Implementation of these recommendations may be useful in protocol development and conduct of high-quality clinical trials in the area of aging and dementia research. They may further provide a platform for the development of education materials that may help guide appropriate clinical trial participation decisions for potential trial participants and the general public.

Using this approach, our expert panel exchanged views, and each independently and anonymously provided feedback through a questionnaire that included open-ended responses. The facilitator/chair reviewed the data and provided a summary report for each round of discussion. The panel then reviewed and discussed the summary report, and consensus was reevaluated through a refined questionnaire. This process continued until all participants reached a consensus.

The experts at each round had a full record of the anonymous issues raised by other experts. Anonymity allowed the experts to express their opinions freely, encouraging openness and revising earlier consensus agreement/disagreement.

2.3 | Committee representation

The committee was assembled through directed invitation guided by the Alzheimer's Association's International Society to Advance Alzheimer's Research and Treatment (ISTAART) Clinical Trials Advancement and Methods Professional Interest Area (CTAM PIA) Executive Leadership. The final CHADS committee composition included seven members of the CTAM PIA including four clinicians, two biostatisticians, a neuroepidemiologist with expertise in clinical trial design and conduct, four members of the Alzheimer's Association leadership, and one each of the following: academic trialist leading a national clinical trial consortium, private practice clinical trialist, pharma industry trialist, ADRD ethicist, non-ADRD (stroke) trialist, and a governmental funding agency (National Institutes of Health) scientist.

TABLE 1 Opening Delphi topics and questions developed by the facilitator/chair

1. Scientific justification

a. Irrespective of whether you agree with the premise or pre-trial data, is there sufficient justification for the trial?

b. Do the data have to come from one lab or more? One site or more?

c. Should the data be published or accessible prior to trial engagement? Or should it be shared with the participants in other ways, and if so what are the checks to ensure validity?

2. Regulatory issues

a. Is trial registration important (both US and international)?

b. Are IRB or other human subject protection certifications important?

c. Is funding or funding source important?

d. Are conflicts of interest for the investigators important?

3. Conduct

a. Should the trial population be defined? How should recruitment be conducted? Are there ways recruitment is conducted that call into question the validity of the clinical trial?

b. Should the intervention be defined? Multi-component testing and supplement packages versus personalized medicine?

c. Should the duration of the trial be defined? As long as you pay you can continue to engage?

d. Should outcomes be prespecified?

e. Should the participant have to pay? If so, what is reasonable to pay for and what is not? Limits?

f. Do we need placebo? If so, should one be able to influence the decision to be randomized to the placebo versus control group?

4. Off-label treatment versus clinical trial?

a. What differentiates an open-label trial from recurrent off-label use of a treatment?

5. Perceptions of approval delay

a. Why should a person or investigator wait for a drug to be tested and approved before being given access to it?

b. Humanitarian use?

6. Do results need to be published? Shared in other ways?

7. Other?

Abbreviation: IRB, institutional review board.

2.4 | Areas/topics addressed

The Modified Delphi process was initiated with a series of general questions developed by the facilitator/chair (Table 1).

3 | RESULTS

3.1 | Delphi round #1

The initial round of the modified Delphi process revealed many areas of consensus among panel members, including (1) a need for

TABLE 2 Areas of agreement in round #1 of the Delphi process

Issue/topic	Agreement % (yes/no)
Intervention should be defined	100/0
Outcomes should be prespecified	100/0
All research-related activities including the trial drug and or intervention should be paid for by the trial	100/0
Participants may be responsible for time committed to the trial, travel costs, and standard of care for the medical condition under study and other medical conditions the subject may have in a legitimate clinical trial	100/0
Risk-benefit information need not be included in advertising, but is necessary in the consent and consent processes	100/0
Public-facing materials should specify whether the use of a medicine is off-label or part of a clinical trial	100/0
Using experimental medicines to support the "Right to Try" Act is appropriate, outside of clinical trial engagement	100/0

prespecifying the intervention and outcomes of the study; (2) appropriateness of costs associated with clinical trial participation; (3) clear delineation of risk-benefit considerations per good clinical practice/human subjects protections (GCP/HSP), which is not necessarily required for advertisement in public-facing materials; (4) clear specification of whether the use of a medicine is off-label or part of a clinical trial in all recruitment materials; and (5) that the use of unproven treatments to support the "Right to Try" legislation is appropriate, outside of clinical trial engagement (Table 2). There was also complete agreement on the need for appropriate regulatory oversight of clinical trials including IRB/REC review, trial registration, and adherence to CONSORT reporting recommendations, but determined to be outside the scope of CHADS as these are otherwise clearly accepted practices.

Areas in which consensus was not initially achieved included the type of information that should be provided to potential participants or should be withheld to maintain scientific rigor, whether placebo should be required for clinical trials, the role of off-label use versus open-label studies, the importance of having preliminary data for efficacy and safety prior to initiating "Right to Try" treatments, and the use of open-label extensions as incentives in clinical trials (Table 3). Questions were revised as part of the modified Delphi approach to provide additional clarification that focused on topics of concern for further discussion in the next round of the process.

3.2 | Delphi round #2

The second round clarified and highlighted additional areas of consensus among panel members, including: (1) sharing of the justification for

the trial with participants; (2) disclosure of funding source and conflict of interest for the investigators to participants; (3) a need for definition of the study population, intervention, and duration of the trial; (4) avoiding coercion through payments for trial participation; and (5) an absolute need for study results to be shared and preferentially published (Table 4). Questions were revised to provide additional clarification that again focused on topics of concern for further discussion.

3.3 | Delphi round #3

The final round of the Delphi process led to consensus agreement and the development of the final CHADS recommendations (Table 5).

4 | DISCUSSION

The modified Delphi process resulted in a series of recommendations that may help identify high-quality clinical trials.^{8,9} This efficient process allowed consensus opinion to be formed by a diverse group of subject experts over the span of a few months. Although many of the issues fall under the purview of existing regulatory guidelines, the committee felt that they required clarification in the context of defining a "high-quality" clinical trial.⁶ The proposed recommendations are intended to serve as a metric for guiding health-care providers and consumers in the selection of appropriate options for those with and/or at risk for ADRD. Areas of specific concern and focus identified included: (1) recognition of whether the unapproved use of an intervention or treatment represented a clinical trial or off-label use under the "Right to Try" Act,^{5,7} (2) trial design, (3) trial conduct including costs and financial considerations/conflicts, (4) adherence to regulatory principles and standards,⁶ and (5) public education materials.

4.1 | Recognition of whether the unapproved use of an intervention or treatment represented a clinical trial or off-label use under the "Right to Try" Act

The distinction between off-label use under the "Right to Try" Act and a clinical trial is a major area of concern.^{5,7} This is a critically important issue in the area of dementia trials, given that, to date, no effective disease-modifying therapies have proven efficacious, marking dementia as a high-priority/high-need area for drug development and expedited approval pathways. The CHADS panel clearly appreciated this fact and the potential importance of off-label use and further respected the purpose of the "Right to Try" Act given the lack of disease-modifying or curative agents for the myriad causes of ADRD.^{5,7} The committee members also understood from their personal experiences with patients and caregivers that the distinction between such uses and legitimate clinical trial research needs to be made quite clear. Clinical trials embed rigorous safety oversight and protections.⁶ Studies focusing on off-label use of existing and/or experimental medications that lack such protections should be suspect.^{3,5,7,10}

TABLE 3 Areas of disagreement in round #1 of the Delphi process

Issue/topic	Agreement % (yes/no)	Discussion
Justification for the trial shared with participants	61/39	<p>Pros</p> <ul style="list-style-type: none"> Participants should be made aware of the rationale for why they are potentially receiving an unapproved medication or intervention <p>Cons</p> <ul style="list-style-type: none"> Providing too many details of the trial including outcomes may skew data by facilitating study of outcome measures or enhancing placebo effects
Should the participant have to pay	80/20	Pros
		Not all studies have adequate grant support and yet the study may be important to do
		Cons
		<ul style="list-style-type: none"> The study should pay for all research-related costs Participants may have to subsume costs for travel, time spent, and standard of care diagnostic procedures and treatment for their condition Financial interests of the investigator and site should be made clear to the research participant and their surrogate
Need for placebo	80/20	<p>Pros</p> <ul style="list-style-type: none"> The inclusion of a placebo arm is necessary for absolute determination of the safety and efficacy of treatments in Phase II & III studies <p>Cons</p> <ul style="list-style-type: none"> High-quality Phase I and open-label studies may provide a wealth of information justifying the design Placebo may not be needed for studies in which the natural history is well known and subject characteristics are matched to historical data
Risk/benefit in advertising	86/14	Pros
		<ul style="list-style-type: none"> Open and full disclosure is recommended whenever possible, and is mandated as part of the full consent process <p>Cons</p> <ul style="list-style-type: none"> Full disclosure may be too extensive for limited advertising efforts in terms of cost and ability to convey detailed information
Differentiating open-label trial from off-label use	86/14	<p>Pros</p> <ul style="list-style-type: none"> All use of experimental (unapproved) therapies should specify whether the use is part of a clinical trial or is being provided off-label, potentially as a "Right-to-Try" effort <p>Cons</p> <ul style="list-style-type: none"> Off-label use and retrospective data analysis can provide important insights and should not be discouraged
Importance of testing a medicine before using it in clinical practice	86/14	Pros
		<ul style="list-style-type: none"> Off-label use of an approved or experimental (unapproved) medicine or intervention may provide an important option to patients to treat otherwise incurable conditions <p>Cons</p> <ul style="list-style-type: none"> Off-label use of medicines (approved or experimental) does not include the safety precautions and oversight of safety inherent in clinical trials. Understanding such safety issues and ensuring proactive safety monitoring is part of the reason why clinical trials are recommended in lieu of off-label use
Importance of an open-label extension (OLE)	57/43	<p>Pros</p> <ul style="list-style-type: none"> OLEs guarantee every subject the opportunity to have access to the experimental medicine irrespective of the need for placebo OLEs allow for additional safety and efficacy analysis that may help move experimental medicines forward <p>Cons</p> <ul style="list-style-type: none"> OLEs may be used coercively to guide engagement in one trial over another competing study

TABLE 4 Areas of agreement in round #2 of the Delphi process

Issue/topic	Agreement % (yes/no)
Justification for the trial shared with participants without overindulging details that may skew results	100/0
Disclosure of funding source is important	100/0
Disclosure of COI for study investigator is important	100/0
Trial population should be defined	100/0
Intervention should be defined	100/0
Duration of trial should be defined	100/0
Coercive subject payments	100/0
Sharing and publication of data	100/0

Abbreviation: COI, conflict of interest.

Potential research participants and/or their health-care surrogates need to understand this distinction clearly, as do health-care providers. Legitimate clinical trials carry explicit indemnification responsibilities in the consent document required for study participation, whereas the consequences of such risks involving the use of an unproven medication outside such legitimate trial participation may fall on the participant and or health-care surrogate.⁵⁻⁷ Efforts to create the illusion of scientific legitimacy for a particular unapproved or unproven treatment may misrepresent off-label use as a clinical trial.³ Clear explanation of this distinction is necessary to allow health-care providers and consumers to understand their options when faced with a diagnosis of an incurable condition with few approved treatments, including ADRD.

4.2 | Trial design considerations

“High-quality” clinical trials in ADRD research should focus on established criteria for clinical trials, with an emphasis on prespecified study populations, defined interventions including dosage and duration, as well as legitimate outcome measures that should not be subject to alteration based on ongoing clinical trial data, but may be changed based on general information from other discoveries in the field prior to analyzing actual trial data.² Efficacy estimates should include supporting documents and also need to include description on how/why they are clinically meaningful. Sample size calculations should provide transparency including software used, point estimates as well as their variability, and the sources of the information and which variables are controlled or stratified. New available safety and or efficacy information from different trials may, however, guide changes in ongoing protocols that may include alterations in study population characteristics, drug dosage, or duration of treatment, and even in some circumstances, changes in outcome measures.² Such changes should not be influenced by the interim study data as this may introduce a substantial bias that would likely require mitigation. Interim data analyses for efficacy and futility should be prespecified with appropriate statistical adjustment

to avoid a type 1 error. Data to be included into the interim analyses (e.g., impute missing data) needs to be discussed. Trials that change or adapt inclusion/exclusion criteria, intervention dose or duration, or outcome measures should be viewed as potentially less than “high-quality” and the alterations in the protocol should be reported to facilitate thorough evaluation of both efficacy and safety. Although such changes may occur in any clinical trial based on all available information with regulatory approval, the failure to disclose such changes and or the impetus to make such changes, or to gain regulatory approval for such changes, would likely indicate a less than “high-quality” study.

4.3 | Trial conduct considerations

One feature distinguishing a “low-quality” versus a “high-quality” clinical trial in ADRD research may be the requirement for payment to participate.³ This refers to payment specifically for the opportunity to participate rather than costs that participants may incur, for example by travelling to a testing site. This most often indicates that the primary motivation for inviting participants involves financial gain for the provider and/or the institution. “High-quality” clinical trials should be adequately supported, precluding such requests from participants and their health-care surrogates. Requests for payment often suggest a lack of funding, which may mean that peers, sponsors, or granting agencies do not find the approach worthy of pursuit. Although it is possible that early-stage discovery may lack funding, a request for payment for research engagement should be construed as a sign that the “study” may not even be a trial or may be of low quality. Conversely, clinical trials that pay excessively for participation may also be “predatory” as they seek to engage participants who may be in need of financial gain themselves. Although most regulatory agencies including IRBs evaluate such payments, there is a wide range of financial incentives across clinical trials, legitimate or otherwise.⁶ The appearance of excessive payments may signal that the trial is of lower quality although such payments may be included in a “high-quality” clinical trial that is pressured to recruit quickly or require certain study population characteristics that may be more motivated by such incentives.

4.4 | Adherence to regulatory principles and standards

Irrespective of the “quality” of a clinical trial, all should adhere to common GCP/HSP regulations that require an overseeing regulatory body, which at minimum requires an appropriate IRB/REC and approved consent process.⁶ The consent document should include contact information for that regulatory body as well as a contact if participants have questions, concerns, or complaints. In addition, “high-quality” studies that intend to appropriately share and or publish their results, should be registered as such with appropriate agencies such as through ClinicalTrials.gov.⁴ Unregistered trials involving the proposed use of unapproved or experimental medicines or interventions should

TABLE 5 Final CHADS consensus recommendations

Recommendation	Rationale
1. High-quality clinical trials should be designed and conducted to be adherent to the reporting principles specified in the published CONSORT statements and basic HSP standards mandated by regulatory authorities.	Regulatory oversight and reporting of results guidances are well established and should be adhered to in all instances.
2. Adequate justification for the trial should be made available to participants including full disclosure of all positive and negative findings, as well as the lack of any relevant data that may influence their decision to participate.	Incomplete justification, presentation of only selected data, and/or the failure to present prior negative data precludes adequate disclosure of study rationale.
3. Outcomes should be prespecified, but specifics may not necessarily be made available to participants to avoid bias in outcome measures.	To avoid statistical bias, changes in outcome measures should only be made prior to data analysis. To prevent "self-study" by participants, discrete information on specific outcome measures may be withheld, but general descriptions should be provided.
4. Participants may subsume costs for time committed to the trial, travel costs, and standard of care for the medical condition under study and other medical conditions the subject may have, but should never be responsible for research-related costs or the experimental medication under the guise of a trial.	Charging patients for study procedures is a clear sign that the study may not be funded, undergone previous peer review, or may be "predatory" for financial gain by the investigators. Charging for the use of experimental or off-label medicines should be considered "for-profit" indicating that it is not part of a legitimate clinical trial.
5. Risk/benefit disclosures are not necessarily required for advertisement but should be mandatory in consent processes.	While good clinical practice and HSP requires full disclosure of risk/benefit considerations, such information may be too detailed to be included in routine trial advertisements.
6. Public-facing materials should specify if the use of a medicine is off-label or part of a clinical trial.	Describing the objective of treatment is necessary in delineating whether the use of an experimental or unapproved medicine/intervention is part of a clinical trial or off-label use.
7. The use of experimental medicines or off-label use of approved medicines, in the spirit of the "Right-to-Try" act, should not be subject to guidances for clinical trial regulation or oversight.	Off-label use as part of the "Right to Try" Act, should be specified as treatment that is not part of any clinical trial.
8. Disclosure of trial registration, HSP oversight, funding source, and COI for the investigators is necessary.	It is critical that potential participants in any clinical trial understand the regulatory oversight and potential for financial benefit that may be driving the investigator to encourage their participation beyond their primary health interests.
9. The trial should have a protocol in which the trial population (I/E criteria), intervention, duration are prespecified and made available to potential participants.	To avoid statistical bias, changes in trial design should only be made prior to data analysis. Participants should not be coerced into changes into continued participation if trial population indications, study intervention, or duration are changed after consent procedures have been finalized. Such changes should be conveyed and re-consent obtained with full disclosure of why such changes have been made to maintain the legitimacy of the trial.
10. Trial participants should not be unduly influenced by payments, enhanced access to medical services which they may not otherwise receive, or other enticements for engagement.	While HSP protections including regulatory oversight provide such protections, the committee noted that there may be a great deal of variation in compensation for trial engagement. While this may at times be related to degree of funding, scrutiny of significant outliers in compensation may help indicate legitimate versus suspect clinical trial conduct.
11. Participants should be informed that the trial results will be published or otherwise made available to the public and research community, and the investigator should be mandated to do so.	If a trial is legitimate, it should be prepared to share and or publish the data derived from research participation. Preconceived intent to collect data on participants receiving off-label use of unapproved medications or interventions indicates an attempt to bypass regulatory oversight, suggesting a lack of legitimacy for the clinical trial.

Abbreviations: COI, conflict of interest; CONSORT, Consolidated Standards of Reporting Trials; HSP, human subjects protections; I/E, inclusion/exclusion.

signal that the trial may not actually be a trial at all, or that it may be of lower quality. Intent to publish or share such results in reputable medical and scientific journals require such registration, and a failure to do so indicates a lower quality study that may be seeking to avoid such requirements.⁴ In addition, financial interests including personal or family gain, institutional gain, or other financial conflicts should be appropriately disclosed to participants.⁶ Studies involving excessive or unexplained financial gains should indicate a “lower-quality” study.

4.5 | Public-facing materials

All public materials providing education regarding the trial should be approved for use through the appropriate regulatory bodies, and the materials should clearly indicate such approval. Public-facing materials advertising a clinical trial should contain a general description of its scientific purpose, the population being studied, the intervention being pursued, a description of the study specifics (what is being asked of participants), and the main study procedures. They should also indicate the overseeing regulatory agencies (local or central IRB/REC), and further specify trial registration including access to verification of such registration.^{4,6} Materials should not promise or suggest positive results, and should instead introduce the study as an optional addition to usual clinical care. Payments or costs of participation should be specified, especially when significant financial burden may be incurred by the participant, care partner, or health-care surrogate. Public-facing materials should avoid potentially coercive excessive payments for participation beyond what would be considered reasonable for the time and effort of participating in the research.

4.6 | Important remaining questions and considerations

Although the current consensus panel recommendations address many critical questions inherent in determining the overall quality of clinical trials in aging and dementia, there remain many other important questions that should be recognized, prompt further discussion, and serve as a focus for future efforts to guide high-quality studies in the field. Given the extensive knowledge accumulated through clinical trials and observational studies, there is much debate on the need to include placebo control groups in future Phase II and III studies. Although the exclusion of placebo controls in Phase I studies is common, it is unclear if current study simulation methods could replace control groups in future studies. Given the variability in disease characteristics and progression across randomized, controlled trials and observational cohorts, it is clear that there remains much work to do in this area of clinical trial design. Additionally, current Food and Drug Administration, European Medicines Agency, and other regulatory guidances maintain requirements for contemporaneous control groups for adjudicating safety and treatment effects in the changing landscape of degenerative disease clinical trials. For now, placebo control groups remain essential for safety and efficacy evaluation.

Other considerations such as standardization of clinical diagnostic criteria and the use of uniform inclusion criteria across trials, controlling for the high number of comorbidities and medications used in older patients, and selection of valid and clinically meaningful outcomes would improve the comparability of study samples and outcomes across trials. Although addressing these considerations would be desirable, this level of uniformity in trial design is currently not feasible for many studies in which the nuances of the sample selection, illness severity, study interventions, and safety concerns may differ broadly. At present, uniform diagnostic criteria, inclusion/exclusion criteria, and outcome measures remain study specific and outside the scope of general recommendations for high-quality aging and dementia clinical trials.

Although the consensus panel appreciated that high-quality trials should maximize inclusion of a wide variety of often frail elderly participants, it is appreciated that depending on the stage of the trial investigation, the type of participant targeted for recruitment, and the often-nuanced risks and benefits of each unique study, general recommendations for maximizing engagement across all studies are not practical. Concerns about the undue influence of caregivers on a participants' and on assessing study outcomes are also important to address, but again general recommendations for judging the quality of a clinical trial in this regard are impractical as most trials conducted in later dementia stages require proxy or surrogate consenting and are dependent on caregiver-reported outcomes. Diversifying trial participants in terms of race/ethnicity and sex is critically important, but diversification can also lead to increased variability as well as small sample size if the analyses have to be conducted separately for each race/ethnic group. Controlling for confounders such as social determinant of health or comorbidities could mitigate the variability to some extent, although the impact of social determinants of health on trial outcomes and efficacy is not well investigated thus far.

Additional important concerns regarding the quality of a clinical trial in aging and dementia include a discussion of the invasiveness and potential risks for study interventions. For each trial we must ask, is this an ethically acceptable treatment for this stage of disease? Given that ADRD are currently incurable, should we only consider oral medications and similar noninvasive treatments as acceptable for high-quality studies, or should we also include injections and infusions, or even invasive stimulation protocols or brain implants? Given the lack of disease-modifying therapies for a wide range of ADRD stages, general recommendations in this area would be premature, but such considerations should be considered on a trial-by-trial basis.

Further work aimed at developing consensus criteria that guide the recognition of high-quality clinical trials in aging and dementia is needed to further guide investigators, regulatory agencies, and the public in expectations for the highest quality clinical trials for ADRD. As the number of potential therapeutics in clinical trials continues to grow, the importance of such issues will also increase. At present, the general recommendations developed by this consensus group appear widely applicable across studies and serve as a basis for continued discussion, debate, and growth in the area of ADRD clinical trial research.

4.7 | General conclusion

There is extensive agreement regarding the characteristics of a high-quality ADRD clinical trial. This consensus guidance may be useful in the protocol development and conduct of "high-quality" clinical trials, and may further provide a foundation for the development of outward-facing educational materials to guide clinical trial participation decisions for prospective clinical trial participants and the general public.

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CONFLICTS OF INTEREST

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from Gerson Lehrman Group; has received travel support through the Alzheimer's Association; has participated on a Data Safety Monitoring Board or Advisory Board for Alzheimer's Clinical Trials Consortium (ACTC), the Research Participant Advisory Board (RPAB) and the Inclusion, Diversity, and Education in Alzheimer's Disease Clinical Trials (IDEA-CT) Committee; and has held leadership positions with the Alzheimer's Association (Director of Scientific Programs & Outreach) and CMT Research Foundation—Chief Scientific Officer. Howard H. Feldman has received grants or contracts from ADCS Clinical Trials grant funding: Annovis (Posiphen), Biohaven (BH 4157), Vivoryon (PQ 912), AC Immune (ACI-24-1301), LuMind (ADC-059-LIFE-DSR); royalties or licenses from Royalty payment received for Feldman HH (filed November 26, 2008), Detecting and Treating Dementia Serial Number 12/3-2691 U.S. Patent No. PCT/US2007/07008. Washington, DC: U.S. Patent and Trademark Office; consulting fees from Eisai Pharmaceuticals, Merck Pharmaceuticals, Arkuda Therapeutics, Axon Neuroscience, Banner Health, Samumed, Samus Therapeutics, Tau Consortium, and Novo Nordisk; travel support from ADDF, Samus, Samumed, Axon, and Novo Nordisk; has participated on a Data Safety Monitoring Board or Advisory Board for Roche/Genentech Pharmaceuticals (DSMB and DMC) and Janssen Research & Development LLC (DSMB). Larry B. Goldstein has received grants or contracts from NIH, consulting fees from Abbott, payment or honoraria from University of South Florida, travel support from American Academy of Neurology, and has held a leadership role for American Academy of Neurology Joint Audit Committee. James Hendrix has received consulting fees from Gerson Lehrman Group; and has patents planned, issued, or pending for US 20190345115. Ruth Peters has received grants or contracts from Grants from Australian National Health and Medical Research Council, the Australian Medical Health Futures Fund, and the University of New South Wales Ageing Futures Institute; and has held a leadership roles as vice chair and chair for the Alzheimer's Association ISAART clinical trials and methodology professional interest area. Julie M. Robillard has received grants or contracts from AGE-WELL, Canadian Consortium on Neurodegeneration in Aging, Alzheimer Society of British Columbia, Social Sciences and Humanities Research Council of Canada, Michael Smith Foundation for Health Research, BC SUPPORT Unit, BC Children's Hospital Research Institute, and has held a leadership roles as Chair, Ethical, Legal, Social Implications Cross-cutting Program of the Canadian Consortium on Neurodegeneration in Aging, Lead, Ethics and Practice, AGE-WELL, Vice-chair, Technology and Dementia Executive Committee, ISTAART PIA, Member, Board of Directors, Medical Device Development Centre of BC. Lon S. Schneider has received support, grants, or contracts from NIH P30 AG066530, USC Alzheimer Disease Research Center (ADRC), Eisai, Eli Lilly, Roche/Genentech, Biogen, Biohaven, Novartis, and Washington University/ NIA DIAN-TU; consulting fees from Abbott, AC Immune, Avraham, Ltd, Boehringer Ingelheim, Cognition Therapeutics, Cortexyme, Eisai, FujiFilm, Immunobrain Checkpoint Ltd, Neurally Inc, Neurim Ltd, Neuronix Ltd, Samus, Takeda, vTv; and has participated on a Data Safety Monitoring Board or Advisory Board for Abbott, AC Immune, Avraham, Ltd, Boehringer Ingelheim, Cognition Therapeutics, Cortexyme, Eisai, FujiFilm, Immunobrain Checkpoint Ltd,

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