

Alzheimer's Disease Clinical Trials

Improving Screen Failure and Recruitment Rates



Jeffrey Zucker
Vice President, Feasibility and Recruitment Optimization



Tom Babic, M.D., Ph.D.
Vice President, Neuroscience



Barbara Zupancic
Director, Global Patient Recruitment and Retention

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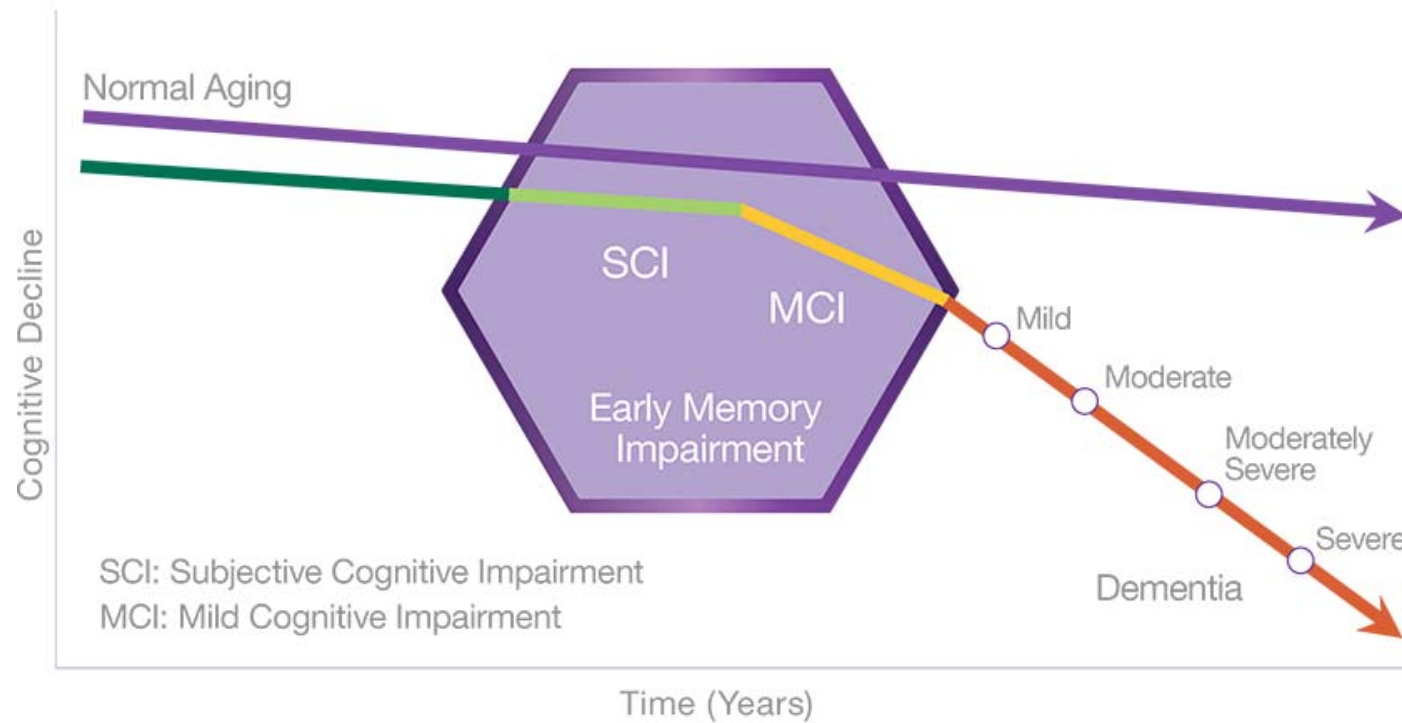
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Early AD-Challenges in Drug Development



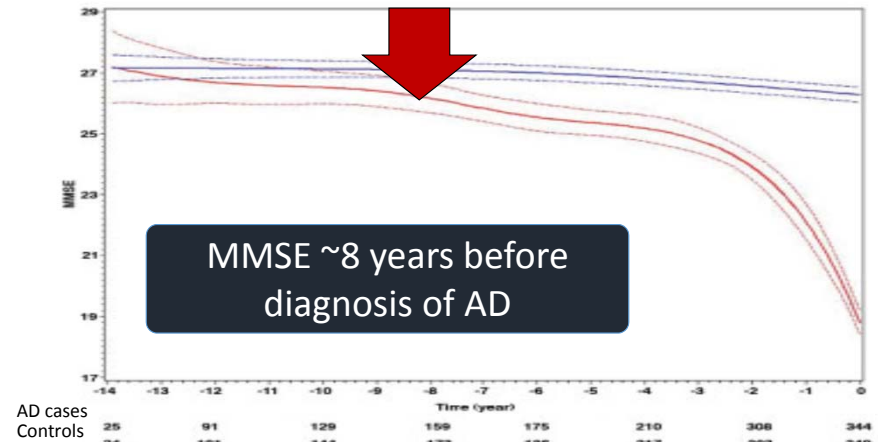
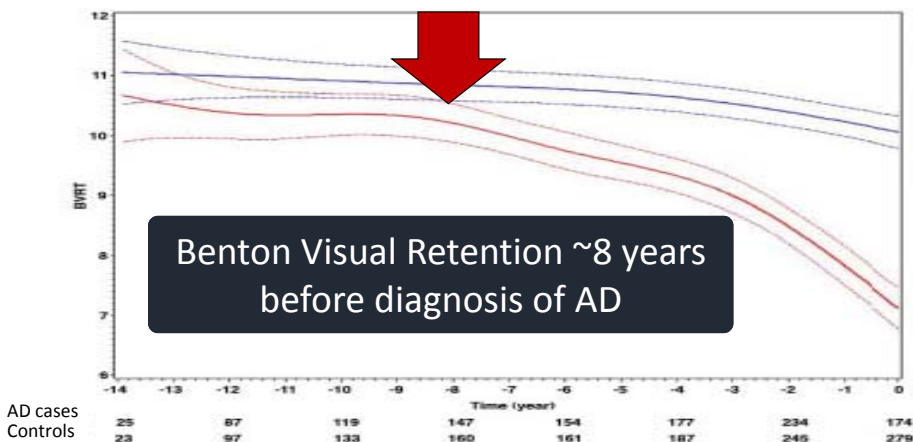
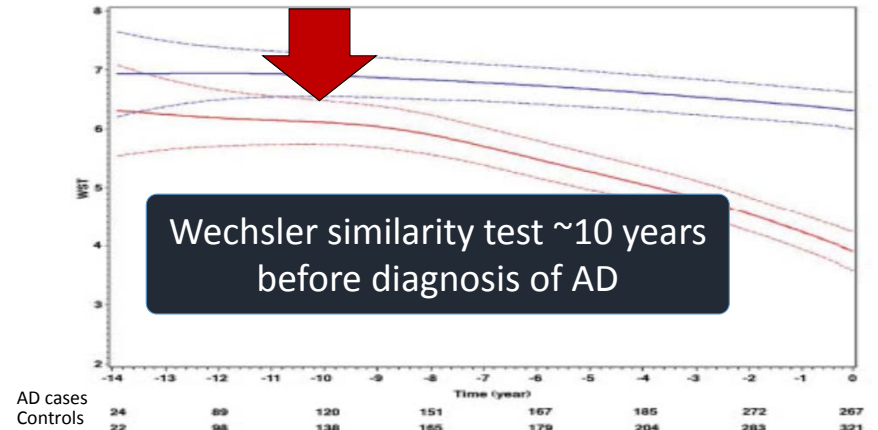
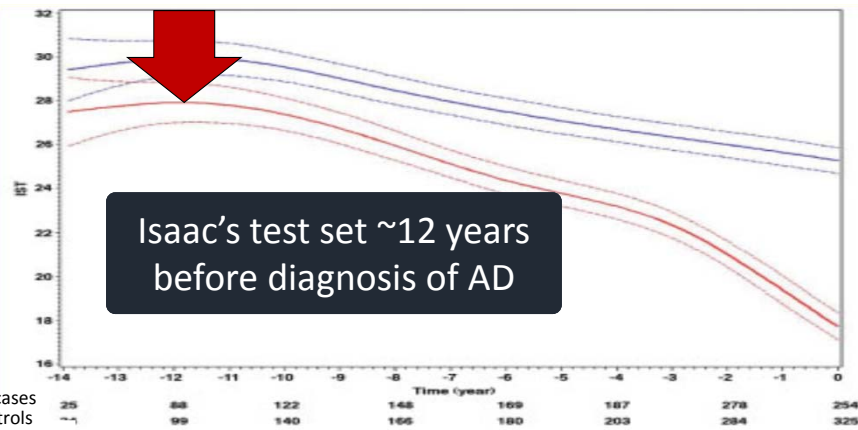
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Early Memory Impairment

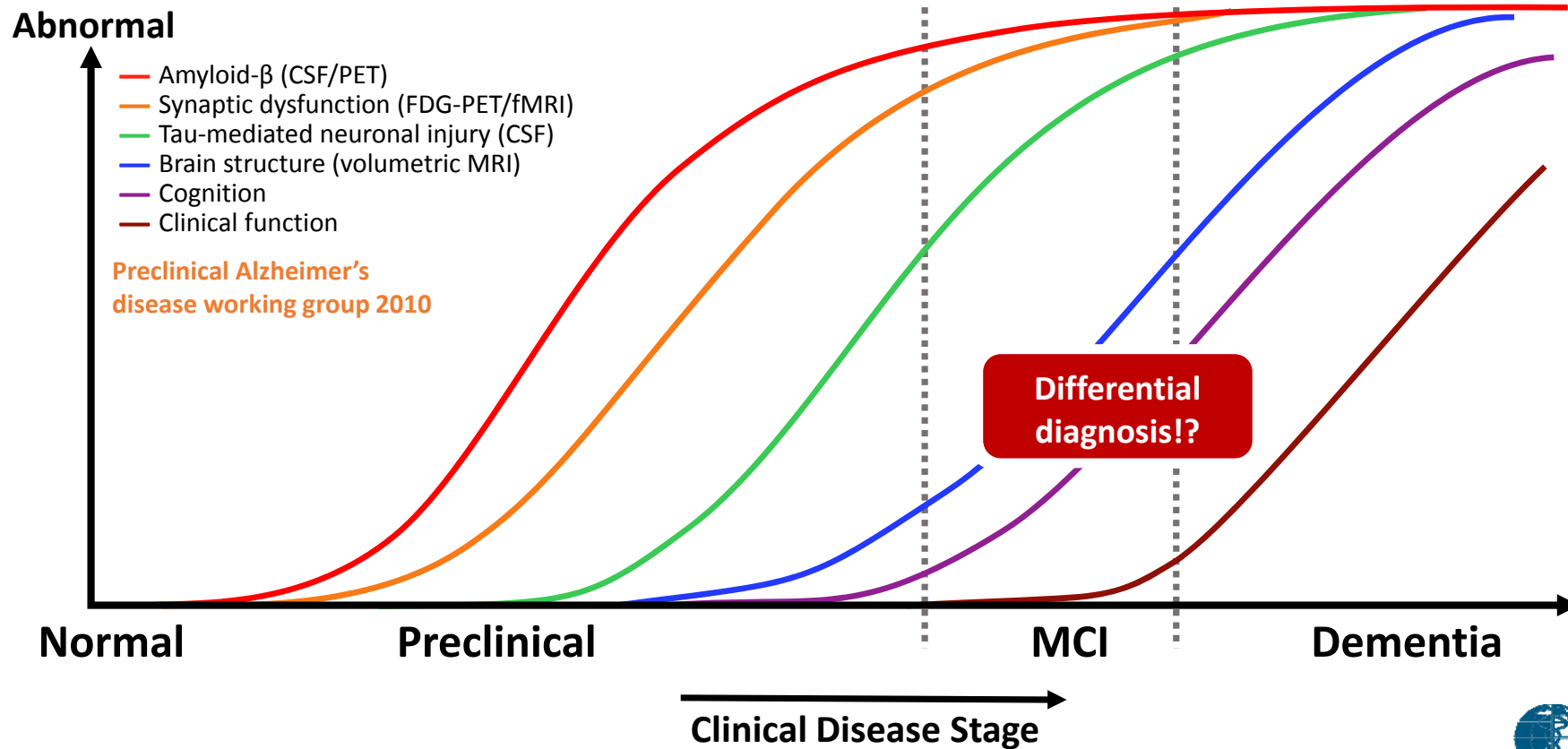


When Do Symptoms of AD Start?

PAQuid Study Amieva H. et al. Ann Neurol 2008



Shift to the Left in Alzheimer's Disease

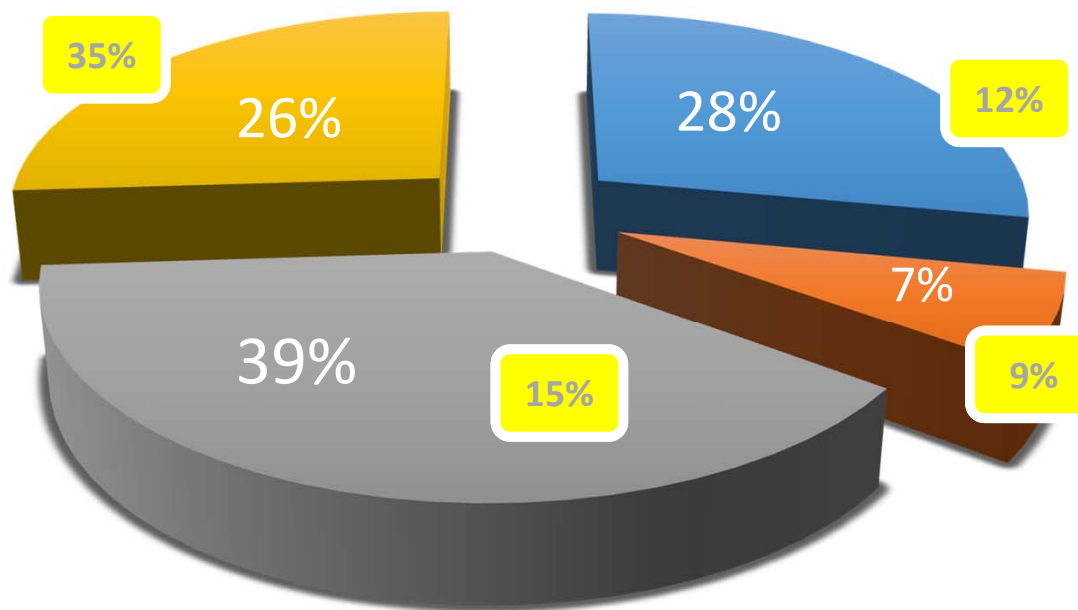


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Cognitive Impairment in Elderly (> 75years)



Fratiglioni 2003

- No report
- Subject reports
- Relative reports
- Both report

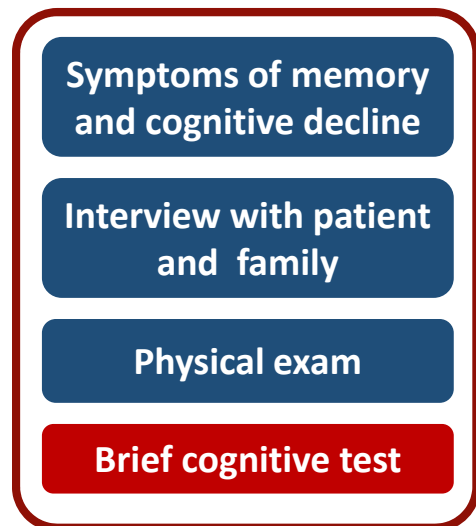
% patients with positive cognitive test

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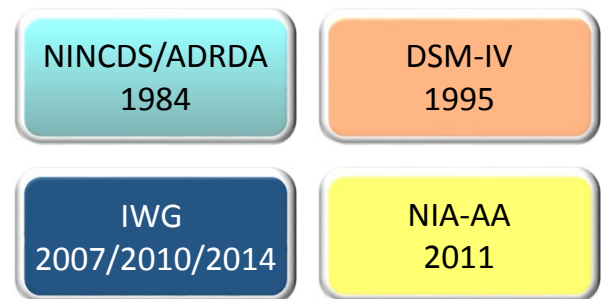
Diagnosis of AD or Dementia Due to AD



Exclusions

- Sudden onset
- Presence of focal neurological signs
- Early onset of:
 - gait disturbances,
 - seizures
 - behavioural changes
 - extrapyramidal signs
- Other diseases with syndrome of dementia

DIAGNOSTIC CRITERIA



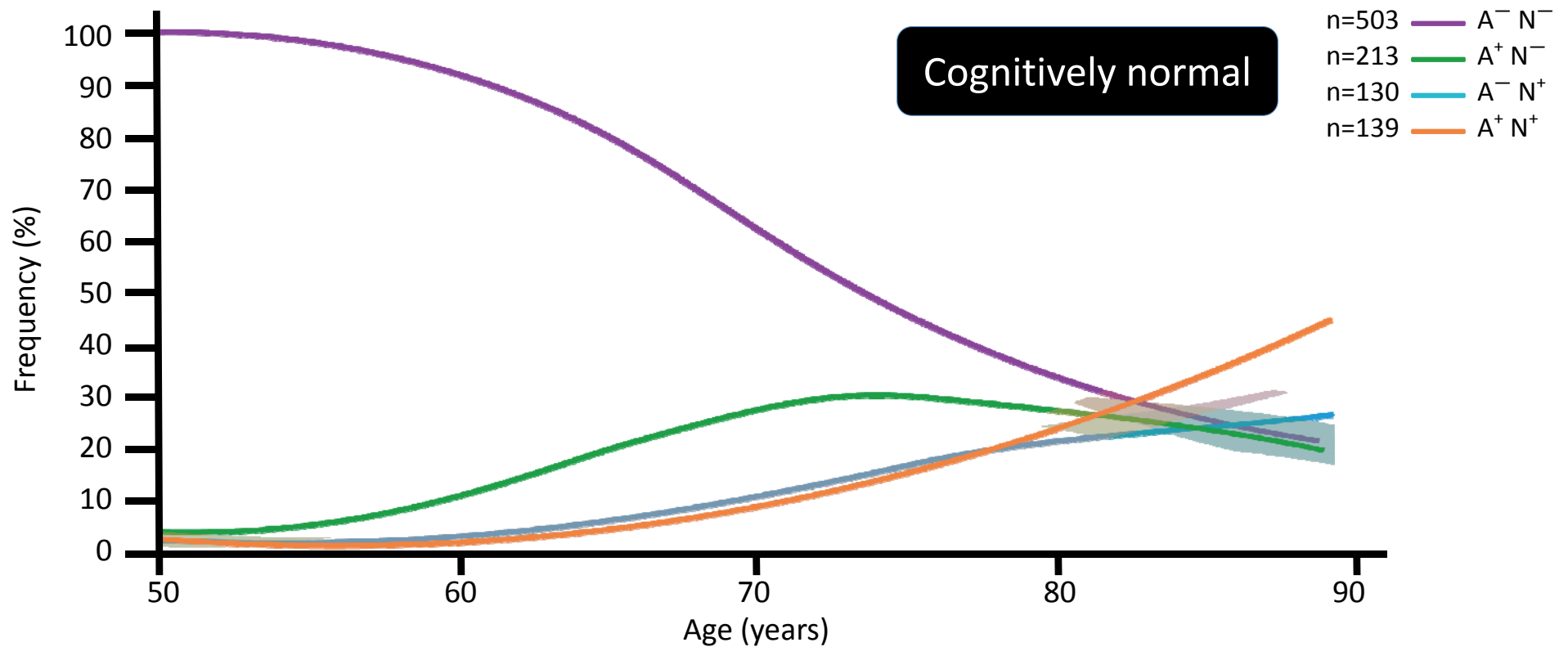
Progressivity of memory (cognitive) decline

Differential diagnostic workup



Evidence of progressive cognitive decline on subsequent evaluations based on information from informants and cognitive testing in the context of either formal neuropsychological evaluation or standardized mental status examinations. (Mc Khan 2011)

Mayo Clinic Study of Aging - MCSA



Inclusion Criteria – Memory Related

- Diagnostic Criteria
 - Petersen criteria
 - IWG (prodromal)
 - NIA-AA – MCI due to AD
- MMSE 25-29(30);
- Global CDR 0.5
- Episodic memory tests
 - Wechsler memory scale –R
 - Logic memory subtest II
 - 16+ years of education - =/< 8
 - 8-15 years of education - =/< 4
 - Free and Cued Selective Reminding Test (FCSRT) Total score ≤ 39 or Free score ≤ 17
 - Pair –associate learning tests
 - RAVLT; DMS48;

MCI

- Diagnostic Criteria
 - NINCDS-ADRDA, DSM IV,
 - IWG
 - NIA - AA
- MMSE 20-26
- Global CDR 0.5 – 1
 - Memory domain 0.5-3
 - Sum of boxes minimal “3”

Mild AD

Dubois B et al. Lancet Neurol

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Clinical Trials in Prodromal AD

SPONSOR molecule	Phase/n	Clinical entry criteria	Biomarker entry criteria	Primary outcome measures
BMS avagacestat	II/263	MMSE >24; CDR 0.5; WMS Logical memory II or FCSRT	CSF Ab ₄₂ < 200pg/ml or T-t/Ab ₄₂ >0.39	Safety CSF markers
ROCHE gantenerumab	III/800	MMSE > 23; CDR 0.5, mBox 0.5 or 1; FCSRT<TR40/FR17	CSF Ab ₄₂ < 600n/ml	CDR-SB; ADAS-cog; biomarkers

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- Avagacestat: 1350 screened; 270 randomised; SF 80%
- Gantenerumab: 3000 screened; 710 randomised; SF 76%

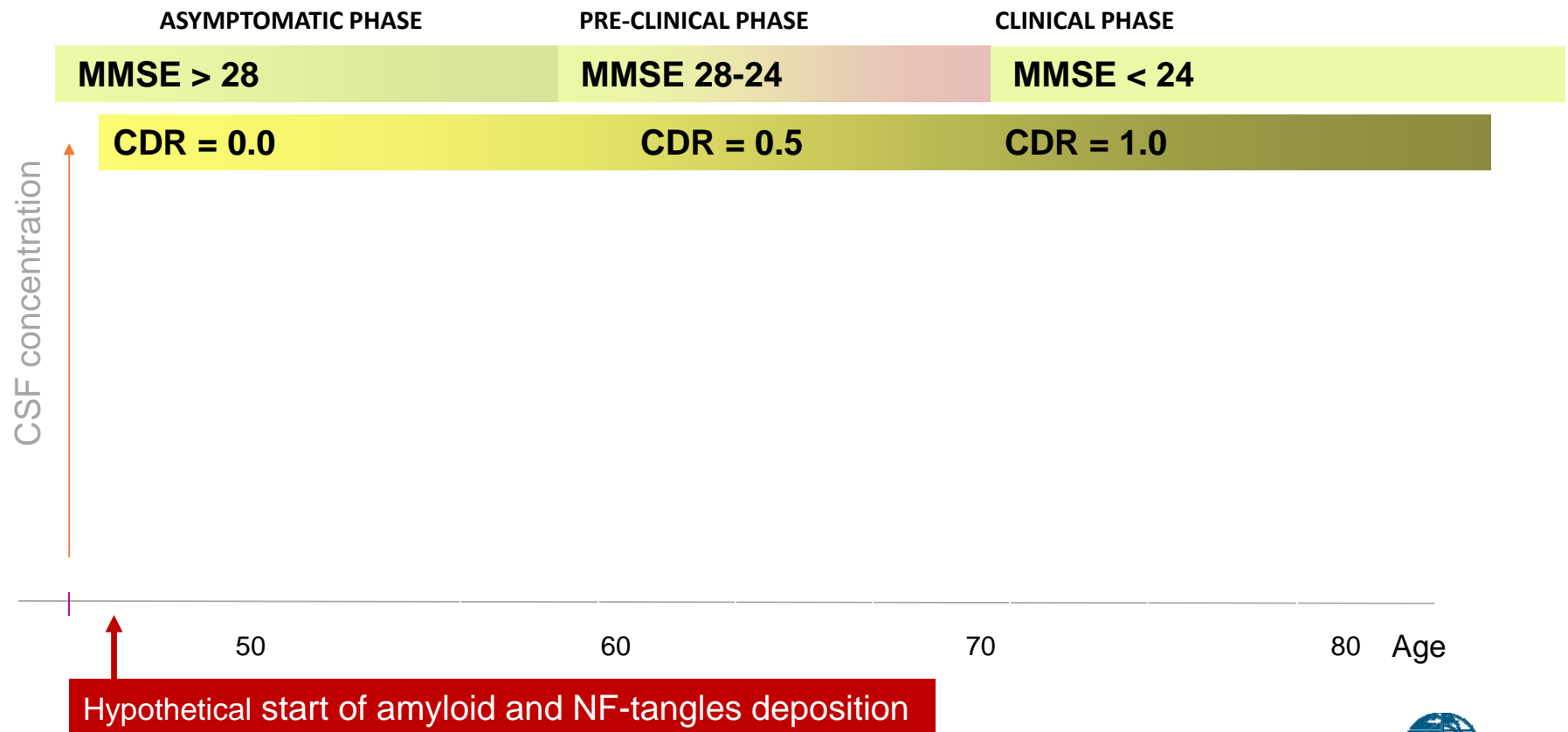
(www.alzforum.org)

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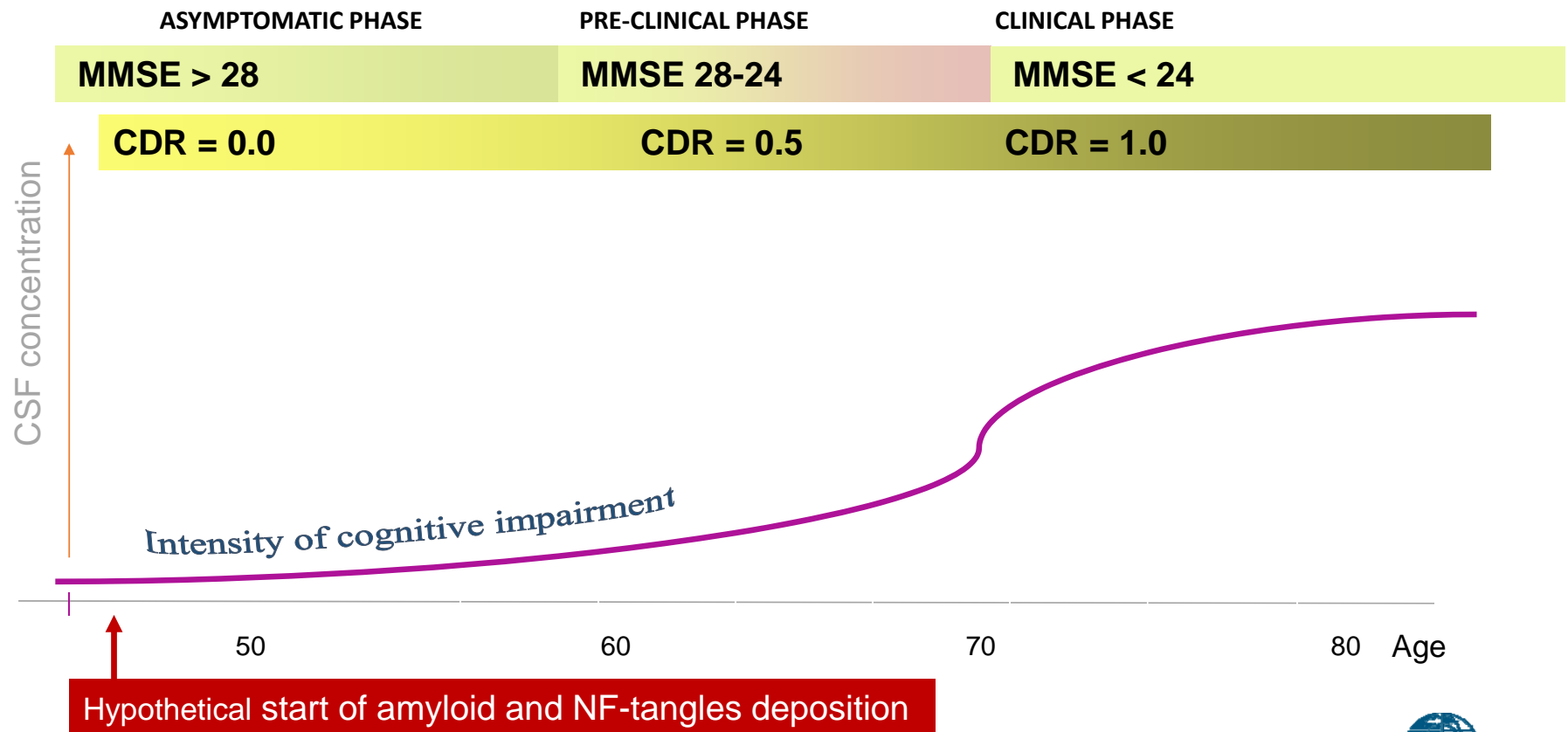


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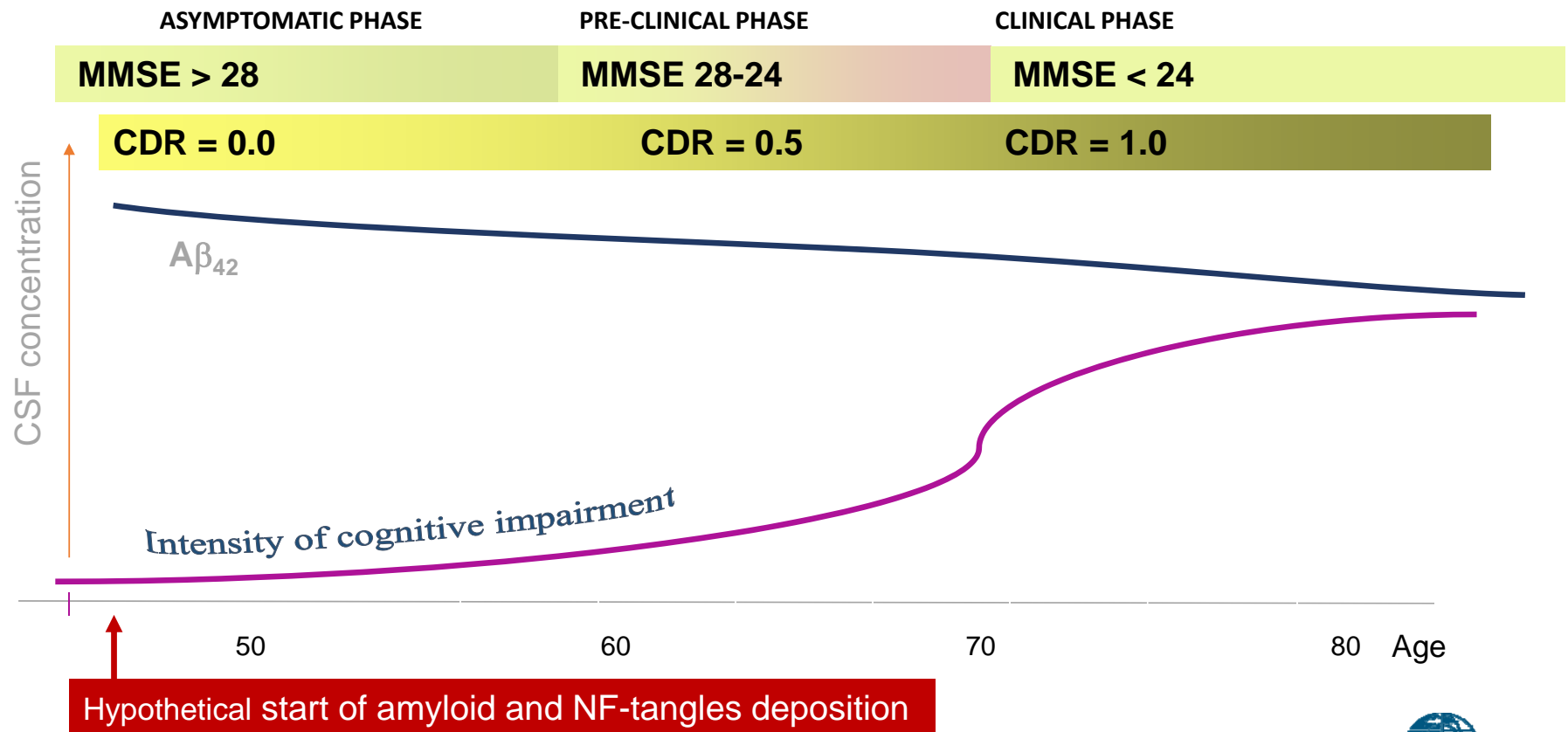
Preclinical, Prodromal and Mild Alzheimer's Disease



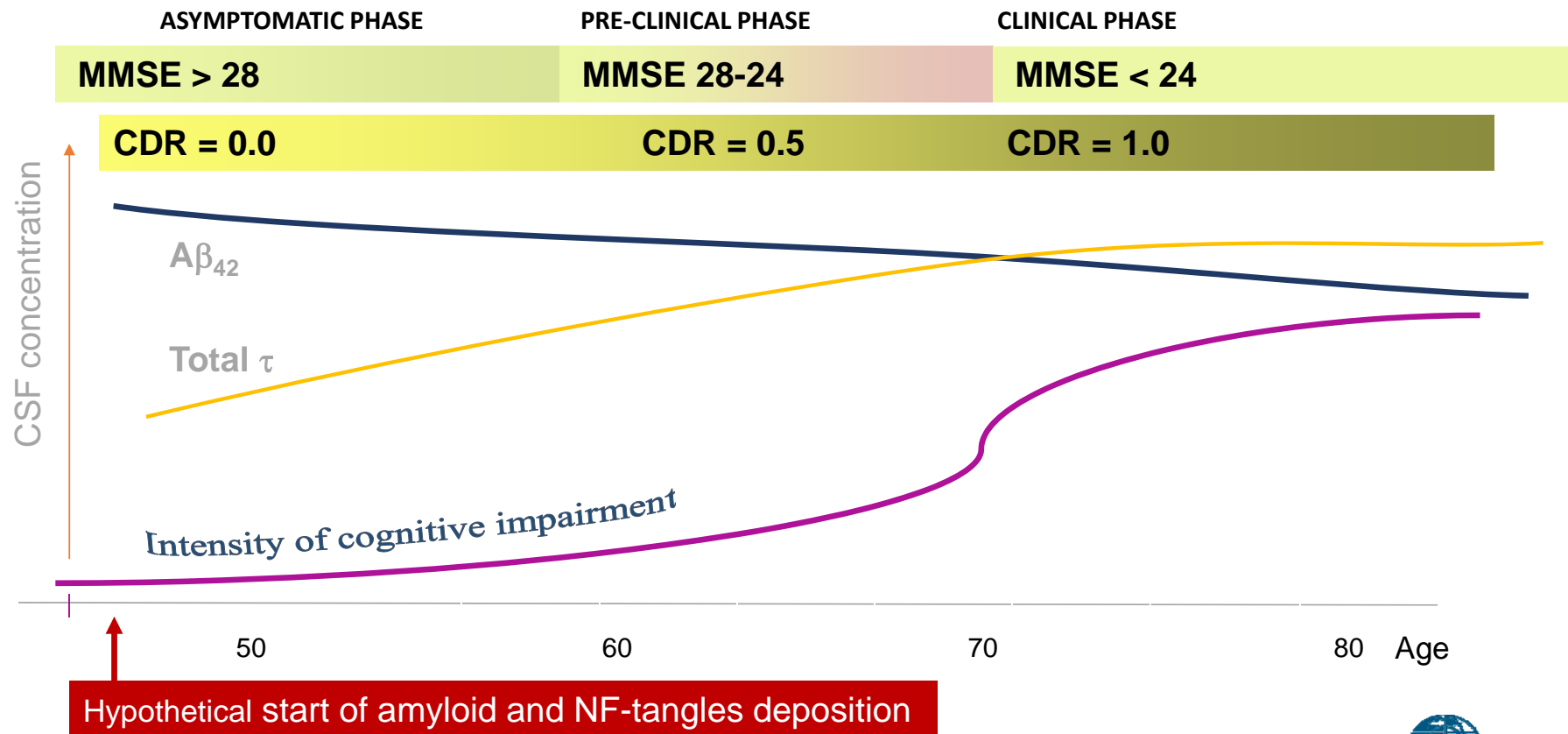
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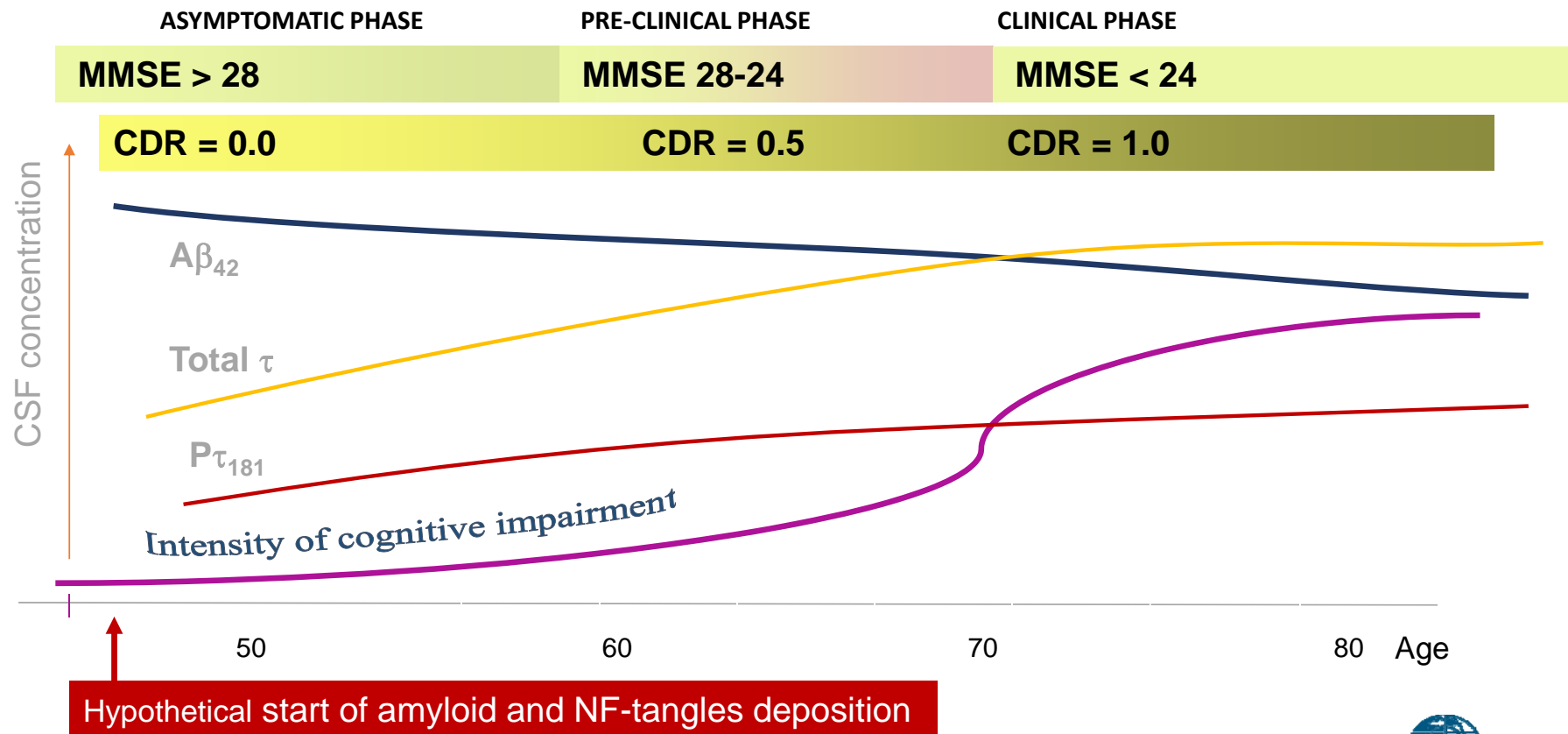
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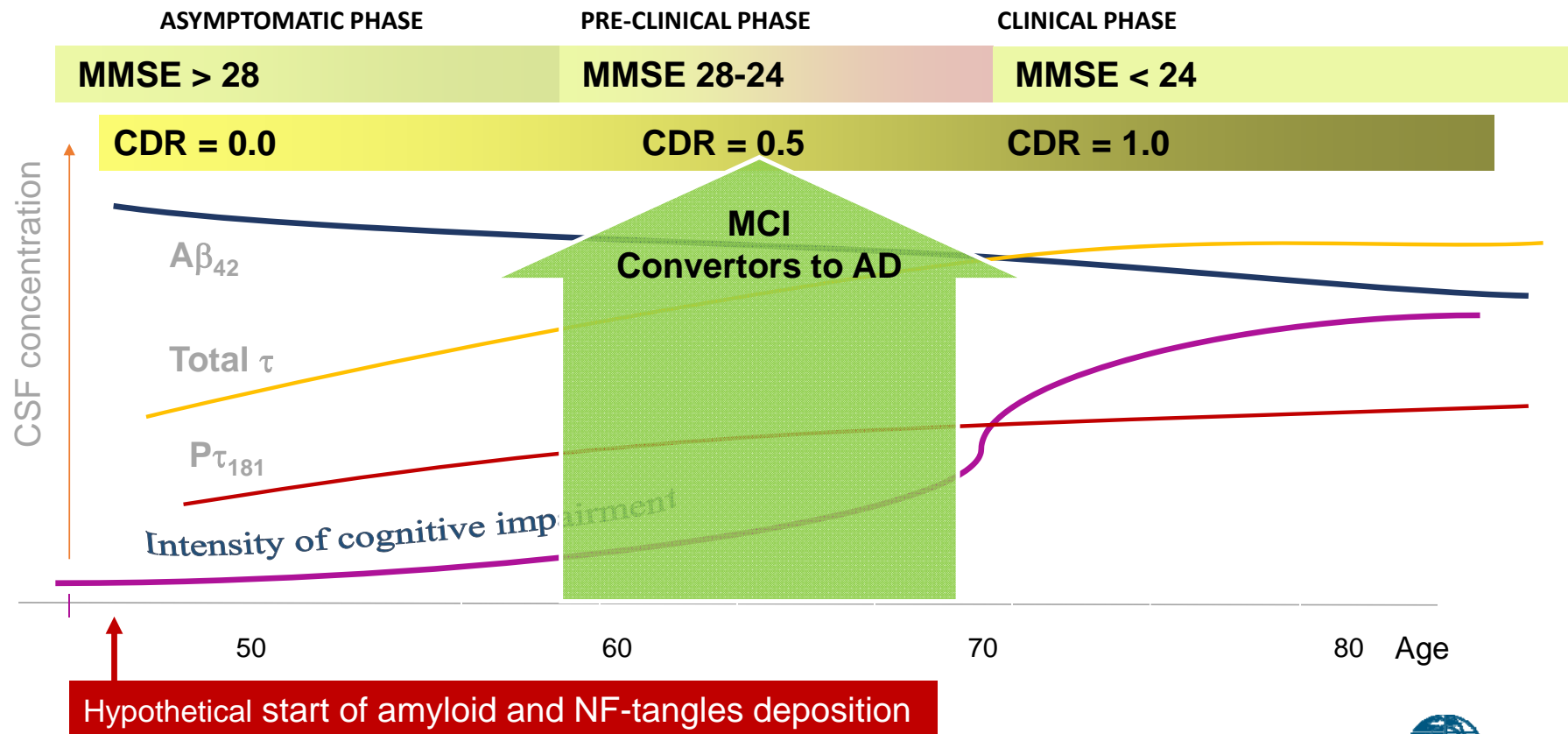
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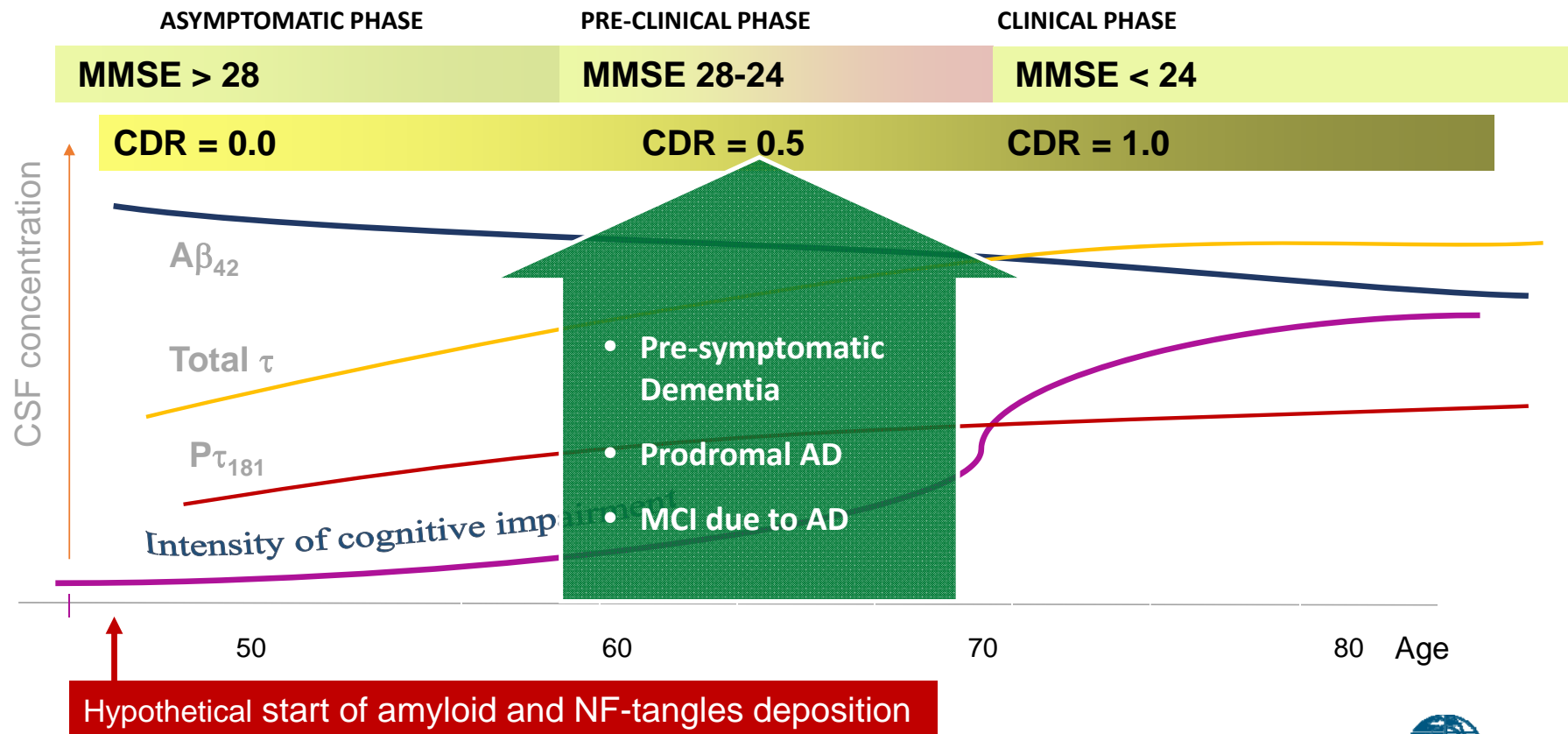
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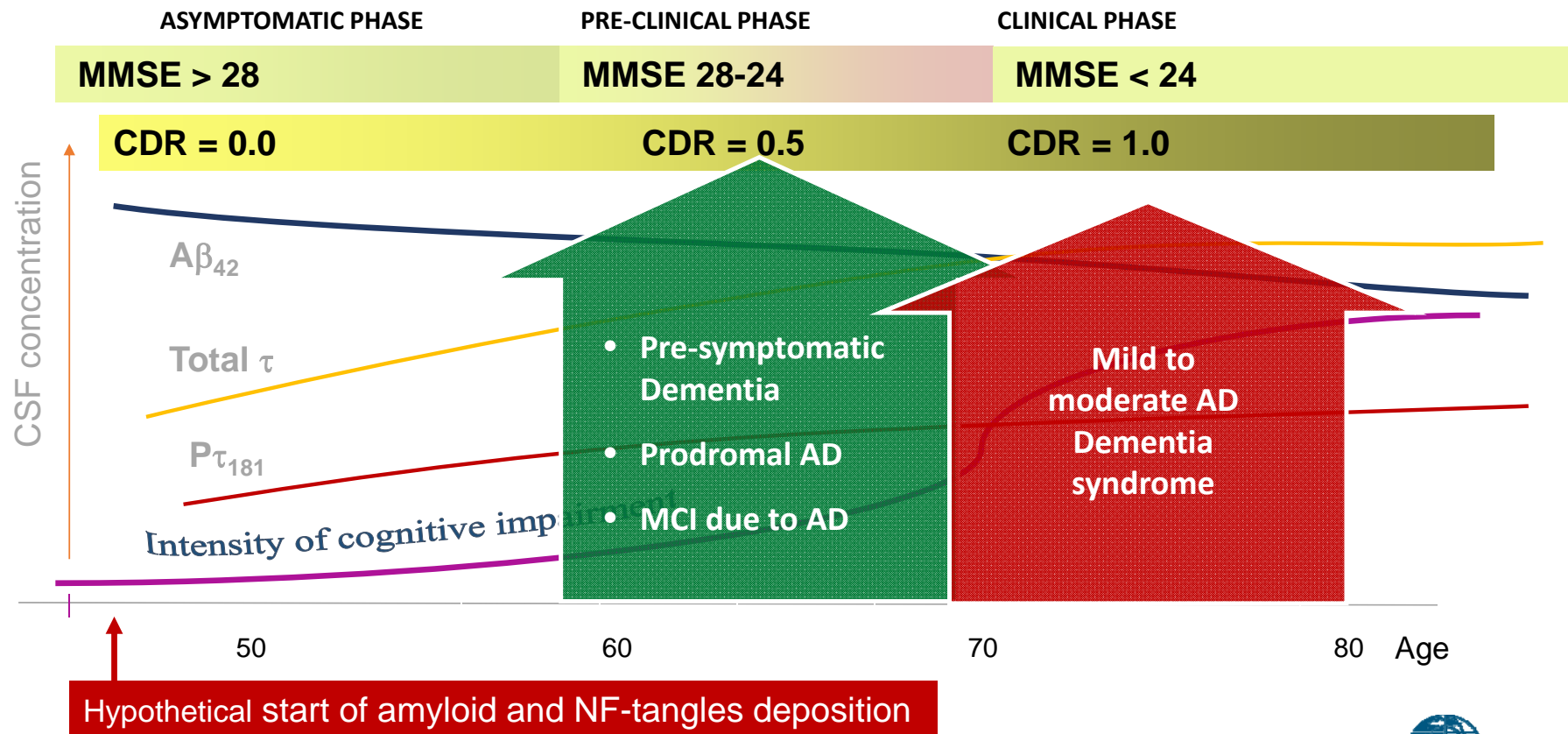
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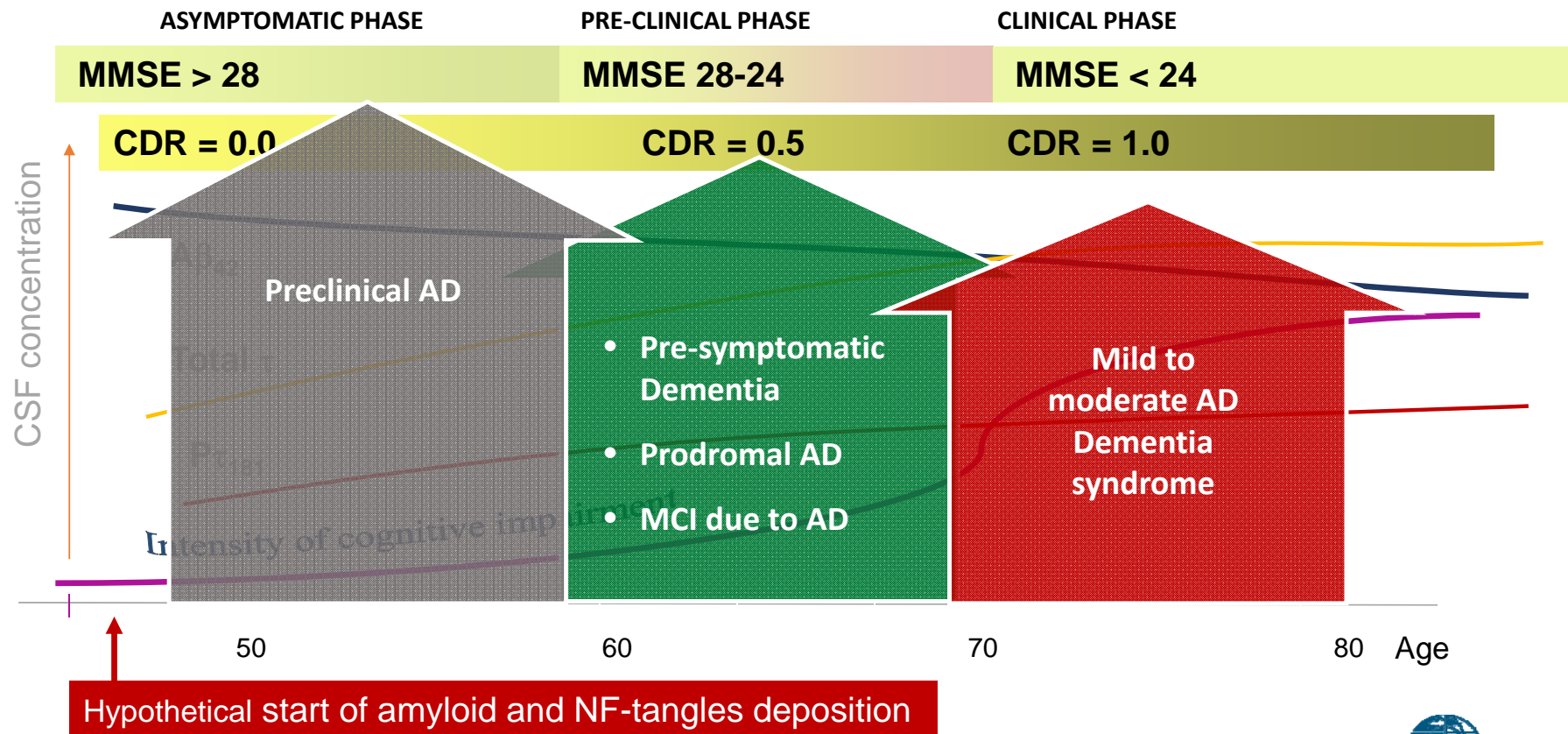
Preclinical, Prodromal and Mild Alzheimer's Disease



Preclinical, Prodromal and Mild Alzheimer's Disease



Preclinical, Prodromal and Mild Alzheimer's Disease



Brief Instrument for Early Dementia Screening

1. Registration from MMSE (0/3)*
2. Orientation in time from MMSE – (5/5)
3. Calculation from MMSE or clock drawing test (0/0)*
4. Recall (3/3)

INTERPRETATION:

- Total score of Orientation in time and Recall is 8/8
- Score of 6 or lower needs a further action.
- *non countable score



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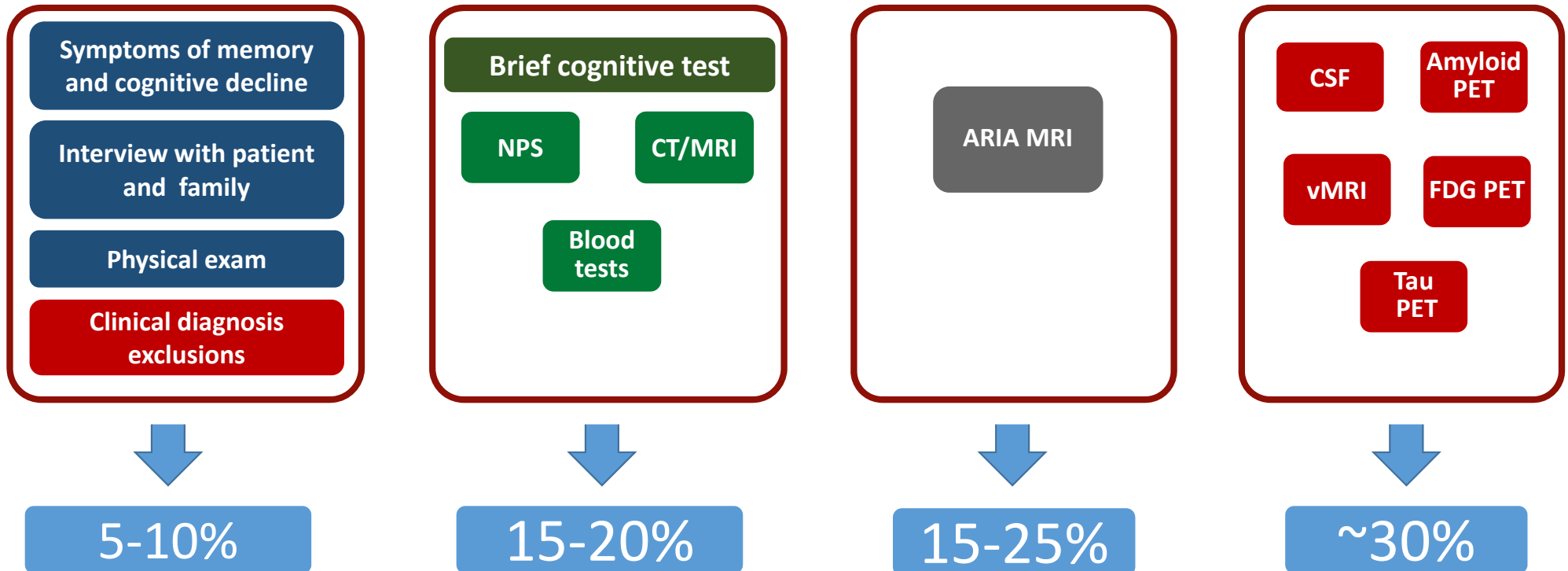
- Total score of Orientation in time and Recall is 8/8
- Score of 6 or lower needs a further action.
- *non countable score



The summation of two subscores (orientation to time and the 3-word recall task) well correlated with FCSRT scores, and it is more strongly associated with dementia and AD than the FCSRT scores and the total MMSE score.

Carcaillon L et al. Dement Geriatr Cogn Disord 2009;27:429–438

Causes of Screening Failures (% of exposed)



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Screen Failure and Retention – Proactive Approach

Predictable

- Medical history
- Medical status
- Dementia history and diagnosis
- Con-medication
- MMSE range
- Study benefits
- Study complexity
- Patient's and caregiver's wish and expectations.
- Logistics
- External pressure

Familiarity with the protocol

**C
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Non predictable

- Structural MRI
- Functional MRI
- Diagnostic Lab
- PET or CSF
- Safety lab/ECG
- AE / new medication
- Paramedical

Semi predictable

- Specific cognition test
- Depression test
- Patient's wish
- Caregiver wish

**R
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Predictable

- Dosing frequency
- Lack of benefit
- Labour intensity
- Length of the study

Semi predictable

- AE of IP
- New medication

Non predictable

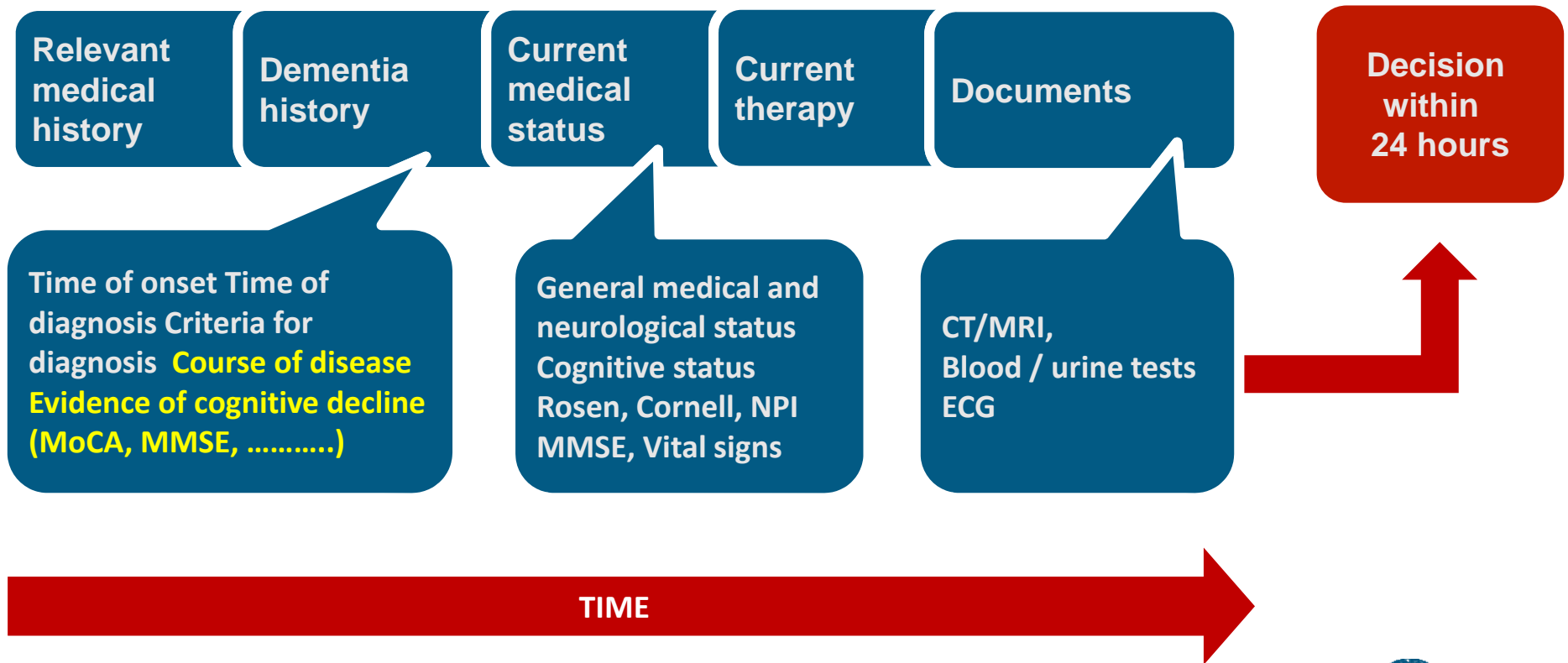
- AE of placebo / IP
- Paramedical

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Centralized Eligibility Review System - CERS



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Journal of Clinical Studies 2016

Therapeutics

Improving Screen Failure and Recruitment Rates in Alzheimer's Disease Clinical Trials



The failures of clinical trials in Alzheimer's Disease (AD) have been attributed to a variety of factors, including an inadequate understanding of mechanisms of action and/or poor target engagement; however, other factors such as inadequate study design, wrong clinical stage of AD matched to the drug's mechanism of action, limited statistical power of endpoint measures, and inclusion of participants who may otherwise not be eligible for the trial, have all contributed to the poor success rate of AD trials. In fact, failure to meet entry criteria in randomised controlled clinical studies in AD focusing on cognition improvement/sparing is a fundamental aspect in the study execution process, leading to protracted timelines and dramatically increased study costs. The importance of appropriate study design and optimisation of recruitment/screen fail rates are especially important as the field moves toward studies of putative disease-modifying agents of AD and patients that are very early in the disease spectrum – studies that have notoriously high screen failure rates (with averages upwards of 85%) and correspondingly low recruitment rates (with averages of 0.19 patients per site per month or less).

Challenges to Recruitment

Studies examining the rates of patient eligibility have established that as little as 10-27% of potential AD patients are actually trial-eligible.¹⁴ Unfortunately, only a portion of AD patients are even marginally aware of research opportunities and many are unable or simply unwilling to participate. Many older adults live alone and may not have access to a caregiver who can accompany them to study visits and aid with various procedures. Indeed, AD trials require not one but two participants: the patient and a study partner, and enrolment of this dyad is imperative to clinical trial success.

Of interest, substantive differences have been noted between enrolled AD samples and the general AD population which reflects the often idiosyncratic subject entry/eligibility criteria specific to any given study. More often than not, the diagnosis of AD in clinical practice is based on the individual clinician's distinctive diagnostic approach rather than specific research criteria. In fact, the greatest challenge for most investigators is how to properly select the right patients for a particular AD study and appropriately translate that patient's medical data and history into protocol-specific entry criteria. This becomes even more important in oligosymptomatic disease presentation in early or prodromal AD, where a patient's spontaneous reports of memory impairment are very often rare, inconsistent, and oftentimes have not been taken seriously.

AD trial recruitment is challenging due to many factors, including medical comorbidities, extensive use

of prescribed and OTC medications, and behavioural complications of AD which can all be exclusionary. Additionally, some AD patients are anxious about lumbar puncture for cerebrospinal fluid examinations or MRI/PET imaging procedures, whereas others might have difficulties with extensive and numerous psychometric tests, which often require between three to five hours to complete, and can result in frustration and emotional anguish upon confrontation of deficits.

Historical Reasons for Screen Fail Rates in AD

The development of symptomatic treatment in mild to moderate AD has traditionally been associated with average screen failure rates ranging between 15-35% in registration clinical trials. Although this range is mostly viewed as manageable by sponsors and CROs, it is not uncommon for trials to have twice the screen fail rates in early AD populations. For example, in a study of early AD patients, screen failure rates have reportedly upwards of 50%.¹⁵ One reason for this higher-than-expected screen fail rates stems from amyloid-related imaging abnormality (ARIA) exclusion criteria, stemming from the failed AN-1792 trial in which dosing in a 372-patient, multinational Phase I/II trial in patients with mild to moderate AD was suspended when four treated AD patients developed brain inflammation that later was demonstrated to reflect specific meningioencephalitis. In addition, this clinical trial programme established procedures that were instituted subsequently in numerous other immunotherapy programmes, and even in studies with dissimilar mechanisms of action, such as the practice of utilising a central reader to assess ARIA at baseline and at regular intervals throughout the trial. Although the original FDA guidance directed clinical trial sponsors to exclude participants with more than two existing brain microhaemorrhages from studies, the Alzheimer's Association working group proposed that research participants with up to four pre-existing microhaemorrhages (or ARIA-H) could enrol in clinical trials after reviewing all publicly available data. Additionally, any patient who develops oedema (or ARIA-E) during the trial must be taken off medication until those complications clear, and then treatment can resume. Any patients developing ARIA-H during the trial may continue to receive treatment, provided that these abnormalities do not worsen symptoms. Because microhaemorrhages cannot be easily seen in routine diagnostic sequences of brain MRI for AD, the additional MRI scans with specific sequences need to be conducted to exclude patients with ARIA-H, resulting in higher screen failure rates (i.e. average rate of 63%).¹⁶

Screen Failure Rates in Prodromal AD/MCI due to AD: Biological substrates of AD can be identified long before patients exhibit clinical signs and symptoms, permitting

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Tomislav Babić, MD, PhD
Vice President, Neuroscience



Henry J. Riordan, Ph.D.
Executive Vice President, Medical and Scientific Affairs

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Barbara Zupancic

Director, Global Patient Recruitment and Retention



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Patient Recruitment and Retention Strategy

The importance of addressing all stages of Alzheimer's disease



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Alzheimer's Disease Insights

- Patients' deficits make research difficult
- Patient Experience - Living a dream
- Caregivers are critical to driving participation
- Research site have insights but need training
- Clinical Trial Participation



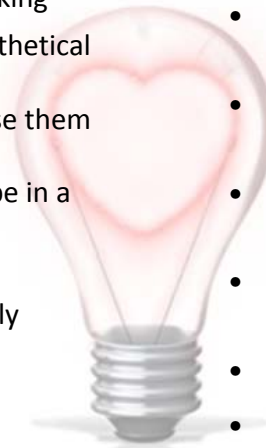
Variations between Mild Cognitive Impairment and Alzheimer's Patient Cohorts- Implications for Recruitment and Retention

MCI Patients

- Patients are generally aware of their diagnosis as well as their symptoms
- Patients are still able to participate in medical decision making
- Patients are also more able to imagine themselves in hypothetical situations, including clinical trials
- Patients more frequently use technology, like iPads, and use them more often
- Patients are able to understand and more were willing to be in a trial
- Caregivers feel lower sense of urgency to treat
- Patient needs are prioritized alongside those of other family members, not higher
- Caregivers are still transitioning to full caregiving role both practically and emotionally
- Caregivers bank on the hope that their loved ones won't progress and cling to normalcy as much as possible, even if it means not getting help
- Caregivers have more negative perception of clinical trials and less sense of trials as a treatment option
- Caregivers play less of a role in decision making

Alzheimer's Patients

- AD Patients are less likely than MCI patients to acknowledge their diagnosis
- AD Patients are less able to participate in medical decision making
- AD Patients have more cognitive changes than previously thought
- AD Patients can't handle new technology or frustration easily and need help
- Caregivers prioritize Mild AD patient needs ahead of other family members' needs
- Caregivers perceive the urgency of treating mild AD
- Caregivers have a more positive perception of clinical trials, and a sense of trials as a treatment option
- Caregivers are hopeful for a medication to preserve the status quo



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Reaching the Audience

- Engage Audience directly online
- Engage Audience in their community
- Engage Medical Community
- Identify Referring Physicians
- Keeping Patients and Caregivers engaged and compliant

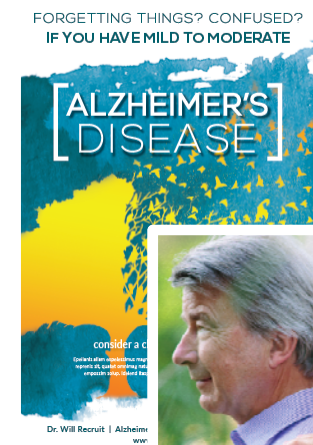
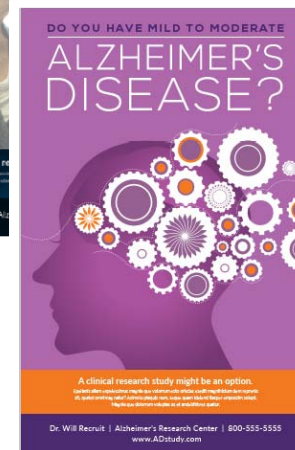
Proactively identify sites that have access to elderly subjects with neuropsychological /cognitive and biomarkers data and have identified subjects that fulfil the criteria for either pre-clinical, prodromal or mild to moderate AD



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Recommendations for Successful Engagement

- Address cognitive changes
- Do not neglect emotional and social needs
- Technology and training
- Take the fear out of treatment
- Utilize communication and study materials



Q & A

Contact:

Lynn Ledwith

Senior Vice President, Global Strategic
Marketing & Commercial Operations

lynnledwith@worldwide.com

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Thank You!

Contact:

Lynn Ledwith

Senior Vice President, Global Strategic
Marketing & Commercial Operations

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