Chapter 1

Alzheimer's Disease Drug Development: A Research and Development Ecosystem

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1.1 Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease with a long preclinical asymptomatic period followed by progressive decline in cognition manifested as mild cognitive impairment (MCI) and then by mild, moderate, and severe dementia [1, 2]. The key pathologies include amyloid (A), tau (T), and neurodegeneration (N) (A/T/N). A myriad of contributing factors have been identified including inflammation, oxidation, genetic and epigenetic factors, hormonal factors, metabolic and bioenergetic changes, autophagy dysfunction, proteostasis, apolipoprotein E (ApoE) effects and lipid abnormalities, and vascular factors.

AD can occur in individuals as young as their 30s but is more commonly of late onset, with AD dementia doubling in frequency every 5 years after age 60 from affecting approximately 1% of individuals at age 60 and increasing to affect approximately 40% of those 85 and older [3]. The current global population of 46.8 million AD dementia patients worldwide is projected to rise to 74.7 million by 2030 with a corresponding increase in cost of care from the current $1 trillion to $2 trillion [4].

Despite the urgent need for treatment for this burgeoning population, until 2021 there were only five drugs approved and on the market (donepezil; rivastigmine; galantamine, memantine, Namzaric™) with no new drugs approved in the United States or Europe since 2003 [5]. One additional agent was approved in China in 2019 (GV-971 [oligomannate]) [6]. In 2021, the ecosystem delivered a new treatment – aducanumab – approved for treatment by the US Food and Drug Administration (FDA) for treatment of MCI due to AD and mild AD dementia. Approval of aducanumab is a breakthrough in AD treatment and a milestone in development of disease-modifying therapies (DMTs) for neurodegenerative disorders (NDDs). This is an important step forward, while still leaving many phases and aspects of AD untreated and introducing an agent that makes exceptional demands on healthcare systems [7]. Aducanumab is expected to have modest impact on the needs of the broader AD population and continuous involvement in new drug discovery for AD is required.

AD drug development takes a long period of time to progress from laboratory studies to possible human availability, is very expensive, and requires a complex ecosystem spanning the translational journey from non-clinical studies, to clinical trials, through regulatory review, to market. The process begins with an unmet medical need and ends with an agent that begins to address the problem; the solution is then subject to reiterative refinement and more unmet needs are identified and addressed (Figure 1.1). The ecosystem has scientific, patient and caregiver, healthcare delivery,

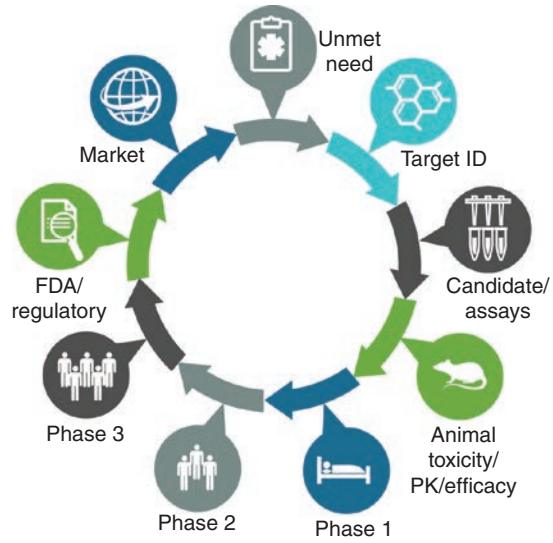

Figure 1.1 The drug-development process from identifying an unmet need to its resolution and reiterative refinement.

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business/financial, advocacy, governmental, and policy dimensions that interact dynamically as the candidate agent progresses from molecule to market. Aducanumab is an example of the successful traversal of this complex process to success. Here we provide an overview of the steps in AD drug development and consider the complex multidimensional infrastructure that supports the process. We begin with a description of the phases of drug discovery and development, followed by the resources needed to advance the process including the funding. We end with a discussion of how the process might be improved.

1.2 Alzheimer's Disease Drug Discovery and Development

1.2.1 Overview of Drug Discovery and Development

Development of a new drug begins with identification of a target for treatment and progresses through development of assays for drugs that may modulate target-related processes, and assessment of the candidate(s) in relevant animal models for efficacy, toxicity, and pharmacokinetics (PK). Agents with desirable drug-like properties are then advanced to Phase 1 first-in-human (FIH) trials to assess PK, safety, and tolerability. Drugs with acceptable features in FIH trials are advanced to Phase 2 proof-of-concept (POC) and dose-ranging studies and then to Phase 3 if the Phase 2 studies suggest that the agent is efficacious and safe. If Phase 3 trials confirm efficacy, the drug is submitted for review to the FDA or other regulatory agencies [8]. A successful review results in marketing approval and the ability to make the agent available to patients and prescribing clinicians [8]. Figure 1.2 shows the elements of this process.

1.2.2 Target Identification and Drug Discovery

Common targets for DMTs in AD are processes that eventually lead to cell dysfunction and death [9, 10]. Targets for cognitive-enhancing agents and treatment for behavioral syndromes of AD commonly include receptors, enzymes, and ion channels. Targets must be "druggable" with properties that can be modulated by small molecules (e.g., drugs) or antibodies, or other biologicals such as antisense oligonucleotides, and other forms of gene therapy [11].

After a target has been identified, an assay with a reporter for interactions suggesting that candidate agents are modulating the target is developed and used to screen candidate therapies. Libraries of compounds are screened for "hits" that have the desired effects in the assay. These libraries are constructed from agents with similar structures and multiple molecular forms, traditional medications (e.g., Chinese traditional medications), natural sources (e.g., bark, seaweed, etc.), repurposed agents that may have AD-related effects, and compounds designed computationally *in silico* [12]. Several hundred thousand compounds may be screened to identify a sufficient number of hits for further development. The hits are reviewed by medicinal chemists for "drug-likeness" including features that predict good absorption and membrane penetration [13, 14]. Compounds with promising characteristics are optimized for molecular features that enhance the likelihood of success as a human therapy – potency, half-life, 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 mechanistic assays is high content analysis, conducted in intact cells using automated microscopy and image analysis. High content analysis can be used to screen for effects on protein aggregation, synaptic integrity, and neuron and synapse number or survival as well as other cellular processes relevant to AD treatment [16].

1.2.3 Non-clinical Assessment

Assessment of the lead candidate in animals establishes the PK characteristics, toxicity, and preliminary efficacy of the molecule. These studies may

Figure 1.2 Phases in the discovery and development of therapeutic agents.

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be done in parallel with or following evidence of proof of mechanism in an animal model (discussed below). 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 at least two species – usually mice and rats. Dogs are sensitive to cardiac effects of drugs and are used to assess possible cardiac toxicity [18]. Laboratory and necropsy studies are performed to thoroughly assess any off-target adverse effects in the animals; special attention is paid to liver, cardiac, bone-marrow, and reproductive organ toxicity. 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 are seen is determined and becomes the basis for dose calculations for the recommended safe starting dose for FIH studies [20].

Development of monoclonal antibodies (mAbs) differs from developing small molecules. Monoclonal antibodies are manufactured to interact with a specific epitope of a target such as a portion of amyloid beta protein (Aβ) or tau protein [21, 22]. Monoclonal antibodies have fewer risks for off-target effects since they are exquisitely targeted to specific molecular sites.

Animal species are used to explore the proof of mechanism of candidate therapies. Although success in animal models has not yet predicted success of a DMT in humans, failure to see the desired effect on AD pathology in an animal model system would make one hesitant to advance the agent to human testing [23]. The most commonly used animal model systems are transgenic (Tg) mice that carry one or more human genes known to cause familial AD. Anti-Aβ approaches can be tested in this model. Tau transgenic model animals as well as many types of gene knock-in (KI) and knock-out (KO) models are available. The National Institute on Aging (NIA) and the National Institutes of Health (NIH) Library have created a publicly available data repository of non-clinical/preclinical studies (AlzPED) that includes the available animal models of AD. The model animals exhibit specific aspects of the AD pathology but not the complex multifactorial AD process observed in humans [24].

Human-derived induced pluripotent stem cells are increasingly used to move the early drug screening process toward a more humanized biological context with the hope of having greater predictability for human responses [25, 26]. The induced pluripotent stem cell models show both Aβ and tau protein accumulation, recapitulating the human disease and creating a more ecologically valid system for drug efficacy studies [25].

1.2.4 Phase 1 Clinical Trials

Phase 1 clinical trials involve the FIH exposure of the drug. In small molecule development programs, the persons participating in the Phase 1 trial are healthy volunteers [27]. If a vaccine is being developed, the FIH testing is usually done with patients with AD dementia. Vaccines can permanently alter the immune system and the unknown consequences of this cannot be risked in young healthy individuals.

At the end of Phase 1, the maximum tolerated dose (MTD), human PK, preliminary drug safety and tolerability, and BBB penetration should be known [28]. Single ascending dose (SAD) studies where cohorts of individuals are exposed to progressively higher doses of the agent are followed by multiple ascending dose (MAD) studies where cohorts are treated for 14–28 days with increasing doses of the agent [29]. A cohort is typically 8–12 individuals randomized in a 4:1 ratio of active agent to placebo. In some MAD approaches, at least one cohort of elderly individuals is included to assess PK, ADME, and toxicity differences in older adults. Phase 1b or 1/2 programs may include cohorts of individuals with AD to gather preliminary information on the effects in patients with the disease state.

Ideally, an MTD is determined at this stage of drug development. Maximum doses can be determined by tolerability and safety limits, volume of administration limits, receptor occupancy studies which show that increasing the dose no longer increases occupancy of a positron emission tomography (PET) ligand, or PK studies that demonstrate that increasing the dose no longer increases the maximum serum concentration or area under the curve. Failure to establish an MTD/maximal dose in Phase 1 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 [30].

Assessing cerebrospinal fluid (CSF) drug levels in Phase 1 is critical to establishing the candidate

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compound's ability to penetrate the human BBB and exert central nervous system (CNS) effects. Treatments should not exit Phase 1 without evidence of BBB penetration and an understanding of plasma/CSF ratios.

1.2.5 Phase 2 Clinical Trials

Phase 2 generally encompasses Phase 2a POC trials and Phase 2b dose-determination studies. At the end of Phase 2, doses to be advanced to Phase 3, target engagement, preliminary information on biomarker or clinical responses, and insight into safety and tolerability in the population of interest should be available [28]. Phase 2 involves patients with AD dementia or prodromal AD/MCI due to AD [31]. The decision to advance an agent to Phase 3 may be based on a clinical outcome or on changes in a biomarker or repertoire of biomarkers considered likely to predict a clinical outcome (no biomarker is currently proven to predict clinical benefit). Alternatively, one can require clinical POC with benefit on a traditional clinical measure such as the AD Assessment Scale – cognitive subscale (ADAS-cog) [32] or Clinical Dementia Rating – sum of boxes (CDR-sb) [33]. Demonstration of clinical benefit typically requires a large long trial virtually equivalent to a Phase 3 trial [34]. Thus, some development programs move from Phase 1 directly to Phase 3, advancing an agent with limited information regarding safety, tolerability, biomarker effects, or dosing.

Biomarkers may be used as Phase 2 outcomes to support decision making for development programs [35]. Target engagement biomarkers are critical to demonstrating that the drug is having the desired pharmacological effect on a near-term target. Without evidence of target engagement, the potential disease-related biological impact of a putative DMT cannot be assessed [36, 37]. Examples of POC studies in AD drug development include demonstration of reduced Aβ production following administration of beta-site amyloid precursor protein cleaving enzyme (BACE) inhibitors or gamma-secretase inhibitors using stable isotope labeled kinetics (SILK) [38], reduced CSF Aβ with BACE inhibitors [39], and increased Aβ fragments in plasma and CSF with gamma-secretase inhibitors and modulators [40]. Candidate target engagement/proof-of-pharmacology (POP) biomarkers include peripheral indicators of inflammation and oxidation for use in trials of anti-inflammatory and antioxidant compounds. Demonstration of target engagement does not guarantee efficacy in later stages of development but provides important de-risking of a candidate agent by showing biological effects that may translate into clinical efficacy.

Populations in AD trials are typically characterized by ApoE genotype to identify the *APOE-4* allele carriers and non-carriers. *APOE-4* carriers have earlier onset of AD and progress more rapidly in the early phases of the illness. Allele status may affect efficacy and side effects and often influences dosing in mAb trials [41–43]. Trials are not typically stratified by genotype, but the statistical analysis plans compare carriers and non-carriers for efficacy and toxicity. Approximately, 65% of biomarker-confirmed AD patients are *APOE-4* carriers; if proportions are markedly lower in trials where biomarkers were not used to verify the diagnosis, the number of non-AD patients inadvertently included in the trial may be high.

Growing information on blood biomarkers suggests that measurement of the $A\beta_{42}/A\beta_{40}$ ratio and plasma levels of hyperphosphorylated tau ($p\text{-}tau_{181}$, $p\text{-}tau_{217}$), total tau, and neurofilament light chain (NfL) may be useful in screening populations for more advanced testing (e.g., Aβ PET imaging) and may eventually be sufficiently accurate to allow their use in diagnosis and trial enrollment. Their possible role in monitoring Aβ-targeted or tau-target therapies is being assessed.

Cognition is mediated by integrated cerebral circuits, and interventions to preserve neurons and synapses – mediated by anti-Aβ, anti-tau, or other mechanisms – will succeed to the extent that they preserve circuit function. Circuit integrity can be assessed by functional MRI (fMRI), quantitative electroencephalography (QEEG), magnetoencephalography (MEG), or fluorodeoxyglucose (FDG) PET [44, 45]. Neurogranin, synaptotagmin, and synaptophysin are synaptic proteins that may represent CSF biomarkers of circuit involvement. These circuit measures can assess the impact of treatment on circuits and may better predict or correlate with the outcome of either cognitive-enhancing agents or DMTs [46].

Biomarkers are used to confirm the diagnosis of AD. The clinical diagnosis of AD dementia based solely on the phenotype of amnestic dementia is not confirmed by Aβ PET or CSF amyloid and tau measures in approximately 25% of patients [41], indicating that they do not have the

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pathobiology of AD. Approximately 50% of MCI patients have abnormal Aβ measures and constitute a prodromal AD population; 50% do not have early AD [47]. AD trials must be comprised of individuals with AD to draw accurate conclusions about efficacy of AD-directed therapies.

MRI is a measure of cerebral atrophy and neurodegeneration. It is used in DMT trials to assess effects on neuronal loss but the results have often been counter-intuitive with greater atrophy in patients for whom other evidence suggests a treatment benefit. MRI is used to monitor amyloid-related imaging abnormalities (ARIA) occurring as a side effect in patients treated with some anti-Aβ mAbs [42]. Other biomarkers commonly used to monitor adverse effects of medications include liver functions, hematological measures, and electrocardiography (ECG).

1.2.6 Phase 3 Clinical Trials

Phase 2 and Phase 3 are often conceived as "learn" (Phase 2) and "confirm" (Phase 3) trials [48]. The learnings of Phase 2 are tested in Phase 3 and, if benefits are confirmed, the agent will be submitted to the FDA for review. Phase 3 trials for DMTs are 12–24 months in duration and typically involve 600–1,000 patients per arm of the study (doses and the placebo comprise 1 arm each). Prevention trials of individuals without cognitive symptoms may be up to 5 years in duration.

1.2.6.1 Phase 3 Trial Populations

Clinical trials in Phase 3 may include preclinical populations of participants with no cognitive symptoms but genetic or biomarker evidence (Aβ PET; CSF amyloid or p-tau changes) of high risk for developing symptomatic AD; prodromal AD populations comprised of participants with MCI and biomarker evidence of AD; or AD dementia with participants exhibiting mild, moderate, or severe AD [8, 49].

The FDA has provided guidance for trials involving early AD – those in the preclinical and prodromal phases [50] (Figure 1.3). FDA Stage 1 describes individuals with positive biomarkers of AD pathophysiology and no symptoms detectable

Stage 1	Stage 2	Stage 3	Stage 4,5,6
Preclinical AD	Preclinical AD	MCI due to AD/ prodromal AD	Mild, moderate, severe AD dementia
Cognitively normal	Subtle cognitive abnormalities	Cognition abnormal	Cognition abnormal
Function normal	Function normal	Subtle functional decline	Function abnormal
Full approval: Longer study shows effects on sensitive cognitive measures (those used in Stage 2)	Persuasive effect on cognitive measures; large magnitude effects or effects on multiple measures making the observations more compelling	Single clinical outcome approvable; effects on clinical and functional aspects of a composite need to be shown	Dual outcomes – cognition plus function or cognition plus global – required
Accelerated approval: Effect on characteristic pathophysiologic changes of AD thought reasonably likely to predict clinical benefit; pattern of effects across multiple biomarkers increases the persuasiveness of the putative effect	Cognitive effects reasonably likely to predict clinical benefit; plus effect on characteristic pathophysiologic changes of AD to add support for accelerated approval	Conventional strategies required (not accelerated)	Conventional strategies required (not accelerated)

Figure 1.3 FDA stages of Alzheimer's disease.

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by even the most sensitive measures; Stage 2 individuals have positive biomarkers and cognitive symptoms that are detectable with very sensitive measures; Stage 3 is characterized by positive biomarkers, abnormal cognition and functional deficits detectable with only the most sensitive measures (this stage is traditionally known as MCI); Stages 4–6 are mild, moderate, and severe AD dementia. The FDA staging creates a framework for assessing treatments in very early AD with outcomes on sensitive measures (biomarkers or clinical assessments) or impact on progression to the next stage.

1.2.6.2 Biomarkers in Phase 3 Trials

Biomarkers are used in Phase 3 to diagnose participants, support disease-modifying activity, and to monitor ARIA in mAb studies. Biomarker evidence of less degeneration and more neuroprotection by the active agent suggests that the drug is a DMT [9, 51]. Biomarkers currently considered as indicative of disease modification in AD include volumetric MRI, FDG PET, CSF NfL chain and total tau, and blood NfL and total tau [52, 53]. Changes on Aβ PET, tau PET, or CSF or blood measures of Aβ protein or p-tau may contribute to the weight of evidence informing the understanding of drug activity and building a narrative for how the agent is achieving disease modification. Aβ and p-tau protein abnormalities are mediators of cell death and changes in these intermediate biomarkers are supportive but not definitive evidence of disease modification.

1.2.6.3 Clinical Outcomes in Phase 3 Trials

The standards for trials of patients with mild-to-moderate AD were created when tacrine – the first agent approved for the treatment of AD – trials were conducted, and these approaches have remained highly influential. The approval process is based on draft guidelines from the FDA of 1990 [54]. These guidelines require that anti-dementia agents show improvement on the core symptoms of AD – memory and cognition – and that the effect is clinically meaningful as shown by a significant drug–placebo difference on a global or a functional rating. Dual outcome requirements are the standard for both DMTs and cognitive enhancer trials for AD dementia trial populations.

New instruments have been added to the repertoire of tools available to assess different trial populations (Table 1.1). The CDR and CDR-sb are composites of cognitive and functional items that have become the standard global outcome for DMT trials [33]. In trials of prodromal AD, the CDR-sb may serve as a single outcome although regulatory authorities consider the contribution

Table 1.1 Clinical assessments commonly used in AD clinical trials

Population	Domain	Instruments
Preclinical (normal cognitive function)	Cognition	Preclinical Alzheimer's Cognitive Composite (PACC)
		API Preclinical Composite Cognitive (PCC) Test Battery
		DIAN-TU Cognitive Composite
	Function	Amsterdam Instrumental ADL scale
	Behavior	Neuropsychiatric Inventory (NPI)
		Mild Behavioral Impairment (MBI) Checklist
Prodromal	Global	Clinical Dementia Rating – sum of boxes (CDR-sb)
	Cognition	Neuropsychological Test Battery (NTB)
		Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)
	Function	Amsterdam Instrumental ADL scale
		ADCS ADL scale (MCI version)
	Behavior	NPI
		MBI checklist

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Table 1.1 (cont.)

Population	Domain	Instruments
Mild-to-moderate AD dementia	Global	CDR-sb
		Clinical Global Impression of Change (CGIC)
	Cognition	NTB
		ADAS-cog
	Function	Amsterdam Instrumental ADL Scale
		ADCS ADL scale
	Behavior	NPI
Severe AD dementia	Global	CDR-sb
		CGIC
	Cognition	Severe Impairment Battery (SIB)
	Function	ADCS ADL scale (severe)
	Behavior	NPI

ADCS – Alzheimer's Disease Cooperative Study; ADL – activities of daily living; API – Alzheimer's Prevention Initiative; DIAN-TU – Dominantly Inherited Alzheimer Network Treatment Unit; MCI – mild cognitive impairment.

of changes in cognition and changes in function to the total score change. The Neuropsychological Test Battery (NTB) has been shown to work well as an as an alternative to the ADAS-cog [55]. The Severe Impairment Battery (SIB) is most commonly used to assess cognition in patients with severe dementia [56]. The Neuropsychiatric Inventory (NPI) is the tool most commonly used to assess behavioral changes in trials of AD and other neurodegenerative disorders. Function is assessed with the Alzheimer's Disease Cooperative Study (ADCS) activities of daily living (ADL) scale [57] or the Amsterdam Instrumental ADL scale [58]. In some trials the Clinical Global Impression of Change (CGIC; or one of its variants) is used as a global measure instead of or in addition to the CDR. Measures of caregiver burden [59], quality of life [60], and resource utilization [61] are commonly included as outcome measures in Phase 3 trials in anticipation of payer discussions.

The emergence of prevention trials involving participants with normal cognitive function requires the use of tools that are very sensitive to small changes in cognition in older adults. Tools in this category include the Preclinical Alzheimer's Cognitive Composite (PACC) [62], Preclinical Composite Cognitive (PCC) Test Battery used in the Alzheimer's Prevention Initiative (API) [63], the Cognitive Composite of the Dominantly Inherited Alzheimer Network Treatment Unit (DIAN-TU) [64], and the European Prevention of AD (EPAD) Neuropsychological Examination (EPE) [65].

1.2.7 Phase 4 Clinical Trials and Post-marketing Studies

Phase 4 studies occur after a drug has been approved by the FDA or other regulatory agency and is available on the market. Regulatory agencies may request a risk evaluation and mitigation strategy to assess safety after marketing approval. Phase 4 studies may be used to extend treatment to a new indication or can be used to extend an indication within the same disease [66, 67]. These strategies comprise life-cycle management of an asset once it is approved. Phase 4 studies may be required to confirm efficacy in agents marketed on the basis of accelerated approval and effects on a biomarker.

1.3 Organization and Funding of the Alzheimer's Disease Drug-Development Ecosystem

1.3.1 Drug Discovery

No agent progresses from discovery in the laboratory to approval for marketing under the stewardship of a single individual or team. The skills sets

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are too diverse and the financial infrastructure required too complex to be accommodated without a mosaic of stakeholders in an ecosystem of support [68].

Target identification begins with study of the neuropathology of AD where the key pathological aspects of AD are evaluated [69]. This type of research is typically conducted in university settings funded by the NIA of the NIH. Philanthropists and advocacy organizations with funding capacity such as the Alzheimer's Association play important roles in supporting basic research directed at the biology of AD. Within the pathology of AD, there are an array of possible drug targets. These are captured in the Common Alzheimer's Disease Research Ontology (CADRO) (https://iadrp.nia.nih.gov/about/cadro) (Table 1.2).

Once a target has been identified, assays are developed, and libraries screened for "hits" that begin the process of developing a candidate agent. This type of screening is done in academic laboratories, biotechnology companies, and pharmaceutical companies. Over the past 10–15 years there has been a shift in pharmaceutical company strategy away from being vertically organized, end-to-end discovery-to-marketing organizations to focusing more on late-stage compounds and Phase 3 opportunities. This shift has been accompanied by an increased emphasis on partnering with academic medical centers (AMCs) and biotechnology companies [70–72]. Products of value in collaborations between biopharmaceutical companies and AMCs include information exchange and intellectual growth, drug candidates, new technology and laboratory processes, data, and biomarker development. Clinical trials are often conducted in AMCs and provide another conduit for collaboration. Academic trainees become familiar with the pharmaceutical industry, an experience that diversifies career choices for them [73]. Independent confirmation and validation of studies performed in academic laboratories are required before investments are made in a promising agent. The Academic Drug Discovery Consortium (ADDC) (www.addconsortium.org) facilitates information exchanges among AMCs with drug discovery programs [74].

Table 1.2 CADRO summary of possible therapeutic targets or treatment of AD

Amyloid beta	Tau	ApoE, lipids, and lipoprotein receptors
Neurotransmitter receptors	Neurogenesis	Inflammation
Oxidative stress	Cell death	Proteostasis/ proteinopathies
Metabolism and bioenergetics	Vasculature	Growth factors and hormones
Synaptic plasticity/ neuroprotection	Gut–brain axis	Circadian rhythm
Environmental factors	Epigenetic regulators	Multi-target
Unknown target	Other	

Source: https://iadrp.nia.nih.gov/about/cadro.

Pharmaceutical companies have active landscape surveillance teams searching for promising emerging compounds that can be licensed, purchased (the compound or the company), partnered, or acquired through merger [75]. Some biotechnology companies specialize in performing assay and screening activities and may create libraries of compounds that can be purchased for further development. Some larger biotechnology companies can escort a compound from early-stage development to later-stage trials. Biopharmaceutical "deals" consist of upfront payment and have risk reduction strategies such as milestone payments that depend on satisfactory progress of the asset. Shared governance is common with assumption of some degree of oversight of the biotech by the pharmaceutical partner with participation in the board of the biotechnology company. Biotechnology companies may be able to take advantage of the partner's expertise in regulatory, legal, commercialization, operations, manufacturing, clinical and medical affairs, and drug safety and pharmacovigilance.

Biotechnology companies typically begin as "spin-offs" from academic programs. The "start-up" focuses on a single product and accesses federal funding through the Small Business Innovation Research (SBIR) program, angel investors, philanthropists, or friends and family investors. Success may attract venture capital that allows the development of the asset to the level where it may attract interest from another biotech, a pharmaceutical company, or larger-scale venture capital investments. Venture capital may come from general funds, funds that specialize in biomedical and life science areas, or dementia-specific funds that specialize in dementia-related investments (e.g.,

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Dementia Discovery Fund, Dolby Ventures, LSP Dementia Fund).

Compounds may languish from lack of support in the early stages of development. Once a compound has been shown to be efficacious in animals, its promise can by explored and eventually realized only if it can be tested in humans. The cost of Phase 1 studies is substantial (~$1,000,000 to $2,500,000) per agent. The studies are typically conducted in healthy volunteers and focus on safety, tolerability, and PK. The information gained in Phase 1 is essential for advancing an agent further, but because it tends to be "recipe like" and does not provide information on treatment of a diseased population, it is often difficult to fund. This creates the "valley of death," where promising agents may not be advanced because of lack of funding, expertise, and infrastructure [76, 77]. Difficulty with fundraising may extend to early Phase 2 testing prior to the generation of disease-related information and beginning clarification of the commercial promise of the agent. Funding agencies have realized and responded to this challenge and support for very early-stage development is increasingly available through the NIA, National Center for Advancing Translational Science, and philanthropic organizations such as the Alzheimer's Drug Discovery Foundation (ADDF) [78, 79].

1.3.2 The Alzheimer's Disease Neuroimaging Initiative

The Alzheimer's Disease Neuroimaging Initiative (ADNI) began in 2004 as a public–private partnership between the NIA and more than 30 private (e.g., pharmaceutical) and not-for-profit enterprises. ADNI has a trial-like structure and was designed to collect brain imaging and biomarker data that could be used to understand the natural history of AD and to model trajectories relevant to planning clinical trials. ADNI has enrolled approximately 325 cognitively normal controls, 425 participants with MCI, and 215 participants with mild AD dementia. Biomarkers collected at 6-month intervals include MRI (structural, diffusion, perfusion, resting state), amyloid PET, tau PET, FDG PET, and genetic and autopsy data. CSF (for measures of Aβ, tau, p-tau, and other proteins) is collected annually. All participants have cognitive and clinical assessments with commonly used clinical trials instruments (Mini-Mental State Examination [MMSE], ADAS-cog, CDR, Everyday Cognition [Ecog], NPI Questionnaire [NPI-Q], and others). Data are collected at 60 participating sites and added to a publicly available database in real time. Trial-like site monitoring and data management ensure data quality.

Among its most important contributions has been ADNI's provision of data to trials sponsors which can be used to model clinical trials and determine necessary sample sizes. Sample sizes for different populations using different clinical instruments have been calculated [80], and the utility of biomarkers, genetic assessments, and MRI atrophy measures in identifying patients with MCI likely to progress to AD dementia has been demonstrated [81–83].

ADNI has worldwide collaborators including ADNI-like organizations in Europe, Japan, Australia, Korea, and Argentina [84]. The similarity of the participants recruited in different global regions has been assessed and the feasibility of using data from different regions shown [85]. Most late-stage trials require globally distributed sites to achieve adequate recruitment, and the baseline features of participants in non-Western countries vary [86, 87] making global data valuable for trial planning.

1.3.3 The Dominantly Inherited Alzheimer's Network – Treatment Unit

The DIAN is an international multi-site study characterizing early clinical and biomarker changes occurring in persons inheriting autosomal-dominant AD (ADAD) mutations. All subjects in the DIAN are either affected by or known to be at 50% risk for inheriting pathogenic presenilin 1 (*PSEN1*), amyloid precursor protein (*APP*), or presenilin 2 (*PSEN2*) mutations. Washington University (St. Louis, Missouri, USA) is the lead site (John Morris, Principal Investigator) and there are 19 participating sites in eight countries recruiting and assessing ADAD participants.

DIAN-TU leverages the existing infrastructure of the ongoing DIAN longitudinal study and builds on important DIAN baseline and rate-of-change data. DIAN-TU has a platform trial design that can introduce new candidate treatments sequentially as each is shown to be effective and matriculates to other studies or is shown to be ineffective and is discontinued. DIAN-TU is led by Randall Bateman of Washington University. Governance is by a steering committee comprised of clinical trial experts, regulatory advisors, and ADAD family-member

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representatives. Funding for the DIAN-TU is provided by the NIA, Alzheimer's Association, and the DIAN Pharma Consortium. The Pharma Consortium was created by the DIAN-TU and collaborating pharmaceutical companies to provide funds, expertise, and drug candidates for the platform [88].

The DIAN-TU platform was initiated as a randomized, blinded, placebo-controlled four-arm trial with a target of 160 asymptomatic to mildly symptomatic mutation carrier participants who are −15 to +10 years of their estimated age at onset of AD dementia [88]. A pooled placebo group derived from the placebo arm for each agent greatly increases efficiency and enhances the participant's likelihood of receiving the active drug compared with traditional designs; this makes participating in the trial more attractive to potential volunteers.

DIAN-TU has introduced innovations including construction of a disease progression model (DPM) to detect changes in cognition with fewer participants, self-administered cognitive testing, a predefined dose escalation algorithm to safely maximize target engagement, adaptive trial design strategies that include both early biomarker and later cognitive interim analyses to inform early efficacy or futility, and novel biomarkers [64].

1.3.4 Alzheimer's Prevention Initiative

The API, led by researchers from Banner Alzheimer's Institute (BAI; Drs. Reiman, Tariot, Langbaum) in partnership with leaders from academia, industry, and other public and private stakeholder organizations was initiated to accelerate the evaluation and approval of prevention therapies. The API ADAD Colombia trial is studying the use of an anti-amyloid treatment – crenezumab – in cognitively normal *PSEN1* mutation carriers and non-carriers from the world's largest ADAD kindred [89]. Mutation carriers are at virtually certain risk for developing AD at young ages. The study is conducted in conjunction with the University of Antioquia in Colombia and Genentech/Roche.

The API Generation Program aims to prevent or delay the onset of symptoms associated with AD in cognitively healthy people with two *APOE-4* alleles, making them at particularly high risk for developing the AD [90]. These studies are part of a collaboration between BAI, Novartis, Amgen, and the NIA. The API has pioneered new cognitive assessments for cognitively normal individuals at risk for AD [91] and developed innovative approaches to genetic counseling [92].

1.3.5 European Prevention of Alzheimer's Disease

The EPAD project, funded by the Innovative Medicines Initiative (IMI), was established to overcome the major hurdles hampering drug development for secondary prevention of AD [65, 93, 94]. EPAD is led by Craig Ritchie at the University of Edinburgh and trial delivery centers throughout Europe participate in the consortium. EPAD incorporates several drug-development innovations: collaborative access to existing European cohorts and registries; development of the EPAD Registry of people at increased risk of developing AD dementia; establishment of the EPAD Longitudinal Cohort Study (LCS) to serve as a trial-ready cohort for POC studies; and establishment of an adaptive, POC trial platform. In addition to providing patients for trials, the LCS provides run-in data for the pre-randomization period in the EPAD POC study, gathers longitudinal data for AD modeling of probability of decline, and generates models that place individuals on the disease probability spectrum [93].

The EPAD POC study emphasizes biomarker effects of candidate agents, but success in the EPAD POC study requires the demonstration of clinical benefit. Drugs deemed successful in the POC study will, therefore, be more likely to achieve clinical and regulatory success in Phase 3. The POC study employs a Bayesian adaptive design that learns from data accrued as the trial progresses. Frequent interim analyses, done in accordance with predefined algorithms and blinded to all trial personnel, allow adaptive randomization of individuals to interventions that appear to show the greatest clinical efficacy, and, potentially, in subpopulations defined by clinical status, biomarkers, or genetics. These interim analyses are used to test for early signals of drug success or futility [93]. The trial design utilizes a shared placebo group to minimize the number of participants assigned to placebo without compromising trial integrity. EPAD has structured involvement of participants as collaborators recognizing the participants' key role [95]. Participant panels establish accountability and transparency between the study goals and the study population, provide an opportunity for researchers to respond to participants' concerns, and create a conduit for

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participants to provide input into the research processes, consent procedures, and dissemination of study results. The EPAD infrastructure may comprise the European component of the Global Alzheimer Platform (discussed below).

1.3.6 Coalition Against Major Disease

The Critical Path Institute (C-Path) is a nonprofit, public–private partnership with the FDA created under the auspices of the FDA's Critical Path Initiative program in 2005. The goal of C-Path is to accelerate the pace and reduce the costs of medical product development through the creation of new measurements, methods, and data standards that aid in the scientific evaluation of the efficacy and safety of new therapies. The Coalition Against Major Diseases (CAMD) was a founding consortium within C-Path and gave rise to the Critical Path for Alzheimer's Disease (CPAD) [96]. CPAD focuses on: (1) regulatory qualification of biomarkers (fluid, imaging, and digital/biosensor observational- and performance-based); (2) Clinical Data Interchange Standards Consortium (CDISC) data standards for AD endpoint assessments; (3) integrated databases for observational and clinical trials data; and (4) quantitative model-based tools for drug development. CPAD efforts led to the qualification by the European Medicines Agency (EMA) for the use of low baseline hippocampal volume for patient enrichment in pre-dementia trials; the creation of an AD drug–disease trial model and clinical trial simulation tool endorsed by the FDA and qualified by the EMA [97]; and the launch of an open database of aggregated CDISC-standardized clinical trial data for AD.

1.3.7 Clinical Trial Infrastructure

Phase 2 clinical trials typically include several hundred participants and Phase 3 trials may require several thousand. Recruitment of large numbers of participants can be achieved only if many sites are involved in the recruitment process; most sites randomize ~0.5 patients per trial per month, contributing six or fewer patients annually to trials [98]. Sites are typically comprised of a site principal investigator (PI), several research coordinators and research assistants, a research nurse, budget manager/financial officer, and a regulatory/institutional review board (IRB) specialist. Sites may be situated in AMCs associated with memory clinics or may be "commercial sites" whose purpose is to attract participants through advertisements and community events for the purpose of conducting trials. Most trials include both academic and commercial sites. Sites must have IRB (local or central) approval to conduct trials and be knowledgeable about informed consent requirements. Sites are monitored for quality during the conduct of the trial by site monitors from the sponsor, the sponsor's contract research organization (CRO), or both.

There are several clinical trial consortia that facilitate trials. The US Alzheimer Clinical Trial Consortium (ACTC) has 30 core academic sites and an extended group of academic and commercial collaborators that conduct NIA-sponsored and industry-sponsored trials. The ACTC is funded by the NIA and consists of a steering committee of the site PIs and cores addressing recruitment, statistics, bioinformatics, imaging, biomarkers, and clinical operations. Paul Aisen (University of Southern California), Reisa Sperling (Harvard University), and Ronald Petersen (Mayo Clinic) provide leadership to the ACTC. The ACTC collaborates with the NIA-funded Trial-Ready Cohort for Preclinical and Prodromal AD (TRC-PAD), a registry of individuals interested in trials who are prescreened through online testing, referred to sites for biomarker confirmation of AD, and comprise a trial-ready cohort for ongoing and emerging trials [99].

The Consortium of Canadian Centres for Clinical Cognitive Research (C5R) is a not-for-profit research network that facilitates collaboration and partnerships between pharmaceutical companies and Canadian dementia researchers. C5R research sites conduct clinical trials and develop treatments for patients with MCI, AD dementia, and other forms of dementia.

The Global Alzheimer Platform (GAP) is a network of over 80 clinical trial sites across North America whose goal is to conduct clinical trials of AD and to optimize clinical trial conduct [100]. GAP provides assistance with site activation, site optimization, recruitment, participant transportation, and participant engagement activities for GAP-enabled trials. GAP has a global vision for more international collaboration and trial conduct.

Neuronet is a European program that connects 18 research projects launched by the IMI, Europe's largest public–private partnership in the

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life sciences. To enhance the productivity and visibility of the IMI neurodegeneration portfolio, Neuronet created a platform for efficient collaboration, communication, and operational synergies among present and future IMI neurodegenerative disease projects. Neuronet is designing systems to map and analyze information regarding actions, initiatives, and partnerships to assess the impact of individual projects, identify remaining gaps, and determine the global value of the program for stakeholders. Neuronet supports the management of the program projects (timelines, dependencies, synergies and key results across projects). Neuronet provides support to the projects by organizing services, expert advice and guidelines/recommendations, opportunities, and transferable best practices. Neuronet promotes enhancement and coordination of communication across the IMI neurodegeneration projects, increasing program visibility, engaging key stakeholders, and establishing relationships with other initiatives in the field.

1.3.8 Contract Research Organizations

CROs play a major role in AD therapeutic and biomarker development and comprise important components of the AD drug-development ecosystem. The growth of CROs reflects the decision of pharmaceutical companies to reduce in-house work forces and rely more on outsourcing. Some pharmaceutical companies have internal trial conduct capability but a majority of them depend on CROs. Trial CROs conduct feasibility studies to assess site capabilities; engage the sites for trials; work with sites to achieve IRB approval; manage contract negotiations and contract review; monitor the sites once the trial is initiated; oversee data collection, capture, and transfer to the sponsor; identify members for data safety monitoring boards; and close sites when the trial is terminated [101]. Some CROs have biostatistical expertise and are contracted to do database management and data analysis. Most Phase 3 trials and some Phase 2 trials are conducted with multi-regional sites, and trial CROs must have multi-regional capability or affiliations with national or regional CROs [102].

Specialty CROs are available for a wide range of services including transgenic mouse testing, Phase 1 clinical trials, regulatory strategy formulation, biomarker measurement, brain imaging interpretation, rater training, and product manufacturing and supply chain management.

1.3.9 Advocacy Organizations

The Alzheimer's Association supports caregivers, funds research, and advocates on the behalf of AD patients and caregivers. It works on a national and local level (through chapters) to provide care and support for those affected by AD and related dementias. As the largest non-profit funder of AD research, the Alzheimer's Association supports research on methods of treatment, prevention, and, ultimately, a cure for AD. From the advocacy perspective, it fights for critical AD research and care initiatives at the state and federal level. In partnership with Bill Gates, the Alzheimer's Association funds the Part the Cloud program that promotes human studies to advance innovative ideas for early-phase human trials (Phase 1 or Phase 2). The association sponsors TrialMatch, a clinical study matching service that connects individuals living with AD, caregivers, and healthy volunteers with research studies. The Alzheimer's Association has partnered with a variety of organizations to support research on amyloid imaging and standardization of CSF biomarker measures, and it has sponsored work groups that advance diagnostic standards [52, 103]. It plays a key role in advocating for better care of AD patients and was a leader in the effort to gain FDA approval for aducanumab.

Alzheimer's Disease International (ADI) is a UK-based globally focused advocacy organization whose goal is to strengthen and support AD and dementia associations worldwide, raise awareness and lower stigma about dementia, make dementia a global health priority, support and empower people living with dementia and their care partners, and increase investment and innovation in dementia research. ADI sponsors the Alzheimer University, a series of workshops for volunteers to help them strengthen their local and national associations. ADI sponsors international and local meetings; publishes globally oriented reports and reviews, helps countries develop national plans for AD and other dementias, promotes "dementia friendly" community programs, and supports research with global impact such as the 10/66 research group [104–106].

Alzheimer Europe is a non-profit non-governmental organization aiming to provide a voice to people with dementia and their caregivers, make

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dementia a European priority, promote a rights-based approach to dementia, support dementia research, and strengthen the European dementia movement. Alzheimer Europe convenes European and local meetings, publishes reports, promotes and collaborates on research [107], and conducts surveys to influence policy and funding decisions [108].

UsAgainstAlzheimer's is a non-profit organization committed to stopping AD by creating urgency from government, industry, and the scientific community in the quest for an AD cure – accomplishing this through leadership, collaboration, advocacy, and strategic investments. Goals of UsAgainstAlzheimer's include improving brain health; increasing the speed, efficiency, and diversity of clinical trials (in collaboration with GAP); advancing national care goals and policies to support caregivers; and mobilizing advocates in many communities (e.g., Women Against AD, Latinos Against AD, etc.).

The Alzheimer's Foundation of America (AFA) provides support, services, and education to individuals, families, and caregivers affected by AD and related dementias nationwide. The AFA conducts support groups (face-to-face and online), webinars, and education programs for patients and caregivers. A signature program is the National Memory Screening Program, which provides, free, confidential memory screenings at sites across the country.

1.3.10 Philanthropy

Advocacy enterprises are one conduit for organized philanthropy. Philanthropists may also make direct contributions to scientists and their laboratories or make contributions as part of a philanthropy group that raises funds and identifies individual scientists or programs worthy of support. Philanthropy often provides seed funds for projects that require preliminary data before proposals for federal or other types of grant support can be developed. Similarly, philanthropy can help overcome "valley of death" challenges (described above) to advance candidate agents to an investment level of development. The Cure Alzheimer's Fund is a non-profit organization dedicated to funding research with the highest probability of preventing, slowing, or reversing AD. The Milken Institute Center for Strategic Philanthropy develops Giving Smarter Guides to help guide philanthropists to high-impact philanthropy. A Giving Smarter Guide for AD has been developed [109].

ADDF (Howard Fillit, Chief Scientific Officer) is a venture philanthropy enterprise that funds treatment-related research at the basic and clinical level. ADDF invests in development of new drugs, biomarkers, and digital technology relevant to drug development. The organization funds early laboratory studies of emerging therapeutics as well as early-stage clinical trials. ADDF emphasizes the importance of an experimental medicine approach to drug development, with early trials focusing on POC and biomarker effects with appropriate statistics for small trials with exploratory aims. ADDF is the largest non-federal funder of clinical trials in the United States and has a shaping influence on AD drug development through its investment strategy [78, 110]. Venture philanthropy invests in early-stage companies, is a company partner, benefits from profits generated, and re-invests any profits in the philanthropy [111].

1.3.11 Regulatory Agencies

Regulatory authorities include the FDA, EMA, Chinese National Medical Products Agency (NMPA), Japanese Pharmaceuticals and Medical Devices Agency (PMDA), and similar agencies in other countries. A key interaction with the FDA is submission of the investigational new drug (IND) when a new agent is to be studied, when an approved product is to be assessed for a new indication, or when a new patient population is to be included in trials. The IND application must include information on animal pharmacology and toxicology studies, product manufacturing, and clinical protocols and investigator information (www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application). The new drug application (NDA) is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the USA.

The FDA corresponds and meets regularly with sponsors throughout the drug-development process. Planned meetings typically occur in the pre-IND period, with the initial IND submission, at end of Phase 2, prior to NDA submission, and with the drug marketing application (Figure 1.4). There is ongoing communication and updates throughout the trial and development process [112].

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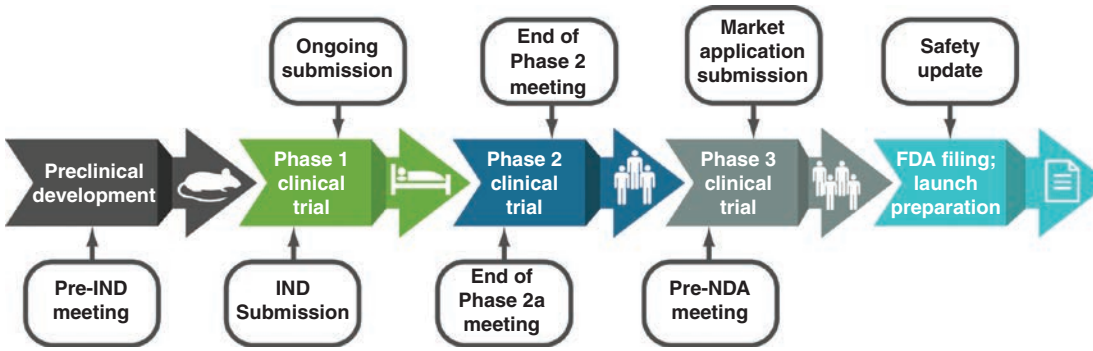

Figure 1.4 Planned meetings with FDA occurring in the course of a drug-development program.

The FDA issues "Guidances" to help sponsors understand FDA policies. Guidance documents usually discuss design, production, labeling, promotion, manufacturing, and testing of regulated products. Guidances provide information on the processing, content and evaluation or approval of submissions, as well as on inspection and enforcement policies. The FDA recently issued an influential Guidance on developing drugs for treatment of early AD [50] describing the stages of early AD to facilitate drug development for the preliminary stages of the illness (see Figure 1.3).

1.3.12 Media and Drug-Development Press

The public becomes aware of scientific advances through media coverage. Members of the lay public are concerned about AD and the consequences of cognitive decline; they do not read the scientific literature and depend on the press and media for scientific information. Social media channels have grown in importance as a source of information [113]. Direct-to-consumer advertising is a source of information for patients and families supported by pharmaceutical companies and providing information about their products. Media releases often have agendas beyond education: scientists want to draw attention to their work; biotechnology companies seek to influence investors; and pharmaceutical companies use media to attract patients in need of their products. Citizens often have no reliable way to assess the accuracy of health information found in the media (social or traditional), on the Internet, or in direct-to-consumer advertising [114]. News on drug development can influence decisions to seek care, invest, join advocacy efforts, or donate funds. For this reason, it is particularly important for scientists to communicate clearly and for citizens to seek informed, objective advice when evaluating news and drawing conclusions based on media releases.

1.3.13 Scientific Publication of Drug-Development Information and Clinical Trials

Scientific publication in peer-reviewed journals is a key part of the life cycle of drug development. Publication of trial results is an ethical responsibility given that participants have taken risks with altruistic motivations to advance the public good. Most journals require that trials submitted for publication have been registered prior to conduct on approved registries such as ClinicalTrials.gov. Nearly all journals expect use of the Consolidated Standards of Reporting Trials (CONSORT) criteria with a checklist of essential elements (Table 1.3) and a figure showing the disposition of participants in the trial (enrollment, intervention, allocation, attrition, completion) [115]. The standardization of trial reporting allows the reader to evaluate the quality of the trial and to compare trials. The CONSORT criteria represent a useful planning document and checklist for trial protocol planning since publication of the trial results will require meeting this standard. Publication of trials in peer-reviewed journals is the principal means of getting treatment-related information into the public domain.

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Table 1.3 CONSORT checklist

Section/topic	Checklist item
Title	Identification as a randomized trial in the title
Abstract	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts)
Background and objectives	Scientific background and explanation of rationale; specific objectives or hypotheses
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 assessed; 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
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), describing any steps taken to conceal the sequence until interventions were assigned
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 how; if relevant, description of the similarity of interventions
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes; methods for additional analyses, such as subgroup analyses and adjusted analyses
Participant flow (with diagram)	For each group, the number 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; why the trial ended or was stopped
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 groups
Outcomes and estimation	For each primary and secondary outcome, results for each group, and the estimated effect size, and its precision (such as 95%); for binary outcomes, presentation of both absolute and relative effect sizes is recommended
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
Limitations	Trial limitations, addressing sources of potential bias, impression, 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
Registration	Registration number and name of trial registry
Protocol	Where the full trial protocol can be accessed, if available
Funding	Sources of funding and other support (such as supply of drugs), role of funders

Adapted from Ref. [115].

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1.4 Aducanumab: The Ecosystem Delivers

Aducanumab (marketed as Aduhelm™) was approved by the FDA on June 4, 2021, as a means of lowering Aβ in the brain. The approval of aducanumab shows the successful interaction of the many stakeholders comprising the AD drug-development ecosystem. Aducanumab emerged from university-based foundational studies involving reverse translation of clinical observations and was further optimized by Neurimmune, a biotechnology company. The rights to advanced development were obtained by Biogen. Trials involving CROs and academic and commercial trial sites were conducted; new biomarkers including Aβ PET were incorporated in the trial design to better define the participant population and the outcome; the FDA conducted extensive reviews of the trials; and the Alzheimer's Association and USAgainstAlzheimer's played key roles in advocating for the approval of aducanumab. The development program of aducanumab had irregularities and some opposed approval. Many lessons emerged from the aducanumab trials that will be applied to other drug-development efforts and will further enhance the AD drug-development ecosystem. The approval of aducanumab is likely to increase confidence in the ability to change the course of AD with pharmacological intervention attracting greater interest from biotechnology and pharmaceutical companies, venture capital, philanthropy, and other sources of financial support.

1.5 Discussion

The drug-development ecosystem described here is not unique to AD; it is characteristic – with some variations – of nearly all drugs. It is successful in the sense that many drugs have traversed the pathway and become approved treatments with major impact on the public health.

Of 210 new molecular entities (NMEs) approved by the FDA between 2010 and 2016, federal funding contributed to development of all. NIH funding was focused primarily on the drug targets rather than on the NMEs themselves [116]. These figures demonstrate the critical role of NIH funding in providing the foundation on which much of the rest of the ecosystem is built. Considering the relatively small number of NMEs entering the AD drug-development pipeline, enhanced investment in AD target discovery is likely to lead to eventual benefit in new therapies [117].

The low rate of successful drug development for AD and other CNS disorders has resulted in a flight of pharmaceutical companies from pursuing treatments for these disorders. From 2009 to 2014 there was a 50% decrease in the number of major pharmaceutical companies working in CNS therapeutic areas [72]. Improvements in the ecosystem including more promising targets and optimized trial processes are required to attract industry sponsors back to AD drug development. Success by companies working on AD therapeutics will encourage other companies to launch programs for AD, and legislative and policy adjustments to incentivize AD drug development will encourage sponsors to include AD drug development in their portfolios. The approval of aducanumab is expected to serve as a stimulus for AD drug-development innovation.

The absence of a well-developed, stable, high-capacity, high-quality clinical trial network with excellent sites throughout the world hinders AD drug development. Organizations such as the ACTC (described above) are funded to test five to six new drugs in each 5-year grant cycle, far below the capacity needed to meet the needs of patients and sponsors. GAP (described above) can manage four to five trials at a time; far below the capacity needed to advance Phase 2 and Phase 3 drugs with a wide range of sponsors. University-based Clinical and Translational Science Award (CTSA) centers in the United States conduct trials in multiple disease states but lack capacity to conduct the trials needed to advance a major portion of the AD drug-development portfolio. The result of these shortfalls is that the sponsor or CRO must identify sites and rebuild the trial network for each trial. This has been likened to rebuilding a soccer stadium for each game. A global continuously functioning trial network that optimizes site function, ensures site quality, and encourages new sites and new principal investigators is needed.

An efficient means of testing drugs in Phase 2 is the use of an adaptive platform trial design [118, 119]. EPAD and DIAN-TU (described above) are examples of this approach. Advantages of platforms include the simultaneous testing of several agents, the use of biomarkers as readouts to determine which agents will continue to be assessed for clinical efficacy and which will be terminated, the use of Bayesian

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statistics to minimize the size and duration of trials for each agent, the pooling of data from placebo groups to minimize the number of patients assigned to placebo, and the ability to study new clinical and biomarker measures. Registries and trial-ready cohorts can be organized to facilitate enrollment in the platform, and assessment of pre-enrollment cognitive trajectories can assist in evaluating drug effects on the course of the disease. Time between trials is minimized as new drugs are continuously introduced as test agents in the platform are terminated or continue to the next phase of development. Trials sites are continuously operational, and the site network can be grown over time. Figure 1.5 illustrates an adaptive platform design for trials. Such a structure requires continuous external financial support at least until the costs can be covered in part by sponsors whose drugs are being assessed. The improvement in patient and caregiver quality of life, continued innovation, eventual generic status of drugs shown to be successful, training opportunities, and economic gains (salaries, etc.) more than justify the costs of supporting such a platform trial enterprise.

The globalization of drug-development research, clinical trials, and the availability of drugs shown to be safe and efficacious is a critical aspect of the AD drug-development ecosystem. Fourteen percent of Phase 2 trials and 42 percent of Phase 3 currently involve sites both in North America and non-North American locations [98]. The United States is the preferred site for trials by sponsors because it has a well-developed trial infrastructure, and its large market and robust reimbursement of drug costs are attractive. Sponsors conduct their trials in the United States to ensure that the data are acceptable to the FDA. Once approved in the United States, some countries require a full development program in their own populations, some require at least safety trials to allow marketing of the agent in their country, and others allow marketing of the agent based on FDA or other regulatory agency approval. This means that treatments will be used by patients in many countries not participating in trials, including those with different body sizes, genetics, diets, nutritional history, and medical care not represented in trials. Even within countries,

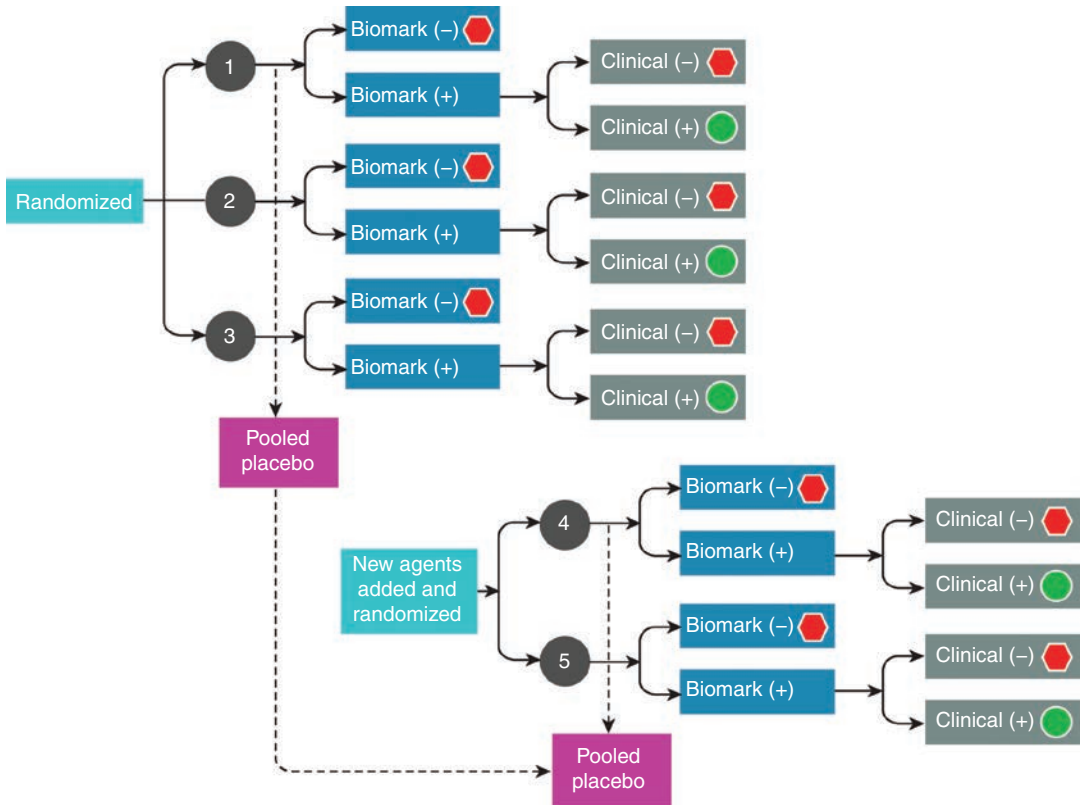

Figure 1.5 Adaptive clinical trial platform.

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such as the United States, the participation in trials by minority members is low and extrapolation from majority-culture trial participants to minority-culture patients is hazardous [120]. Diversifying trial participants within countries and globally is an unmet need that must be resolved to advance health equity among the world's populations.

Training of translational neuroscientists with experience, knowledge, skills, and passion for drug development is another unmet need that must be addressed if future generations are to have ever better therapeutic options. Few training programs exist specifically for trialists, most residencies provide no exposure to trials, and although most academic dementia programs conduct trials, the involvement of trainees is variable. The need for new staff with trial skills far outstrips the current capacity to develop this workforce [121]. Many aspects of college curricula can be translated into contributions to drug development (Figure 1.6). Biology addresses drug targets; chemistry is key to candidate development; veterinary medicine is required for animal care; psychology contributes to outcomes; physicians trained in several specialties are required for trials; and business, law, ethics, regulatory science, and governmental affairs all prepare students for potential roles in drug development. Few under-graduate or graduate programs acquaint students with career opportunities for drug development [122].

Clinical trials and drug development are key components of the larger concept of translational science or translational medicine that conceptualizes accelerating advances in science to improve public health [123]. There is a perceived gap between the increasing investment in science and the relative lack of new therapies in disorders such as AD; translational science aims to address this gap. In drug development, the translation from basic science to animal testing is T1; the translation of animal observation to humans in trials is T2; the translation from trials to care is T3; and the translation from care to public health and policy is T4 [124] (Figure 1.7). To achieve the laudable and important goal of improving public health, drug-development science must be complemented by advances in recruitment science, implementation science,

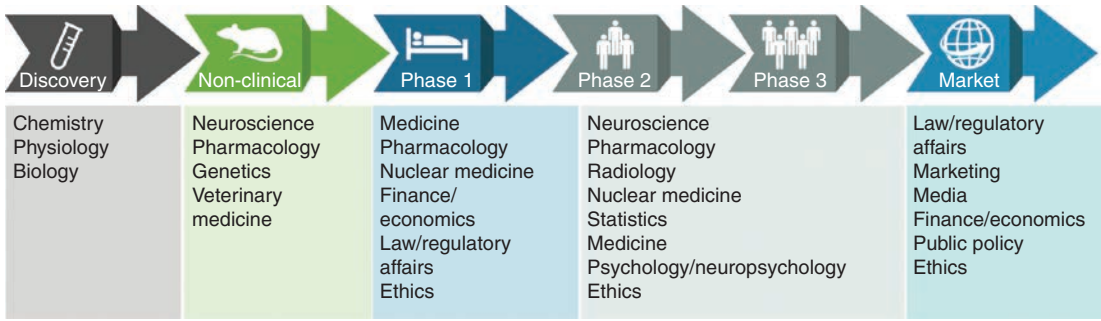

Figure 1.6 Alignment between skills needed for drug development and college curricula.

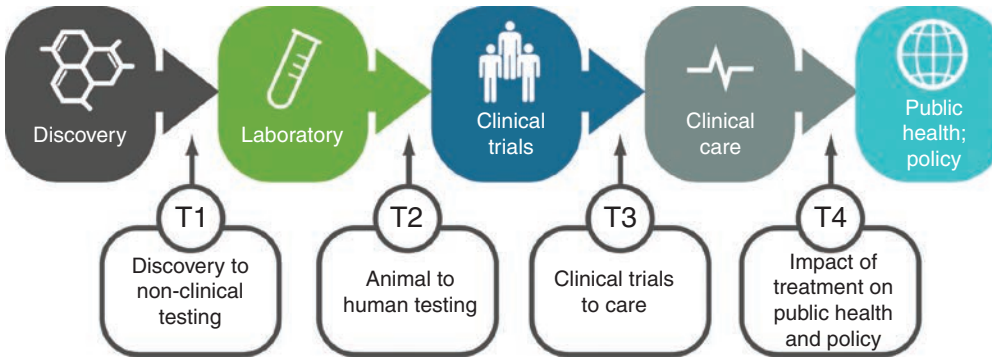

Figure 1.7 Steps in the translational research process.

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regulatory science, science of behavior change, and other key approaches to ensure that new advances in treatment of AD and other related dementias reach all those in need of therapy [125–128].

1.6 Summary

Drug development for AD depends on a complex, dynamic, interactive ecosystem with many stakeholders (Figure 1.8). The system is successful in advancing drugs, biomarkers, and trials. The approval of aducanumab is an example of the successful working of the ecosystem to advance a new therapy for AD. Other promising agents are emerging from the pipeline and success will encourage more sponsors to enter the AD and related dementias therapeutic area. The ecosystem lacks optimal coordination among the many participants and accelerating drug development depends on building infrastructure and advancing training that will ensure the resources and expertise for future AD drug development.

Disclosures

Dr. Cummings has provided consultation to Acadia, Actinogen, Acumen, Alector, Alkahest, AriBio, Avanir, Axsome, Behren Therapeutics, Biogen, Biohaven, Cassava, Cerecin, Cerevel, Cortexyme, EIP Pharma, Eisai, Foresight, GemVax, Genentech, Green Valley, Grifols, Janssen, Karuna, LSP, Merck, Novo Nordisk, Ono, Otsuka, ReMYND, Resverlogix, Roche, Signant Health, Sunovion, Suven, and Vaxxinity pharmaceutical, investment, and assessment companies. Dr. Cummings has stock options in ADAMAS, AnnovisBio, MedAvante, BiOasis. Dr. Cummings owns the copyright of the Neuropsychiatric Inventory. Dr. Cummings is supported by NIGMS grant P20GM109025; NINDS grant U01NS093334; NIA grant R01AG0 53798; NIA grant P20AG068053, and ADDF Goodes Prize.

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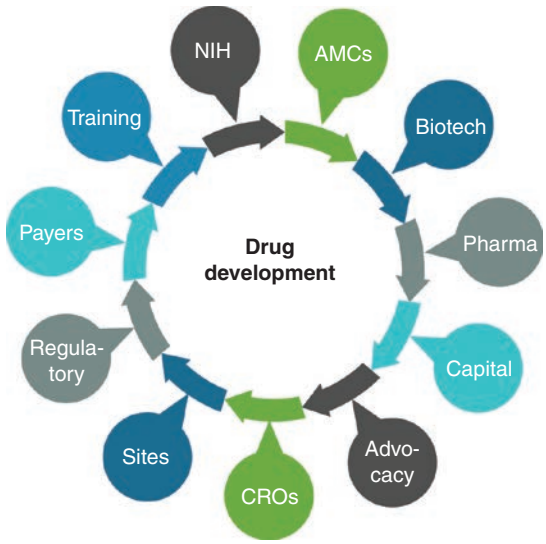

Figure 1.8 Stakeholders involved in AD drug development.

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