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

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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

<table>
<thead>
<tr>
<th>Trial Duration* (Average, Years)</th>
<th>AD Trial Duration Breakout (Average, years)</th>
<th>Screen Failure Rate (Average, %)</th>
<th>Enrollment Rate (Average, pat/site/month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular*</td>
<td>1.5</td>
<td>AD (SMT) 0.5</td>
<td>Psychiatry 1.8</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>1.5</td>
<td>Mild AD (DMT) 0.9</td>
<td>Cardiovascular 1.7</td>
</tr>
<tr>
<td>Neurology</td>
<td>1.8</td>
<td>AD (SMT) 2.4</td>
<td>Psychiatry 1.7</td>
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<tr>
<td>Oncology</td>
<td>2.3</td>
<td>Mild AD (DMT) 2.2</td>
<td>Oncology 1.0</td>
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### Stringent and evolving screening criteria (Aβ+, comorbidity exclusions, narrow cognitive ranges) contribute to high screen failure rates and slow enrollment

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

*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)

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;
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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\(^1,2\)

The disease process may begin more than 20 years before clinical symptoms occur\(^3\)

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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.

- CSF, cerebrospinal fluid; FMRI, FDG, F-lucose; 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

TRADITIONAL METHODS
- Clinic
- Local databases

CLINICAL/RESEARCH INTEGRATION
- Dedicated dementia centres
- Research embedded in clinic

PATIENT/PROFESSIONAL AWARENESS
- Media - TV/Radio/newspapers
- Social media – twitter/facebook
- Patient networks
- Initiatives – Dementia Friends

PRE-SCREENING
- Telephone/in person questionnaire - Historical data
  - 77%SF -> 40%SF
- Remote cognitive screen
  - AI
  - Blood biomarker

Reduce screen failure rate

Increase rate of identification

Enhance trial conduct
AD registries
• UK registry
• Alz Prevention Registry
• Brain Health Registry
• Global Alzheimer’s Platform
• Healthy Brains

AD cohorts
• European Prevention of AD
• TRC-PAD
  Trial Ready Cohort for Preclinical / Prodromal AD

link potential participants and recruiter

38,022 total volunteers
80,145 screenings
10,752 participants have enrolled in studies to date

provide trial-ready participants
Cohorts + adaptive platforms maximise recruitment efficacy

**DIAN-XR**
1722 enrolled
443 in families

2008

EXTEND TO 4 YRS

2014

DOSE ESCALATION

2018

DRUG C HALTED
COG RUN IN DEVELOPED

2022

**DIAN-L**
20 sites
5 continents

531 enrolled
275 active

**DIAN-TU**
4 YEARS
21 sites
6 countries

194 randomised

**DRUG A**

**DRUG B**

**DRUG C**

**DRUG D**

**Webinars**

**Conferences**

collaboration between NIH, academic centers, industry, and Alzheimer’s Association
Innovation in Design and Recruitment

We need a strategy in order to recruit these healthy people that do not go to the office...

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

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 (JPD).
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

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**

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.
“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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