

# The changing diagnostic criteria for Alzheimer's disease – regulatory challenges

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*November 24, 2014*



# Disclaimer

- No Col
- The content of this talk is my own and refers to the **Discussion paper on the clinical investigation of medicines for the treatment of Alzheimer's disease and other dementias (EMA/CHMP/539931/2014; 23 October 2014).**
- All information discussed is in the discussion paper or publically available.



# Outline

- **Patient characteristics and selection of population**
- **Assessment of therapeutic efficacy**
  - Symptomatic improvement
  - Disease modifying effects
- **Design features**



# Defining populations

- **AD diagnostic criteria**
  - NIA-AA/IWG guidelines: clinicobiological entity
  - ICD 10, DSM 5 (major and mild neurocognitive disorder)
  - Consensus for research purposes and trial enrichment:

## Core clinical diagnosis + biomarkers

- Disease continuum



Preclinical	prodromal/MCI	mild	moderate	severe AD
		MMSE 21-26	10-20	≤ 9



# Comparison IWG and NIA-AA criteria for clinical diagnosis of Alzheimer’s disease (Morris 2014)

## Similarities

Incorporate biomarkers for AD into the diagnostic process

Move towards an aetiological diagnosis for MCI

‘Prodromal AD’ (IWG)

‘MCI due to AD’ (NIA-AA)

## Differences

IWG

NIA-AA

‘AD’ refers only to symptomatic stage

‘AD’ refers to the pathologic process, whether asymptomatic or symptomatic

Replace ‘MCI’ with ‘Prodromal AD’

Retain ‘MCI’

Requires objective impairment in memory

Subjective and/or objective impairment in memory and/or nonmemory domains

Biomarker abnormalities required for diagnosis

Biomarker abnormalities support diagnosis but not required

DuBois B *et al. Lancet Neurol* 2010; 9:1118–1127; McKhann GM *et al. Alzheimer’s & Dementia* 2011; 7:263–29; Albert M *et al. Alzheimers & Dementia* 2011; 7:270–279; Sperling R *et al. Alzheimer’s & Dementia* 2011; 7:280–292.



# Similarities and Differences of IWG and NIA-AA criteria

- **Similarities**

- the recognition of a preclinical stage of the disease
- the acceptance of a diagnosis of AD prior to dementia
- the incorporation of AD biomarkers to diagnose (IWG) or provide support for the diagnosis (NIA-AA) of AD

- **Differences**

- IWG: objective memory impairment and positive biomarker mandatory
- NIA-AA: subjective or objective memory impairment, positive biomarker supportive but not mandatory
- IWG: pathophysiological biomarkers
- NIA-AA: biomarker algorithm
- IWG: prodromal patients do not have any functional impairment
- NIA-AA: “mild problems” in iADL also in patients with MCI



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- NIA-AA: biomarker algorithm
- **IWG: prodromal patients do not have any functional impairment**
- **NIA-AA: “mild problems” in iADL also in patients with MCI**



## Which criteria are the most sensitive and specific?

- This is not settled yet.
- These differences may lead to different populations.
- We can always describe them.
- EMA does not need to endorse a specific set of diagnostic criteria, thus from a regulatory perspective any recommendation of diagnostic criteria particularly for early AD (i.e. prodromal AD/ MCI due to AD and preclinical AD) is kept open.
- Highest sensitivity and specificity should be strived for!
- It is important to have homogeneous inclusion criteria to enable global development programs.





## Impact on approach to demonstrate therapeutic efficacy

- Different requirements to assess therapeutic efficacy are distinguished according to
  - the potential claims of treatment, e.g. **symptomatic improvement** or **disease modification** and **prevention** and
  - **the stage of the disease** (preclinical, prodromal/MCI, mild, moderate or severe dementia)

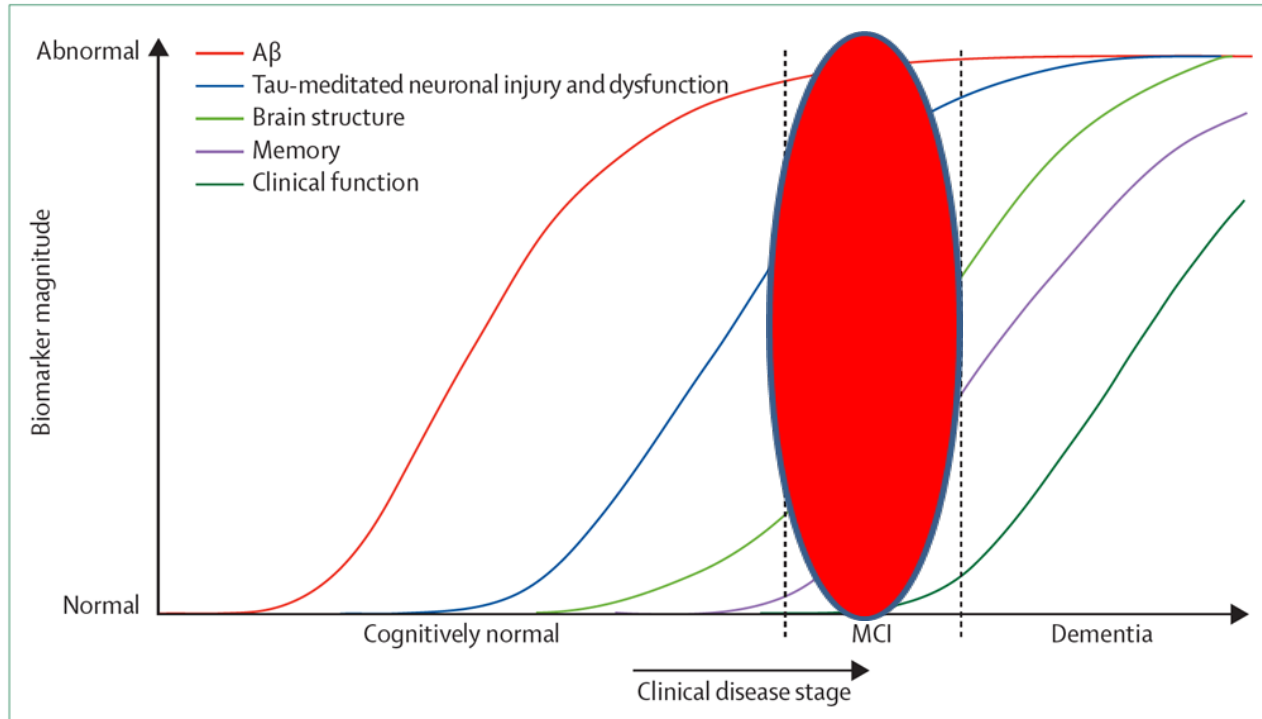


# Symptomatic improvement

- **Dementia Trials**
  - **Co-primary outcome measures**
    - Cognition
    - Function
  - **Response criteria for clinical relevance**
    - proportion of patients with meaningful benefit
  - **Secondary endpoints**
    - Global domain, additional symptoms (e.g. agitation)
- **Trials in prodromal/ MCI due to AD**
  - Co-primary approach more challenging
  - Should still apply in principle



# AD Progression Model (Jack 2013)

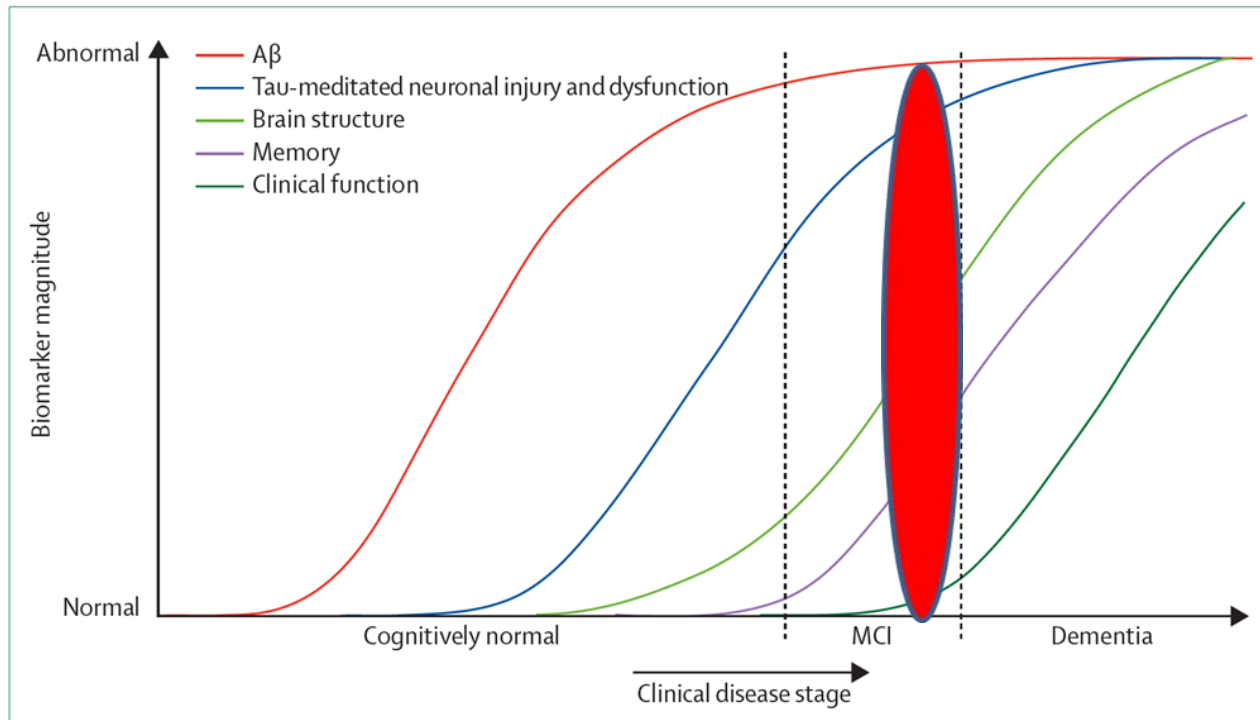


**Figure 2: Dynamic biomarkers of the Alzheimer's pathological cascade**

Aβ is identified by CSF Aβ<sub>42</sub> or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.



# AD Progression Model

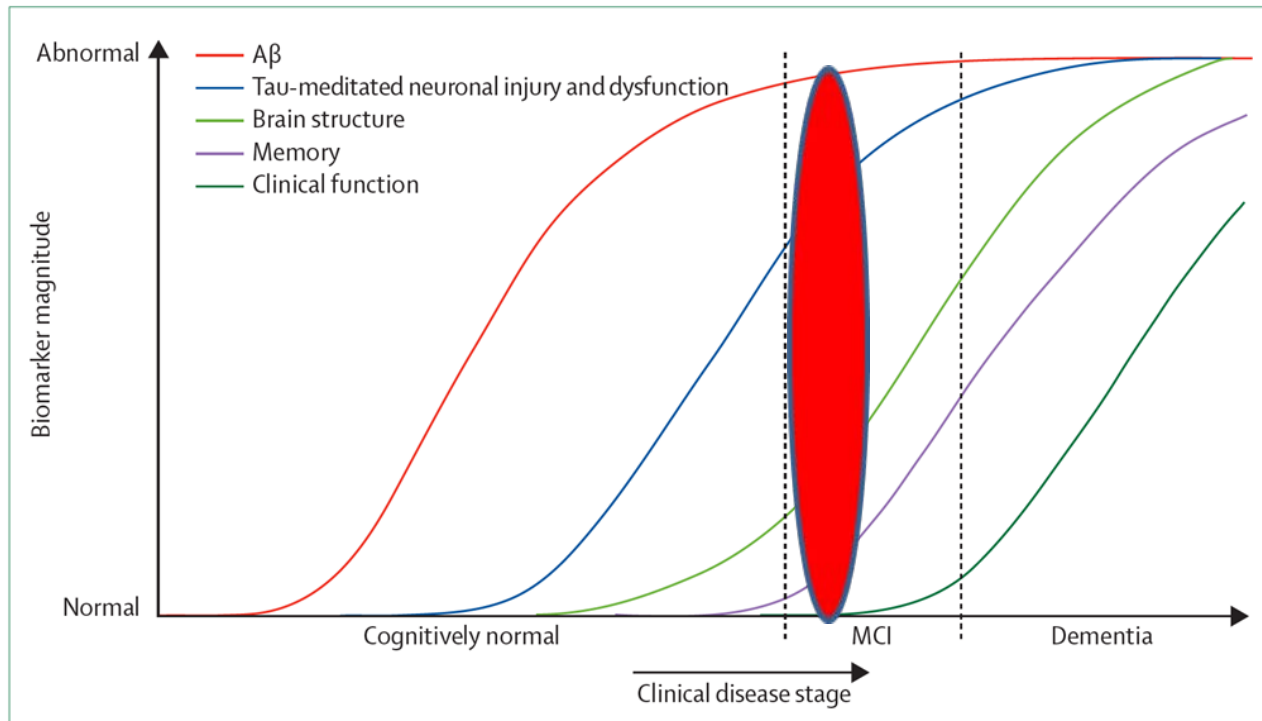


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# Clinical endpoints

- **Earliest Symptoms**
  - Subtle cognitive deficits
  - No detectable functional impairment
  - Most to gain (potentially)
  
- **Use of isolated cognitive measures, composite scales**
  - Several scales under development
  - Small effect sizes
  - Hard to interpret clinical meaningfulness



# Design features

- **Symptomatic improvement**

- **Dementia stage of AD**

Standard clinical trial design: DB, placebo-controlled, parallel group, dual outcome approach, active comparator,

Alternative: add-on designs

Duration of treatment: 6 months

- **Prodromal AD/MCI due to AD**

Placebo is the comparator of choice

Duration of treatment: 6 months may not be enough, assessment of efficacy and safety at regular intervals, maintenance of effect is important



# Disease modification

- It may be difficult to differentiate unambiguously between symptomatic and disease modifying effects only on the clinical endpoints
- From a regulatory point of view, a medicinal product can be considered as disease modifying, if the progression of the disease as measured by assessment tools addressing both cognition and function is reduced or slowed down and if these results are linked to a significant effect on adequately qualified and validated biomarkers.
- Suitable study designs are needed
- Two-step approach a way forward?





# Disease modification

- **Co-primary outcome measures**
  - Cognition
  - Function
- **Response criteria for clinical relevance**
  - proportion of patients with meaningful benefit
- **Secondary endpoints**
  - Global domain
  - **Biomarkers**



# Design features

- **Disease modification**

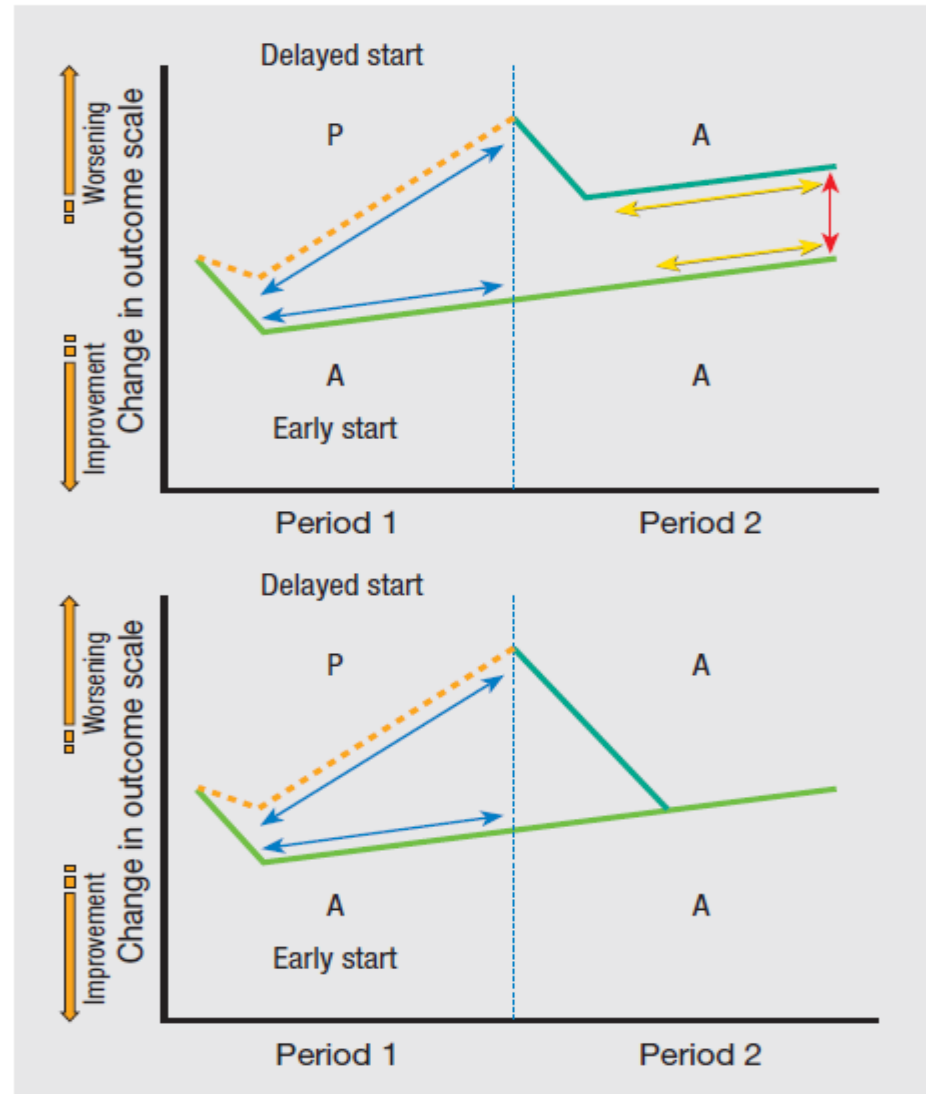
- **Prodromal AD/MCI due to AD and mild to moderate dementia**

- Placebo-controlled trials are mandatory, stratification for standard of care
- Standard parallel design might be problematic
- Slope analysis assumes a linear model over time and a constant treatment effect
- Randomized withdrawal or randomized delayed start design
- Time to event analysis
- Study duration: 18 months for mild to moderate AD , 24 months for prodromal AD?



# Delayed start design

- Stanzione P et al. 2011



# Design features

- **Prevention trials in preclinical patients**

Time to event approach: onset of dementia or onset of cognitive impairment,  
**even longer study durations?**

**Scientific advice is recommended.**



# Combination treatment

- **A trial where the combination is compared to two monotherapy arms**
- **May be difficult for DM therapies**
- **Exclusion of monotherapy arms needs to be justified**
  - lack of efficacy in previous monotherapy programs
  - convincing phase 2 data demonstrating additive/synergistic effects of the combination over each monotherapy arm not only on biomarkers but also on clinical parameters



# Points for discussion

- **Do IWG and NIA/AA criteria identify different populations?**
- **The co-primary endpoint approach in early disease stages?**
- **What is the optimal study duration in early disease stages?**
- **The concept of disease modification: what is the best approach?**



**Thank you for your attention!**

