Defeating dementia: progress and challenges on the road to 2025

Clinical Trials panel

Moderator: Dr Steven Hyman

Harvard University Distinguished Professor and Director, Stanley Center at the Broad Institute of Harvard and MIT

#DefeatingDementia

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Dr Lynne Hughes

Vice President and Head, Global Medical Strategy CNS, IQVIA

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Alzheimer's Disease Trials are Inherently Complex

Across a range of criteria, Alzheimer's trials are more challenging than other disease areas

- AD trials are **longer** and have **more stringent screening** criteria relative to other disease areas
- Ideal patients/subjects are **difficult to identify**
- **High screen failure** rates lead to slow trial enrollment
- **High cost/screened patient**: $34,000- preclinical, $30,000- pAD

AD trials are concentrated in the US and Western EU, but no single market performs strongly among all the metrics

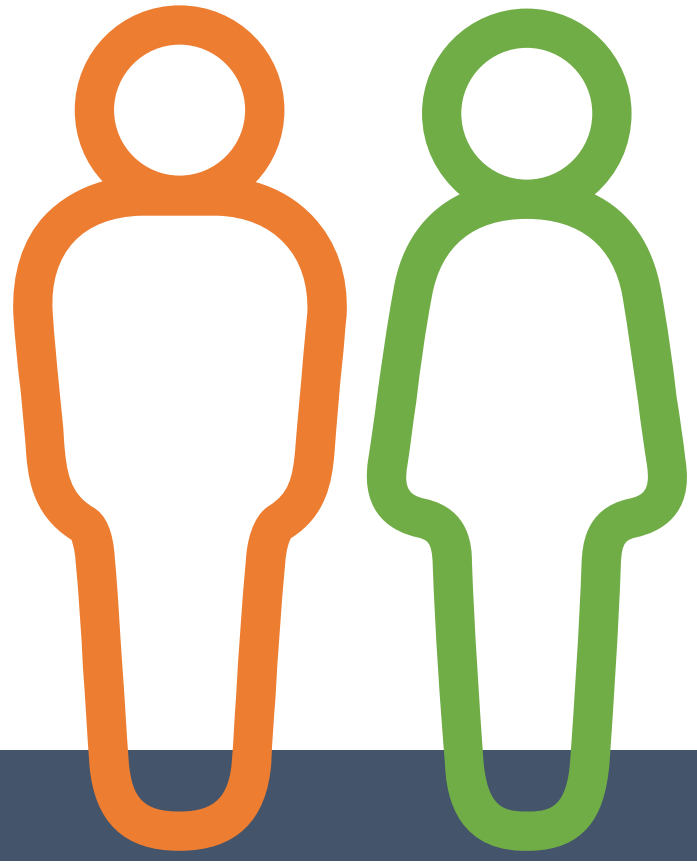
Developed markets conduct more trials due to:	Access to PET infrastructure & ligand availability
	Principal Investigators with AD trial experience
	Limited language and cultural barriers
	Stable regulatory environment

Alzheimer's Disease Clinical Trial Subjects…

Face a high time commitment and burdensome testing throughout the screening and trial itself

Trial subjects must make several multi-hour visits to undergo screening procedures

- Stringent criteria results in high screen failure rates:
  - For MCI : 75 % fail screening
  - For preclinical subjects : 90 % fail screening

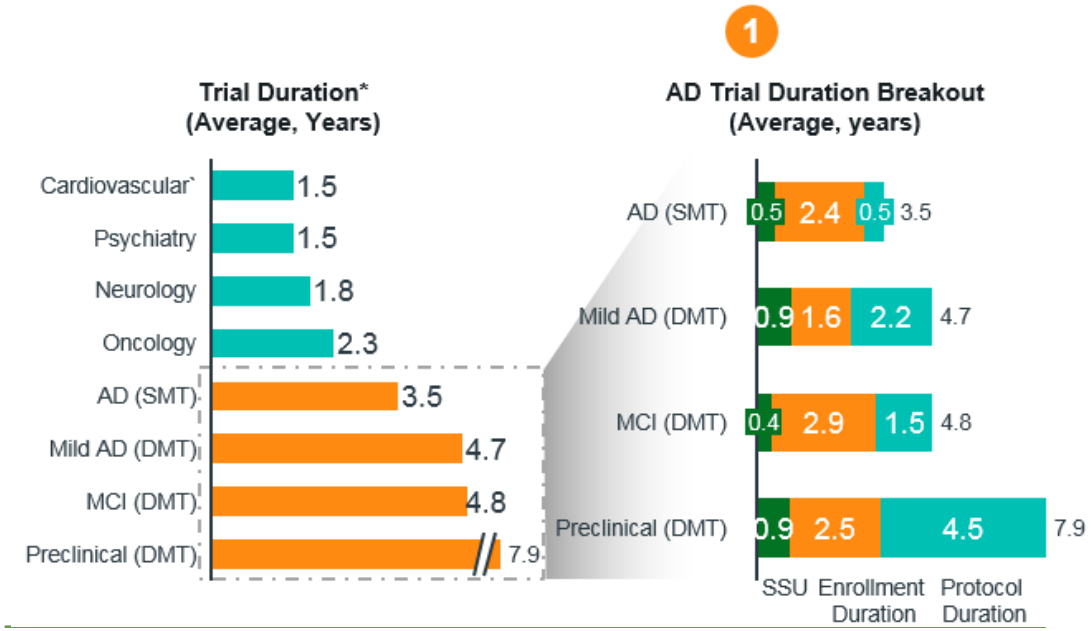


Protocols for early stage trials require subject to undergo scans and cognitive assessment every few months

- Monthly visits for infusions, rating scale assessments
- Monthly visits for MRI scans
- Half yearly visits for PET scans

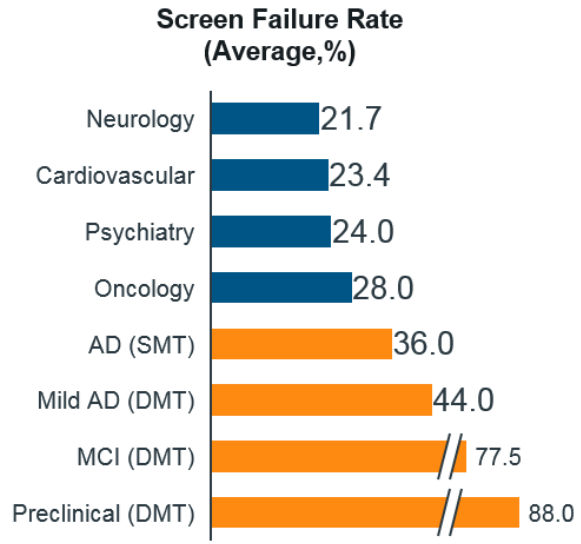
Disease Modifying Therapy (DMT) AD Trials are Slower to Enroll and Take Longer than Trials in Other Therapeutic Areas

AD summary across key CT metrics

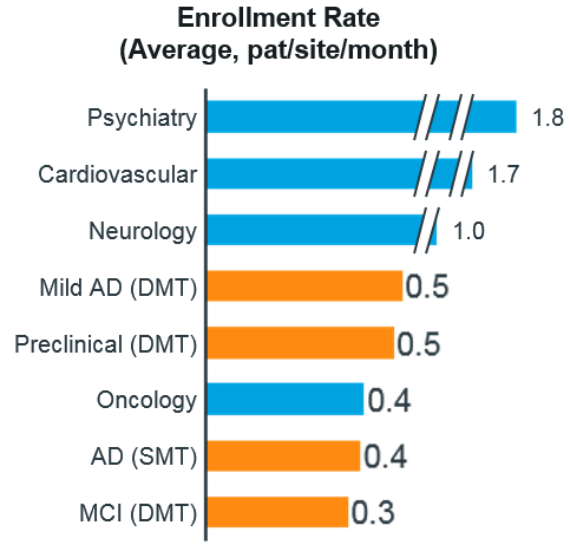


Long response period is required to effectively show slowing of AD progression, leading to long protocol duration

Long enrollment periods exacerbate this issue, making AD DMT trials to be significantly longer than other disease areas



Stringent and evolving screening criteria (Aβ+, comorbidity exclusions, narrow cognitive ranges) contribute to high screen failure rates and slow enrollment



Patients may be asymptomatic and/or perceive early cognitive decline as natural aging, hindering enrollment speed

Source: Citeline (clinical trial metrics from over 40,000 sources) – total duration; Infosario (internal IQVIA CRO database) - Enrollment rate, screen failure and drop-out rate; Aβ – Amyloid-beta; DMT – disease modifying therapy; SMT – symptom modifying therapy; *Duration: Site selection to study completion; Note: MCI trials are MCI/prodromal AD trials, referring to trials in patients with MCI along with biomarker positivity (i.e. prodromal AD)

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Dr Samantha Budd Haerberlein

Vice President, Biogen

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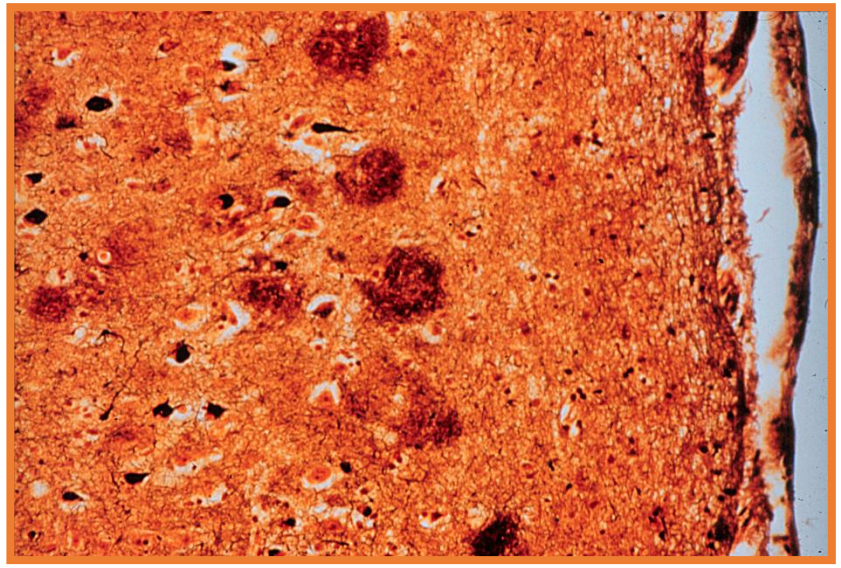
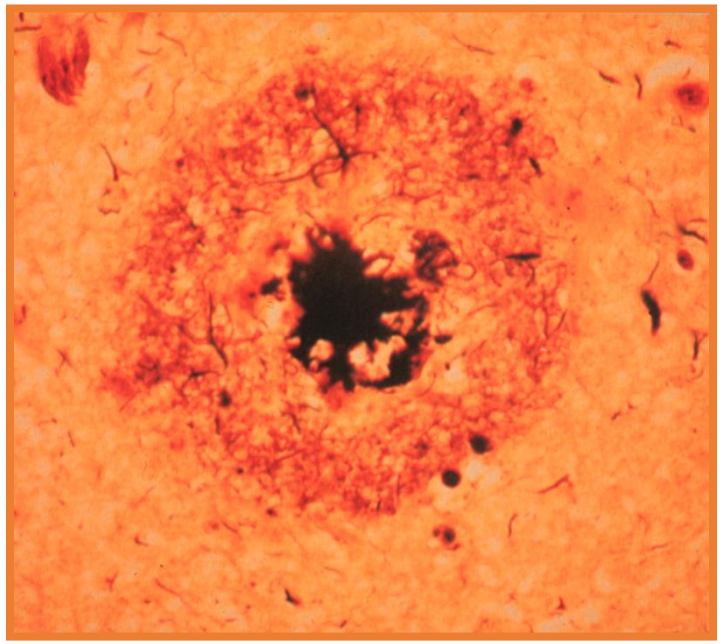
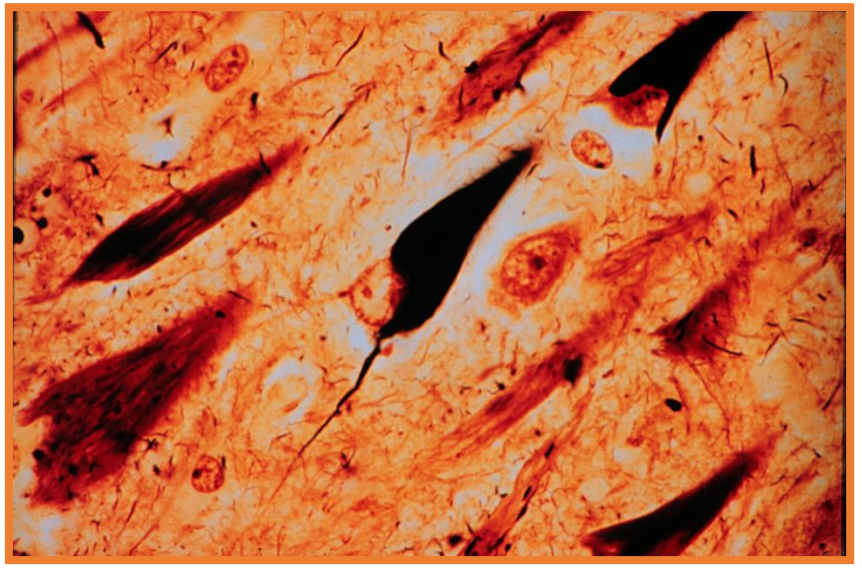
Alzheimer's Disease

- Plaque and tangle disease
  - Plaques – amyloid protein
  - Tangles – Tau protein





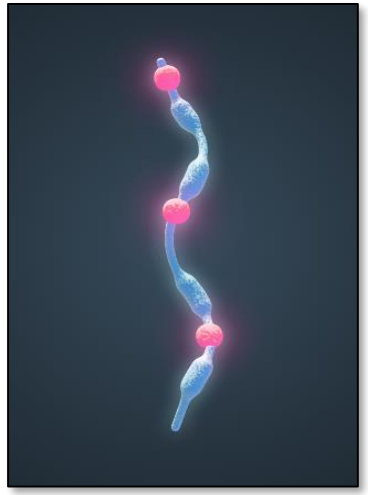


Pathological changes can occur in the brain decades before any cognitive symptoms of Alzheimer's disease are evident[1,2]

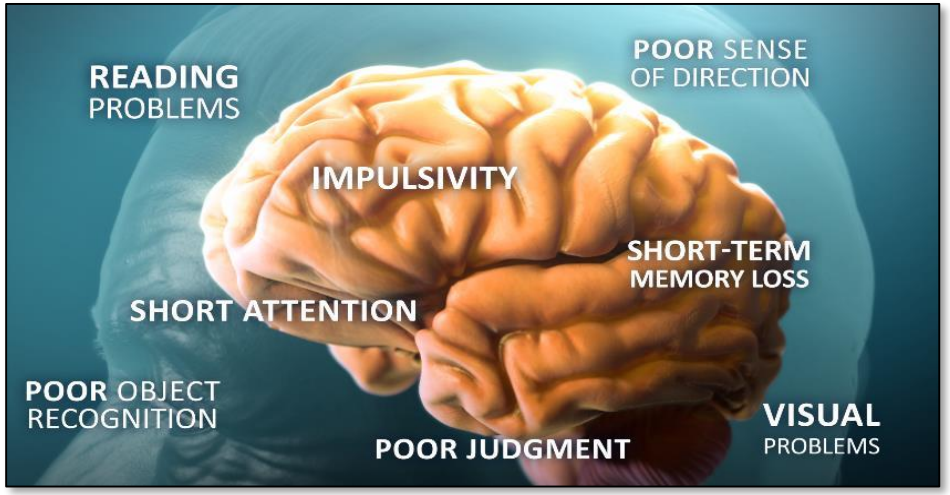
–20 years **–15 years** **Onset of disease**

Aβ

Tau



Symptoms across stages



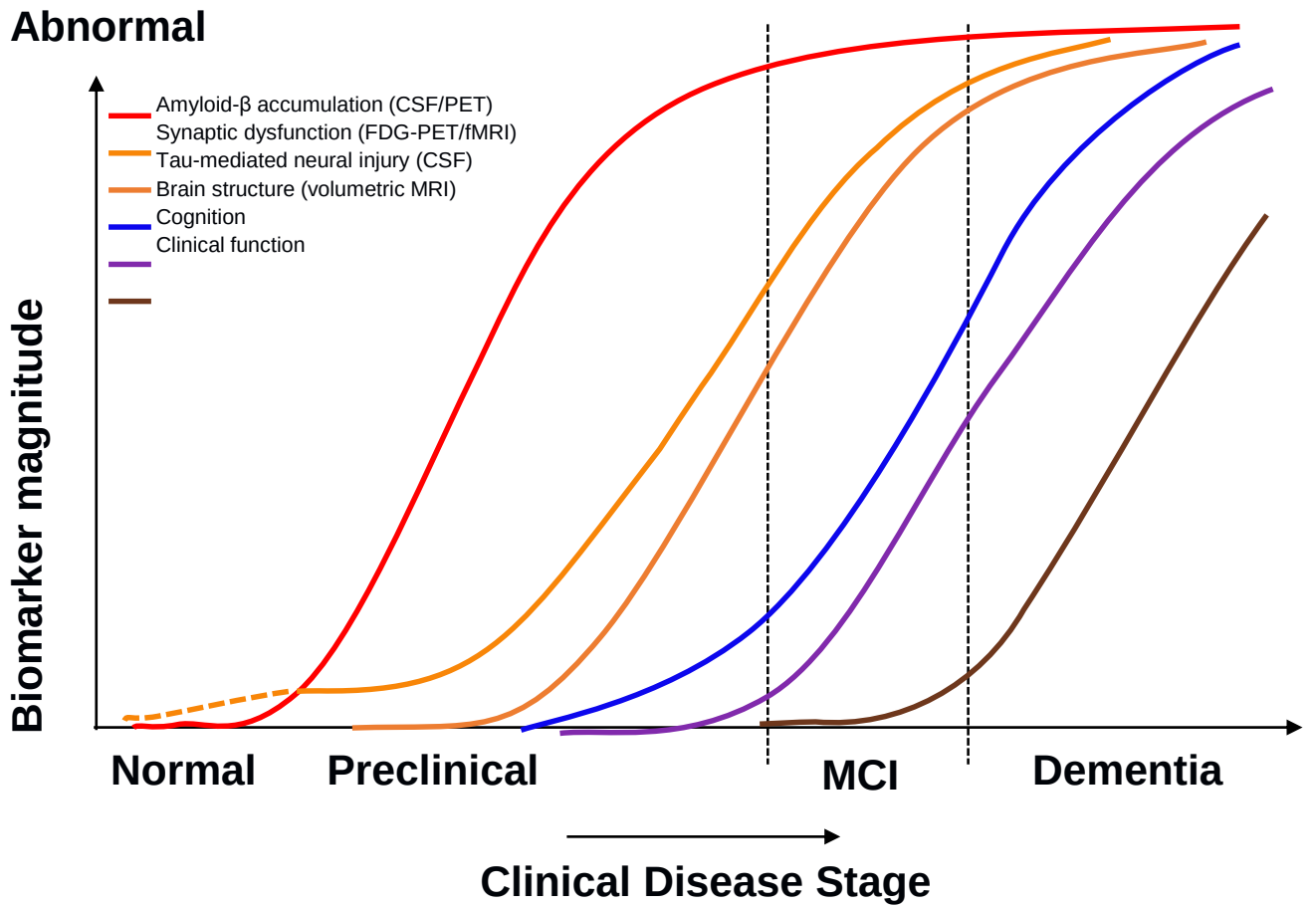
The disease process may begin more than 20 years before clinical symptoms occur[3]

Images from: Understanding Alzheimer's Disease. Available from: https://www.youtube.com/watch?v=jBvWadjjwXs. Accessed June 4 2017.

1. Jack CR, et al. Brain. 2009:132;1355–1365; 2. Dubois B, et al. Alzheimer's & Dementia. 2016;12:292–323; 3. Bateman RJ et al. N Engl J Med 2012;367:795–804.

Biomarker changes precede clinically relevant changes in cognition

- **Biomarker technologies now enable the detection of key pathologies in living humans.**
- **Initial clinical trials targeted later stages of Alzheimer's disease.**



- Image adapted from: Sperling RA et al. Alzheimers Dement. 2011;7:280-292.
- Lannfelt L et al. Alzheimers Res Ther. 2014;6-16; Panza F et al. Expert Rev Clin Immunol. 2014;10:405-419; Panza F et al. Expert Rev Neurother. 2014;14:973-986; Moreth J et al. Immun Ageing. 2013;10:18.
- CSF, cerebrospinal fluid; fMRI, FDG, fludeoxyglucose; functional magnetic resonance imaging; mAbs, monoclonal antibodies; MRI, magnetic resonance imaging.

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Dr Catherine Mummery

Clinical Director Neurology, UCL Dementia Research Centre

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Recruitment to trials: the challenge

- Mismatch between clinic and trial criteria – 'only the fittest'
- Earlier stage of disease requires new methods of identification
- High volume screening esp. preclinical: 10% success rate

Reduce screen failure rate

Pre-screening

Telephone/in person questionnaire - Historical data

77%SF -> 40%SF

Remote cognitive screen

? AI

? blood biomarker

TRADITIONAL METHODS

- **Clinic**
- **Local databases**

Clinical/Research integration

Dedicated dementia centres

Research embedded in clinic

Enhance trial conduct

Patient/Professional Awareness

Media - TV/Radio/newspapers

Social media – twitter/facebook

Patient networks

Initiatives – Dementia Friends

Increase rate of identification

AD registries

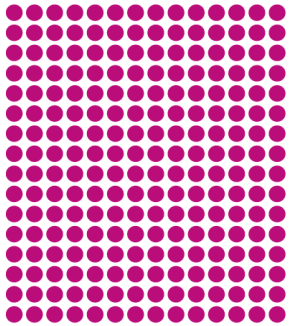
link potential participants and recruiter

- UK registry

Join dementia research

- Alz Prevention Registry
- Brain Health Registry
- Global Alzheimer's Platform
- Healthy Brains

38,022
total volunteers



80,145
screenings

10,752
participants have enrolled in studies to date

AD cohorts

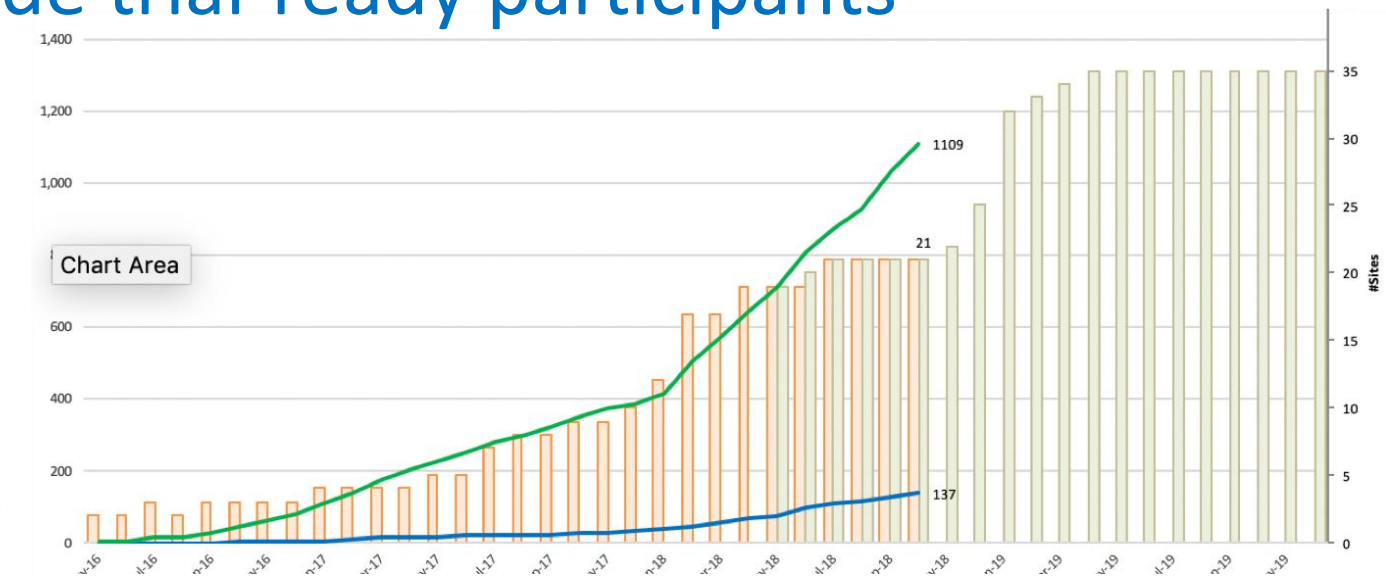
provide trial-ready participants

- European Prevention of AD

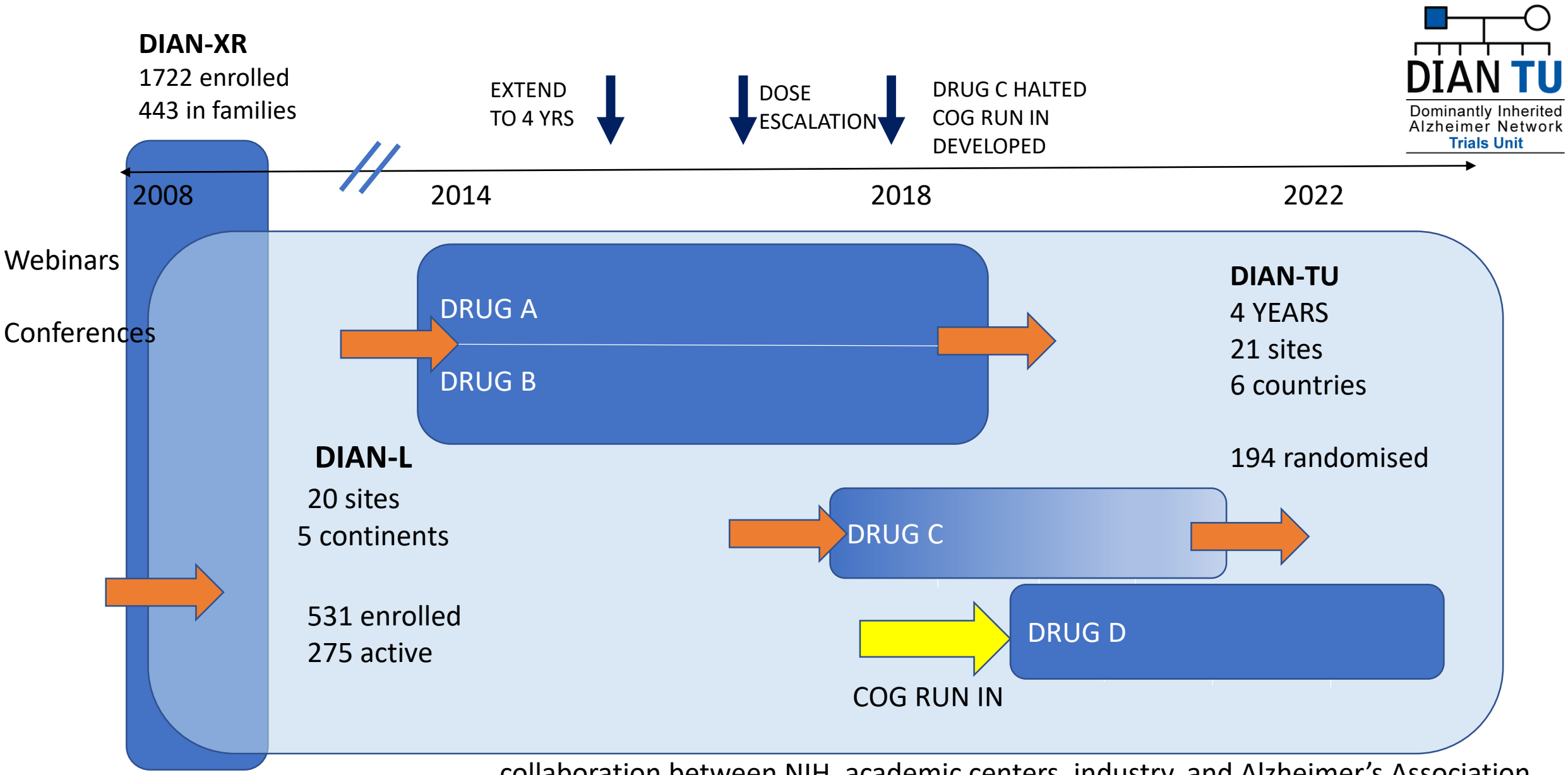
EPAD
European Prevention of Alzheimer's Dementia Consortium

- TRC-PAD

Trial Ready Cohort for Preclinical / Prodromal AD



Cohorts + adaptive platforms maximise recruitment efficacy



collaboration between NIH, academic centers, industry, and Alzheimer's Association

Innovation in Design and Recruitment

We need **a strategy** in order to recruite these **healthy people** that do not go to the office…

AD Risk Calculator

1. Promote **Awareness** of the General population about the **primary prevention**…
2. Take profit of popular activities such as *marathons, football match, concerts*…
3. Include **the AD risk check-up (APOE vs blood biomarker)** in the Healthy Check-up over 50
4. Use of **AD biomarkers** (CSF or PET scan or blood) in selected population at risk

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Professor Ricardo Allegri

Cognitive Neurologist, FLENI

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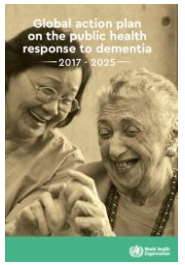
Healthcare Systems and Government Actions

World Health Organization

Alzheimer's Disease International

alzheimer's association

Alzheimer's Research UK



World Dementia Council
Leading the Global Action Against Dementia

Research, Open Science and Data Global Team

Aim

To foster and promote: a culture of open science and collaborative global research into dementia; a strategic approach to research across the spectrum of the disease; and research into interconnected dementia related issues.

Action areas

1

Facilitate the global expansion of research programmes, such as the EU Joint Programme – Neurodegenerative Diseases Research (JPND).

2

Develop a global WDC statement promoting open science, i.e. facilitating data sharing and collaboration.

3

Promote the use of national healthcare and administrative databases amongst public and private payers and commissioners to anticipate impact of treatments and care in real life.

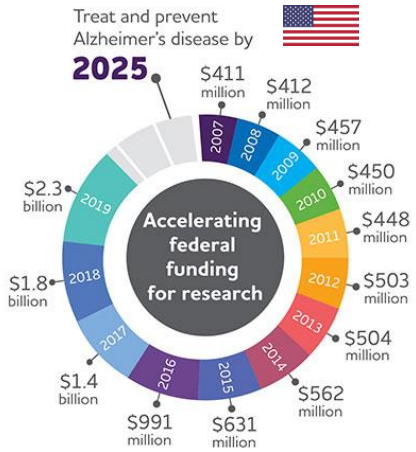
Healthcare Systems and Government Actions

World Health Organization

Alzheimer's Disease International

alzheimer's association

Alzheimer's Research UK



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Action areas

4

Encourage stakeholders to be advocates for improved increased collaboration around dementia research and address barriers to them doing so.

5

Influence and encourage governments to invest in public intervention trials designed to demonstrate the potential for reducing the risk of dementia, in partnership with the Risk Reduction Global Team.

Healthcare Systems and Government Actions

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"Without clinical trials and the help of human volunteers, there can be no better treatments, no prevention and no cure for Alzheimer's disease"

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Questions?

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