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Review Article

Advances in designs for Alzheimer's disease clinical trials

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Abstract: There is an urgent need to identify new treatments for the rapidly growing population of people with Alzheimer's disease (AD). Innovations in clinical trial designs many help to reduce development time, provide more definitive answers regarding drug efficacy, and facilitate prioritizing compounds to be advanced to Phase III clinical trials. Standard designs compare drug and placebo changes from baseline on a rating scale. Baysian adaptive clinical trials allow the use of data collected in the trial to modify doses, sample size, trial duration, and entry criteria in an on-going way as the data are collected. Disease-modification is supported by findings on staggered start and delayed withdrawal designs. Futility designs can use historical controls and may shorten trial duration. Combination therapy designs may allow investigation of additive or synergistic treatment effects. Novel trial selection criteria allow investigation of treatment effects in asymptomatic or minimally symptomatic, prodromal AD populations. The Clinical Dementia Rating-Sum of Boxes (CDR-SOB) can be considered as a single trial outcome in early disease populations. Alternate forms of the Alzheimer's Disease Assessment Scale-Cognitive Portion (ADAS-cog), computerized measures, and pharmacoeconomic scales provide new and relevant information on drug effects. Comparative dose strategies are used in trials of symptomatic agents, and novel methods including withdrawal designs, symptom emergence analyses, and sequential designs are being utilized to assess the efficacy of putative psychotropic agents. The choice of trial design is driven by the question to be answered by the clinical trial; an increasing number of design approaches are available and may be useful in accelerating and refining AD drug development.

Keywords: Clinical trials, Alzheimer's disease, designs, drug development

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 antidementia 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 affect 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 PSI 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-

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

Table 1. Computerized assessments used in AD clinical trials

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

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

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 bapineuzumab trial [72]. Amyloid imaging using Pittsburgh Compound B (PiB) has been used in a Phase II trial of bapineuzumab [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 psychotropic properties. Patients with no symptoms at baseline may have less emergence of new behavioral symptoms when treated with psychotropic or disease- modifying agents. Reduction of emergence of behavioral changes can function as an outcome to determine benefit of medications with psychotropic 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 placebo 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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References

[1] World Health Organization, Alzheimer's Disease International. Dementia: A Public Health Priority. Geneva 2012; www.alz.co.uk/WHO-dementia-report.

[2] PhRMA. Medicines in development for Alzheimer's disease. PhRMA 2010; http://www.phrma.org/research/medicines-development-alzheimers-disease.

[3] Thompson PA, Wright DE, Counsell CE, Zajicek J. Statistical analysis, trial design and duration in Alzheimer's disease clinical trials. Int Psychogeriatr 2012; 24: 689-697.

[4] Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984; 141: 1356-1364.

[5] O'Bryant SE, Lacritz LH, Hall J, Waring SC, Chan W, Khodr ZG, Massman PJ, Hobson V, Cullum CM. Validation of the new interpretive guidelines for the clinical dementia rating scale sum of boxes score in the national Alzheimer's coordinating center database. Arch Neurol 2010; 67: 746-749.

[6] Galasko D, Bennett D, Sano M, Ernesto C, Thomas R, Grundman M, Ferris S. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997; 11 Suppl 2: S33-S39.

[7] Gauthier S, Gélinas I, Gauthier L. Functional disability in Alzheimer's disease. Int Psychogeriatr 1997; 9 Suppl 1: 163-165.

[8] Leber P. Guidelines for the Clinical Evaluation of Antidementia Drugs. United States Food and Drug Administration, Washington, DC 1990; First draft.

[9] Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ; Memantine Study Group. Memantine in moderate-to-severe Alzheimer's

disease. N Engl J Med 2003; 348: 1333-1341.
[10] Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I; Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA 2004; 291: 317-324.
[11] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-198.
[12] Padmanabhan SK, Berry S, Dragalin V, Krams M. A Bayesian dose-finding design adapting to efficacy and tolerability response. J Biopharm Stat 2012; 22: 276-293.
[13] Wang SJ, Hung HM, O'Neill R. Adaptive design clinical trials and trial logistics models in CNS drug development. Eur Neuropsychopharmacol 2011; 21: 159-166.
[14] Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. Clin Pharmacol Ther 2009; 86: 97-100.
[15] Esserman LJ, Woodcock J. Accelerating identification and regulatory approval of investigational cancer drugs. JAMA 2011; 306: 2608-2609.
[16] Leonov S, Miller S. An adaptive optimal design for the E_{max} model and its application in clinical trials. J Biopharm Stat 2009; 19: 360-385.
[17] Wang SJ, Hung HM, O'Neill R. Regulatory perspectives on multiplicity in adaptive design clinical trials throughout a drug development program. J Biopharm Stat 2011; 21: 846-859.
[18] Berry SM, Spinelli W, Littman GS, Liang JZ, Fardipour P, Berry DA, Lewis RJ, Krams M. A Bayesian dose-finding trial with adaptive dose expansion to flexibly assess efficacy and safety of an investigational drug. Clin Trial 2010; 7: 121-135.
[19] Bodick N, Forette F, Hadler D, Harvey RJ, Leber P, McKeith IG, Riekkinen PJ, Rossor MN, Scheltens P, Shimohama S, Spiegel R, Tanaka S, Thal LJ, Urata Y, Whitehouse P, Wilcock G. Protocols to demonstrate slowing of Alzheimer disease progression. Position paper from the International Working Group on Harmonization of Dementia Drug Guidelines. The Disease Progression Sub-Group. Alzheimer Dis Assoc Disord 1997; 11 Suppl 3: 50-53.
[20] Leber P. Observations and suggestions on antidementia drug development. Alzheimer Dis Assoc Disord 1996; 10 Suppl 1: 31-35.
[21] Cummings JL. Defining and labeling disease-modifying treatments for Alzheimer's disease. Alzheimers Dement 2009; 5: 406-418.
[22] Olanow CW, Rascol O, Hauser R, Feigin PD, Jankovic J, Lang A, Langston W, Melamed E, Poewe W, Stocchi F, Tolosa E; ADAGIO Study Investigators. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. N Engl J Med 2009; 361: 1268-1278.
[23] Zhang RY, Leon AC, Chuang-Stein C, Romano SJ. A new proposal for randomized start design to investigate disease-modifying therapies for Alzheimer disease. Clin Trials 2011; 8: 5-14.
[24] McDermott MP, Hall WJ, Oakes D, Eberly S. Design and analysis of two-period studies of potentially disease-modifying treatments. Control Clin Trials 2002; 23: 635-649.
[25] Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, Woodbury P, Growdon J, Cotman CW, Pfeiffer E, Schneider LS, Thal LJ. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N Engl J Med 1997; 336: 1216-1222.
[26] Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, Galasko D, Jin S, Kaye J, Levey A, Pfeiffer E, Sano M, van Dyck CH, Thal LJ; Alzheimer's Disease Cooperative Study Group. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005; 352: 2379-2388.
[27] Tilley BC, Palesch YY, Kieburtz K, Ravina B, Huang P, Elm JJ, Shannon K, Wooten GF, Tanner CM, Goetz GC; NET-PD Investigators. Optimizing the ongoing search for new treatments for Parkinson disease: using futility designs. Neurology 2006; 66: 628-633.
[28] Czaplinski A, Haverkamp LJ, Yen AA, Simpson EP, Lai EC, Appel SH. The value of database controls in pilot or futility studies in ALS. Neurology 2006; 67: 1827-1832.
[29] Levy G, Kaufmann P, Buchsbaum R, Montes J, Barsdorf A, Arbing R, Battista V, Zhou X, Mitsumoto H, Levin B, Thompson JL. A two-stage design for a phase II clinical trial of coenzyme Q10 in ALS. Neurology 2006; 66: 660-663.
[30] Kaufmann P, Thompson JL, Levy G, Buchsbaum R, Shefner J, Krivickas LS, Katz J, Rollins Y, Barohn RJ, Jackson CE, Tiryaki E, Lomen-Hoerth C, Armon C, Tandan R, Rudnicki SA, Rezania K, Sufit R, Pestronk A, Novella SP, Heiman-Patterson T, Kasarskis EJ, Pioro EP, Montes J, Arbing R, Vecchio D, Barsdorf A, Mitsumoto H, Levin B; QALS Study Group. Phase II trial of CoQ10 for ALS finds insufficient evidence to justify phase III. Ann Neurol 2009; 66: 235-244.
[31] Schneider LS, Sano M. Current Alzheimer's disease clinical trials: methods and placebo outcomes. Alzheimers Dement 2009; 5: 388-397.
[32] Gordon PH, Cheung YK, Levin B, Andrews H, Doorish C, Macarthur RB, Montes J, Bednarz K, Florence J, Rowin J, Boylan K, Mozaffar T, Tandan R, Mitsumoto H, Kelvin EA, Chapin J, Bedlack R, Rivner M, McCluskey LF, Pestronk A, Graves M, Sorenson EJ, Barohn RJ, Belsh JM, Lou JS, Levine T, Saperstein D, Miller RG, Scelsa SN; Combination Drug Selection Trial Study Group. A novel, efficient, randomized

selection trial comparing combinations of drug therapy for ALS. Amyotroph Lateral Scler 2008; 9: 212-222.
[33] Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007; 6: 734-746.
[34] Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, Delacourte A, Frisoni G, Fox NC, Galasko D, Gauthier S, Hampel H, Jicha GA, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Sarazin M, de Souza LC, Stern Y, Visser PJ, Scheltens P. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 2010; 9: 1118-1127.
[35] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7: 280-292.
[36] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7: 270-279.
[37] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7: 263-269.
[38] Reiman EM, Langbaum JB, Tariot PN. Alzheimer's prevention initiative: a proposal to evaluate presymptomatic treatments as quickly as possible. Biomark Med 2010; 4: 3-14.
[39] Bateman RJ, Aisen PS, De Strooper B, Fox NC, Lemere CA, Ringman JM, Salloway S, Sperling RA, Windisch M, Xiong C. Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. Alzheimers Res Ther 2011; 3: 1-13.
[40] Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns NJ, Xie X, Blazey TM, Holtzman DM, Santacruz A, Buckles V, Oliver A, Moulder K, Aisen PS, Ghetti B, Klunk WE, McDade E, Martins RN, Masters CL, Mayeux R, Ringman JM, Rossor MN, Schofield PR, Sperling RA, Salloway S, Morris JC; the Dominantly Inherited Alzheimer Network. Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease. N Engl J Med 2012; 11.
[41] Reiman EM, Brinton RD, Katz R, Petersen RC, Negash S, Mungas D, Aisen PS. Considerations in the design of clinical trials for cognitive aging. J Gerontol A Biol Sci Med Sci 2012; 67: 766-772.
[42] Spiegel R, Berres M, Miserez AR, Monsch AU; the Alzheimer's Disease Neuroimaging Initiative. For debate: substituting placebo controls in long-term Alzheimer's prevention trials. Alzheimers Res Ther 2011; 3: 9.
[43] Bernick C, Cummings J, Raman R, Sun X, Aisen P. Age and Rate of Cognitive Decline in Alzheimer Disease: Implications for Clinical Trials. Arch Neurol. Published online 2012; 19.
[44] Schultz T, Yang E, Farnum M, Lobanov V, Verbeeck R, Raghavan N, Samtani MN, Novak G, Shi Y, Narayan V, Dibernardo A. A Novel Subject Synchronization Clinical Trial Design for Alzheimer's Disease. J Alzheimers Dis 2012; 30: 1 -10.
[45] Harrison J, Minassian SL, Jenkins L, Black RS, Koller M, Grundman M. Arch Neurol 2007; 64: 1323-1329.
[46] Balsis S, Unger AA, Benge JF, Geraci L, Doody RS. Gaining precision on the Alzheimer's Disease Assessment Scale-cognitive: A comparison of item response theory-based scores and total scores. Alzheimers Dement 2012; 8: 288-294.
[47] Skinner J, Carvalho JO, Potter GG, Thames A, Zelinski E, Crane PK, Gibbons LE; for the Alzheimer's Disease Neuroimaging Initiative. The Alzheimer's Disease Assessment Scale-Cognitive-Plus (ADAS-Cog-Plus): an expansion of the ADAS-Cog to improve responsiveness in MCI. Brain Imaging Behav 2012.
[48] Samtani MN, Farnum M, Lobanov V, Yang E, Raghavan N, Dibernardo A, Narayan V; Alzheimer's Disease Neuroimaging Initiative. An improved model for disease progression in patients from the Alzheimer's disease neuroimaging initiative. J Clin Pharmacol 2012; 52: 629-644.
[49] Monsell SE, Liu D, Weintraub S, Kukull WA. Comparing measures of decline to dementia in amnestic MCI subjects in the National Alzheimer's Coordinating Center (NACC) Uniform Data Set. Int Psychogeriatr 2012; 16: 1-8.
[50] Grill JD, Di L, Lu PH, Lee C, Ringman J, Apostolova LG, Chow N, Kohannim O, Cummings JL, Thompson PM, Elashoff D; Alzheimer's Disease Neuroimaging Initiative. Estimating sample sizes for predementia Alzheimer's trials based

on the Alzheimer's Disease Neuroimaging Initiative. Neurobiol Aging 2012.
[51] Cedarbaum JM, Jaros M, Hernandez C, Coley N, Andrieu S, Grundman M, Vellas B; Alzheimer's Disease Neuroimaging Initiative. Rationale for use of the Clinical Dementia Rating sum of boxes as a primary outcome measure for Alzheimer's disease clinical trials. Alzheimers Dement 2012.
[52] Coley N, Andrieu S, Jaros M, Weiner M, Cedarbaum J, Vellas B. Suitability of the clinical dementia rating-sum of boxes as a single primary endpoint for Alzheimer's disease trials. Alzheimers Dement 2011; 7: 602-610.
[53] Levinson D, Reeves D, Watson J, Harrison M. Automated neuropsychological assessment metrics (ANAM) measures of cognitive effects of Alzheimer's disease. Arch Clin Neuropsychol 2005; 20: 403-408.
[54] Saxton J, Morrow L, Eschman A, Archer G, Luther J, Zuccolotto A. Computer assessment of mild cognitive impairment. Postgrad Med 2009; 121: 177-185.
[55] Tornatore JB, Hill E, Laboff J, McGann ME. Self-administered screening for mild cognitive impairment: Initial validation of a computerized test battery. J Neuropsychiatr Clin Neurosci 2005; 17: 98-105.
[56] Fowler KS, Saling MM, Conway EL Semple JM, Louis WJ. Computerized neuropsychological tests in the early detection of dementia: prospective findings. J Int Neuropsychol Soc 1997; 3: 139-146.
[57] De Jager CA, Milwain E, Budge M. Early detection of isolated memory deficits in the elderly: the need for more sensitive neuropsychological tests. Psychol Med 2002; 32: 483-491.
[58] Gualtieri CT, Johnson LG. Neurocognitive testing supports a broader concept of mild cognitive impairment. Am J Alzheimers Dis Other Demen 2005; 20: 359-366.
[59] Gualtieri CT, Johnson LG. Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. Arch Clin Neuropsychol 2006; 21: 623-643.
[60] Ballard C, O'Brien J, Gray A, Cormack F, Ayre G, Rowan E, Thompson P, Bucks R, McKeith I, Walker M, Tovee M. Arch Neurol 2001; 58: 977 -982.
[61] DeLepeliere J, Heyrman J, Baro F, Buntinx F. A combination of tests for the diagnosis of dementia had a significant diagnostic value. J Clin Epidemiol 2005; 58: 217-225.
[62] Falleti MG, Maruff P, Collie A, Darby D. Practice effects associated with the repeated assessment of cognitive function using the CogState battery at 10-minute, one week and one month test-retest intervals. J Clin Exp Neuropsychol 2006; 28: 1095-1112.
[63] Darby D, Maruff P, Collie A, McStephen M. Mild cognitive impairment can be detected by multiple assessments in a single day. Neurology 2002; 59: 1042-1046.
[64] Lichtenberg PA, Johnson AS, Erlanger DM, Kaushik T, Maddens ME, Imam K, Barth J, Webbe FM. Enhancing cognitive screening in geriatric care: use of an internet-based system. Int J Healthcare Inf Sys Informatics 2006; 1: 47 -57.
[65] Darby D, Brodtmann A, Woodward M, Budge M, Maruff P. Using cognitive decline in novel trial designs for primary prevention and early disease-modifying therapy trials of Alzheimer's disease. Int Psychogeriatr 2011; 11: 1-10.
[66] Fillit H, Cummings J, Neumann P, McLaughlin T, Salavtore P, Leibman C. Novel approaches to incorporating pharmacoeconomic studies into phase III clinical trials for Alzheimer's disease. J Nutr Health Aging 2010; 14: 640-647.
[67] Reiman EM, Langbaum JB, Tariot PN. Alzheimer's prevention initiative: a proposal to evaluate presymptomatic treatments as quickly as possible. Biomark Med 2010; 4: 3-14.
[68] Bateman RJ, Siemers ER, Mawuenyega KG, Wen G, Browning KR, Sigurdson WC, Yarasheski KE, Friedrich SW, Demattos RB, May PC, Paul SM, Holtzman DM. A gamma-secretase inhibitor decreases amyloid-beta production in the central nervous system. Ann Neurol 2009; 66: 48-54.
[69] Blennow K, Zetterberg H, Rinne JO, Salloway S, Wei J, Black R, Grundman M, Liu E; for the AAB-001 201/202 Investigators. Effect of immunotherapy with bapineuzumab on cerebrospinal fluid biomarker levels in patients with mild to moderate Alzheimer disease. Arch Neurol 2012.
[70] Gilman S, Koller M, Black RS, Jenkins L, Griffith SG, Fox NC, Eisner L, Kirby L, Rovira MB, Forette F, Orgogozo JM; AN1792(QS-21)-201 Study Team. Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. Neurology 2005; 64: 1553-1562.
[71] Lannfelt L, Blennow K, Zetterberg H, Batsman S, Ames D, Harrison J, Masters CL, Targum S, Bush AI, Murdoch R, Wilson J, Ritchie CW; PBT2 -201-EURO study group. Safety, efficacy, and biomarker findings of PBT2 in targeting Abeta as a modifying therapy for Alzheimer's disease: a phase IIa, double-blind, randomised, placebo-controlled trial. Lancet Neurol 2008; 7: 779-786.
[72] Salloway S, Sperling R, Gilman S, Fox NC, Blennow K, Raskind M, Sabbagh M, Honig LS, Doody R, van Dyck CH, Mulnard R, Barakos J, Gregg KM, Liu E, Lieberburg I, Schenk D, Black R, Grundman M; Bapineuzumab 201 Clinical Trial Investigators. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. Neurology 2009; 73: 2061-2070.
[73] Rinne JO, Brooks DJ, Rossor MN, Fox NC, Bullock R, Klunk WE, Mathis CA, Blennow K, Barakos J, Okello AA, Rodriguez Martinez de Liano

S, Liu E, Koller M, Gregg KM, Schenk D, Black R, Grundman M. 11C-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study. Lancet Neurol 2010; 9: 363-372.

[74] Ostrowitzki S, Deptula D, Thurfjell L, Barkhof F, Bohrmann B, Brooks DJ, Klunk WE, Ashford E, Yoo K, Xu ZX, Loetscher H, Santarelli L. Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab. Arch Neurol 2012; 69: 198-207.

[75] Siemers E, DeMattos RB, May PC, Dean RA. Role of biochemical Alzheimer's disease biomarkers as end points in clinical trials. Biomark Med 2010; 4: 81-89.

[76] Beckett LA, Harvey DJ, Gamst A, Donohue M, Kornak J, Zhang H, Kuo JH; Alzheimer's Disease Neuroimaging Initiative. The Alzheimer's Disease Neuroimaging Initiative: Annual change in biomarkers and clinical outcomes. Alzheimers Dement 2010; 6: 257-264.

[77] Sperling RA, Jack CR Jr, Black SE, Frosch MP, Greenberg SM, Hyman BT, Scheltens P, Carrillo MC, Thies W, Bednar MM, Black RS, Brashear HR, Grundman M, Siemers ER, Feldman HH, Schindler RJ. Alzheimers Dement 2011; 7: 367-385.

[78] Sperling R, Salloway S, Brooks DJ, Tampieri D, Barakos J, Fox NC, Raskind M, Sabbagh M, Honig LS, Porsteinsson AP, Lieberburg I, Arrighi HM, Morris KA, Lu Y, Liu E, Gregg KM, Brashear HR, Kinney GG, Black R, Grundman M. Lancet Neurol 2012; 11: 241-249.

[79] Farlow M, Veloso F, Moline M, Yardley J, Brand-Schieber E, Bibbiani F, Zou H, Hsu T, Satlin A. Safety and tolerability of donepezil 23 mg in moderate to severe Alzheimer's disease. BMC Neurol 2011; 11: 57.

[80] Cummings J, Froelich L, Black SE, Bakchine S, Bellelli G, Molinuevo JL, Kressig RW, Downs P, Caputo A, Strohmaier C. Randomized, double-blind, parallel-group, 48-week study for efficacy and safety of a higher-dose rivastigmine patch (15 vs. 10 cm) in Alzheimer's disease. Dement Geriatr Cogn Disord 2012; 33: 341-353.

[81] Devanand DP, Pelton GH, Cunqueiro K, Sackeim HA, Marder K. A 6-month, randomized, double-blind, placebo-controlled pilot discontinuation trial following response to haloperidol treatment of psychosis and agitation in Alzheimer's disease. Int J Geriatr Psychiatry 2011; 26: 937-943.

[82] Tariot PN, Schneider LS, Cummings J, Thomas RG, Raman R, Jakimovich LJ, Loy R, Bartocci B, Fleisher A, Ismail MS, Porsteinsson A, Weiner M, Jack CR Jr, Thal L, Aisen PS; Alzheimer's Disease Cooperative Study Group. Chronic divalproex sodium to attenuate agitation and clinical progression of Alzheimer disease. Arch Gen Psychiatry 2011; 68: 853-861.

[83] Fava M, Evins AE, Dorer DJ, Schoenfeld DA. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. Psychother Psychosom 2003; 72: 115-127.

[84] Tamura RN, Huang X. An examination of the efficiency of the sequential parallel design in psychiatric clinical trials. Clin Trials 2007; 4: 309-317.