Early-stage Alzheimer disease: getting trial-ready

Paul S. Aisen ✉, Gustavo A. Jimenez-Maggiora, Michael S. Rafii, Sarah Walter and Rema Raman

Abstract | Slowing the progression of Alzheimer disease (AD) might be the greatest unmet medical need of our time. Although one AD therapeutic has received a controversial accelerated approval from the FDA, more effective and accessible therapies are urgently needed. Consensus is growing that for meaningful disease modification in AD, therapeutic intervention must be initiated at very early (preclinical or prodromal) stages of the disease. Although the methods for such early-stage clinical trials have been developed, identification and recruitment of the required asymptomatic or minimally symptomatic study participants takes many years and requires substantial funds. As an example, in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease Trial (the first phase III trial to be performed in preclinical AD), 3.5 years and more than 5,900 screens were required to recruit and randomize 1,169 participants. A new clinical trials infrastructure is required to increase the efficiency of recruitment and accelerate therapeutic progress. Collaborations in North America, Europe and Asia are now addressing this need by establishing trial-ready cohorts of individuals with preclinical and prodromal AD. These collaborations are employing innovative methods to engage the target population, assess risk of brain amyloid accumulation, select participants for biomarker studies and determine eligibility for trials. In the future, these programmes could provide effective tools for pursuing the primary prevention of AD. Here, we review the lessons learned from the AD trial-ready cohorts that have been established to date, with the aim of informing ongoing and future efforts towards efficient, cost-effective trial recruitment.

Alzheimer disease (AD), a progressive and fatal age-related neurodegenerative disease characterized by amyloid deposits in the brain and neurofibrillary tangles within neurons, is among the world's most important health-care challenges. After 30 years of AD therapeutic research, accelerated approval of one anti-amyloid drug has been achieved but effective and broadly available therapies continue to be urgently needed[1,2]. Candidate treatments that effectively target the core pathologies of AD have yielded generally disappointing results in clinical trials, a failure that might be attributed to intervention too late in the course of the disease[3]. All pivotal trials to date have been conducted in individuals with symptomatic AD characterized by advanced, irreversible neurodegeneration. However, the accumulation of fibrillar amyloid in brain is the initial defining change in the AD continuum, occurring many years prior to the onset of symptoms of cognitive impairment[4]. The results of long-term follow-up studies show that most cognitively healthy individuals with elevated brain amyloid will develop symptomatic AD over a period of 10–15 years[5], supporting the development of anti-amyloid interventions for this preclinical (presymptomatic) stage. The beneficial impact of anti-amyloid treatment is expected to be optimized when initiated prior to substantial irreversible neurodegeneration and before considerable accumulation of co-pathologies such as Lewy bodies, TDP43 proteinopathy and vascular disease[6].

AD is thus considered a continuum of gradual changes progressing over about 25 years from onset of pathology to death[7] (FIG. 1). Amyloid initiates the process, with initially subtle cognitive decline accompanied by multiple neurobiological processes, including tau pathology, brain atrophy and synaptic dysfunction, proceeding thereafter. Accurate cognitive and biomarker measures now allow the longitudinal tracking of these processes. Cognitively healthy individuals who have biomarker evidence of AD pathology are referred to as having preclinical (or presymptomatic) AD. Individuals with mild cognitive impairment and biomarker evidence of AD are referred to as having prodromal AD. As the accumulation of fibrillar deposits of amyloid mark

Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA.

✉*e-mail: paisen@usc.edu*

https://doi.org/10.1038/s41582-022-00645-6

Key points

- Trial-ready cohorts are an effective strategy for the identification of participants eligible for clinical trials in early-stage Alzheimer disease (AD).
- Building these cohorts requires considerable planning and technological infrastructure to facilitate recruitment, remote longitudinal assessment, data management and data storage.
- Trial-ready cohorts exist for genetically determined populations at risk of AD, such as those with familial AD and Down syndrome; the longitudinal data from these cohorts is improving our understanding of the disease progression in early stages, informing clinical trial design and accelerating recruitment to intervention studies.
- So far, the challenges experienced by trial-ready cohorts for early-stage AD have included difficulties recruiting an ethnically and racially representative cohort; and for online cohorts, difficulty retaining participants.
- The results of ongoing work will reveal the success of strategies to improve cohort diversity and retention, and the rates of referral to clinical trials.

Earned media coverage
Publicity gained through promotional efforts other than advertising (paid media) or branding (owned media).

the onset of AD brain pathology, amyloid PET scanning is often used to look for biomarker evidence of AD; biofluid assays, in particular the ratio of $A\beta_{1-42}$ to $A\beta_{1-40}$ in cerebrospinal fluid (CSF) or even in plasma, might also be used. Tests of episodic memory (such as paragraph recall) are most commonly used to identify the typical early (predementia) cognitive impairment associated with AD.

The Anti-Amyloid Therapy in Asymptomatic Alzheimer's (A4) study, a public–private partnership funded by Eli Lilly, the National Institute on Aging (NIA), the Alzheimer's Association and other organizations, was designed and implemented to test the efficacy of the monoclonal antibody solanezumab in presymptomatic AD[8]. The final results from A4 are expected in early 2023. The trial is the first international phase III study of a candidate disease-modifying agent at this earliest detectable stage of disease. The A4 experience to date has demonstrated the feasibility of performing clinical trials in presymptomatic AD, but has also revealed the substantial barriers that must be overcome before such trials can be performed routinely. The recruitment plan for A4 involved inviting individuals aged 65 years or over for screening with florbetapir amyloid PET scans. As candidates for the study needed to be clinically healthy, memory clinics and other health-care settings were not appropriate sources; instead, outreach efforts focused on earned media coverage[9], local and national advertising (including social media activities). On the basis of analysis of data from the Alzheimer Disease Neuroimaging Initiative, the A4 study team anticipated that 30% of candidates would have amyloid elevation detected by PET, and this estimate proved accurate. However, recruitment of the target of 1,150 participants took over 3 years and required more than 4,000 PET scans[10]; the diversity of participants screened and then randomized was also minimal. Thus, efforts to perform trials at the earliest stage of AD face an enormous bottleneck: the painfully slow recruitment of diverse asymptomatic or minimally symptomatic individuals with biomarker-confirmed AD.

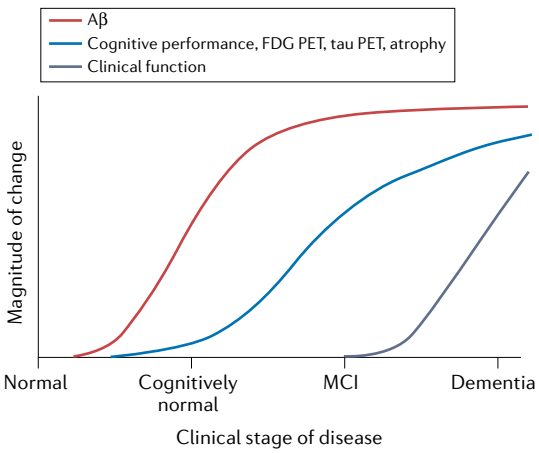

Fig. 1 | **The continuum of Alzheimer disease.** The figure illustrates the changes in Alzheimer disease pathologies in the brain and clinical symptoms that occur over time, highlighting the window of time during which changes in biomarkers are measurably different from those in healthy ageing but cognitive symptoms have not yet emerged. This window provides an important opportunity for the testing of clinical interventions. Aβ, amyloid-β; FDG, fluorodeoxyglucose; MCI, mild cognitive impairment. Reprinted from REF.[7].

A promising approach to alleviation of the bottleneck is the establishment of trial-ready cohorts of candidates for early intervention trials[11]. A trial-ready cohort is a group of individuals who meet general eligibility requirements for clinical trials in the target population. For AD, building these cohorts involves characterizing individuals with cognitive testing and assessing key biomarkers such as PET or CSF measures of amyloid pathology. Existing trial-ready cohort programmes have leveraged online tools that allow web-based recruitment and data collection, minimizing participant burden. In the future, the process could be streamlined further by the use of plasma assays to select individuals at risk of amyloid accumulation, thus reducing the number of costly and burdensome biomarker confirmation procedures (amyloid PET scans or lumbar punctures) required. The scientific community has recognized the promise of early intervention trials in AD, but also the enormous effort required to identify and enrol the target population. The establishment of trial-ready cohorts, particularly those consisting of individuals with biomarker-confirmed preclinical or prodromal AD and an interest in joining clinical trials, is a strategy for addressing the major bottleneck slowing early intervention programmes. In this Review, we aim to make further progress towards efficient trials in early-stage AD by examining and learning from the approaches that have been used to establish AD trial-ready cohorts thus far, and highlighting considerations for the design and implementation of future efforts.

Existing trial-ready cohorts

Building a trial-ready cohort enables investigators to establish and maintain a connection with individuals who meet criteria for trial enrolment in advance of the initiation of actual trial screening at a clinical site. A small number of trial-ready cohorts for AD research have been established to date and each has a different design. The process of recruitment into a trial-ready cohort often begins with remote contact through web-based activities and continues through in-person

evaluation and longitudinal follow-up until trial screening. Genetic and biomarker testing, essential for selection of participants for most early intervention AD trials, are conducted during the evaluation of candidates for the trial-ready cohort. Longitudinal cognitive and clinical assessments are performed during the period before screening for trials begins; if collected in a manner compliant with regulatory requirements, these data might establish individual pre-randomization trajectories that can strengthen later study designs and analysis of trial outcomes.

Sporadic AD

TRC-PAD. The Trial-Ready Cohort for Preclinical and Prodromal Alzheimer's Disease (TRC-PAD) was launched, with funding from the NIA, to reduce the time and expense of recruiting into early intervention trials in response (in part) to the experience of the A4 trial[12]. The overarching aim of TRC-PAD is to use web-based longitudinal data collection to assess AD risk and select individuals for biomarker testing and in-person follow-up in a trial-ready cohort, facilitating recruitment into early-stage intervention trials. Participants from TRC-PAD are now being actively recruited into therapeutic trials such as the AHEAD study, a public–private partnership with funding from the NIA and Eisai that is testing the amyloid-reducing monoclonal antibody lecanemab in asymptomatic individuals with intermediate or elevated levels of brain amyloid[13].

TRC-PAD (FIG. 2) builds on the major existing registries of individuals with interest in AD trials by inviting participants to join a longitudinal online registry, the Alzheimer Prevention Trials Webstudy (APT Webstudy). The APT Webstudy platform then collects unsupervised demographic, cognitive and clinical data from each participant, enabling the statistical estimation of the risk of amyloid elevation in brain[14]. Predictors of amyloid status from the A4 pre-randomization dataset were used to make the initial risk estimates in TRC-PAD, with refinements to be incorporated as new datasets become available[15].

The criteria for referral to the APT Webstudy included age of at least 50 years, absence of known dementia diagnosis and potential interest in participating in therapeutic trials[14]. Recruitment was initiated in 2018 using referrals from existing online registries for individuals interested in AD research — for example, the Alzheimer's Prevention Registry from the Banner Alzheimer's Institute, TrialMatch from the Alzheimer's Association and the Brain Health Registry at the University of California San Francisco — as well as earned media and social media outreach. Between 8,000 and 18,000 new participants have consented to the APT Webstudy each year, resulting in a total of 45,000 participants as of 7 February 2022. The mean age of this cohort is 64.6 years (s.d. 8.6 years). Within the cohort, 73% of participants are women, 91% self-report as non-Hispanic white, 61% have a self-reported family history of AD or dementia, and 38% returned for their first quarterly follow-up assessment[16].

A network of 50 US sites was established for in-person evaluation of the APT Webstudy participants who live within driving distance of a clinical trial site and are identified as being at high risk of developing AD. Participants are referred to clinical trial sites using the 'Site Referral System' (SRS). The SRS is a software system that allows the coordinating centre to deliver to clinical site personnel the contact information for eligible Webstudy participants. During the in-person evaluation, cognitive testing with the Preclinical Alzheimer's Cognitive Composite (PACC) and apolipoprotein E (APOE) genotyping is performed. APOE and PACC data are then included in an algorithmic reassessment

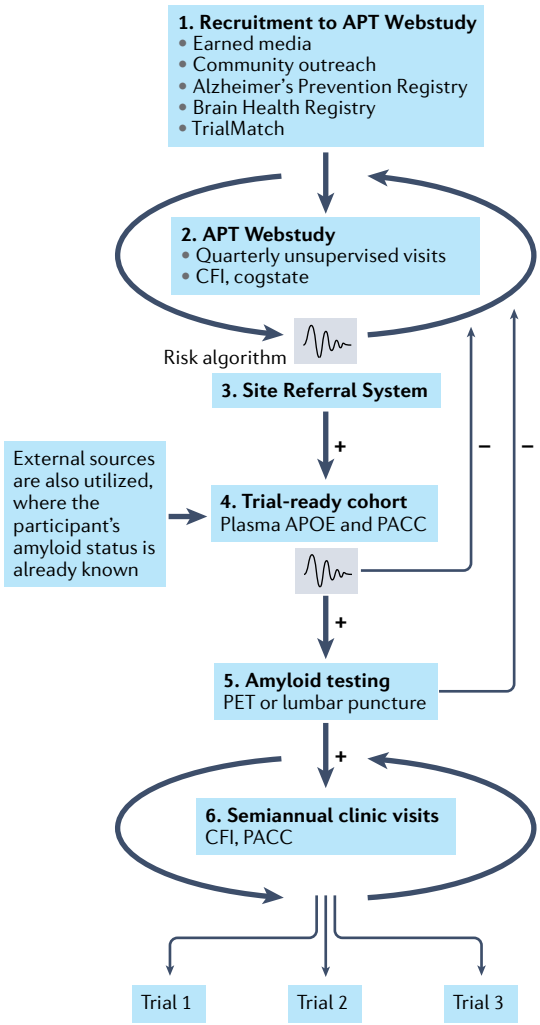

Fig. 2 | **The Trial-Ready Cohort for Preclinical and Prodromal Alzheimer's Disease.** Participants for Trial-Ready Cohort for Preclinical and Prodromal Alzheimer's Disease are recruited primarily from existing registries and remotely consent to be followed in the Alzheimer Prevention Trials Webstudy (APT Webstudy) for quarterly unsupervised assessments (1, 2). Algorithms are run to select participants for referral for in-person assessment, managed through the Site Referral System (3). Screening for the in-person cohort includes cognitive and clinical assessments and amyloid testing (4). Eligible participants are enrolled for semi-annual clinic visits (5), until an appropriate clinical trial becomes available at their site. APOE, apolipoprotein E; CFI, Cognitive Function Index; PACC, Preclinical Alzheimer's Cognitive Composite. Adapted from REF.[12].

Table 1 | **Demographics of participants in key trial-ready cohorts**

Category	EPAD Registry[25]	J-TRC[22]	APT Webstudy[16]	TRC-PAD[16]
Total consented participants	1,188	3,081	45,207	418
Mean age in years (s.d.)	65.77 (7.09)	62.3 (8.8)	64.68 (8.62)	71.8 (5.3)
Female participants	676 (56.9%)	1,688 (54.8%)	33,248 (73.5%)	242 (57.9%)
Participants with a family history of AD	815 (68.6%)	1,241 (40.3%)	27,360 (60.5%)	NR
Race and ethnicity				
Asian	–	–	838 (1.9%)	6 (1.4%)
African American	–	–	804 (1.8%)	10 (2.4%)
American Indian or Alaska Native	–	–	97 (0.2%)	0 (0%)
Hawaiian/Pacific Islander	–	–	72 (0.2%)	1 (0.2%)
Hispanic or Latino	–	–	1,697 (3.8%)	21 (5.0%)
White	–	–	40,784 (90.2%)	398 (95.2%)
Education				
Advanced degree	–	–	17,831 (39.4%)	190 (45.5%)
College or some college	–	–	20,408 (45.1%)	189 (45.2%)
High school or less	–	–	6,558 (14.5%)	38 (9.1%)

AD, Alzheimer disease; APT Webstudy, Alzheimer Prevention Trials Webstudy; EPAD, European Prevention of Alzheimer's Dementia; J-TRC, Japanese Trial-Ready Cohort; NR, not reported; TRC-PAD, Trial-Ready Cohort for the Prevention of Alzheimer's Dementia.

of the risk of elevated brain amyloid to select individuals for biomarker testing with amyloid PET or CSF amyloid peptide assays. Individuals with biomarker results that qualify them for trial enrolment are then followed up semi-annually until screened for an available early-stage trial[12]. As of February 2022, 802 participants from the APT Webstudy had been referred for in-person screening and 416 in-person screening visits had been conducted. Of the participants who were screened, 141 were eligible for TRC-PAD on the basis of biomarker results and enrolled into the cohort. Of the participants enrolled in TRC-PAD, 30% have subsequently been screened for or enrolled in a clinical trial. The movement of individuals from the APT Webstudy through the SRS to the TRC-PAD in-person visits has been markedly slowed by disruptions resulting from the COVID-19 pandemic. The pandemic has also had a substantial effect on the initiation of new studies and enrolment to existing AD clinical trials[17].

The development of plasma assays that accurately reflect AD pathology in brain has been an enormous advance in the field in the past 5 years. Assessment of the plasma $A\beta_{1-42}$ to $A\beta_{1-40}$ ratio by mass spectrometric methods has now been identified as a sensitive and specific indicator of brain fibrillar amyloid load as determined by amyloid PET[18,19]. Immunoassays for phosphorylated tau (p-tau) species, particularly p-tau_{217} and p-tau_{231} are also excellent markers of AD pathology[20]. Plasma specimens from the first few hundred individuals undergoing biomarker testing in TRC-PAD are being analysed using the leading candidate assays, and the best performing assay based on cost, feasibility and predictive value will be incorporated into the second stage of the TRC-PAD algorithm[15]. This change is expected to substantially reduce the number of negative PET scans and lumbar punctures required to reach full enrolment.

The APT Webstudy Registry, as most participant registries, has two limitations: difficulty in achieving diverse and representative enrolment and loss of participants to follow-up[16]. A significant lack of diversity in race, ethnicity and education can be observed among the APT Webstudy participants; as a result, the sample does not represent the diversity of the US population eligible for the study (TABLE 1). In addition, long-term retention in the APT Webstudy has been low at 38%[16], limiting the availability of key variables including longitudinal data on cognitive performance and subjective cognitive symptoms for use in risk assessments. Efforts are underway to address these deficiencies (discussed below). Evidence-based testing of novel retention strategies, for example evaluating the use of engagement videos, and implementation of innovative and targeted recruitment strategies, are ongoing.

The effect of the global pandemic on in-person TRC-PAD visits presents another major challenge for the programme and has required modifications to be made to the platform design. Most US clinical trial sites, particularly academic sites (which account for the majority of TRC-PAD sites), prioritized therapeutic trial visits over observational study visits during the pandemic. Consequently, biomarker testing has been fairly limited across the programme. The TRC-PAD site referral system has now been modified to accommodate direct referral from the APT Webstudy to therapeutic trial screening visits, bypassing the TRC-PAD visits, supporting the overarching aim of facilitating faster clinical trial recruitment.

J-TRC. The Japanese Trial-Ready Cohort (J-TRC) was launched in October 2019. This cohort represents an international collaboration between investigators at the University of Tokyo, Japan, and the TRC-PAD investigators, with the aim of adapting the informatics and biostatistics approaches developed for TRC-PAD to build an exploratory cohort to accelerate recruitment of older Japanese individuals into clinical trials. The informatics teams from the two groups collaborated to establish the required infrastructure, perform a culturally appropriate translation and adaptation of the web-based virtual cohort technology, develop a population-based risk algorithm to support participant selection, and build the electronic data capture system used to support data collection for the in-person cohort. These efforts were facilitated by the use of cloud-based technology, which expedited the implementation of the J-TRC informatics infrastructure in compliance with local data privacy and security regulations. Similarly, the biostatistics teams from the two groups collaborated to develop the statistical modelling approaches[21]. Recruitment to J-TRC used multiple mechanisms to promote the study and recruit participants, resulting in 3,081 consented participants as of June 2020 (REF.[22]). Eligible participants had a mean age

Subjective cognitive symptoms
Self-reported experience of worsening or more frequent memory loss.

of 62.3 years (s.d. 8.8 years), 54.79% were women and 40.28% had a family history of AD or dementia.

EPAD Registry. The European Prevention of Alzheimer's Dementia (EPAD) Project of the Innovative Medicines Initiative was a public–private consortium established with the aim of facilitating the successful development of new treatments for the secondary prevention of AD dementia. The EPAD Project had four aims: improving access to cohorts and registries, developing an EPAD Registry, establishing a longitudinal cohort and performing an adaptive proof-of-concept trial[23]. Here we focus on the experience of EPAD Registry's longitudinal cohort, the EPAD Longitudinal Study (EPAD-LCS), which was launched in 2016 and was the first trial-ready cohort of participants with preclinical AD. Participants for EPAD-LCS were preselected from ongoing parent cohorts[24]. The aim of this trial-ready cohort was not only to provide participants for the EPAD proof-of-concept trial, but to facilitate longitudinal modelling of the disease. EPAD-LCS used data from the pre-existing population-based cohorts and custom algorithms to identify participants at greatest risk of future AD, but did not require participants to have evidence of elevated amyloid for enrolment (FIG. 3). The minimum requirements were indicators of risk in four of the data variables: age, gender, education, apolipoprotein E ε4 (*APOE* ε4) genotype, family history of dementia, diagnosis of cognitive disorder, CSF biomarkers, MRI hippocampal volume, and memory test scores. An analysis of prescreening methods in four of the referral cohorts found variance in referral rates, but similar rates of amyloid elevation in participants with the same risk factors[25].

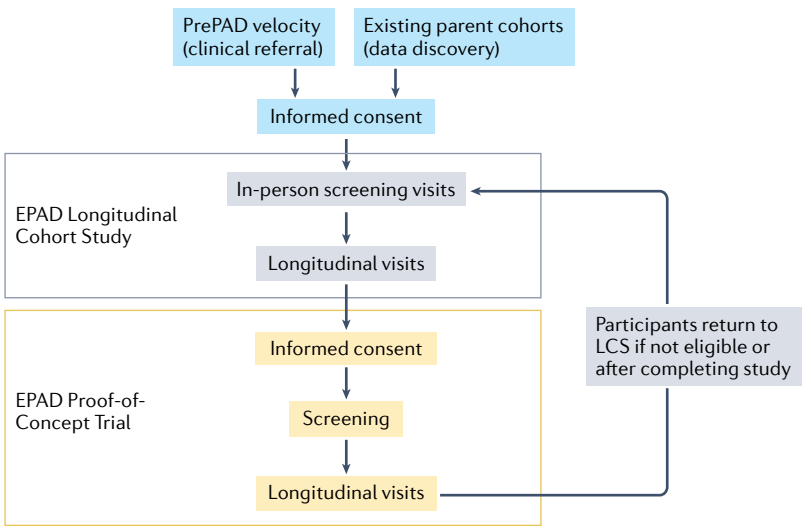

Fig. 3 | **Intended flow of participants to European Prevention of Alzheimer's Dementia Longitudinal Cohort Study and Proof-of-Concept trial.** Participants were identified from multiple cohorts, some community-based and prescreened for age, familial history and other risk factors. Participants were then referred for in-person screening and assessment for enrolment in the European Prevention of Alzheimer's Dementia (EPAD) Longitudinal Cohort Study. The intention was that participants from the cohort would be screened for enrolment into the EPAD proof-of-concept trial; however, EPAD Registry funding was discontinued in 2019 and the trial was not initiated. Participants were instead referred to appropriate clinical trials that were available at their local research centre. Adapted from REF.[24].

Older individuals were more likely to have elevated amyloid, but with increased age, more barriers to participation were also present. Family history of dementia was identified as a strong predictor of amyloid elevation and 15% of prescreened participants invited to join the EPAD Registry were determined to have elevated amyloid[26,27].

EPAD-LCS involved in-person visits every 6 months, with the aim of referring participants into the embedded clinical trials. Overall, 1,828 participants were enrolled in the EPAD-LCS over 4 years, across 31 research sites and ten European countries, with 99% of participants self-identifying as white[25]. Amyloid-positive individuals constituted 35% of the cohort and the majority of these individuals were also cognitively healthy, which the authors attribute to recruiting from population-based cohorts[23,24,28]. The EPAD Project also established participant advisory groups, with local groups nested in different regions reporting to a central board, to provide feedback on study recruitment materials and representation of the programme in the public. The study team viewed feedback from these participants as critical to the success of the platform[29]. The EPAD Project's 5 years of funding ended in 2019 without achieving the goal of referral of LCS participants into therapeutic trials[30]. Participants are being encouraged to enrol in clinical trials available locally, and the data have been released as part of the Neuronet knowledge base and will make a substantial contribution to advancing our understanding of trial-ready cohort design and infrastructure.

Genetically determined AD

Some trial-ready cohorts were designed to enrol individuals with a known genetically determined elevated risk of AD and include an observational cohort with expansion to clinical trial enrolment. Although enrolment strategies for these genetically high-risk populations will differ from the strategies used to enrol individuals from the general population, the value of identifying and following cohorts of well-characterized individuals who are candidates for therapeutic trials is similar in both cases. Experiences from building trial-ready cohorts of genetically high-risk participants to date inform ongoing efforts in sporadic disease.

DIAN-TU. Rare mutations cause an early-onset, autosomal dominant form of AD (ADAD). Data from the Dominantly Inherited Alzheimer's Network (DIAN) observational cohort has elucidated the natural history of ADAD including the identification of changes in standard AD biomarkers such as biofluid or PET measures of amyloid or tau pathology decades before the onset of dementia[31]. Over a 9-year period, the DIAN observational cohort enrolled 411 participants, including participants with an ADAD-associated genetic mutation[32]. Of the 251 mutation carriers, 55.4% were women, 59.8% were cognitively healthy and the mean duration of education was 14.2 years. The DIAN Trials Unit (DIAN-TU) platform was launched to accelerate identification of effective drugs for treatment and prevention of ADAD[33,34] — the genetically characterized participants in the DIAN observational study can be viewed as a trial-ready cohort. In 2012, a phase II–III

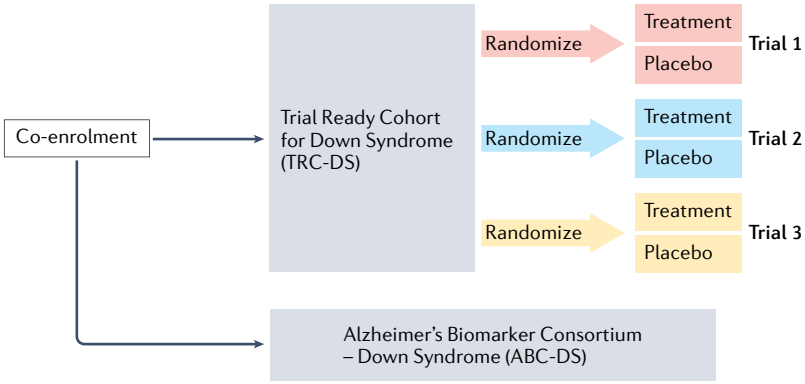

Fig. 4 | **Trial-ready cohort for Down syndrome schema.** Participants can co-enrol in the Alzheimer's Biomarker Consortium – Down Syndrome (ABC-DS) and the Trial Ready Cohort for Down Syndrome (TRC-DS). Within the TRC-DS, participants are followed up longitudinally until an appropriate clinical trial becomes available. The longitudinal data will then be used as run-in data for the trial, minimizing the burden of repeat testing for participants and increasing the efficiency of study design. Reprinted from REF.[78].

double-blind, randomized, pooled-placebo controlled trial began by testing two drugs — solanezumab (an antibody targeting soluble Aβ) and gantenerumab (an antibody targeting fibrillar Aβ)[35]. The antibodies demonstrated biomarker target engagement, and in 2014, the study transitioned within the DIAN-TU platform to become the Adaptive Prevention Trial, a 4-year phase III trial to determine whether antibody administration would prevent cognitive decline in individuals with presymptomatic AD[35]. Topline results released in 2020 showed that both of the trial's investigational drugs missed their primary end points[35,36]. The DIAN-TU is preparing to launch two new drug arms as the Next Generation (NexGen) Prevention Trial. The NexGen Trial will be a multicentre, double-blind, randomized, pooled-placebo controlled, phase II trial of two potential disease-modifying therapies in 160 mutation carriers at risk of or with mild symptomatic ADAD[37].

TRC-DS. Individuals with Down syndrome are at very high risk of developing AD pathology and have a greater than 95% lifetime risk of developing AD dementia[38,39]. The Alzheimer's Biomarker Consortium–Down Syndrome (ABC-DS) Project is setting the stage for secondary prevention trials for Down syndrome-related AD by collecting longitudinal AD biomarker data (for example, MRI, amyloid and tau PET, plasma and CSF amyloid and tau measures) from more than 500 adults with Down syndrome[40] (FIG. 4). FIGURE 4 illustrates the participant flow for the Trial-Ready Cohort for Down Syndrome (TRC-DS), recently launched by the Alzheimer's Clinical Trial Consortium–Down Syndrome (ACTC-DS)[41]. The ACTC-DS is a network of 16 international clinical trial sites (including all ABC-DS sites) with extensive experience in clinical studies in adults with Down syndrome[42]. To facilitate recruitment into the first ACTC-DS trial and other trials in this population, TRC-DS will enrol 120 adults with Down syndrome and no dementia into a longitudinal run-in study. This study will involve MRI, amyloid PET, tau PET, cognitive testing and biofluid biomarker analysis in preparation for upcoming randomized, placebo-controlled clinical trials. Enrolment to TRC-DS was delayed as a result of the COVID-19 pandemic, in particular the elevated risk of severe outcomes of COVID-19 in individuals with Down syndrome compared with the general population[43,44]. The first screening visit for TRC-DS took place in September 2021.

Building future trial-ready cohorts

The experience to date with TRC-PAD, EPAD Registry, J-PAD, DIAN and TRC-DS described above has highlighted various considerations for the optimal design and implementation of trial-ready cohorts on a national and global scale. These considerations relate to data capture and management approaches, regulatory requirements, representative recruitment, participant retention, use of optimal remote and unsupervised assessments, and the use of appropriate statistical models in risk assessment.

Informatics

Large AD trial-ready cohorts rely heavily on informatics infrastructure to achieve programme objectives, aims and milestones. Effective planning by the study team is required to accommodate evolving requirements and the multitude and volume of data types. Specific issues include ensuring data confidentiality and security, constructing connections between unsupervised web-based components and in-person electronic data capture systems, and designing automated selection and presentation systems to facilitate the biomarker confirmation process. Data security and confidentiality are crucial to building and maintaining participant engagement and trust. Reports of the increasing incidence of cybersecurity attacks in health care are a frequent reminder of the threat posed by bad actors[45]. Adopting a risk-based approach to security that combines robust governance, awareness training, procedural and technical controls, regular security audits, and security incident response simulations is imperative. Protecting personal health information requires a shared commitment by all stakeholders, including institutions, study teams and participants.

Several approaches have been used to build informatics infrastructure to establish exploratory cohorts for clinical trials, including local and national registries, virtual cohorts and federated networks[27,46–50]. Despite apparent differences, these approaches share a common workflow. Step one is to build an exploratory cohort. Step two is to facilitate the selection and engagement of potential trial participants who satisfy prespecified criteria. Step three is to enable recruitment of selected participants into clinical trials. The chosen approach dictates the requirements of the underlying informatics infrastructure.

When building exploratory cohorts, key design considerations include the amount, frequency and type of data to be collected. As new data types are introduced, such as digital, imaging and fluid biomarker data, a modular approach to system and database design will support evolution. Rigid, monolithic database designs will struggle to adapt to change. A semi-structured data lake storage model provides the necessary flexibility to manage this

Virtual cohort
Collection of participants in a virtual cohort study conducted using remote assessments.

Federated networks
A type of network used to facilitate data access and sharing across member institutions.

Data lake
Large-capacity semi-structured data repository.

Data fidelity
Preservation of raw data to avoid data loss that may occur data during processing operations.

Real-time data ingestion
Real-time physical transfer of data from its source to a target repository.

level of heterogeneity. This method, originally proposed for the management of large transactional datasets ('big data'), has become a generalized solution for management of heterogeneous data that offers benefits such as cost-effectiveness, high scalability, data fidelity, real-time data ingestion and fault tolerance[51]. Mature examples of this method implement tiered access layers to ensure that sensitive participant data is protected[52]. The use of a semi-structured data storage approach also facilitates the iterative development and application of rules-based and inference-based participant selection methods.

In the case of TRC-PAD, a hybrid multitiered approach that combines the characteristics of virtual and in-person cohorts was used to build the exploratory cohort[12] (FIG. 5). In the first tier, participants enrol in a virtual cohort that includes web-based longitudinal assessments. Pseudonymized participant data are ingested into a data lake and are used to support a risk-based selection algorithm. Selected participants are referred to performance sites in their vicinity for recruitment and screening into the in-person cohort, the second tier of the exploratory cohort. At this point, sites also have the option of referring selected participants directly to ongoing clinical trials. Closely tracking each participant's journey through this hybrid workflow is a key objective for the underlying TRC-PAD informatics infrastructure[53].

Recruitment

To engage individuals with minimal or no symptoms of disease, we must move away from models that recruit participants from medical settings. Effective tools for the recruitment of asymptomatic populations include community events, earned media and social media[54,55]. Existing registries of individuals with an interest in AD therapeutic research are invaluable sources. A recruitment initiative that has proven to be very effective is the use of national earned media followed by local media featuring local researchers and participants[9]. Another important successful recruitment strategy is the use of local newspapers, including outreach from a 'trusted' source. For example, in the A4 study a letter to the syndicated advice column 'Dear Abby' resulted in over 11,000 phone calls, more than 700 referrals to study sites and several hundred screens[9]. The column is run by the daughter of the original Dear Abby, who died from AD.

Several registries of individuals interested in AD research have been built through community events, paid and earned media, and have established mechanisms for referring participants directly into clinical trials. For example, in the UK, anyone over the age of 18 years can register at Join Dementia Research to learn about clinical trial and research opportunities. The largest registries in the USA are the Alzheimer's Association TrialMatch, the Brain Health Registry and the Alzheimer's Prevention Registry. TrialMatch is a free, online clinical studies matching service that connects individuals living with AD, care-givers and healthy volunteers with more than 700 active studies in AD and other dementias. TrialMatch has over 370,000 people registered, and around 52% are cognitively healthy individuals[14]. Individuals can find existing studies by searching on their own, or can opt-in to being notified when a study is recruiting participants that fit their profile. Among TrialMatch users, 75% provide their information and permission to be contacted, either by phone or by email. The Alzheimer's Prevention Registry is an internet-based participant registry with over 350,000 participants, of whom 94% report no cognitive impairment[49]. The registry initially began referring participants to clinical trials by sending study announcement emails, and now uses direct referral of participants to clinical trials by allowing participants to share their information to clinical trial sites through the Alzheimer's Prevention Registry website. The Alzheimer's Prevention Registry and TrialMatch were the greatest contributors of participants referred into the APT Webstudy; overall, 67% of APT Webstudy participants came from existing registries such as these[14]. Family history seems to be a common reason for participants joining registries; 50–80% of individuals signed up for registries reported a family history of AD[14,48,49].

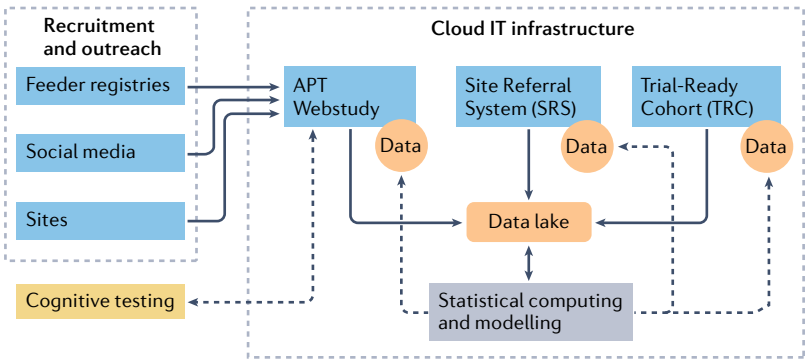

Fig. 5 | **The Trial-Ready Cohort for Preclinical and Prodromal Alzheimer's Disease informatics platform: an example of a modular approach.** The Trial-Ready Cohort for Preclinical and Prodromal Alzheimer's Disease informatics platform takes a modular approach to system and database design to support the evolution of the platform and the heterogeneity of the data. Key features include cloud IT infrastructure and a semi-structured 'data lake' storage model. At each of the three stages — the Alzheimer Prevention Trials (APT) Webstudy, the Site Referral System and the Trial-Ready Cohort — de-identified participant data is ingested into a data lake and is used to support a risk-based selection algorithm. Adapted from REF.[53].

Diversity

AD therapeutic trials in both academic and industry settings have been unsuccessful in recruiting and then enrolling individuals who are representative of the population at risk[9,41]. As a consequence, results from AD randomized, controlled trials do not provide adequate data or permit evidence-based assessments of safety and efficacy by race, ethnicity or socioeconomic status. Although web-based registries have achieved more diversity than most AD clinical trials, the majority of participants in web-based national registries self-report as white, are women, and have more than 15 years of education[14,16,48,49]. The EPAD Registry, despite prescreening in part through community-based registries, still enrolled 99% white and highly educated participants[25]. Major efforts are now underway by the TRC-PAD investigators to address this deficiency using a multifaceted approach that includes community partnerships

and data-driven assessment of study designs to reduce enrolment barriers. Results from these efforts will be reported within the next year. The training and education of future clinical trialists are also critical, and the IMPACT-AD programme aims to increase the diversity of study investigators and teams in clinical trials in AD-related dementias[56]. The TRC-PAD programme is currently developing a recruitment and retention study platform informed by data and evidence, with the aim of identifying and testing effective strategies to enrol and retain diverse cohorts eligible for randomized clinical trials. The proof-of-concept trial has recently been completed and results will be presented within the next year. Similar efforts are underway at other local and national web-based registries[57].

Retention

Web-based registries generally suffer from substantial attrition over time, with only 30–50% of participants returning for their next follow-up interaction; however, trial-ready cohorts that involve in-person follow-up have shown much higher retention of participants; for example, in the EPAD Registry, all but 14% of participants returned for the first follow-up visit[25]. The continued success of the web registries will depend on an ability to retain participants, use the longitudinal unsupervised clinical and cognitive data to identify individuals at risk and then successfully enrol them into appropriate clinical trials. Although several tactics for retaining research participants have been used[58,59], there is very little evidence on the efficacy of such tactics[60]. The TRC-PAD retention trial platform aims to test various retention strategies in an evidence-based framework and the first online retention trial of APT Webstudy participants has been completed. Additional engagement methods under development through this platform include various financial and non-financial rewards, access to expert information and updates on therapeutic research.

Risk assessment

The current procedures for the assessment of risk through biomarker confirmation require either a PET scan or lumbar puncture to assess levels of amyloid in brain. Both procedures are burdensome to participants as well as challenging and costly in terms of research infrastructure. Application of statistical learning theory and decision-tree-based machine learning approaches, such as extreme gradient boosting, to large datasets such as the publicly available A4 pre-randomization data has enabled development of predictive models of amyloid burden[15]. The estimates from these models, along with specific inclusion and exclusion criteria, have enabled the establishment of study-based statistical algorithms that select individuals for biomarker testing and minimize screen failures within TRC-PAD. Additionally, advances in plasma biomarkers of AD pathology, including the $A\beta_{1-42}$ to $A\beta_{1-40}$ ratio and p-tau_{217} assays, have the potential to greatly facilitate prescreening. Adaptation of these statistical models on the basis of accrued biomarker confirmation data will continue to improve efficiency.

Statistical learning theory
A framework for machine learning drawing from the fields of statistics and functional analysis.

Decision-tree-based machine learning
Also called 'induction of decision trees'; one of the predictive modelling approaches used in statistics, data mining and machine learning.

Extreme gradient boosting
A tree-based algorithm and a machine learning technique used in regression and classification tasks

Remote assessment

Sensitive measures of episodic memory and executive function, along with reports of subjective concerns about memory function, are useful in determining risk of biomarker positivity. Such measures have been adapted to enable longitudinal, unsupervised data collection using web-based programmes[61–63]. This approach was successfully implemented in the APT Webstudy. The use of completely web-based assessments of cognitive performance using the Cogstate Brief Battery has been shown to be feasible and improves prediction of elevated brain amyloid[64]. This test battery comprises four simple playing card tasks that measure psychomotor speed and recent memory, and is used to assess cognition and memory function. The One-Card Learning Test has shown particular sensitivity to amyloid-related cognitive decline in individuals with preclinical and prodromal AD[65]. The Cognitive Function Instrument is a 15-item participant-reported questionnaire[64,66] that assesses subjective concerns about memory. It captures the participant's perceived ability to perform high-level functional tasks in daily life, as well as their sense of overall cognitive functional ability. The participant self-reported score on the Cognitive Function Instrument has been validated as providing an early indication of future cognitive decline[64], and has been incorporated into the APT Webstudy to contribute to risk assessment.

Biomarker testing

To optimize trial recruitment, standardized approaches to PET imaging, CSF analysis and plasma assays need to be employed in trial-ready cohorts, ideally the assay and thresholds for eligibility would be identical to the target therapeutic trials. For example, TRC-PAD uses a multistage selection and screening process that includes a series of adaptive algorithms that assess participant data at multiple points[12,15]. Newly acquired data are used to update participant risk predictions and rankings, and inform the decision-making process used to graduate participants from one stage of TRC-PAD to the next (FIG. 2). Screening is conducted in multiple phases, first confirming clinical and cognitive eligibility and performing apolipoprotein E genetic testing; after a validation phase, plasma assays will also be included in this phase of risk assessment. Using this information, the participant's risk level is updated and reviewed centrally before screening proceeds to amyloid testing, either by PET imaging or CSF collection by lumbar puncture. Following procedures that were designed and refined for the A4 study[8], participants are then told whether they are eligible for the trial-ready cohort. Optimization of the TRC-PAD assessments, disclosure and risk estimation procedures continues.

Disclosure of results

As AD biomarker test accuracy improves and in response to participant feedback, AD clinical research is increasingly sharing individual test results with participants, with the aim of facilitating recruitment and retention[67,68]. Ethical sharing of research results requires engaging with participants to ensure comprehension, including a discussion of what is known and not known about future

risk or clinical meaningfulness, as well as follow-up to ensure that the possible negative impact of disclosure is managed. The EPAD Registry did not disclose risk to asymptomatic individuals but did disclose AD biomarker results if the participant became symptomatic during longitudinal participation[24]. DIAN allowed participants to decide whether or not to learn their genetic status, with most participants choosing not to learn their status[69]. The A4 study developed strict disclosure protocols to minimize potential harmful effects of participants learning that they had elevated brain amyloid levels, and prior to randomization, the study team communicated to participants whether their levels of amyloid in the brain were 'elevated' or 'not elevated'[70]. Qualitative and long-term follow-up studies embedded within A4 have so far demonstrated that these protocols achieve participant comprehension that having elevated amyloid represents an increased (but uncertain) risk of developing AD[71]. A4 participants discussed changes to health behaviour and future plans as a result of learning their amyloid status[72]; however, for participants who learned that they had elevated amyloid, a significant short-term psychological effect of the news was not observed when compared with participants who learned they did not have elevated amyloid[70]. Adapted versions of the A4 procedures for disclosure of biomarker results were implemented in the TRC-PAD programme[12]. Maximizing disclosure of genetic and biomarker results, preceded by educational efforts, is expected to improve participant recruitment, diversity and retention in trial-ready cohort programmes[73].

Connection to trials

Logistically, the ultimate aim of connecting trial-ready cohorts with trial enrolment is best facilitated by systems that comply with applicable regulatory requirements and provide seamless data connections to clinical trial data capture systems[74]. In the USA, these systems must comply with the Code of Federal Regulations Title 21, Part 11 (21 CFR part 11)[75], which establishes the controls and conditions required by the FDA to assure the integrity and validity of electronic records and electronic signatures included in clinical trials submission packages. This informatics approach allows run-in data from trial-ready cohorts to be used in trial datasets. Links between participant data across cohorts can be supported via the use of a common immutable identification number system, such as the NIA's global unique identifier (NIA GUID)[76]. These systems use cryptographic methods to protect participant privacy by preventing the storage or transfer of identifying information. This approach allows screening data from clinical trials to be imported into the exploratory cohort to inform the training dataset that is used to increase the performance of risk-based participant selection algorithms[15].

Conclusions and future directions

Trial-ready cohorts of individuals with biomarker-confirmed preclinical or prodromal AD represent a primary tool for timely recruitment of clinical trial participants. As such individuals are asymptomatic or mildly symptomatic, connections must extend beyond the traditional health system model, and therefore, the use of web-based programmes can be a valuable approach. The EPAD Registry experience showed that population-based referrals can work, but large numbers of participants are needed to find sufficient numbers who are eligible for the trial-ready cohort. TRC-PAD demonstrated that statistical modelling of predictors, including demographic data, subjective cognitive symptoms, cognitive performance and genetic markers as well as emerging plasma biomarker measures, can allow selection of individuals for biomarker (PET or CSF) testing. Plasma measures might eventually supplant PET and CSF tests as the indicator of biomarker status.

A critical piece of infrastructure for efficient movement of participants from registries to trial-ready cohorts to clinical trials is the establishment of agreements and protocols to allow sharing of information. In a seamless, 21 CFR part 11-compliant cohort trial data system, cohort data can readily be used as run-in or covariate data in trials. Maintaining this infrastructure for secure management of sensitive data requires a highly qualified and dedicated team and ongoing financial support. When funding is not continued, as with the EPAD Registry, the ability to understand the efficacy of trial-ready cohorts to accelerate clinical trial enrolment is lost.

Data from trials, particularly pre-randomization data, can facilitate the aims of trial-ready cohort programmes. Key TRC-PAD aims involve using biomarker data to validate predictors and adjust risk algorithms. However, the flexible design of the cohort, which allows participants to move directly from the referral stage to trial screening when feasible, can enable trial-ready cohort biomarker confirmation to be bypassed; this route from referral to screening has been a major path during the pandemic, when many sites prioritized trial visits over trial-ready cohort observational activities. Therefore, transfer of biomarker data from trial screening visits into the TRC-PAD data system became important. The establishment of trial-ready cohort protocols at trial sites also provides a potential mechanism for long-term follow-up of trial participants after completion of study visits. This use of the trial-ready cohorts could support long-term safety and efficacy assessments and provide an opportunity for obtaining eventual neuropathological correlation with clinical and biomarker data.

Primary prevention of AD by monitoring individuals in middle age for risk and evidence of amyloid dysregulation, and intervening with anti-amyloid strategies, can now be envisioned. To facilitate the trials necessary to establish the efficacy of primary prevention, longitudinal observational studies must first fill gaps in our knowledge of predisease indicators. The trial-ready cohort programmes for early intervention trials provide an infrastructure that can be adapted to this purpose, and could also be modified for trials of different therapeutic approaches such as anti-tau, anti-inflammatory or non-pharmacological interventions.

Experience to date shows that longitudinal web-based observational programmes that are connected to trial site networks can efficiently maintain connections to large numbers of potential candidates for prevention trials.

Growing evidence suggests that plasma assays such as those that measure Aβ peptides or phosphotau species can be used to detect early neurobiological changes of AD prior to CSF and PET amyloid biomarker positivity. The continuing development of accurate metabolic profiling of amyloid dysregulation might also provide a path to blood-based indicators of risk of later amyloid accumulation[77] enabling selection of candidates for primary prevention treatment. Remote plasma testing, using commercial clinical test sites to obtain, process and ship specimens to central laboratories, could thus facilitate large-scale prescreening of participants for primary prevention trials, with streamlined referral to trial-ready cohorts and clinical trial sites. Many millions of people worldwide require effective treatments to slow the progression of AD. This enormous public health need necessitates continued progress towards the efficient recruitment of appropriate individuals into trials.

Published online 4 April 2022

1. Cummings, J., Lee, G., Zhong, K., Fonseca, J. & Taghva, K. Alzheimer's disease drug development pipeline: 2021. *Alzheimers Dement.* **7**, e12179 (2021).
2. Cummings, J. et al. Aducanumab: appropriate use recommendations. *J. Prev. Alzheimers Dis.* **8**, 398–410 (2021).
3. Sperling, R. A., Jack, C. R. Jr & Aisen, P. S. Testing the right target and right drug at the right stage. *Sci. Transl. Med.* **3**, 111cm133 (2011).
4. Rowe, C. C. et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiol. Aging* **31**, 1275–1283 (2010).
5. Donohue, M. C. et al. Association between elevated brain amyloid and subsequent cognitive decline among cognitively normal persons. *JAMA* **317**, 2305–2316 (2017).
6. DeTure, M. A. & Dickson, D. W. The neuropathological diagnosis of Alzheimer's disease. *Mol. Neurodegener.* **14**, 32 (2019).
7. Aisen, P. S. et al. On the path to 2025: understanding the Alzheimer's disease continuum. *Alzheimers Res. Ther.* **9**, 60 (2017).
8. Sperling, R. A. et al. The A4 study: stopping AD before symptoms begin? *Sci. Transl. Med.* **6**, 228fs213 (2014).
9. Raman, R. et al. Disparities by race and ethnicity among adults recruited for a preclinical Alzheimer disease trial. *JAMA Netw. Open* **4**, e2114364 (2021).
10. Sperling, R. A. et al. Association of factors with elevated amyloid burden in clinically normal older individuals. *JAMA Neurol.* **77**, 735–745 (2020).
This article presents the results from prerandomization data from the first preclinical study of AD, summarizing key differences in factors associated with elevated brain amyloid in cognitively healthy participants.
11. Aisen, P. et al. Registries and cohorts to accelerate early phase Alzheimer's trials. A report from the E.U./U.S. Clinical Trials in Alzheimer's Disease Task Force. *J. Prev. Alzheimers Dis.* **3**, 68–74 (2016).
12. Aisen, P. S. et al. The Trial-Ready Cohort for Preclinical/Prodromal Alzheimer's Disease (TRC-PAD) project: an overview. *J. Prev. Alzheimers Dis.* **7**, 208–212 (2020).
This article discusses the design, approach and rationale for the trial-ready cohort for preclinical/prodromal AD.
13. US National Library of Medicine. *ClinicalTrials.gov* https://ClinicalTrials.gov/show/NCT04468659 (2022).
14. Walter, S. et al. Recruitment into the Alzheimer Prevention Trials (APT) webstudy for a Trial-Ready Cohort for Preclinical and Prodromal Alzheimer's Disease (TRC-PAD). *J. Prev. Alzheimers Dis.* **7**, 219–225 (2020).
15. Langford, O. et al. Predicting amyloid burden to accelerate recruitment of secondary prevention clinical trials. *J. Prev. Alzheimers Dis.* **7**, 213–218 (2020).
16. Walter, S. et al. The Trial-Ready Cohort for Preclinical and Prodromal Alzheimer's Disease (TRC-PAD): experience from the first 3 years. *J. Prev. Alzheimers Dis.* **7**, 234–241 (2020).
17. Weinberg, M. S. et al. Clinical trials and tribulations in the COVID-19 era. *Am. J. Geriatr. Psychiatry* **28**, 913–920 (2020).
18. Ovod, V. et al. Amyloid β concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis. *Alzheimers Dement.* **13**, 841–849 (2017).
19. Nakamura, A. et al. High performance plasma amyloid-β biomarkers for Alzheimer's disease. *Nature* **554**, 249–254 (2018).
20. Palmqvist, S. et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. *JAMA* **324**, 772–781 (2020).
21. Sato, K. et al. Predicting amyloid risk by machine learning algorithms based on the A4 screen data: application to the Japanese Trial-Ready Cohort study. *Alzheimers Dement.* **7**, e12135 (2021).
22. Sato, K. et al. Efficacy and cost-effectiveness of promotion methods to recruit participants to an online screening registry for Alzheimer disease prevention trials: observational study. *J. Med. Internet Res.* **23**, e26284 (2021).
23. Ritchie, C. W. et al. Development of interventions for the secondary prevention of Alzheimer's dementia: the European Prevention of Alzheimer's Dementia (EPAD) project. *Lancet Psychiatry* **3**, 179–186 (2016).
This article discusses the design, approach and rationale for the European Prevention of Alzheimer's Dementia project, which includes a trial-ready cohort and intended run-in data for a clinical trial.
24. Solomon, A. et al. European Prevention of Alzheimer's Dementia longitudinal cohort study (EPAD LCS): study protocol. *BMJ Open* **8**, e021017 (2019).
25. Ingala, S. et al. Application of the ATN classification scheme in a population without dementia: findings from the EPAD cohort. *Alzheimers Dement.* **17**, 1189–1204 (2021).
26. Vermunt, L. et al. Prescreening for European Prevention of Alzheimer Dementia (EPAD) trial-ready cohort: impact of AD risk factors and recruitment settings. *Alzheimers Res. Ther.* **12**, 8 (2020).
27. Vermunt, L. et al. European Prevention of Alzheimer's Dementia Registry: recruitment and prescreening approach for a longitudinal cohort and prevention trials. *Alzheimers Dement.* **14**, 837–842 (2018).
28. Ritchie, C. W. et al. The European Prevention of Alzheimer's Dementia (EPAD) Longitudinal Cohort study: baseline data release V500.0. *J. Prev. Alzheimers Dis.* **7**, 8–13 (2020).
29. Gregory, S. et al. Research participants as collaborators: background, experience and policies from the PREVENT Dementia and EPAD programmes. *Dementia* **17**, 1045–1054 (2018).
30. Alzforum. In the wake of COVID-19: trials interrupted, delayed, cancelled. https://www.alzforum.org/news/community-news/wake-covid-19-trials-interrupted-delayed-cancelled (2020).
31. Bateman, R. J. et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N. Engl. J. Med.* **367**, 795–804 (2012).
32. McDade, E. et al. Longitudinal cognitive and biomarker changes in dominantly inherited Alzheimer disease. *Neurology* **91**, e1295–e1306 (2018).
33. Mills, S. M. et al. Preclinical trials in autosomal dominant AD: implementation of the DIAN-TU trial. *Rev. Neurol.* **169**, 737–743 (2013).
34. Morris, J. C. et al. Developing an international network for Alzheimer research: the Dominantly Inherited Alzheimer Network. *Clin. Investig.* **2**, 975–984 (2012).
This article discusses the design, approach and rationale for the Dominantly Inherited Alzheimer Network, a longitudinal study with a platform to provide run-in data for clinical trials in a rare group of individuals with genetically determined early-onset AD.
35. Salloway, S. et al. A trial of gantenerumab or solanezumab in dominantly inherited Alzheimer's disease. *Nat. Med.* **27**, 1187–1196 (2021).
36. Alzforum. In DIAN-TU, gantenerumab brings down tau. By a Lot. Open extension planned. https://www.alzforum.org/news/conference-coverage/dian-tu-gantenerumab-brings-down-tau-lot-open-extension-planned (2020).
37. Bateman, R. J. et al. The DIAN-TU next generation Alzheimer's prevention trial: adaptive design and disease progression model. *Alzheimers Dement.* **13**, 8–19 (2017).
38. McCarron, M. et al. A prospective 20-year longitudinal follow-up of dementia in persons with Down syndrome. *J. Intellect. Disabil. Res.* **61**, 843–852 (2017).
39. Hithersay, R. et al. Association of dementia with mortality among adults with Down syndrome older than 35 years. *JAMA Neurol.* **76**, 152–160 (2019).
40. Handen, B. L. et al. The Alzheimer's Biomarker Consortium–Down Syndrome: rationale and methodology. *Alzheimers Dement.* **12**, e12065 (2020).
41. US National Library of Medicine. *ClinicalTrials.gov* https://ClinicalTrials.gov/show/NCT04165109 (2022).
42. Rafii, M. S., Zaman, S. & Handen, B. L. Integrating biomarker outcomes into clinical trials for Alzheimer's disease in Down syndrome. *J. Prev. Alzheimers Dis.* **8**, 48–51 (2021).
This article discusses the design, approach and rationale for longitudinal studies with biomarker assessments for individuals with Down syndrome, who have a genetically determined risk of developing the pathology of AD.
43. Malle, L. et al. Individuals with Down syndrome hospitalized with COVID-19 have more severe disease. *Genet. Med.* **23**, 576–580 (2021).
44. Clift, A. K., Coupland, C. A. C., Keogh, R. H., Hemingway, H. & Hippisley-Cox, J. COVID-19 mortality risk in Down syndrome: results from a cohort study of 8 million adults. *Ann. Intern. Med.* **174**, 572–576 (2021).
45. Argaw, S. T. et al. Cybersecurity of hospitals: discussing the challenges and working towards mitigating the risks. *BMC Med. Inf. Decis. Mak.* **20**, 146 (2020).
46. Grill, J. D. et al. Constructing a local potential participant registry to improve Alzheimer's disease clinical research recruitment. *J. Alzheimers Dis.* **63**, 1055–1063 (2018).
47. Visweswaran, S. et al. Accrual to Clinical Trials (ACT): a Clinical and Translational Science Award Consortium network. *JAMIA Open* **1**, 147–152 (2018).
48. Weiner, M. W. et al. The Brain Health Registry: an internet-based platform for recruitment, assessment, and longitudinal monitoring of participants for neuroscience studies. *Alzheimers Dement.* **14**, 1063–1076 (2018).
49. Langbaum, J. B. et al. The Alzheimer's Prevention Registry: a large internet-based participant recruitment registry to accelerate referrals to Alzheimer's-focused studies. *J. Prev. Alzheimers Dis.* **7**, 242–250 (2020).
50. Schneider, R. B. et al. A virtual cohort study of individuals at genetic risk for Parkinson's disease: study protocol and design. *J. Parkinsons Dis.* **10**, 1195–1207 (2020).
51. Sawadogo, P. & Darmont, J. On data lake architectures and metadata management. *J. Intell. Inf. Syst.* **56**, 97–120 (2021).
52. Che, H. & Duan, Y. On the logical design of a prototypical data lake system for biological resources. *Front. Bioeng. Biotechnol.* **8**, 553904 (2020).
53. Jimenez-Maggiora, G. A. et al. TRC-PAD: accelerating recruitment of AD clinical trials through innovative information technology. *J. Prev. Alzheimers Dis.* **7**, 226–233 (2020).
54. Andrasik, M. P. et al. Increasing Black, Indigenous and People of Color participation in clinical trials through community engagement and recruitment goal establishment. *PLoS ONE* **16**, e0258858 (2021).
55. Hays, J. et al. The Women's Health Initiative recruitment methods and results. *Ann. Epidemiol.* **13**, S18–S77 (2003).

56. Berkness, T. et al. The Institute on Methods and Protocols for Advancement of Clinical Trials in ADRD (IMPACT-AD): a novel clinical trials training program. *J. Prev. Alzheimers Dis.* **8**, 286–291 (2021).
57. Cocroft, S. et al. Racially diverse participant registries to facilitate the recruitment of African Americans into presymptomatic Alzheimer's disease studies. *Alzheimers Dement.* **16**, 1107–1114 (2020).
58. Robinson, K. A. et al. Updated systematic review identifies substantial number of retention strategies: using more strategies retains more study participants. *J. Clin. Epidemiol.* **68**, 1481–1487 (2015).
59. Gilmore-Bykovskyi, A. L. et al. Recruitment and retention of underrepresented populations in Alzheimer's disease research: a systematic review. *Alzheimers Dement.* **5**, 751–770 (2019). **Systematic review of the literature for published reports describing the recruitment and retention of individuals from under-represented backgrounds in AD-related dementias (ADRD) research or under-represented participants' perspectives regarding participation in ADRD research.**
60. Brueton, V. C. et al. Strategies to improve retention in randomised trials: a Cochrane systematic review and meta-analysis. *BMJ Open.* **4**, e003821 (2014).
61. Cromer, J. A. et al. Comparison of cognitive performance on the Cogstate Brief Battery when taken in-clinic, in-group, and unsupervised. *Clin. Neuropsychol.* **29**, 542–558 (2015).
62. Perin, S. et al. Unsupervised assessment of cognition in the Healthy Brain Project: implications for web-based registries of individuals at risk for Alzheimer's disease. *Alzheimers Dement.* **6**, e12043 (2020).
63. Nosheny, R. L. et al. Validation of online functional measures in cognitively impaired older adults. *Alzheimers Dement.* **16**, 1426–1437 (2020).
64. Amariglio, R. E. et al. Tracking early decline in cognitive function in older individuals at risk for Alzheimer disease dementia: the Alzheimer's Disease Cooperative Study Cognitive Function Instrument. *JAMA Neurol.* **72**, 446–454 (2015).
65. Darby, D. G. et al. Episodic memory decline predicts cortical amyloid status in community-dwelling older adults. *J. Alzheimers Dis.* **27**, 627–637 (2011).
66. Walsh, S. P., Raman, R., Jones, K. B. & Aisen, P. S. Alzheimer's Disease Cooperative Study Group ADCS Prevention Instrument Project: the Mail-In Cognitive Function Screening Instrument (MCFSI). *Alzheimer Dis. Assoc. Disord.* **20**, S170–S178 (2006).
67. Ott, B. R., Pelosi, M. A., Tremont, G. & Snyder, P. J. A survey of knowledge and views concerning genetic and amyloid PET status disclosure. *Alzheimers Dement.* **2**, 23–29 (2016).
68. Shalowitz, D. I. & Miller, F. G. Communicating the results of clinical research to participants: attitudes, practices, and future directions. *PLoS Med.* **5**, e91 (2008).
69. Aschenbrenner, A. J. et al. Awareness of genetic risk in the Dominantly Inherited Alzheimer Network (DIAN). *Alzheimers Dement.* **16**, 219–228 (2020).
70. Grill, J. D. et al. Short-term psychological outcomes of disclosing amyloid imaging results to research participants who do not have cognitive impairment. *JAMA Neurol.* **77**, 1504–1513 (2020).
71. Mozersky, J., Sankar, P., Harkins, K., Hachey, S. & Karlawish, J. Comprehension of an elevated amyloid positron emission tomography biomarker result by cognitively normal older adults. *JAMA Neurol.* **75**, 44–50 (2018).
72. Largent, E. A. et al. Cognitively unimpaired adults' reactions to disclosure of amyloid PET scan results. *PLoS ONE* **15**, e0229137 (2020).
73. Milne, R. et al. Ethical issues in the development of readiness cohorts in Alzheimer's disease research. *J. Prev. Alzheimers Dis.* **4**, 125–131 (2017).
74. Jimenez-Maggiora, G. A., Bruschi, S., Qiu, H., So, J.-S. & Aisen, P. S. ATRI EDC: a novel cloud-native remote data capture system for large multicenter Alzheimer's disease and Alzheimer's disease-related dementias clinical trials. *JAMIA Open* **5**, ooab119 (2022).
75. FDA. CFR - Code of Federal Regulations Title 21. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11 (2022).
76. Babcock, D. *The Role of GUIDs in Data Sharing* (National Institute of Neurological Disorders and Stroke, 2019).
77. Paterson, R. W. et al. SILK studies–capturing the turnover of proteins linked to neurodegenerative diseases. *Nat. Rev. Neurol.* **15**, 419–427 (2019).
78. Rafii, M. S. Alzheimer's disease in Down syndrome: progress in the design and conduct of drug prevention trials. *CNS Drugs* **34**, 785–794 (2020).

Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
The authors have received grants from the National Institute on Aging and research support from Eisai, Janssen and Lilly. P.S.A. has consulted for Abbvie, Biogen, ImmunoBrain Checkpoint, Merck, Rainbow Medical, Roche and Shionogi.

Peer review information
Nature Reviews Neurology thanks Oskar Hansson, who co-reviewed with Gemma Salvadó; Frederik Barkhof; and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

RELATED LINKS
Alzheimer's Prevention Registry: https://www.endalznow.org/
Alzheimer Prevention Trials Webstudy: www.aptwebstudy.org
Join Dementia Research: https://www.joindementiaresearch.nihr.ac.uk
Neuronet: https://kb.imi-neuronet.org/
TrialMatch: https://www.alz.org/alzheimers-dementia/research_progress/clinical-trials/trialmatch