



**Clinical Trials for Disease-Modifying Therapies in Alzheimer's Disease:  
A Primer, Lessons Learned, and a Blueprint for the Future**

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## Review

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# Clinical Trials for Disease-Modifying Therapies in Alzheimer's Disease: A Primer, Lessons Learned, and a Blueprint for the Future

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**Abstract.** Alzheimer's disease (AD) has no currently approved disease-modifying therapies (DMTs), and treatments to prevent, delay the onset, or slow the progression are urgently needed. A delay of 5 years if available by 2025 would decrease the total number of patients with AD by 50% in 2050. To meet the definition of DMT, an agent must produce an enduring change in the course of AD; clinical trials of DMTs have the goal of demonstrating this effect. AD drug discovery entails target identification followed by high throughput screening and lead optimization of drug-like compounds. Once an optimized agent is available and has been assessed for efficacy and toxicity in animals, it progresses through Phase I testing with healthy volunteers, Phase II learning trials to establish proof-of-mechanism and dose, and Phase III confirmatory trials to demonstrate efficacy and safety in larger populations. Phase III is followed by Food and Drug Administration review and, if appropriate, market access. Trial populations include cognitively normal at-risk participants in prevention trials, mildly impaired participants with biomarker evidence of AD in prodromal AD trials, and subjects with cognitive and functional impairment in AD dementia trials. Biomarkers are critical in trials of DMTs, assisting in participant characterization and diagnosis, target engagement and proof-of-pharmacology, demonstration of disease-modification, and monitoring side effects. Clinical trial designs include randomized, parallel group; delayed start; staggered withdrawal; and adaptive. Lessons learned from completed trials inform future trials and increase the likelihood of success.

**Keywords:** Alzheimer's disease, biomarkers, clinical trials, disease modifying therapies, proof-of-concept, target engagement

## INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease that produces gradual decline in cognition and function [1, 2]. The most common form, late onset AD, becomes symptomatic in late life but biomarker studies show that the amyloid

protein considered the major risk factor for the disease begins to accumulate in the brain up to 20 years before symptoms begin [3].

The total number of individuals with AD will double every 20 years [4]. The annual cost of AD currently exceeds \$230 billion and the total annual cost will exceed \$1 trillion by 2050 if means of preventing, delaying, slowing the progression, or improving the symptoms are not found [5].

There is a high rate of negative clinical trials in AD drug development programs; 99% of drugs tested

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between 2002 and 2014 showed no drug-placebo difference and only one drug was approved by the US Food and Drug Administration (FDA) during that period [6]. Drugs in the AD pipeline include agents intended to intervene in the basic biology of AD and modify disease progression, symptomatic cognitive enhancers, and drugs to treat neuropsychiatric symptoms [7, 8].

The greatest need in AD drug development is for disease-modifying therapies (DMTs) that will delay or slow the clinical course of AD by intervening in the processes leading to cell death [9]. Approximately two-thirds of the current AD drug development pipeline involves DMTs—either immunotherapies or small molecule agents administered orally [7, 8]. In this paper, we describe the methods for AD clinical trials of DMTs, review past failures to identify lessons for AD drug development, and look ahead to new approaches to improving AD drug development and optimizing success in bringing new treatments to patients with AD or those at high risk for the disorder.

## OVERVIEW

Figure 1 shows the overview of an AD treatment discovery and development program beginning with identification of a target and proceeding through preclinical (sometimes called non-clinical) characterization; to Phase I, Phase II, and Phase III clinical trials; and to regulatory review and patient access

through marketing. On average, development for an AD treatment requires 13 years and is expected to cost \$5.6 billion U.S. dollars. Preclinical evaluation requires approximately 2 years, Phase I averages 2.8 months, Phase II requires 27.7 months, Phase III is typically 50.9 months, and FDA review requires 18 months [10]. These figures are for AD drugs of all types and likely under-estimate the time taken to develop an AD DMT.

The biography of new agents can be divided into *discovery* phases extending from the first characterization of the compound to the final optimization of the lead candidate and *development* extending from preclinical/animal testing to Phase I First-in-Human (FIH) studies through Food and Drug Administration (FDA) review and to Phase IV for those agents undergoing post-approval assessment.

## DRUG DISCOVERY

### *Target identification and drug discovery*

A DMT must intervene in the basic biology of AD leading to cell death [9]. Common targets in AD are processes of production, oligomerization, or clearance of the amyloid- $\beta$  protein (A $\beta$ ); the development of neurofibrillary tangles from the tau protein; processes associated with cellular metabolism; neuroinflammation; oxidative injury to membranes; or cell maintenance and regeneration strategies such as

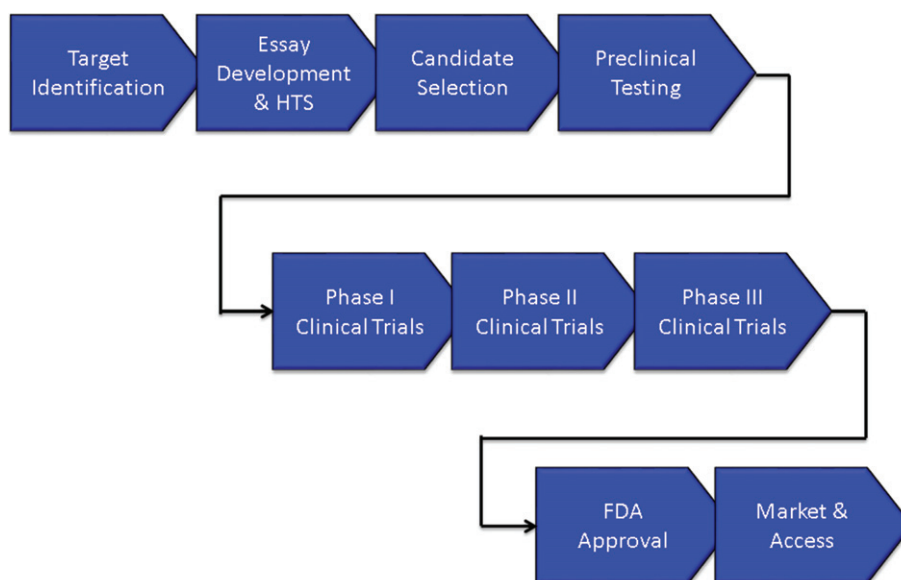


Fig. 1. Overview of the drug development process.

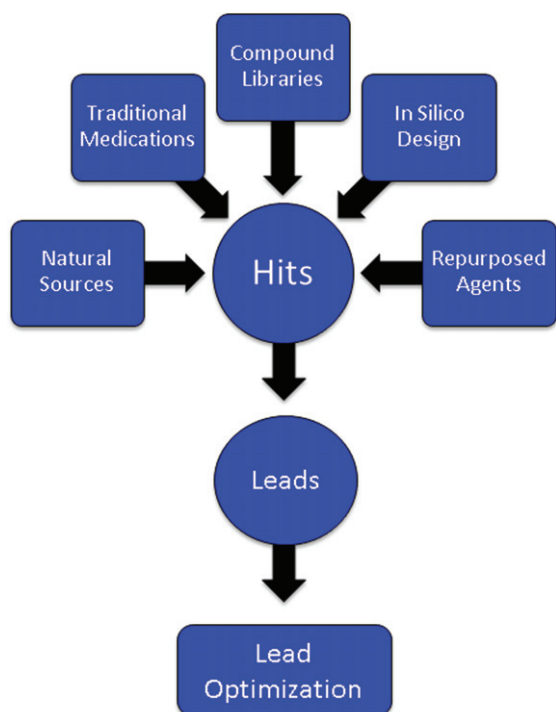


Fig. 2. Origin of compounds that are assayed through high throughput screening to produce “hits” that are then subject to medicinal chemistry refinement to produce leads and optimized leads.

stem cells or growth factors. Targets must be “drug-gable” to provide the basis for a drug discovery and development programs; druggable targets have properties that can be modulated by small molecules (e.g., drugs) or antibodies [11].

After a target has been identified, an assay is developed for the proposed mechanism of action (MOA) such as inhibition of the  $\beta$ -secretase enzyme necessary for  $A\beta$  production, modulation of the  $\gamma$ -secretase enzyme also critical to  $A\beta$  generation, inhibition of oligomerization of  $A\beta$  into its most toxic form, phosphorylation of the tau protein required for the formation of neurofibrillary tangles, activation of microglia in the inflammatory process, or manipulation of cell survival through growth factors. Large numbers of compounds (“libraries”) are screened for “hits” that have the desired effects in the assay (Fig. 2). Libraries are constructed from pharmacophores with multiple molecular forms, traditional medications (e.g., Traditional Chinese Medicines), natural sources and biodiversity, repurposed agents that may have AD-related effects, and compounds designed by computer where structure-activity relationships can be modeled *in silico* [12]. Several hundred thousand compounds may be screened to

identify a sufficient number of hits to provide a foundation for further development. The hits are reviewed by medicinal chemists for “drug-likeness” including features that predict good absorption and membrane penetration [13, 14]. Agents with promising characteristics are optimized for molecular features that enhance the likelihood of being successful as a drug for human therapy—potency, half-life, predictable toxicity, blood-brain barrier (BBB) penetration, etc. Once a lead compound and several backups are identified, testing in animals can begin [15].

An alternative to high-throughput screening with biological assays is high content analysis (HCA), conducted in intact cells using automated microscopy and image analysis. HCA can be used to screen for effects on protein aggregation, synaptic integrity, neuron and synapse number, and apoptosis as well as other cellular processes relevant to AD treatment [16]. HCA may more closely reflect the neurological environment in which drugs must act when administered in the human setting.

#### Preclinical assessment

Assessment of the lead candidate in animals establishes the pharmacokinetic characteristics, toxicity, and efficacy of the molecule in the test species. Testing involves both short-term and long-term treatment in a wide range of doses to establish the absorption, distribution, metabolism, excretion (ADME), and toxicity of the potential treatment [17]. Testing is required in two species, usually mice and rats. Dogs have a high sensitivity to cardiac effects of drugs and are the usual assay species for cardiac toxicity [18]. Special attention is paid to liver and bone marrow toxicity; laboratory and necropsy studies are performed to thoroughly assess any off-target adverse effects in the animals. In addition, panels of enzymes, ion channels, and other biological mechanisms are used to search for unanticipated off-target effects of the candidate therapy [19]. If no unusual toxicity is identified, the highest drug dose level at which no adverse events (NOAEL) are seen is determined and becomes the basis for dose calculations for the maximum recommended safe starting dose (MRSD) for FIH studies [20].

Development of monoclonal antibodies (mAb) differs from that of the approach to developing small molecules. Monoclonal antibodies are manufactured to interact with a specific epitope of a target such as a portion of the  $A\beta$  molecule to limit its oligomerization into a more toxic form, facilitate its removal

by brain microglia, or bind with peripheral A $\beta$  to form a “peripheral sink” to remove AD from the brain [21, 22]. Monoclonal antibodies have fewer risks for off-target effects since they are exquisitely targeted to specific molecular sites.

Animal species are also used to explore the efficacy of candidate therapies. Throughout the drug development process, every effort is made to minimize the use of animals and to develop alternatives to animal observations in the assessment of both the toxicity and efficacy of candidate therapies. Although success in animal models has not yet predicted success of a DMT in humans, the failure to see the desired effect in an animal model system of AD biology would constitute a reason not to advance the molecular candidate to human testing [23]. The most commonly used animal model systems are transgenic (tg) mice that have one or more human genes known to cause familial AD in their genome. The amyloid precursor protein/presenilin 1 double tg is a widely used test animal. These genetically modified mice begin to deposit brain amyloid by 6 months of age and by 9 months of age show mild cognitive impairment. Anti-amyloid approaches can be tested in this model. Triple tg and 5x tg as well as many types of gene knock-in (KI) and knock-out (KO) species have been developed. The model animals exhibit specific aspects of the AD pathology observed in humans. Tg animals develop brain amyloidosis with plaques similar to those of humans but typically have little tau formation, inflammation, or cell death characteristic of human AD. They provide a means of assessing the anti-amyloid effect of the agent but not its likely success in the complex multifactorial AD process observed in humans [24].

Human-derived induced pluripotent stem (iPS) cells are increasingly used to screen drugs and to move the early screening process toward a more human biological context with the hope of having greater predictability for human response. The stem cells may be derived from fibroblasts of patients with autosomal dominant AD and the induced stem cells undergo directed transformation to neurons which bear the genetic abnormality and can be the substrate for drug efficacy assessment, or skin cells from unaffected donors can be transformed into iPS cells and then into neurons and an amyloid-related mutation is introduced to create a platform for treatment assessment [25, 26]. The cells are grown in gels allowing 3-dimensional growth and spontaneously form organoid structures with brain-like features. The iPS cell platforms show both amyloid and tau pro-

tein accumulation further recapitulating the human disease and creating a more ecologically valid system for drug efficacy assessment [25].

If the candidate agent has acceptable ADME and toxicity characteristics and shows desirable activity in the model used to assess efficacy, it will be advanced to human testing.

## CLINICAL TRIALS

### *Introduction*

The development phase—and to a lesser extent the discovery phase—of drug creation is guided by a Target Product Profile (TPP) [27]. The TPP defines the desirable features of a drug and its use including the primary indication, patient population, treatment duration, delivery mode, dosage, regimen, tolerability, risk/side effects, tolerability, and differentiating features in a competitive landscape. A minimally acceptable profile and an ideal profile are identified. Failure to achieve the minimally acceptable profile may lead to discontinuation of the development program. Using the TPP, the indication and proposed package insert are constructed and the development program is designed in reverse to insure that all the features of the TPP are fully defined for the compound in the course of development.

Clinical trials must be reported in a specific format called the Consolidated Standards of Reporting Trials (CONSORT) when they are submitted to journals [28]. The International Committee of Medical Journal Editors has subscribed to these requirements to achieve standardized reporting of clinical trials. Table 1 provides the CONSORT checklist of elements to be included in any report of a clinical trial. Anticipation of the features to be reported allows the checklist to function as a useful guide to planning a clinical trial.

The National Institutes of Health (NIH) has developed a template that can be used to plan a clinical trial including all elements necessary to meet Good Clinical Practice (GCP) guidelines and CONSORT requirements ([http://osp.od.nih.gov/sites/default/files/Protocol\\_Template\\_05Feb2016\\_508.pdf](http://osp.od.nih.gov/sites/default/files/Protocol_Template_05Feb2016_508.pdf)). This extensive template serves as a precise guide to clinical trial planning and presentation for Institutional Review Board, funder, and FDA review.

### *Phase I*

Phase I involves the FIH exposure of the drug. In small molecule development programs, the persons

Table 1  
CONSORT checklist [28]

Section / Topic	Checklist Item
Introduction	
Background and objectives	Scientific background and explanation of rationale; specific objectives or hypotheses
Methods	
Trial design	Description of trial design (such as parallel, factorial) including allocation ratio; important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	Eligibility criteria for participants; settings and locations where the data were collected
Interventions	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	Completely defined pre-specified primary and secondary outcome measures, including how and when they were accessed; any changes to trial outcomes after the trial commenced, with reasons
Sample size	How sample size was determined; When applicable, explanation of any interim analyses and stopping guidelines
Random sequence generation	Method used to generate the random allocation sequence; type of randomization; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers)
Randomization implementation	Who generated the random allocation sequence, who enrolled the participants, and who assigned participants to interventions
Blinding	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and; if relevant, description of the similarity of interventions
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes
Results	
Participant flow diagram	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome; for each group, losses and exclusions after randomization, together with reasons
Recruitment	Dates defining the periods of recruitment and follow-up
Baseline data	A table showing baseline demographic and clinical characteristics for each group
Numbers analyzed	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned group
Outcomes and estimation	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval); for binary outcomes, presentation of both absolute and relative effect sizes
Ancillary analyses	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms (28))
Discussion	
Limitations	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalizability	Generalizability (external validity, applicability) of the trial findings
Interpretation	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Other Information	
Registration	Registration number and name of trial registry
Funding	Sources of funding and other support (such as supply of drugs); role of funders

participating in the Phase I trial are normal healthy volunteers [29]. If a mAb or vaccine is being developed, the FIH testing is usually done with patients with AD. Immunotherapies can permanently alter the immune system—this is more likely with a vaccine than a mAb—and the unknown consequences of this cannot be risked in young healthy individuals.

Single ascending dose (SAD) studies where cohorts of individuals are exposed to a single dose of progressively higher doses of the agent are followed by multiple ascending dose (MAD) studies

where cohorts are treated for 14–28 days with progressively higher doses of the agent [30]. A cohort is typically 8–12 individuals randomized in a 4:1 ratio of active agent to placebo. SAD studies and some portions of MAD studies are conducted in specially designed Phase I in-patient units. Serial blood samples as well as urine and stool samples are collected to determine ADME characteristics in humans. Patient reports, physical examination, electrocardiography, and blood tests are collected to determine the safety and tolerability of each dose.

Ideally, a maximum tolerated dose (MTD) is determined at this stage of drug development. There are several ways of determining the lowest dose to be tested in Phase I; typically a dose representing 1/10 of the NOAEL observed in the most sensitive animal species is the beginning dose and the dose is doubled in each successive cohort [20]. The MTD informs future studies since it represents the upper limit of dosing. Low, medium, and high doses are typically advanced to Phase II. Failure to establish an MTD in Phase I can lead to future challenges in the development process; if later trials are negative, it may be difficult to know whether the agent is ineffective or was not given in a sufficient dose.

Assessing CSF drug levels in Phase I can provide important insights about a candidate compound's ability to penetrate the human BBB and exert CNS effects. Treatments should not exit Phase I without evidence of BBB penetration and an understanding of plasma/CSF ratios. Consisting of tight junctions joining the endothelial cells of the central nervous system, the BBB creates a physical barrier that severely restricts the size and ionic properties of molecules permitted to cross into the brain [31]. Augmenting the physical barrier is a complex network of enzymes and transport proteins, such as P-glycoprotein (P-gp), breast cancer resistance protein, and multidrug resistance protein that metabolize and expel molecules that are able to pass through the physical barrier. The BBB thus represents a significant obstacle for agents intended to reach targets deep within the brain parenchyma and failure to penetrate the BBB has contributed to failed development programs [32].

The challenges of BBB penetration require confirmation of drug delivery into the brain in early phase testing. Lumbar CSF measures provide an approximation of the brain exposure in humans. Levels of unbound, pharmacologically active drug in CSF can be drawn during continuous intravenous infusion or at fixed time points after systemic delivery [33]. Differences in the human and rodent BBB, particularly the robustness of the P-gp system, leads to differences in human CSF levels and makes extrapolations between human and animal data problematic [34]. Observations made from CSF in the healthy state must later be confirmed in the disease state as differences in cerebral blood flow, activity of efflux transport proteins, and BBB permeability with disease may fundamentally alter drug delivery [35].

## Phase II

Drugs that appear safe and have acceptable ADME and safety profiles when tested in normal human volunteers are advanced to Phase II to be tested in the population of interest, AD. Repurposed agents that have been gone through Phase I while being developed for another indication (e.g., hypertension, cancer, Parkinson's disease, diabetes, etc.) may enter directly into Phase II or occasionally directly into Phase III [36, 37].

Phase II generally encompasses Phase IIa proof-of-concept (POC) trials and Phase IIb dose-finding studies. The goal of Phase II is to gain confidence in the treatment and provide information for Phase III trials. Phase II involves patients with AD dementia or prodromal AD [38]. A conundrum has evolved for Phase II trials of AD DMTs. The decision to advance an agent to Phase II could be based on a Phase IIa study with a biomarker outcome, using the biomarker to decide if there is a sufficient likelihood of clinical success. The challenge with this approach is that there is no AD biomarker that has gained surrogate status and none is known to predict a clinical outcome. Alternately, one can require clinical POC with benefit on a traditional clinical measure such as the AD Assessment Scale – cognitive portion (ADAS-cog) [39] or Clinical Dementia Rating – Sum of Boxes (CDR-sb) [40]. To show clinical benefit typically requires a large long trial equivalent to a Phase III trial [41]. Thus, some development programs move from Phase I directly to Phase III. This often results in a Phase III program that is advancing an agent with limited information regarding safety, tolerability, biomarker effects, or dosing. This strategy may contribute to the high failure rate of AD drug development and the absence of any successful DMTs [6].

Increasingly, biomarkers are used in Phase II to support decision making for development programs (Fig. 3). Biomarkers are used to confirm the diagnosis of AD. The clinical diagnosis of AD dementia is not confirmed by amyloid or CSF amyloid and tau measures in approximately 25% of patients diagnosed clinically with AD [42], indicating that they do not have the pathobiology of AD. Approximately 50% of mild cognitive impairment patients have abnormal amyloid measures and constitute a prodromal AD population—50% do not have early AD [43]. AD trials must have individuals with AD to draw accurate conclusions about efficacy of AD-directed therapies. Figure 4 shows normal and AD-type amyloid positron

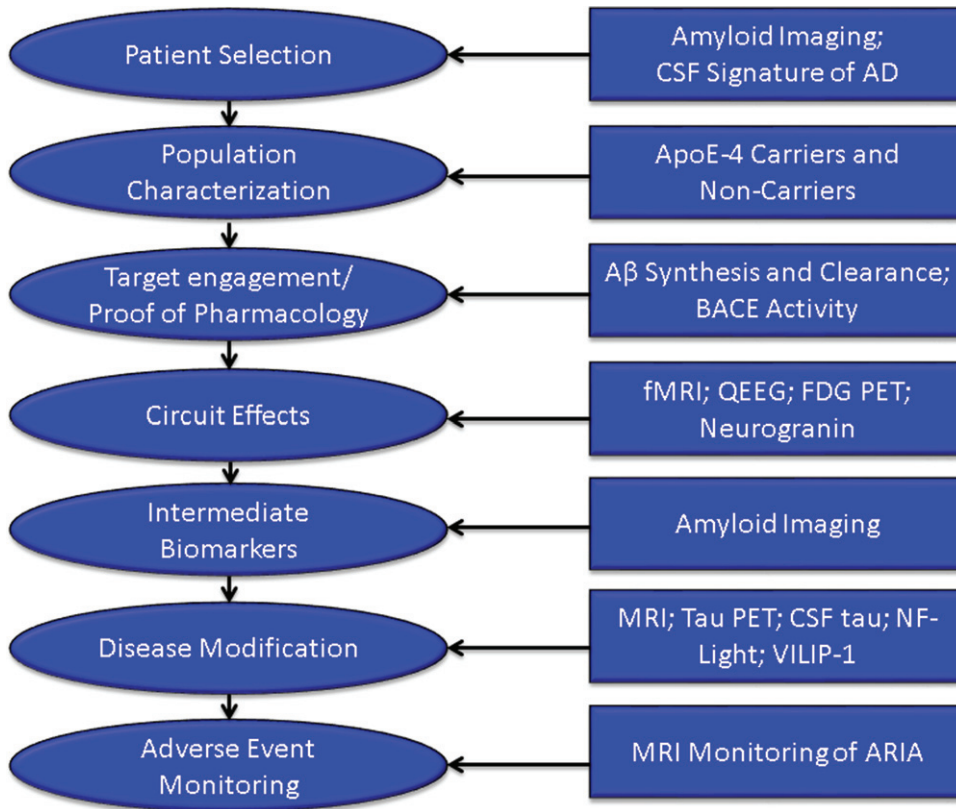


Fig. 3. Roles of biomarkers in Phase II of drug development (BACE inhibition is included as an example of one type of target engagement biomarker; each drug mechanism will have a corresponding target engagement/proof of pharmacology biomarker), CSF, cerebrospinal fluid; AD, Alzheimer's disease; fMRI, functional magnetic resonance imaging; QEEG, quantitative electroencephalography; FDG PET, fluorodeoxyglucose positron emission tomography; NF-light, neurofilament light chain protein; ARIA, amyloid-related imaging abnormalities.

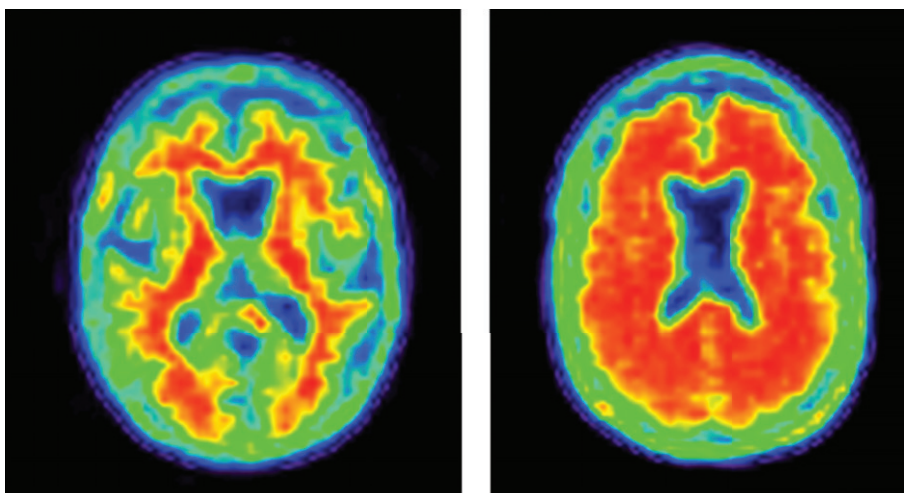


Fig. 4. Negative (normal) and positive (abnormal; consistent with AD) amyloid PET images.



emission tomography (PET) used to support the diagnosis of AD.

Populations in AD trials are typically divided by apolipoprotein E (ApoE) genotype into ApoE4 allele carriers and noncarriers. Allele status may affect efficacy and side effects and often influences dosing in mAb trials [42, 44, 45]. Recruitment may not be stratified by genotype but the statistical analysis plans will contrast carriers and noncarriers for efficacy and toxicity.

Target engagement biomarkers are critical to demonstrating that the drug is having the desired clinical effect on the near-term target. Without target engagement, the disease-modifying properties of the drug cannot be assessed. For example, if a beta-site cleavage enzyme (BACE) inhibitor is not producing BACE inhibition or is not affecting amyloid synthesis, then the hypothesis that BACE inhibition will produce disease-modification cannot be assessed. Amyloid deposition is an intermediate biomarker of drug efficacy. It may not be immediately related to cell death but appears necessary to establish an environment in which cell death occurs. Effects on amyloid deposition can serve as an intermediate biomarker of anti-plaque effects of anti-amyloid drug activity. In the PRIME study of aducanumab, for example, reduced brain amyloid was demonstrated after 6 months of therapy and was more marked after 12 months of treatment [43].

Cognition is mediated by integrated cerebral circuits and preservation of circuit integrity is a precondition for a beneficial cognitive impact of therapy. Circuit function can be assessed by fMRI or quantitative electroencephalography [46, 47]. Fluorodeoxyglucose PET reflects synaptic integrity and is a measure of circuit synaptic function [48]. Neurogranin is a measure of synaptic integrity that may represent a fluid biomarker of circuit preservation. These circuit measures can assess the circuit level impact of therapy and may better predict the cognitive outcome [49].

Biomarkers suggesting that an agent has produced disease modification are those that are closely correlated with processes leading to cell death. A drug-placebo difference in these biomarkers in favor of less degeneration and more neuroprotection by the active agent indicates that the drug is a DMT [9].

Biomarkers currently considered as indicative of disease-modification in AD include volumetric MRI as well as measures of tau protein aggregation (tau PET, CSF tau), neurofilament light chain protein, and VILIP-1 [50–54].

Finally, MRI is used to monitor amyloid-related imaging abnormalities (ARIA) occurring as a side effect in patients treated with some anti-amyloid mAbs [44]. Other biomarkers commonly used to monitor adverse events of medications include liver functions, hematologic measures, and electrocardiography.

At the end of Phase II, the ADME, safety, tolerability, and target engagement of the test agent should be known. Dosing should be narrowed to one or two doses before proceeding to Phase III. Understanding these aspects of the candidate therapy at the end of Phase II builds confidence in the therapeutic approach and makes it more likely that the agent will succeed in Phase III.

### *Phase III*

Phase II and Phase III are often conceived as “learn” and “confirm” trials [55]. The learnings of Phase II are tested in Phase III and, if benefits are confirmed, the agent will be submitted to the FDA for review. Phase III trials for DMTs are 12 to 24 months in duration and typically involve 600–1000 patients per arm of the study (each dose and the placebo comprise 1 arm each). The reasons for failure of drugs to advance from Phase III to regulatory review include lack of efficacy (50%), unacceptable toxicity (14%), and commercial, strategic, and operational issues (31%) [56]. These figures are for all classes of agents (not limited to AD-directed drugs); they emphasize the importance of accruing efficacy data in Phase II. Drugs that have genetic connections to the neurobiology of the disease and that have biomarkers to inform drug development decisions are more likely to advance from one phase to the next than drugs that lack this information [57].

As noted above, biomarkers are used in Phase III to diagnose participants, support disease-modifying activity, and monitor amyloid-related imaging abnormalities in mAb studies.

### *Phase IV and post-marketing studies*

Phase IV studies occur after the drug has been approved by the FDA or other regulatory agency and is available on the market. Phase IV studies may be used to extend treatment to a new indication, for example, the assessment and eventual approval of rivastigmine for the treatment of Parkinson’s disease dementia after its approval for mild-moderate AD dementia [58]. Phase IV trials can also be used to

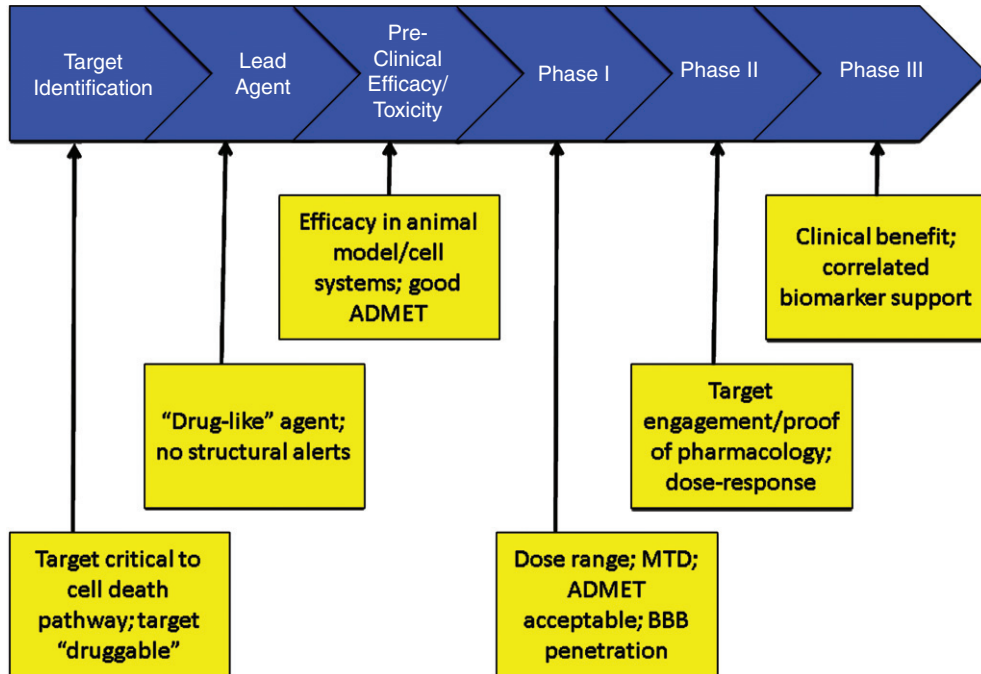


Fig. 5. Critical data to be accrued in each stage of drug discovery and development (ADMET – absorption, distribution, metabolism, excretion, toxicity; BBB – blood brain barrier; MTD – maximum tolerated dose).

extend an indication within the same disease such as the extension of donepezil and rivastigmine into severe AD after approval for mild-moderate AD [59, 60]. The FDA may also require demonstration of efficacy with Phase IV studies after approval of an agent on the basis of a change in a biomarker that is considered reasonably likely to predict a clinical benefit. This type of conditional approval is a consideration in prevention treatments where trial outcomes will emphasize biomarkers in populations without clinical symptoms.

If there are safety concerns, the FDA may require the sponsor to construct a Risk Evaluation and Management Strategy (REMS) to be monitor the safety of an agent once it is marketed [61]. Figure 5 summarizes the critical data to be accrued at each stage of drug development that should be known before proceeding to the next stage.

### TRIALS OF DISEASE-MODIFYING THERAPIES IN ALZHEIMER'S DISEASE

#### *Defining disease modification*

A DMT is defined as an intervention that produces an enduring change in the clinical progression

of AD by interfering in the underlying pathophysiological mechanisms of the disease process that lead to neuronal death [9]. DMT efficacy is demonstrated through clinical trial designs and biomarkers. Evidence of disease modification in the drug development process is based on clinical trial designs such as staggered start and delayed withdrawal or with parallel designs incorporating combined clinical outcomes and correlated biomarker evidence of an effect on the underlying pathophysiological processes of the disease. Most development programs rely on biomarkers to provide support for DM rather than using clinical trial design strategies. The biological change associated with disease modification (DM) is neuroprotection, and biomarker support for DM depends on demonstration of neuronal preservation. DM and neuronal preservation cannot be observed directly and must be inferred from biomarker evidence. To support DM, the biomarker must be indicative of a change in the processes leading to the loss of neurons. Biomarkers commonly used in clinical trials of DMT are discussed above (Fig. 3).

DM is not equivalent to "cure" or to prevention of decline; DM refers to a permanent change in disease trajectory that will delay the onset of symptoms or slow progression in symptomatic patients.

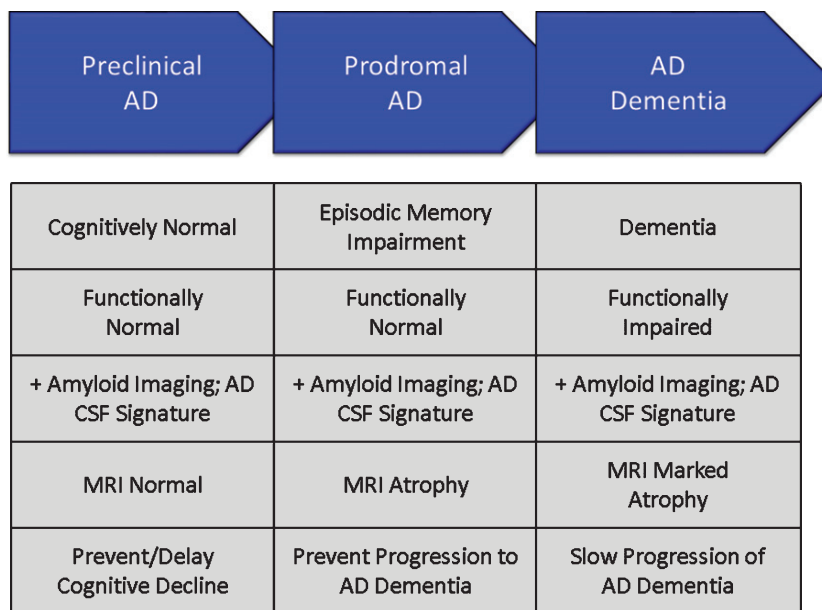


Fig. 6. Phases of Alzheimer's disease (AD) as defined by cognitive, functional, and biomarker observations. Trial goals for each phase are noted.

A delay of 5 years would equate to decreasing the total number of affected individuals by 50%. If the treatment is available by 2025 the annual savings to the US economy by 2050 is projected to be \$369 billion [62].

### Populations

Phases of AD are recognized; these are not distinct stages but represent a seamless progression from a high risk state in which amyloid is present in the brain in the form of neuritic plaques, to prodromal AD with episodic memory impairment (in the typical presentation of AD) and biomarker evidence of AD, to AD dementia with cognitive and functional impairment characterized as mild, moderate or severe [38] (Fig. 6). Although these phases represent progression along a seamless spectrum of severity, they are artificially divided for purposes of clinical trials. Tools and outcomes appropriate for one phase of disease (e.g., preclinical) are not the same as those one would choose for later phases (e.g., mild-moderate AD). Table 2 provides examples of cognitive and functional measures used as outcome measures for different phases of AD [39, 40, 63–70].

Clinical outcomes in AD dementia trials are well established and have been used to demonstrate efficacy of cholinesterase inhibitors and memantine. Cognitive measures for mild-moderate AD dementia

include the ADAS-cog [39] and the Neuropsychological Test Battery [66]. Common secondary measures include the CDR-sb [40], Clinical Global Impression of Change (CGIC), and the Neuropsychiatric Inventory [71]. Dual outcomes are required in AD dementia trials and include a cognitive measure with a functional or global outcome.

Prodromal trials commonly use a composite endpoint comprised of cognitive and functional elements or of cognitive elements derived from several scales. Composite endpoints include the CDR-sb [40], the AD Composite Scale (ADCOMS) [69], and the integrated AD Rating Scale (iADRS) [70]. The FDA has indicated that demonstration of both cognitive and functional benefit is necessary for drug approval in the prodromal phase of AD; a drug-placebo difference on a composite scale should not depend entirely on differences in cognition [72]. Some trials of DMTs include both patients with prodromal AD and those with mild AD dementia; the differences in these populations is arbitrary, and the groups can be usefully combined to facilitate recruitment of a broader population and show benefit in patients who have more than minimal impairment.

Prevention trials include primary prevention studies involving participants with no cognitive symptoms and no state biomarker changes of AD or secondary prevention studies including participants who have no cognitive symptoms but in whom

Table 2  
Outcome tools used for the progressive phases of Alzheimer’s disease [39, 40, 63–70]

Feature	Preclinical AD	Prodromal AD	AD Dementia
Cognition	Preclinical Alzheimer Cognitive Composite (PACC); Alzheimer Prevention Initiative Cognitive Composite (APCC) Test	Clinical Dementia Rating- Sum of Boxes (CDR-sb); AD Composite Score (ADCOMS); Integrated AD Rating Scale (iADRS)	Alzheimer’s Disease Assessment Scale – Cognitive Subscale (ADAS-cog); Severe Impairment Battery (SIB); Neuropsychological Test Battery (NTB)
Function	None	Alzheimer’s Disease Cooperative Study – Activities of Daily Living (ADCS ADL) Scale, Mild Cognitive Impairment (MCI)	Alzheimer’s Disease Cooperative Study – Activities of Daily Living (ADCS ADL) Scale; Disability Assessment for Dementia (DAD)
Trial Outcome	Drug-placebo difference in biomarker considered reasonably likely to predict clinical benefit; Reduction in cognitive decline compared to placebo	Drug-placebo difference in a composite outcome plus biomarker outcomes supportive of disease modification (composite differences between drug and placebo should not be due exclusively to cognitive benefits of therapy)	Drug-placebo difference in dual cognitive and functional or global outcomes plus biomarker outcomes supportive of disease modification

amyloid imaging or CSF amyloid measures show that amyloidosis is present. Studies of asymptomatic participants with autosomal dominant mutations often have mixtures of some patients with amyloid abnormalities and some without, offering the possibility of evaluating a DMT as either primary or secondary prevention [73, 74]. Highly sensitive cognitive measures are combined with biomarkers to determine the impact of anti-amyloid therapies [63, 67, 73, 74]. Participants in this stage of preclinical or presymptomatic AD show very mild cognitive decline that may provide an opportunity to establish a drug-placebo difference in cognitive change [75, 76]. Biomarkers reasonably likely to predict future cognitive decline include amyloid imaging and tau imaging. Tau PET correlates better with cognitive decline and MRI measures of brain atrophy and may provide more insight into DM than amyloid measures [77, 78].

*Clinical trial design*

The most common Phase III design for DMT trials is the randomized, parallel group, placebo controlled, two or more arm, 18–24 month trial. The primary outcome is the drug-placebo difference at trial end on co-primary clinical and functional outcomes or clinical and global outcomes. Biomarker measures typically include MRI volumetrics; amyloid PET (if the agent has a mechanism expected to impact fibrillar amyloid); and CSF Aβ, total tau, and p-tau. Additional biomarkers might be chosen depending on drug MOA and specifics of the trial. Drug-placebo differences at trial end are analyzed for both clinical

and biomarker outcomes. Analyses that offer supporting data expected in DM include change in slope of decline, increasing drug-placebo difference over time, and delay to milestones captured in the data (e.g., in a trial of prodromal patients, the percent of patients at each time point who have progressed to a diagnosis of dementia or advanced from a CDR score of 0.5 to a CDR score of 1). These supporting analyses can be affected by symptomatic agents and do not by themselves prove DM. Clinical and biomarker data are expected to be correlated if they are mediated by the same mechanism [79].

The delayed start and staggered withdrawal designs provide evidence of DM without depending on biomarkers. They demonstrate an enduring change in the course of the disease in comparison with a group begun on treatment earlier (in the case of the delayed start design) or withdrawn from therapy (in the case of the staggered withdrawal design) [80–82]. These trials have been difficult to implement and have had limited use in programs attempting to show DM. The switch from placebo to active therapy when a trial is terminated and participants enter an open label extension (all are on active therapy) provides an opportunity for a delayed start observation [83], although the absence of blinding at this stage of the trial could bias the observations. This open-label delayed start analysis could add support to a claim of DM without providing definitive evidence.

Adaptive clinical trial designs use data from the ongoing trial to make decisions about trial conduct. For example, the Dominantly Inherited AD-Treatment Unit (DIAN-TU) uses an adaptive strategy for dose-selection of test agents [84]. Adaptive strategies can

be used for dose, treatment duration, sample size, and entry criteria. The decision structure must be comprehensively pre-specified but adaptive designs have the advantage of responding to the in-trial observations and can save time and resources while optimizing the opportunity to demonstrate a drug-placebo difference [85].

Another resource-saving strategy in clinical trial design and analysis is the incorporation of futility analyses at a time when a sufficient number of patients have been exposed to treatment for a sufficiently long period time to predict the possible outcomes. If the drug-placebo difference at the time of the analysis suggests that the study has a very low possibility of finding a drug-placebo difference at trial conclusion, the trial can be stopped [64, 86]. Futility analyses avoid exposing patients to agents and potential side effects when a positive conclusion of the trial is deemed highly unlikely. Criteria for futility are evolving; they must be liberal enough to insure that potentially viable drugs are not terminated prematurely and conservative enough that trials with very little chance of success are not continued.

The sample size of the trial is determined by the anticipated effect size of the intervention, the variability of the key measurements, and the desired length of the trial. Assuming that a slowing of 20% or more is clinically meaningful for participants and families, the typical trial for a DMT anticipates including 600–1000 subjects per arm and observing them for 18–24 months [87]. Individuals with more severe disease have faster rates of decline. Prodromal patients who are ApoE4 carriers decline more rapidly than those who are not carriers [88]. The decline in the placebo group is critical to assessing the efficacy of the intervention and decline on placebo is a critical determinant of the success of a trial.

## LESSONS LEARNED FROM TRIALS OF DMTS

There have been frequent failures in attempts to develop new drugs for AD, and 100% of DMT development programs have failed [6]. Every trial, however, is a learning opportunity and many lessons have been learned that will assist in future drug development [89].

### *Animal models of AD provide limited evidence of efficacy*

Animal models of AD are an important means of investigating efficacy and toxicity in the preclinical

state prior to exposing humans to possibly toxic or ineffective compounds. Many of the tg animal models overexpress the amyloid protein leading to cortical plaques similar to those observed in human AD [90]. These genetically engineered animals have abnormalities of amyloid metabolism but generally lack other aspects of human AD; they lack tau or cell death and have limited inflammatory changes [91]. The tg mice have mild cognitive changes but do not develop severe dementia equivalent to the human disease. Many types of therapy have been successful in reducing amyloid abnormalities in these animals and have often lead to improved cognitive performance on tests such as Morris Water Maze or Novel Object Recognition [90]. None of these successes at the pre-clinical level has predicted success at the human level. The animals serve as important gateways in the drug development process showing that they impact specific pathways; advancing a drug to human testing that did not succeed as expected in animals would be unwise. The models, however, recreate limited aspects of human AD such as amyloidosis and cannot be taken as models of the full spectrum of pathology of human AD or predictors of human benefit [23].

Another concern with regard to animal models is their reproducibility [92]. If an experiment cannot be reproduced within a single model or across related models then its ability to predict human outcomes is suspect. Strain, age, gender, handler behavior, diet, and light conditions may all influence animal behavior. Randomization and sample size are important aspects of animal trial design that have sometimes been ignored [93]. Lack of rigor with regard to these aspects of animal model testing may contribute to the lack of reproducibility both across models and in translating results from animals to humans.

### *Establish BBB penetration in Phase I*

BBB penetration is shown in preclinical studies by the effects of drug on behavioral studies and post-exposure necropsy. Differences between rodent and human BBB function, especially activity of p-gp transporter make extrapolation of animal model results to humans uncertain, requiring demonstration of BBB penetration in Phase I FIH studies [34]. Tarenflurbil is an example of an agent advanced as treatment for AD with *in vivo* activity in animal models but likely low entrance into the CNS in humans [94]. Before candidate agents exit Phase I, investigators should establish BBB penetration, the plasma/CSF ratio, and the relationship of predicted

human brain exposure to concentrations associated with benefit in animal models.

#### *Determine a maximum tolerated dose in Phase I*

Dose escalation studies in Phase I and dose refinement studies in Phase II should provide confidence in the dose(s) selected for Phase III. In particular, it is important to establish a MTD whenever possible to ensure that the highest possible doses have been explored. In some cases, occupancy studies may allow conclusions about dosing without an MTD if the receptor is fully occupied at lower doses. In other situations, solubility or physical features may limit the administered dose and the MTD cannot be determined. Beyond these exceptional circumstances, an MTD should be determined. Without an MTD, failure to show a drug-placebo difference in Phase II or Phase III will raise questions about the adequacy of the dose.

#### *The diagnosis of AD should be supported by biomarkers*

An important learning is the relatively large number of individuals who have a prodromal AD or AD dementia phenotype but are not amyloid-bearing when studied with amyloid PET [42]. These non-amyloid individuals have suspected non-Alzheimer pathology (SNAP) and are presumed not to have AD. They should be excluded from trials of agents for AD. Table 3 shows the percentage of patients meeting clinical criteria for prodromal AD or mild AD dementia who are amyloid-bearing [42]. Amyloid is more common in those with ApoE genotypes but genetic characterization is insufficient to ensure the presence of amyloid. To be confident that the trial population has AD, amyloid imaging or CSF evidence of the AD A $\beta$ /tau signature should be collected (Fig. 4).

#### *Assure target engagement in Phase II*

DM is supported by an impact on “downstream” measures of cell death such as MRI atrophy, CSF tau, or possibly other biomarkers of neuronal degeneration such as neurofilament light chain protein [54]. These downstream consequences can reasonably be expected only if the “upstream” target of the pharmacologic intervention is successful. Target engagement measures will depend on the MOA of the candidate therapy. BACE inhibitors, gamma secretase inhibitors, and gamma secretase modulators will

Table 3

Amyloid PET findings in patients meeting clinical criteria for prodromal AD or mild AD dementia (stratified by ApoE genotype) [42]

Group	Amyloid Positive	Amyloid Negative
All	61%	39%
All prodromal AD	50%	50%
Prodromal ApoE4 carriers	71%	29%
Prodromal ApoE4 non-carriers	31%	69%
All mild AD dementia	75%	25%
Mild AD dementia ApoE4 carriers	90%	10%
Mild AD dementia ApoE4 non- carriers	58%	42%

have an effect on amyloid production as measured by stable isotope-labeled kinetics (SILK) [95]. BACE inhibitors will also inhibit BACE activity as measured in the CSF and reflected in sA $\beta$ PP $\beta$ , a by-product of BACE activity; gamma secretase modulators result in A $\beta$  fragments of 15/16 amino acid lengths in the CSF which are not normally present in AD [95–97]. Proof of pharmacology is one goal of Phase II and compounds should not be advanced to Phase III without well documented support for a pharmacologic effect.

#### *Establish a dose-response relationship in Phase II*

Dosing approaches in Phase II ideally establish a low dose that is ineffective, one or two mid-range doses that are effective, and a high dose that is not tolerated and not acceptable. A dose-response on clinical or biomarker measures increases confidence in the pharmacology of the molecule. Regulatory agencies usually seek assurance that patients are given the lowest effective dose to ensure that they are not being exposed to unnecessary side effects. Doses established in Phase II inform decisions of which dose should be advanced to Phase III. Drug formulation decisions should be completed in Phase II prior to Phase III.

#### *Collect multiple biomarkers to assess outcomes*

Knowledge of the neurobiology of AD is incomplete. Systems biology studies demonstrate that AD biology is complex [98] and biomarkers provide limited windows onto this complex and ill-understood disease. Although working models of the order of events in AD have been constructed, none have been proven and none have guided successful DMT development. Agnostic approaches to biomarkers (e.g., amyloid; tau, neurodegeneration; A/T/N) are used to

acknowledge the exploratory nature of our biomarker documentation of drug effects [99]. To support DM as the outcome of a therapy, trial sponsors should collect A/T/N biomarker data, emerging biomarkers, and biomarkers specifically linked to the mechanism of the intervention to gain a comprehensive view of the impact of treatment.

#### *Recruitment is a major challenge*

Trial recruitment is a difficult process and each population—cognitively normal at-risk participants for prevention trials, minimally impaired biomarker positive participants for prodromal AD trials, and cognitive and functionally impaired participants for AD dementia trials—have unique requirements for identification, recruitment, informed consent, and retention in the trial. There are too few highly functioning trial sites in the world. The world's populations are generally poorly educated about clinical trials and often have few opportunities to participate. Many trials spend more time in the recruitment phase of the trial than in the drug exposure phase. Slow recruitment slows the cycle time of trials and increases their cost. Many AD-concerned organizations are constructing responses to this challenge. The Global Alzheimer Platform (GAP) network of trial sites in the US and the European Prevention of Alzheimer's Disease (EPAD) initiatives are among the leaders of the attempt to reduce recruitment times and accelerate trials [100, 101].

#### *Global trials have greater variability*

One response to slow recruitment is to include many trial sites with each site recruiting only a few participants to the trial. In most trials, each site is expected to contribute 6–12 participants, but many sites contribute only 1 or 2 participants. This amplifies “noise” in the data and decreases the ability to demonstrate a drug-placebo difference.

Globalization of trials creates another set of challenges. Sites distributed around the world are culturally and linguistically diverse, have different standards of health care, and include participants with different histories of nutrition and levels of education. Trial sites are highly variable in terms of experience, expertise, training, and infrastructure. Local hospital and university institutional review boards (IRBs) may have limited experience with hosting and reviewing AD trials [102]. Global sites impose challenges in terms of drug manufacturing and distribution, supply

lines, biomarker collection, laboratory availability, and data collection and quality assurance. The result of this complexity is that populations recruited into trials from around the world vary in terms of age, education, genotype, and other clinical characteristics, and they progress somewhat differently in clinical trials [103, 104]. North America and Western European trial populations are similar and results are likely to be most interpretable if these populations comprise the majority of the study population.

Efficacy and safety data are needed on all populations where the agents will be marketed; smaller trials in local populations may be the best way to address these needs.

#### *Comprehensive trial networks are needed to conduct AD trials*

Conducting clinical trials is demanding and requires expertise, commitment, and infrastructure. Some academic medical centers support trials while others do not, industry sponsors support trials but tend not to support trial infrastructure. In the US, the National Center for Advancing Translational Sciences (NCATS) sponsors Clinical and Translational Science Awards (CTSAs) to provide trial infrastructure in major university medical centers [105]. Trial networks are currently re-created for each trial and raters are re-trained on the same outcomes for each trial. Each institution often has its own IRB for reviewing trials. Legal review of contracts further slows trial initiation. Construction of a highly efficient trial network with standing non-redundant training, and a central IRB are goals of GAP and EPAD [100, 101].

#### *Negative trials may indicate an ineffective drug or a failed trial*

The failure to show a drug-placebo difference at the end of a trial may be due to lack of efficacy of the candidate therapy or flawed conduct of the clinical trial. Table 4 summarizes the reasons for negative outcomes in trials. Drug-related reasons for negative trials include lack of efficacy and excessive toxicity [106]. In some cases, the dose range has not been adequately explored in early drug development and a negative trial opens the question of whether the agent might have been efficacious at higher doses. Such agents must return to Phase I for dose escalation trials and sponsors rarely have an interest in pursuing this alternative. Trial-related reasons for failed tri-

als of DMTs include lack of decline in the placebo group, enrollment of non-AD patients, and excessive measurement variability.

*Placebo decline determines drug-placebo difference*

Successful DMTs will slow the course of decline in AD. Slowing of decline is established by contrasting the decline in the active treatment group with the trajectory of the placebo group. The placebo trajectory will determine the drug-placebo difference at end of trial. The rate of decline of the placebo group is a crucial consideration in understanding the treatment effect. Placebo groups with SNAP patients do no decline as rapidly as those with confirmed AD, emphasizing the importance of confirming the diag-

nosis of AD in trial participants [107]. Slow decline in the placebo group will minimize the drug-placebo difference and the agent will appear less efficacious than when compared with a more rapidly declining group. Similarly, an unusually rapidly declining placebo group may lead to an overestimation of drug efficacy since the drug-placebo difference will be exaggerated and this may not be reproduced in a later trial. A meta-analysis of placebo decline showed that patients with mild AD are expected to decline 5.6 points on the ADAS-cog or 3 points on the Mini-Mental State Examination in 18 months [108]. This figure is based on trials that included patients without biologically confirmed AD and may underestimate the decline in those confirmed with amyloid imaging or CSF studies to have AD.

Table 4

Reasons for failure to show a drug-placebo difference at the end of a clinical trial of a disease-modifying agent. AD, Alzheimer’s disease

<p>Drug-related</p> <ul style="list-style-type: none"> <li>• Lack of efficacy of the agent</li> <li>• Inappropriately low dosing of an effective agent</li> <li>• Excessive toxicity or lack of tolerability leading to high discontinuation rates in the active treatment arms</li> <li>• Excessive toxicity or lack of tolerability leading to early termination of the trial</li> </ul> <p>Trial-related</p> <ul style="list-style-type: none"> <li>• Lack of decline in the placebo group</li> <li>• Recruitment of non-AD patients into trials requiring an AD substrate for drug benefit to occur</li> <li>• Excessive measurement variability</li> <li>• Lack of measurable effect of active comparator drugs (if available)</li> </ul>
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*Phase II subgroup analyses do not provide guidance for Phase III*

Negative trials are often analyzed to detect treatment-responsive subgroups that can be exploited in future trials. This approach entails substantial risk of being misled by spurious trial specific results. Subgroups are not subject to the same recruitment or randomization as the original group, the sample sizes of subgroups are often small leading to underpowered results, and the outcome measures are typically not optimized for a specific subgroup. Basing a Phase III program on a subgroup analysis of a Phase II trial with a negative outcome has usually resulted in a negative Phase III trial.

Table 5

Questions to ask to determine how much confidence can be placed in a subgroup analysis [109–111]

Guide: Questions to Ask of Subgroup Claims	Supportive of Subgroup Claim if “Yes”
<p>Design</p> <ul style="list-style-type: none"> <li>Was the subgroup variable a baseline characteristic?</li> <li>Was the subgroup variable a stratification factor at randomization?</li> <li>Was the subgroup hypothesis specified a priori?</li> <li>Was the subgroup analysis one of a small number of subgroup hypotheses tested (<math>\leq 5</math>)?</li> </ul> <p>Analysis</p> <ul style="list-style-type: none"> <li>Can chance explain the subgroup difference?</li> <li>Was the test of interaction significant (<math>p &lt; 0.05</math>)?</li> <li>Was the significant interaction effect independent, if there were multiple significant interactions?</li> </ul> <p>Context</p> <ul style="list-style-type: none"> <li>Was the direction of the subgroup effect correctly pre-specified?</li> <li>Was the subgroup effect consistent with evidence from previous related studies?</li> <li>Was the subgroup effect consistent across related outcomes?</li> <li>Was there indirect evidence to support the apparent subgroup effect – for example, biological rationale, laboratory tests, animal studies?</li> </ul> <p>Systematic reviews</p> <ul style="list-style-type: none"> <li>Is the subgroup difference suggested by comparisons within rather than between studies?</li> </ul>	



To reduce the risk of being misled, one can apply guidelines for interpretation of Phase II subgroup analyses. Table 5 shows the principal recommendations for subgroup analysis [109–111]. Subgroup analyses suggesting benefit in one group of patients require conducting a Phase II trial for this subgroup to gain additional confidence in this treatment approach.

## BLUEPRINT OF A DEVELOPMENT PROGRAM FOR A DMT

This primer of DMT trials plus the lessons learned from negative trials suggest a blueprint for future trials of DMTs. The key elements of success for a DMT development program include:

- Comprehensive understanding of target biology
- Selective, potent agents impacting a key element of AD biology leading to cell death
- Disciplined conduct of a drug development program organized around a TPP
- Success in preclinical models of AD
- Acceptable ADME and toxicity in preclinical studies
- Acceptable ADME and toxicity in FIH studies
- BBB penetration demonstrated with relevant extrapolated brain exposures achieved in Phase I
- MTD established in Phase I
- Use of biomarkers in Phase II and III to establish accurate diagnosis of AD
- POC established in Phase II with target engagement and proof-of-pharmacology
- Dose-response shown in Phase II
- Trials implemented in high functioning trial network
- Globalization-dependent variability minimized in Phases II and III
- Demonstration of robust clinical and correlated DM-type biomarker response in Phase III
- Report Phase II and III trials using CONSORT criteria
- Continued assessment of safety and clinical utility after market introduction

## SUMMARY

Development of DMTs for AD is a difficult, long, and expensive process. No development program has yet succeeded. A systematic approach to drug development advancing the scientific understanding of the candidate molecule from preclinical studies

through Phases I, II, and III of clinical trials can increase the probability of success and de-risk development programs. Biomarkers for diagnosis, target engagement and proof-of-pharmacology, outcome assessment, and side effect monitoring assist in drug development. Excellent conduct of trials and awareness of the trial pitfalls are critical to development success. New therapeutic targets such as tau-related processes and the use of combination therapies may enhance the chances of successful DMT development. Quality development and trial strategies for drugs that are potent, selective, and impactful on the biology of AD are necessary to bring urgently needed new treatments to patients with AD and those at risk for the disease.

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