Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder that is becoming increasingly common as the global population ages, is reaching epidemic proportions, and imposes a major public health challenge [1]. It is imperative that new pharmacologic therapies be developed for treatment of AD. Finding means of preventing or delaying the onset, slowing the progression, and improving the symptoms of this disorder are critically important. There are currently approximately 80 drugs in development for AD and being assessed in over 200 clinical trials [2].

The only mechanism to achieve regulatory approval for use of new agents in the treatment of AD is through well conducted clinical trials. Clinical trial innovation is critical to shortening the development cycles of new therapies and accelerating both the development of effective new therapies and identification of drugs that have limited or no therapeutic potential and should not be advanced in development programs.

This review describes innovations in clinical trial methodology applicable to disease modifying therapies, symptomatic cognitive enhancer treatments, and psychopharmacologic interventions for behavioral disturbances in AD. Novel trial designs used in non-AD neurodegenerative disorders and that may be applicable to AD are included. The purpose of the review is to describe innovations in AD clinical trial designs, promote consideration of optimal clinical trial processes, and provide a conceptual framework for considering novel clinical trial designs. In addition to innovative clinical trial designs, novel populations included in clinical trials and biomarkers as outcomes of clinical trials are noted. Novel clinical outcomes that comprise alternatives to the standard measures are described.
Standard AD clinical trial design

The most typical AD clinical trial design was created in the development programs for cholinesterase inhibitors (e.g., donepezil, rivastigmine, galantamine) and memantine [3]. These are double-blind, placebo controlled, parallel group clinical trials with dual outcomes including a cognitive measure (typically the Alzheimer’s Disease Assessment Scale cognitive portion (ADAS-cog) [4]), and a global or Activities of Daily Living (ADL) outcome (e.g., Clinical Dementia Rating (CDR) and Clinical Dementia Rating Sum of Boxes (CDR-SOB) [5]; Alzheimer’s Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) [6] scale; or Disability Assessment for Dementia (DAD) [7]). This dual-outcome approach specifying a statistically significant drug-placebo difference on the core clinical symptoms of AD as represented by the ADAS-cog and a measure of clinical meaningfulness as measured by a global or activities of daily living measure were included in the original draft criteria for the development of anti-dementia agents [8]. In the typical design, patients are randomized to drug or placebo and the change from baseline in the placebo group is compared to change from baseline in the treatment group after a three, six or twelve month period, depending on the length of the trial. The sample size of the trial is determined by the anticipated number of patients required to show a statistically significant difference between groups at the end of the study measurement period. The sample size requirements are related to the expected effect size.

Memantine was approved after the cholinesterase inhibitors were on the market and were commonly used in the treatment of AD. The memantine development program included one mono-therapy trial [9] and one add-on trial administering memantine to patients on standard doses of donepezil [10]. Since then, most clinical trials have accepted standard of care with a cholinesterase inhibitor with or without memantine at baseline; patients are randomized to the novel treatment or placebo as add-on treatments to the standard of care.

Patient populations included in these trials typically suffered from mild-to-moderate AD with Mini-Mental State Examination (MMSE) [11] scores of 10-26. All cholinesterase inhibitors are approved by the Food and Drug Administration (FDA) for mild-to-moderate AD. Donepezil is approved for use in patients with severe AD and memantine is approved for use in patients with moderate-to-severe AD.

Novel clinical trial designs as considered in this review comprise designs that deviate from this standard model.

Novel clinical trial designs for disease modifying agents

Adaptive or bayesian clinical trial designs

Adaptive or Bayesian trial designs refer to clinical trial designs that use accumulating data to guide modification of aspects of the study as it continues [12]. The adaptive trial design allows learning from the accumulating data and application of what is learned within the ongoing trial without undermining the validity and integrity of the trial. The adaptive process is prospectively planned and performed in a comprehensively pre-specified manner [13]. Adaptive clinical trial designs have been successfully used in oncology drug development programs with I-SPY I and I-SPY II as notable examples of the successful implementation of adaptive trial designs for serial testing of multiple antineoplastic agents [14, 15].

Adaptive clinical trial designs can be used for dose finding; response to side-effect occurrence; adjustment of trial duration to allow them to be shortened or lengthened depending on attaining pre-specified outcomes; or modification of entry criteria if pre-specified patient groups can be identified as responders or non-responders. Adaptive approaches have been used in Phase I first-in-human studies to maximize information about dose-response relationships [16] and in Phase II trials to flexibly assess efficacy and safety of investigational agents [17, 18].

Adaptive trials often require more time in the preparation phase since the decision framework for the trial must be pre-specified in the statistical analysis plan [13]. Adaptive trials provide the basis for advancing agents into more conventional trials in Phase III or for terminating a development program.

Staggered start and delayed withdrawal designs

Staggered start and delayed withdrawal designs were originally proposed by Paul Leber as a way
of providing evidence of disease modification without relying on biomarkers [19, 20]. In the staggered start/delayed start design patients are randomized to drug or placebo at baseline and after a pre-specified period the placebo group is treated with the active agent. If the delayed start group “catches up” with the group receiving treatment from the onset of the trial, no disease modification effect has been observed and the agent is deemed to have symptomatic benefits only. If the delayed start group does not catch up with the group receiving treatment from the onset, then it is concluded that disease modification has occurred.

In the staggered withdrawal design, patients in an active treatment arm are withdrawn from therapy and if they return to the functional level of an untreated group then no disease modification can be inferred. If after withdrawal, however, the treatment group continues to function at a higher level than an untreated group then data supporting disease modification have been generated [21]. These trial designs, while conceptually compelling, have rarely been implemented since the periods of treatment, delay to treatment, and observation after withdrawal of treatment are difficult to determine and add substantial uncertainty to the design implementation. Progress is being made in the utilization of these designs. A clinical trial of rasagiline in Parkinson’s disease utilized a delayed start design [22]. Two dose groups (1 mg and 2 mg per day) were compared with a placebo group. Early treatment with 1 mg per day provided benefits that were consistent with a disease-modifying effect. No similar pattern was observed in the 2 mg group leaving the disease-modifying efficacy of rasagiline unproven. The study established the methodology for implementing a delayed start trial in patients with a neurodegenerative disease.

Conceptual advances have been made in modeling randomized start and two period trials with specification of the design parameters, duration, and patient numbers required to establish disease-modifying effects [23, 24]. These modeling exercises may provide useful guidance for implementation of delayed start and staggered withdrawal designs in AD clinical trials.

**Time-to-onset designs**

Analysis of the drug/placebo differences in changes on a rating scale at trial end is the most common measure of drug efficacy. An alternate approach is the time-to-onset design where the difference between drug and placebo to time of onset of a predetermined disease milestone is the basis for comparison. Time to group progression from CDR 2 to CDR 3, death, nursing home placement or onset of severe disability has been used to compare vitamin E, selegiline, and placebo [25], and time-to-onset of AD dementia from mild cognitive impairment (MCI) was used to compare vitamin E, donepezil and placebo [26].

No agents have gained regulatory acceptance based on time-to-onset types of designs but they can be considered as one element of a drug development program. They generally require longer observation periods and larger sample sizes than conventional designs. Outcomes may be seen as more clinically relevant and embody trial outcomes important to payers. Use of time-to-onset designs in psychotropic treatment trials is described below.

**Futility designs**

A futility study compares the outcome of a single treated group against a predetermined threshold value reflective of a clinically meaningful change [27]. Futility studies may use a placebo control arm but often use historical controls to establish the threshold for clinical meaningfulness. A single dose or multiple doses may be included in futility studies. The advantage of futility studies is that fewer patients may be observed for shorter periods of time in Phase II to facilitate decisions about which agents should be prioritized to advance to Phase III. Futility studies have been successfully used in Parkinson’s disease [27] and in amyotrophic lateral sclerosis (ALS) [28, 29]. In a unique ALS trial testing CoQ10, an adaptive design was used for Phase I of a two phase trial to identify a promising dose, and a futility design was used in Phase II to determine whether the agent should be advanced to Phase III testing [30].

Futility designs have promise for use in AD drug development programs. An important caution in the application of futility designs using historical controls is that placebo groups have often varied substantially from trial to trial [31]. Careful matching between the selection criteria of the historical controls and the selection criteria for
the futility study is critical to insure that accurate inferences can be drawn.

**Combination therapy designs**

Multiple complex sequential and interactive pathways are involved in the neurobiology of AD. Intervention with a single agent may be insufficient to impact the disease course and simultaneous use of multiple agents may be required to achieve an optimal therapeutic benefit. As noted above, most contemporary clinical trials of AD are add-on treatments allowing both standard of care and novel therapeutic agents in the trial design. However, add-on designs do not provide the same information as combination therapy approaches where the combination can be compared to the effects of agents used singularly with all arms initiated simultaneously.

Combination treatments have been used in Phase II clinical trials of ALS showing their potential applicability in neurodegenerative disease. A celecoxib-creatine combination was selected over a minocycline-creatine combination for further study based on a trial comparing the two combinations’ progression to historical controls. Both combination therapies exceeded the futility threshold. The design was efficient requiring only sixty participants per treatment arm [32].

**Novel patient selection criteria for AD Trials**

Novel patient populations that are being identified for inclusion in AD clinical trials include prevention trials for those at high genetic risk for AD, prevention trials in those with a trait biomarker showing the presence of the AD pathological process but insufficient to cause clinical symptoms, and those with prodromal AD exhibiting symptoms of a hippocampal type of amnestic disorder and with a biomarker indicative of AD. These participant groups reflect the evolving definition of AD into a spectrum of severity from asymptomatic individuals with a positive biomarker, to minimally symptomatic persons with a biomarker of AD, to AD dementia [33-37].

**Prevention trials**

Prevention trials currently being implemented or planned include a study of crenezumab to delay the onset of cognitive impairment in patients carrying a presenilin 1 (PS1) mutation. The trial will be sixteen months long and will access multiple clinical and biomarker endpoints to provide preliminary evidence of efficacy [38]. The PS1 mutation is fully penetrant and all carriers develop the clinical syndrome of AD dementia. The time of onset of disease is relatively stereotyped within families and can be predicted for clinical trial purposes. By making the PS1 mutation the inclusion criterion the population will consist of some patients who have amyloid biomarkers at baseline (low cerebrospinal fluid (CSF), amyloid beta protein (Aβ42), or positive amyloid imaging) and some who do not. Differential efficacy of crenezumab in these two circumstances — before or after the onset of the Aβ pathophysiology — is an important dimension of this study.

A similar strategy is being used in the treatment portion of the Dominantly Inherited Alzheimer Network (DIAN) [39, 40]. In this trial, patients with PS1, presenilin 2 (PS2), or amyloid precursor protein (APP) mutations will be enrolled in clinical trials of disease-modifying agents and the impact on biomarkers determined. Clinical measures will be collected as secondary outcomes. Three agents will be compared with placebo in an innovative four-arm design.

The Alzheimer Disease Cooperative Study (ADCS) intends to conduct a study using trait markers of amyloid pathology (positive amyloid imaging) to identify patients at high risk for progressing from the preclinical asymptomatic state with Alzheimer’s type changes in the brain to symptomatic forms of AD [41].

Two other genetically informed trials include a plan to test individuals with high genetic risk for AD. In one trial persons homozygous for the apolipoprotein E4 (ApoE4) allele will be randomized to drug or placebo. The homozygous carrier state places an individual at great risk for the development of AD, and delay of onset of cognitive symptoms will be monitored as an outcome. The Takeda/Zinfandel study will use age, ApoE4 carrier status, and TOMM 40 gene status to stratify patients into high and low risk groups. High risk groups will be randomized to pioglitazone or placebo and followed for five years. The trial population will include 6,000 participants. The outcome is time to onset of AD-type cognitive decline.

These prevention trials capitalize on advancing understanding of the genetics of AD, bio-
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markers for AD, and new preventative disease-modifying treatments for AD.

A challenge to prevention trials is the difficulty of keeping patients at high risk on placebo for prolonged periods of observation. A recently proposed alternative is to use mathematical models to forecast outcomes of presymptomatic AD patients from their baseline data. This placebo group simulation approach (PGSA) would allow the forecasted outcomes to be compared with outcomes observed on candidate therapies [42]. This approach may have an advantage over the use of historical controls in futility designs in that it is based on the patient’s own observed clinical features.

Prodromal AD

Prodromal AD, a concept introduced by International Work Group (IWG) led by Bruno Dubois, refers to patients who have a hippocampal type of amnestic disorder and a biomarker indicative of the presence of AD but are not functionally impaired and do not meet criteria for AD dementia [33, 34]. Prodromal AD is similar to the syndrome of mild cognitive impairment (MCI) due to AD using criteria proposed by the National Institute on Aging (NIA) and Alzheimer’s Association (AA) workgroup [36]. Prodromal AD comprises a clinical-biological concept with a specific clinical phenotype supported by defined biomarkers. Prodromal AD populations are currently in clinical trials for immunotherapies, small molecules, and a medical food. Like the prevention trials utilizing asymptomatic at-risk populations, the prodromal trials represent a novel advance in AD clinical trial methodology using a pre-dementia population.

Synchronized populations

A challenge in AD trial design is the variable rate of progression observed among AD patients. Some patients progress rapidly while others exhibit indolent courses. Age, for example, has recently been shown to have an effect on progression with older patients in clinical trials progressing substantially more slowly than younger patients [43]. Recent designs propose novel subject synchronization criteria allowing for both the level of disease severity and the rate of progression to be integrated into the clinical trial design [44]. Inclusion of such features in clinical trials may allow more definitive outcomes, shorter trial durations, or smaller trial populations.

Novel clinical outcomes in AD trials

Preliminary data suggest that the ADAS-cog shows less change in earlier AD populations compared to patients with moderate AD dementia [45]. For more mild patients in AD clinical trials including individuals with no symptoms but at risk for progression to symptomatic phases of AD and individuals with prodromal AD the standardized use of the ADAS-cog may not be an optimal means of observing a drug-placebo difference. A variety of alternative approaches to analyzing the ADAS-cog have been suggested as means of improving the sensitivity to change of this instrument in mildly affected AD populations [46, 47]. None of these has been validated prospectively in a clinical trial. Further evolution of the ADAS-cog as a clinical trial outcome for early AD trials is anticipated [48].

Examination of the psychometric properties of the CDR-SOB indicates that this measure, which assesses both cognitive and functional features of AD, has psychometric properties that make it appropriate as an outcome for patients meeting criteria for MCI [49]. The calculated sample size for a 24-month MCI trial of a drug showing a 25 percent treatment affect would be 458 patients per arm using the CDR-SOB as an outcome compared to 1,046 patients if the ADAS-cog (11 item) was used as the outcome. If the CDR-SOB was combined with low CSF amyloid beta protein 1-42 (Aβ42) then only 282 patients were predicted to be required per arm compared to 639 patients per arm if the ADAS-cog plus CSF Aβ42 was used [50]. These calculations indicate that sample sizes in trials using the CDR-SOB or a combination of the CDR-SOB and biomarkers for outcomes clinical trials in patients with MCI or prodromal AD are feasible.

Patients with no or minimal symptoms have no functional compromise and use of traditional dual outcomes (function plus cognition or global plus cognition) may not be appropriate. A single clinical outcome, such as the CDR-SOB, may be viewed or indicative of treatment benefit in patients with pre-dementia AD [51, 52].

Computerized measures may add sensitivity to clinical trials and may be particularly useful
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Table 1. Computerized assessments used in AD clinical trials

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Domains</th>
<th>Strength</th>
<th>Weakness</th>
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<tbody>
<tr>
<td>Automated Neuropsychological Assessment Metrics (ANAM) (^{53})</td>
<td>Psychomotor speed, memory, attention; notably weak — language, delayed recall</td>
<td>Correctly classified 100% of AD patients vs. age-matched control</td>
<td>Weakness; patients often exhibited procedural confusion</td>
</tr>
<tr>
<td>Computer Assessment of Mild Cognitive Impairment (CAMCI) (^{54})</td>
<td>Attention, executive function, memory, processing speed</td>
<td>High sensitivity (86%) and specificity (94%) in MCI detection</td>
<td>Only one published study available, no data available in AD population</td>
</tr>
<tr>
<td>Computer-Administered Neuropsychological Screen for Mild Cognitive Impairment (CANS-MCI) (^{55})</td>
<td>Language, memory, executive function</td>
<td>Strong correlation with conventional tests</td>
<td>Only one published study available, no longitudinal data available</td>
</tr>
<tr>
<td>Cambridge Neuropsychological Test Automated Battery (CANTAB) (^{56,57})</td>
<td>Working memory, attention, visuospatial memory</td>
<td>Early detection of memory deficits</td>
<td>Study data is available for only a small selection of subtests</td>
</tr>
<tr>
<td>Central Nervous System Vital Signs (CNSVS) (^{58})</td>
<td>Memory, psychomotor speed, reaction time, cognitive flexibility, complex attention</td>
<td>Discrimination of normal control vs. MCI, MCI vs. mild AD</td>
<td>Lack of normative data for older age groups</td>
</tr>
<tr>
<td>Cognitive Drug Research (CDR/COGDRAS) (^{59})</td>
<td>Memory, attention, reaction time</td>
<td>Sensitivity in discriminating DAT vs. other forms of dementia</td>
<td>Adds little diagnostic value to basic clinical workup</td>
</tr>
<tr>
<td>CogState (^{60})</td>
<td>Working memory, executive function, attention, reaction time; notably weak – verbal ability</td>
<td>Designed for repeat administration</td>
<td>Difficult to distinguish early MCI from healthy controls without several rounds of administration</td>
</tr>
<tr>
<td>Cognitive Skills Index (CSI) (^{61})</td>
<td>Memory, attention, response speed, processing speed</td>
<td>Correlated well with diagnosis in geriatric clinic setting</td>
<td>All stimuli are presented non-verbally</td>
</tr>
<tr>
<td>MicroCog (Aeromedical Consultation Services) (^{62})</td>
<td>Memory, attention, reaction time, spatial ability, reasoning and calculation</td>
<td>Cognitive scoring significantly correlated with Full IQ component WAIS-III</td>
<td>Significant anxiety / frustration in cognitively impaired subjects</td>
</tr>
<tr>
<td>Mindstreams (Neurotrax) (^{63})</td>
<td>Memory, executive function, visuospatial, verbal fluency, attention, motor skills, information processing</td>
<td>Effective in detection of MCI / mild AD even when depressive symptoms are present</td>
<td>Length of time required for completion (45-60 min)</td>
</tr>
</tbody>
</table>

where a preliminary clinical benefit is being sought in a Phase II proof-of-concept trial. These measures might be used to track cognitive function among cognitively normal elders where a change in cognition will trigger a conventional clinical assessment [52]. A variety of computerized assessments are under development for application in AD trials (Table 1) [53-63]. Computerized neuropsychological assessment devices offer several advantages over conventional pen and paper tests. With only minimal rater training requirements (if any), computerized batteries offer a high degree of standardization in both administration and scoring. Their level of sensitivity toward metrics such as psychomotor speed and reaction time is impossible by human evaluators. A few shortcomings of the technology may be identified. There is often a lack of equivalence in subjects’ computer experience and there can be large practice effects associated with computerized test scores [64]. In the elderly population which predominately comprises AD trials, unfamiliar response modality, and physical design of the interface can also impact test performance. To compound this practical challenge, there is a shortage of established psychometric standards for computerized assessments. Ultimately, the decision of
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whether to incorporate computerized assessment or paper and pen assessments must be directly based upon the protocol in question – the format which optimizes endpoint assessment in that particular trial should be chosen.

Given the growing interest in demonstrating clinically meaningful value of new treatments, pharmacoeconomic, quality of life, and caregiver burden instruments are increasingly included among outcome measures in clinical trials [66].

Biomarkers in clinical trials

Biomarkers are increasingly used in clinical trials. They are employed as study entry criteria, outcomes, and side-effect monitoring. Biomarkers are the pre-specified outcomes for primary prevention trials involving patients without clinical symptoms but at high risk for symptomatic forms of AD [67, 39, 40]. A variety of candidate biomarkers have been examined as outcomes in AD trials. Diminished production of Aβ42 has been used as an outcome in proof-of-pharmacology studies of gamma-secretase inhibitors using the stable isotope labeled kinetics (SILK) technique [68]. Diminished CSF tau has been observed in studies of bapineuzamab [69] and AN1792 [70]. Diminished CSF Aβ42 was described in a trial of PBT2 [71]. Magnetic resonance imaging (MRI) volumetrics were used as an outcome in a Phase II bapineuzamab trial [72]. Amyloid imaging using Pittsburgh Compound B (PiB) has been used in a Phase II trial of bapineuzamab [73] and a Phase Ib trial of gantenerumab [74]. Serum levels of Aβ42 increase with many types of immunotherapeutic interventions and may comprise a pharmacodynamic measure relevant to treatment response [75]. The annual rate of change of AD biomarkers, as observed in the Alzheimer’s Disease Neuroimaging Initiative (ADNI), have been established and provides a guideline that might be useful in establishing sample size for adequately powered trials or as historical controls for futility trials [76].

MRI has played a key role in monitoring of amyloid-related imaging abnormalities (ARIA) in clinical trials [77, 78].

Innovations in trials of cognitive enhancing agents

Establishing the efficacy of higher doses of existing approved therapies has been the object of recent clinical trials. The efficacy of the 23 mg dose of donepezil was established in patients with moderate-to-severe AD, and the 13.3 mg rivastigmine patch was established as efficacious in patients with mild-to-moderate AD exhibiting cognitive and functional decline [79, 80]. Both of these designs used active comparator arms rather than placebo comparison groups. The 23 mg donepezil tablet was compared to 10 mg of donepezil, and the 13.3 mg rivastigmine patch was compared to the 9.5 mg rivastigmine patch.

Active comparator designs are valuable in establishing whether a novel therapy or new dose exceeds the benefit of established therapy. They are an effective trial design for a line extension approach within an approved indication.

Novel outcomes for trials of treatments of behavioral disturbances in AD

Neuropsychiatric symptoms are common in AD and no drugs have been approved for treatment of behavioral disturbances in this disorder. It is imperative that treatments be developed for disabling AD-related behavioral disturbances including agitation, psychosis, depression, and sleep disorders.

Novel designs have emerged in this area of AD drug development. Devanand and colleagues [81] used an antipsychotic discontinuation design to determine if patients with AD who are withdrawn from risperidone exhibit behavioral deterioration [81]. This withdrawal design is novel compared to the usual approach of initiating therapy and comparing the drug and placebo groups following treatment introduction.

The emergence of new behavioral disturbances over time is characteristic of AD. Behaviors present at baseline may be reduced by agents with psychotrophic properties. Patients with no symptoms at baseline may have less emergence of new behavioral symptoms when treated with psychotrophic or disease-modifying agents. Reduction of emergence of behavioral changes can function as an outcome to determine benefit of medications with psychotrophic or disease-modifying effects. Tariot and co-workers [82] tested sodium valproate in a delay-to-onset design accessing the emergence of agitation and psychosis in patients lacking these symptoms at baseline. No benefit of valproate treatment was
established, but the design parameters may be of value in other AD clinical trials focusing on symptom management.

A persistent problem in establishing efficacy of psychotropic agents in AD clinical trials is the high rate of improvement observed in patients in the placebo group. This response is likely multi-factorial in nature including placebo response of the caregiver, benefit from participation in the clinical trial and its associated high level of clinical care, regression to the mean, and issues in trial conduct. A novel design that seeks to minimize the placebo group response is the parallel sequential comparative design [83, 84]. In Phase I of this design there is a traditional comparison of treatment and placebo groups. At the end of Phase I, the placebo non-responders are re-randomized to treatment or placebo. The final comparison is between active treatment and placebo in the non-responders of Phase I. The placebo response in Phase I may approach 40 percent, while the placebo response in Phase II has characteristically been approximately 10 percent. This design has not been utilized in AD clinical trials but has promise as a means of reducing problematic placebo group responses.

Summary

The great need for new therapies for AD and the requirement to accelerate treatment development require innovation in clinical trial design. There have been a number of advances in clinical trial design that promise to improve trial conduct and outcomes in drug development programs for AD. The investigator has an increasing repertoire of designs from which to choose; and the final choice of trial design will be determined by the specific question that the trial is required to answer in the drug development program.

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