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Dementia: a European Regulatory Perspective – Challenges, Opportunities, Requirements

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ISCTM Autumn Conference, Toronto, October 2008

Critique on Regulatory Decisions in Dementia

- **Trend to question the clinical relevance of improvement shown with AchEI and Memantine**
  - **All studies methodological flawed**
    - **Assessment tools**
    - **Endpoints**
    - **Drop outs/missing data**
    - **Statistical evaluation**
  - **Overestimation of effects of active treatment**
  - **Despite of these limitations treatment effects are small and not clinically meaningful**
  - **Long-term safety issues**

Revision of the Guidance Document

- addresses different types of dementia
- differences in severity
  - MCI/preclinical/prodromal/very mild DAT
  - mild
  - moderate
  - severe
- disease modification
- discussion on biomarkers as surrogate endpoints
- discussion on adequate study designs

Diagnosis of Dementia

Box 1: General criteria for diagnosing dementia[4]

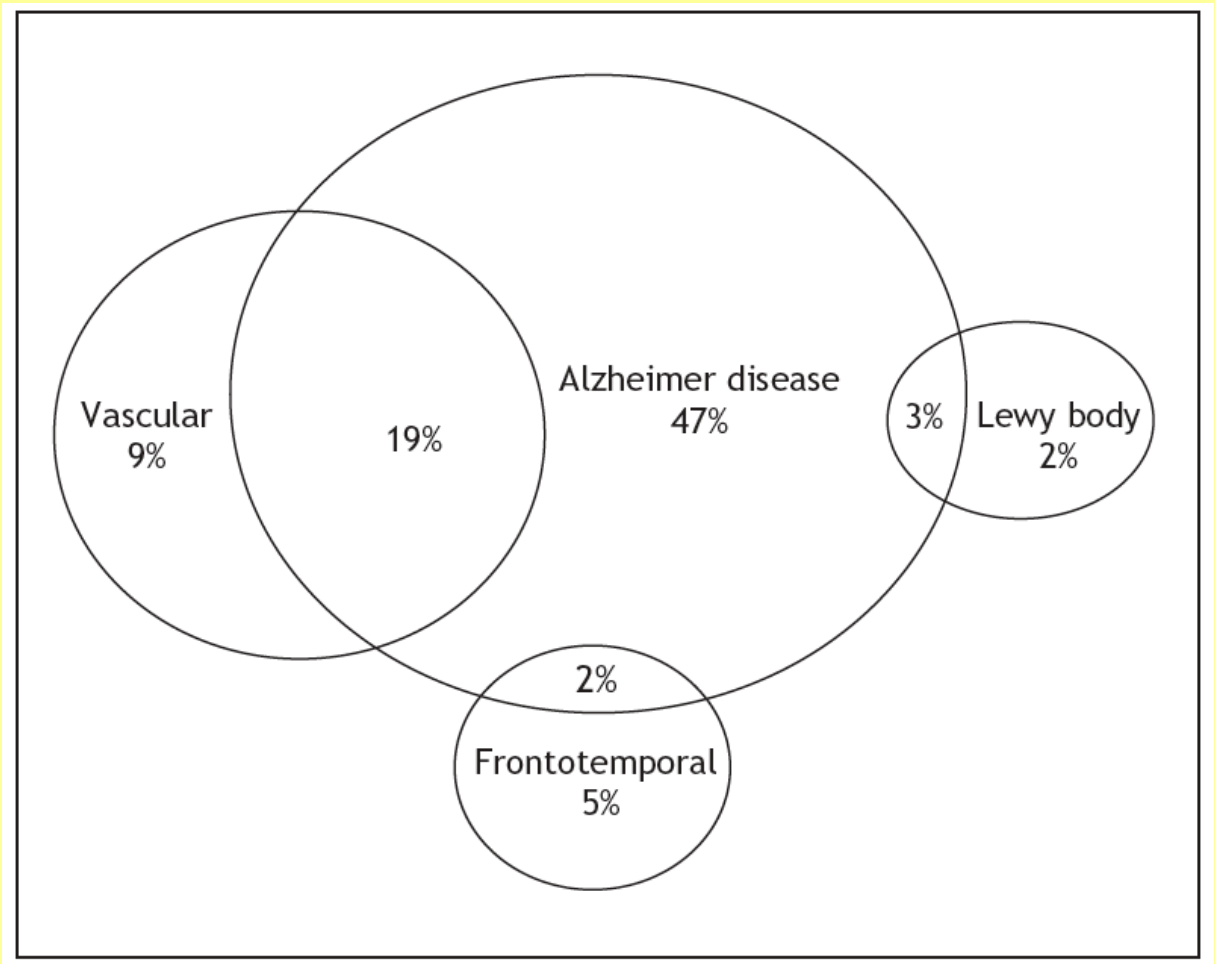
A. The development of multiple cognitive deficits manifested by both:

1. Memory impairment (impaired ability to learn new information or to recall previously learned information).
2. One or more of the following cognitive disturbances:
   - aphasia (language disturbance)
   - apraxia (impaired ability to carry out motor activities despite intact motor function)
   - agnosia (failure to recognize or identify objects despite intact sensory function)
   - disturbance in executive function (e.g., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria A1 and A2 each cause major impairment in social or occupational functioning and represent a substantial decline from a previous level of functioning.

C. The deficits do not occur exclusively during the course of a delirium.

Subtypes of Dementia
(Canadian Population)



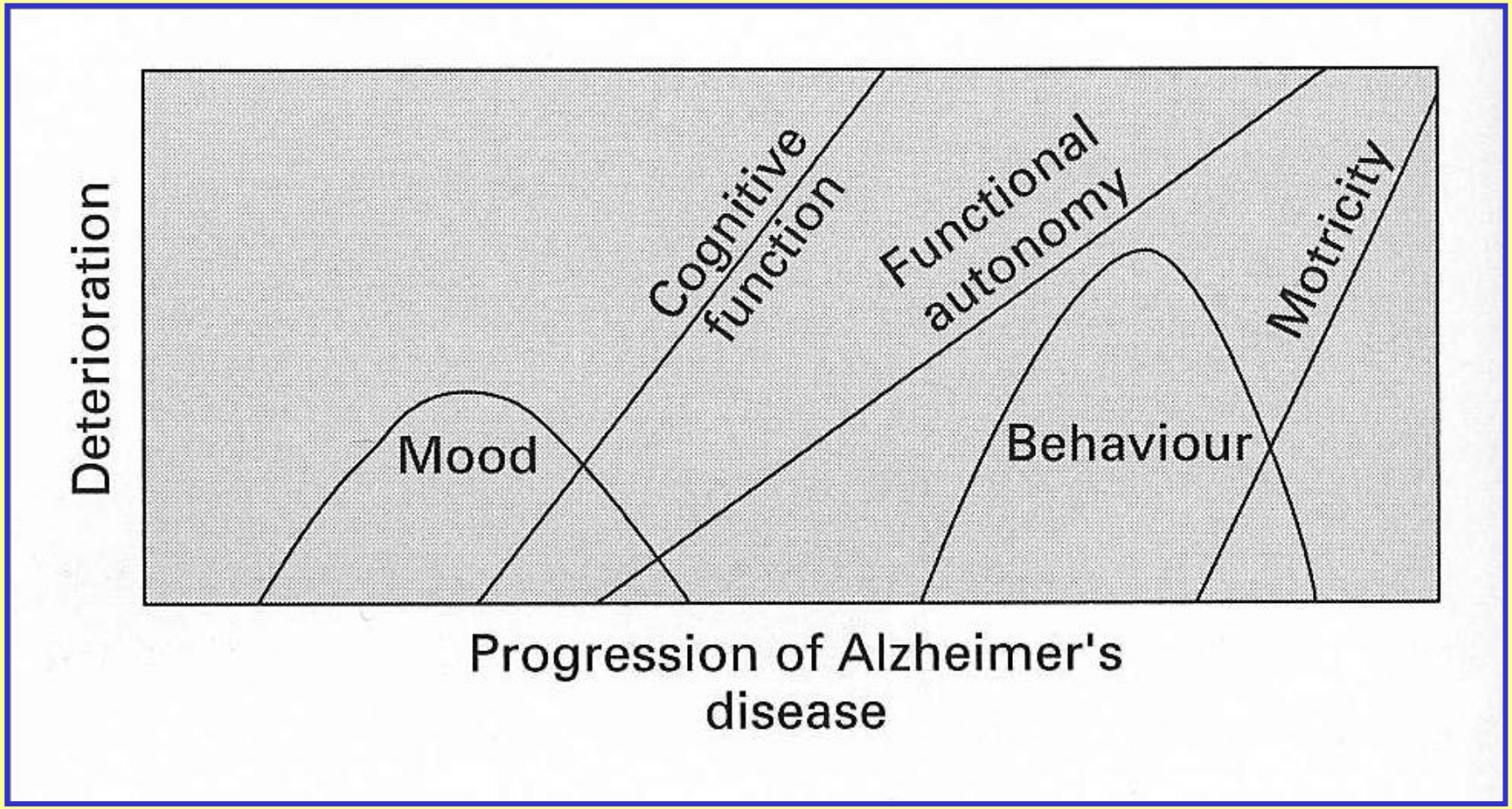
Trial population:

High specificity of diagnostic criteria more important than high sensitivity !!!

Clinical Milestones in Alzheimer‘s Disease

- Emergence of cognitive symptoms
- Conversion from amnestic MCI/preclinical dementia to diagnosable dementia
- Loss of „instrumental acitivities of daily living“
- Further deterioration in cognitive and functional domains to states worser than expected
- Emergence of behavioural abnormalities
- Nursing home placement
- Loss of self-care ADL
- Death

Disease Course and Symptoms in the different domains

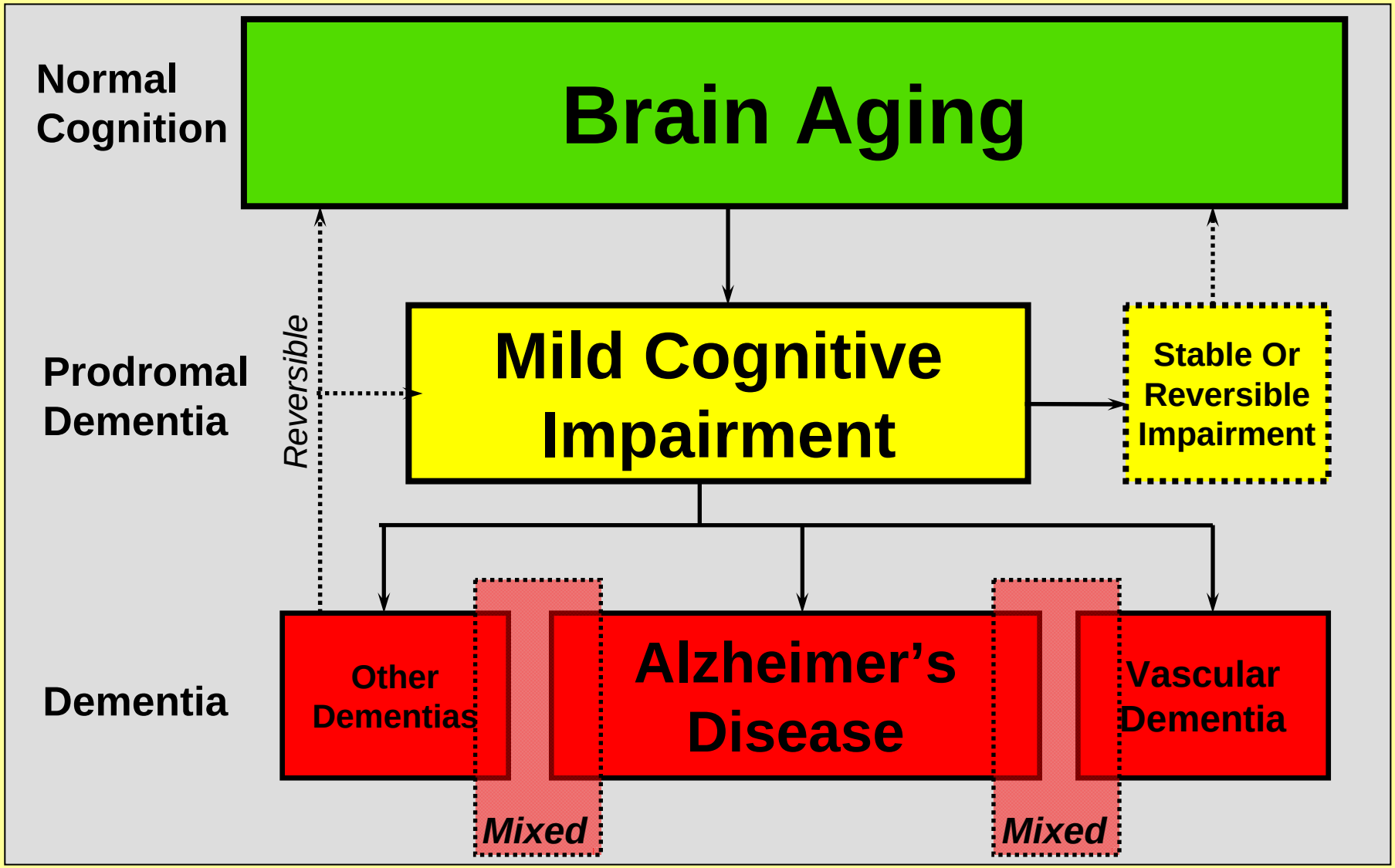


modified from: Gauthier, S: Trial Designs and Outcome in Dementia Therapeutic Research, Taylor & Francis 2006, p.38

Which population do we study ?

- **Diagnostic criteria**
  - MCI / aMCI / preclinical DAT / prodromal DAT
  - DAT
- **Severity**
  - Mild
  - Moderate
  - Severe
- **Study design**
  - Assessment tools
  - Domains of assessment
  - Duration of trials
  - Placebo/active comparator/add-on
  - Statistical evaluation
  - Clinical relevance

MCI is Prodromal Dementia ?



Clinical Heterogeneity of MCI

MCI
Amnestic

→ **Alzheimer's disease**

MCI
Single non-memory domain
or
Multiple domains slightly impaired

→
- Normal Aging
- Alzheimer's disease
- Vascular dementia
- Frontotemporal dementia
- Lewy body dementia
- Primary progressive aphasia
- Parkinson's disease

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Revision of Diagnostic Criteria
Dubois B, Feldman HH, Jucova C et al. 2007

- **Core diagnostic Criterion:**
  Early and significant episodic memory impairment

- **At least one supportive criterion of**
  - **MTL atrophy shown with MRI**
  - **Abnormal CSF (amyloid-ß, tau, phospho-tau)**
  - **Specific pattern shown with PET**
  - **Proven DAT mutation**

- **Validation studies necessary !!!**

Possible Cornerstones in the Treatment of Patients with Dementia

- **NfG on Medicinal Products for Treatment of Alzheimer‘s Disease**
  - **Symptomatic Improvement**
  - **Slowing or arrest of progression**
  - **Primary prevention**

NEW: http://www.emea.europa.eu

Alzheimer's Disease: Efficacy (Symptomatic Improvement)

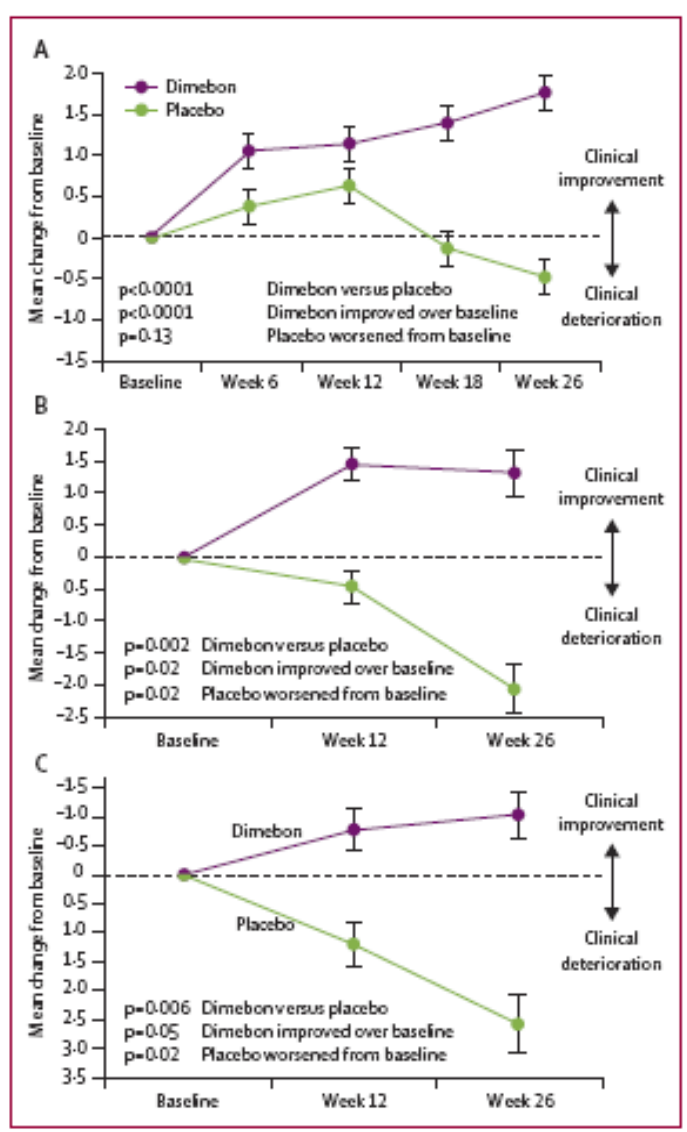
- 2 primary Endpoints
  - mandatory: **cognitive** domain
    functional domain
  - both endpoints should show significant differences
- Response criteria for clinical relevance:
  proportion of patients with meaningful benefit ?
- Duration of treatment: at least 6 months
- secondary endpoints
  - global domain
  - additional symptoms

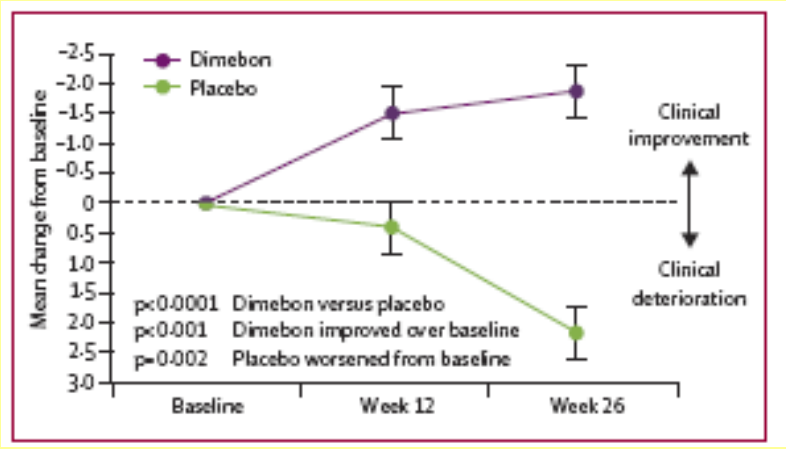
Dimebon in mild to moderate AD

MMSE

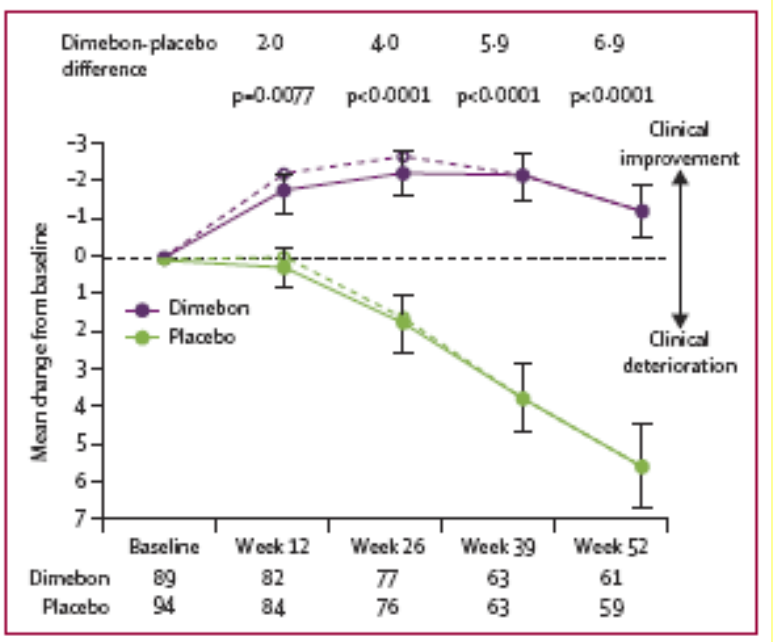
ADCS-ADL

NPI





ADAScog



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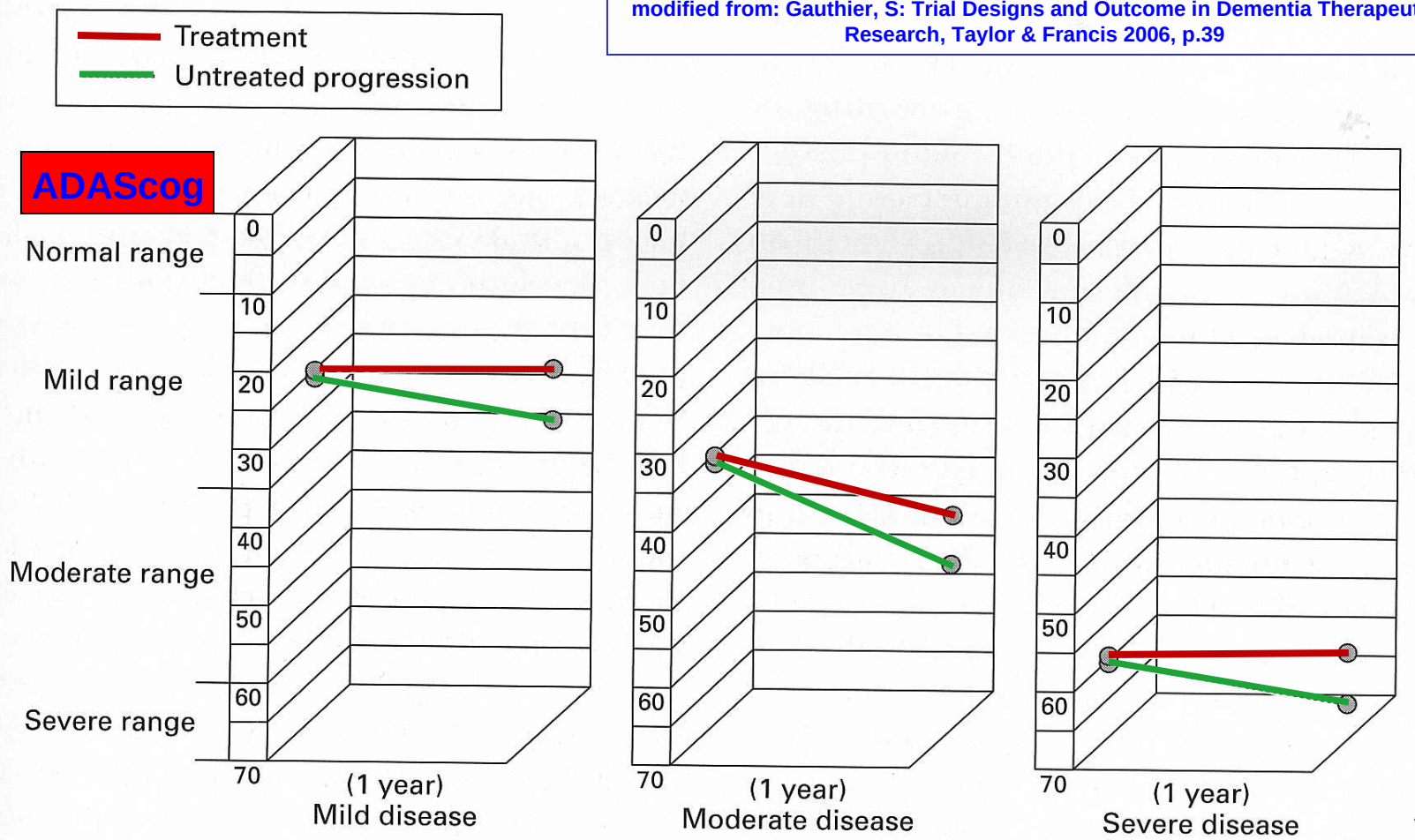
Scales used in Clinical Trials

- ***Cognition***
  - ADAScog
  - Neuropsychological Test Battery (NTB)
  - Severe Impairment Battery (SIB)
- ***Functional***
  - Alzheimer Disease Cooperative Study ADL Scale (ADCS-ADL)
  - Alzheimer‘s Disease Functional Assessment and Change Scale (ADFACS)
  - Disability Scale in Dementia (DAD)
  - Nurses Observation Scale for Geriatric Patients (NOSGER)
- ***Global***
  - CIBIC-plus

Deterioration in Cognition in different stages of Disease Severity

modified from: Gauthier, S: Trial Designs and Outcome in Dementia Therapeutic Research, Taylor & Francis 2006, p.39



Assessment of overall benefit

- **Response-Criteria:**

  e.g.. ADAScog ≥ 4 + Score ≤ 3 of CIBIC + no change in DAD

- **Effect size**

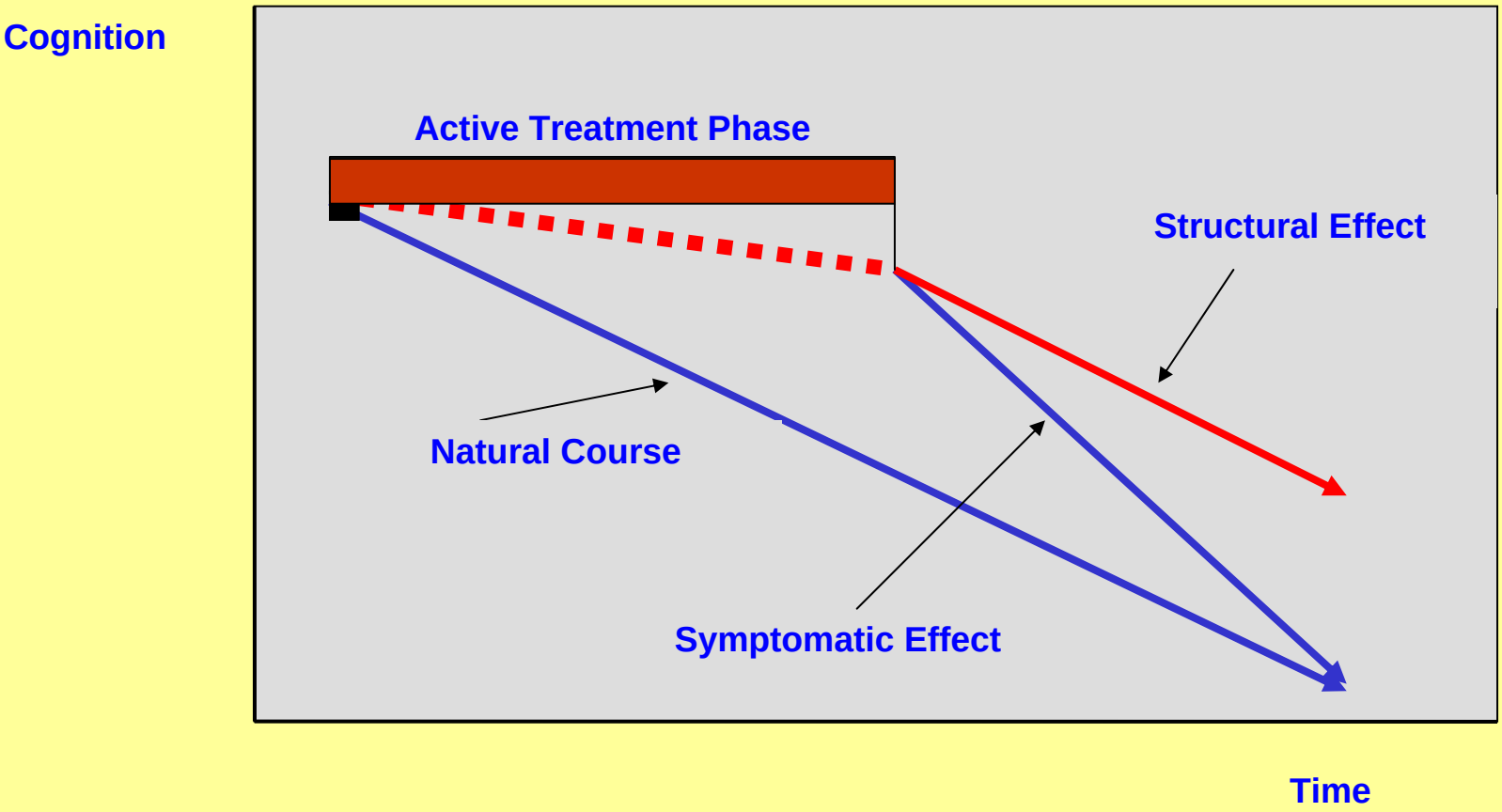
- **Numbers Needed to Treat**

  (e.g. patients showing improvement of ADAScog ≥ 4)

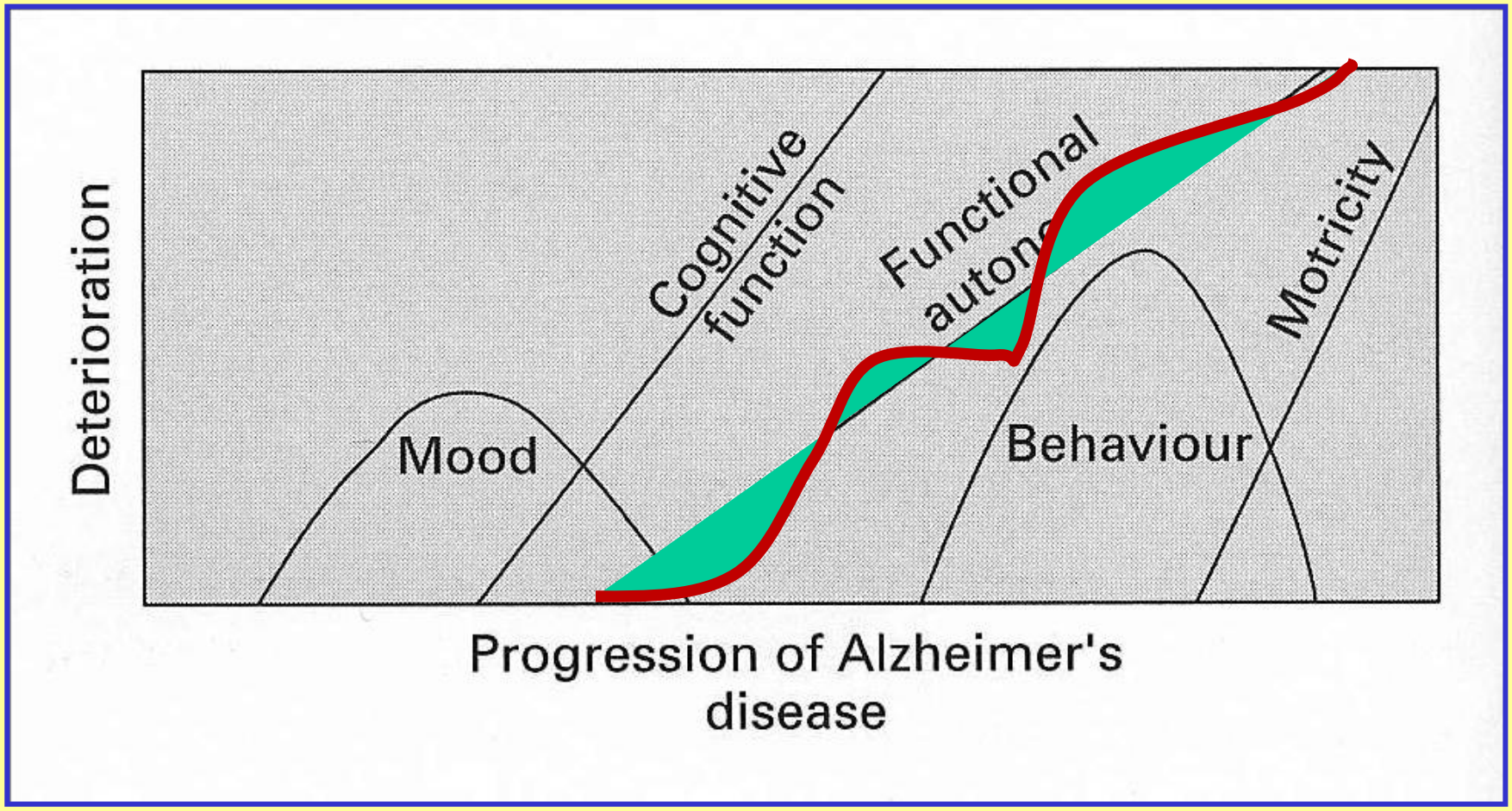
Alzheimer's Disease:
Efficacy (Disease Modification)

- 2 primary Endpoints
  - mandatory: **cognitive** domain
    functional domain
  - both endpoints should show significant differences
- Response criteria for clinical relevance:
  proportion of patients with meaningful benefit ?
- Duration of treatment: 18 months (?)
- secondary endpoints
  - global domain
  - Biomarkers
    - **e.g. serial volumetric MRI**
  - Quality of Life
  - additional symptoms

„Randomized withdrawal design“



Disease Course and Symptoms in the different domains



modified from: Gauthier, S: Trial Designs and Outcome in Dementia Therapeutic Research, Taylor & Francis 2006, p.38

Issues with Trials in Early Phases

- **Clinical Endpoints of interest may be difficult to use**
  - **Long follow-up measurement**
  - **Expensive measurements**
  - **Rare events**
  - **High drop-out rates**
  - **…..**

Biomarkers the way out?

- **Surrogate (replacement) Endpoint**
  - **Easier/quicker to measure**
  - **Reduce trial duration, size and expenditures**
  - **Should be measured accurately and reproducible**
  - **Change in proportion to what it represents**

Biomarkers can be used as tools to

- Understand the biology of a disease
- Understand the effects of medicinal products
- Provide information on sub-populations of patients that might respond to treatment or be susceptible to side effects (individualized medicine)
- Developing better diagnostics and medicinal products
- Improve methodology of clinical trials

Ideal Surrogate Endpoints

Fleming TR, Ann Int Med, 1996

- …proposed surrogate endpoint must ***not merely be a correlate*** of the true clinical outcome
- effect of intervention on a ***valid*** surrogate endpoint must **reliably predict the effect** on a clinical outcome of interest
- treatment effect on the clinical outcome should be explained by its effect on the surrogate marker

How to validate a „Surrogate Endpoint“

Bucher HC et al., JAMA (1999) 282, 771-778

(1) Plausible connection between basic science and clinical trials

(2) Is there a strong, independent, consistent association between surrogate endpoint and clinical outcome (necessary, not sufficient)

(3) Evidence from randomized trials that improvements in the surrogate endpoint leads consistently to improvement of the target outcome

(4) Large, precise, and lasting treatment effects

(5) Are the likely benefits worth the potential harms and costs

Validierung	Therapie	Indikation	Einfluss auf Surrogat-endpunkt	Einfluss auf klinischen Endpunkt
validiert	Antihypertensiva	Hypertonie	Blutdruck ↓	Schlaganfälle und Myokardinfarkte ↓
	Statine	Hyperlipidämie	LDL-Cholesterol ↓	Myokardinfarkte ↓ Überleben ↑
	Orale Antidiabetika	Diabetes	Hb-A1c ↓	kardiovaskuläre Komplikationen ↓
	Bisphosphonate	postmenopausale Osteoporose	Knochendichte ↑	Frakturen ↓
	Antiretrovirale Substanzen	AIDS	$CD4^+$-T-Lympho-zytenzahl ↑	Krankheitsprogres-sion ↓
nicht validiert, bzw. fehl-geschlagen	Encainid, Flecainid, Moricizin (Klasse – 1C-Antiarrhythmika)	ventrikuläre Rhyth-musstörungen nach Myokardinfarkt	ventrikuläre Extrasystolen ↓	2,5-fache Erhöhung der Mortalität
	Milrinon (Phosphodiesterase-hemmer)	Herzinsuffizienz	verbesserte kardiale Funktion (Herzindex ↑)	28%ige Erhöhung der Mortalität
	Hochdosis-Diuretikatherapie	Hypertonie	Blutdruck ↓	KHK-Risiko ↑
	Fibrate	Hyperlipidämie	Cholesterol ↓	Gesamtmortalität ↑
	Dexfenfluramin	Adipositas	Gewichtsverlust	Herzklappenschäden, pulmonale Hypertonie
	Natriumfluorid	postmenopausale Osteoporose	Knochendichte ↑	Frakturrate ↑
	Vakzin-Studie mit AN1792	Alzheimer-Demenz	Hirnatrophie erhöht statt vermindert	Kognition gebessert, Meningoenzephalitis

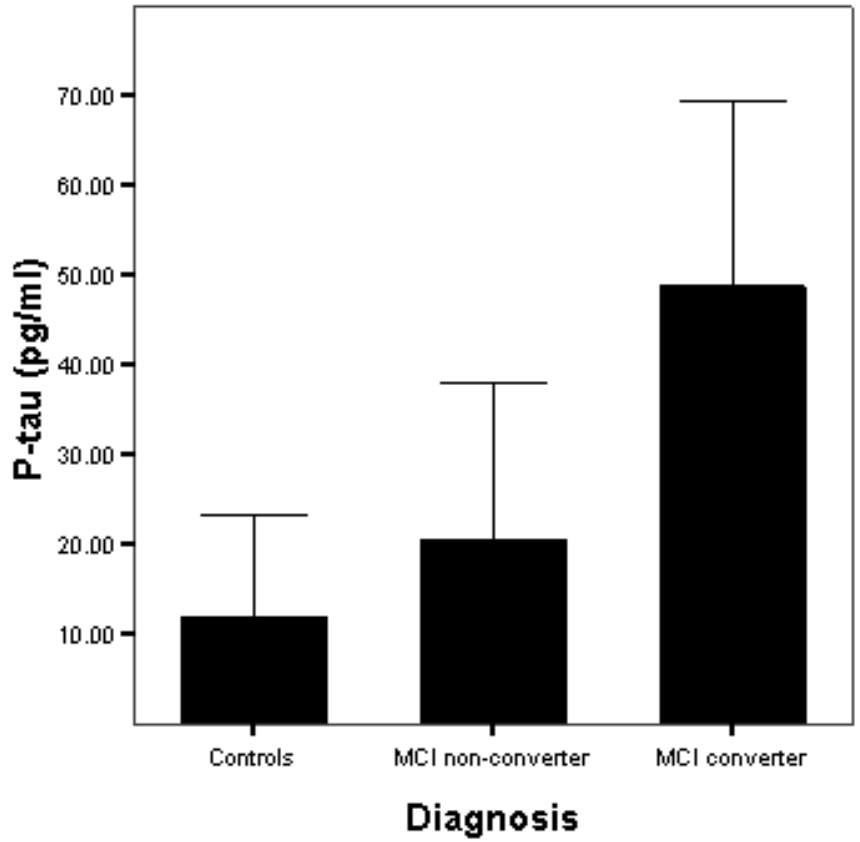
CSF-Biomarkers

- **β-Amyloid I-42** ↓
  - Differentiate from „normal aging“
  - No prediction of time to conversion
  - No correlation with severity
  - Discrimination DAT to other dementias difficult (recent improvement ?: Bibl M, Brain (2006) 129: 1177-1187)

- **total-τ-Protein** ↑ **phospho-τ-Protein** ↑
  - Differentiate from „normal aging“
  - No prediction of time to conversion
  - No correlation with severity
  - Discrimination DAT to other dementias difficult
  - May change with treatment (Gilman S, Neurology (2005) 64: 1553-1562)

phospho-tau and MCI

4 centers, n: 144 - 56 HC, 88 MCI (43 conv / 45 non-conv)



from:

Ewers M et al.

Neurology, 69, 2205-2212 (2007)

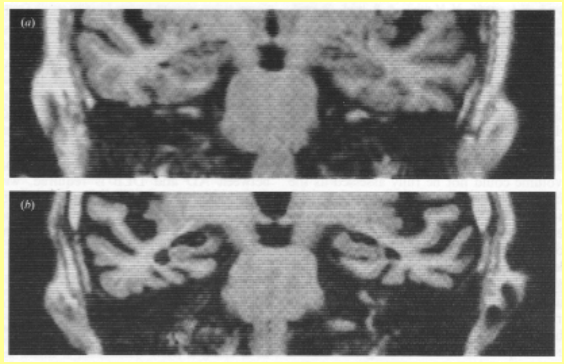
A priori cut off point:

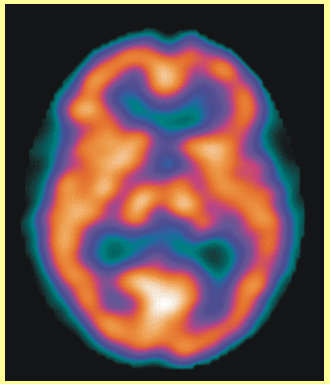
27,32pg/ml

Centers: München, Heidelberg, Amsterdam, Pitea

Surrogate Endpoints: Neuroimaging

- **Structural MRI**
  - Hippocampus
  - Entorhinal cortex
- **Functional Imaging**
  - PET/SPECT
  - MRS
  - fMRI





- **Links need to be established:**
  - Imaging tool and desired clinical outcome
  - Imaging tool and disease modification

Imaging of Amyloid Load by PET

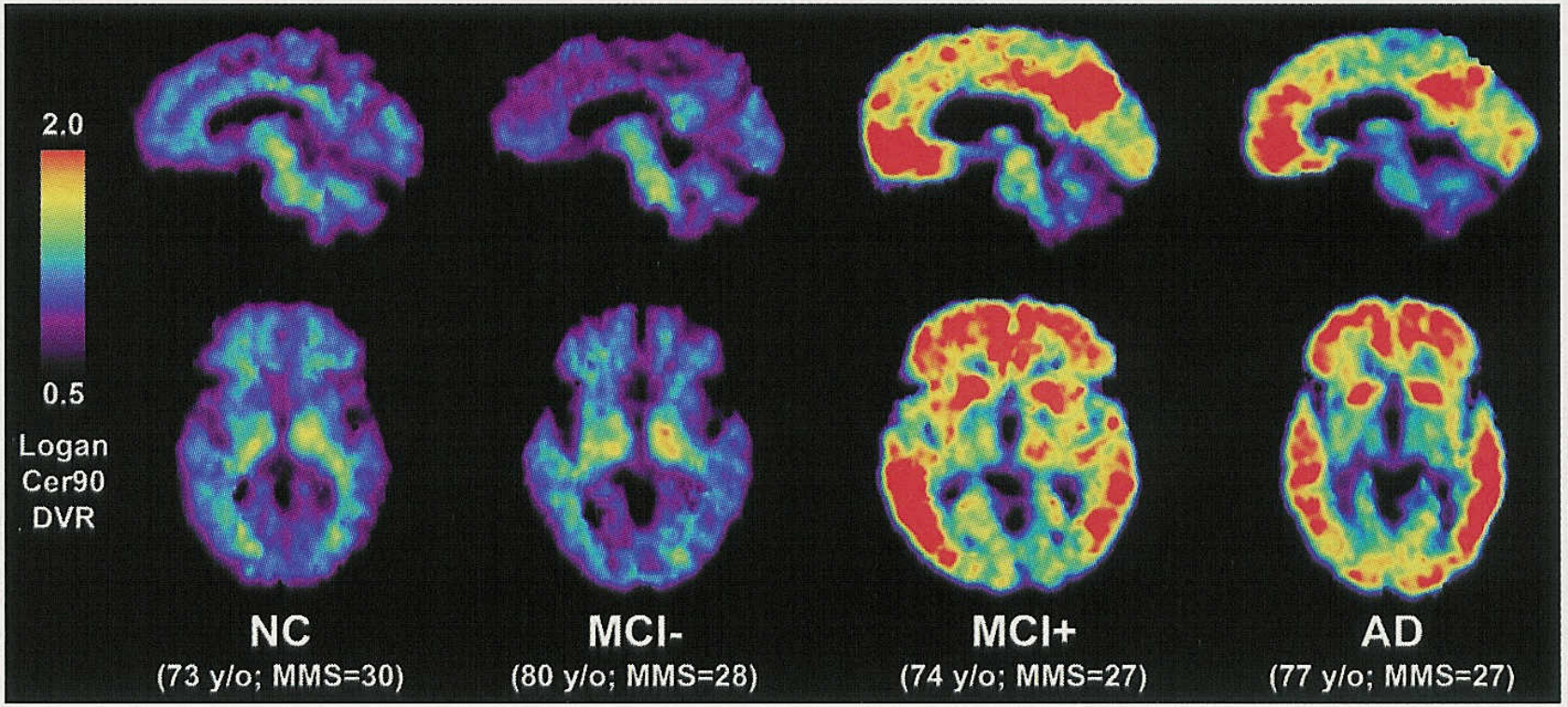
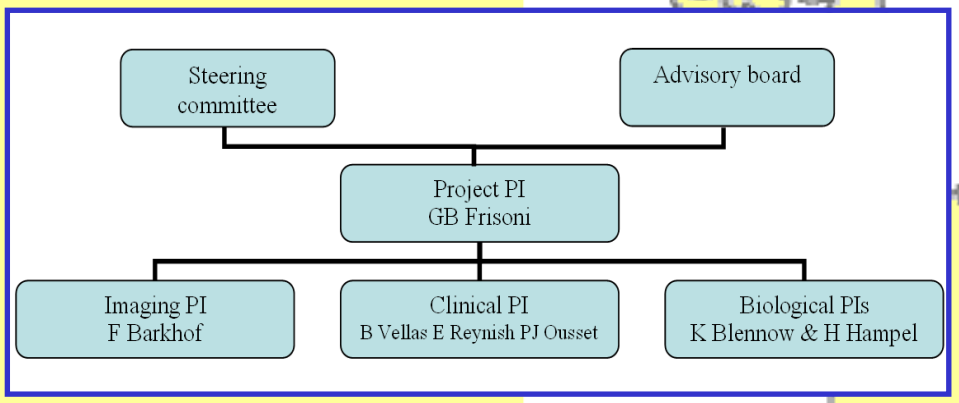


Figure 1 PET images produced using Pittsburgh Compound-B (PIB) shown in sagittal (top) and transaxial (bottom) views. Shown from left to right are a cognitively normal control (NC), an MCI subject with no evidence of amyloid deposition (MCI–), an MCI subject with heavy amyloid deposition (MCI+), and a case with mild Alzheimer disease (AD). *Courtesy University of Pittsburgh Amyloid Imaging Group.*

from: Blennow & Zetterberg:, Nature Medicine 2006, 12, 753-754

Pilot E-ADNI
Phase III biomarker validation



- Stockholm – Wahlund/Winblad
- Göteborg – Blennow Bio co-PI
- Copenhagen - Waldemar
- Amsterdam – Barkhof MR imag PI
- Munich – Hampel Bio co-PI
- Brescia – Frisoni Project PI
- Toulouse – Vellas Clinical PI
- Roma – Rossini

Regulatory view: still no sufficiently validated surrogates for phase III pivotal studies in patients with Alzheimer's disease available!

- Cerebrospinal fluid markers (e.g. phospho-τ ⬆ and β-Amyloid I-42 ⬇)
  - helpful as trait markers with high sensitivity and specificity
  - yet no value as state markers
- Brain imaging (e.g. MRI of medial temporal lobe)
  - helpful as trait markers for enrichment of populations at risk
  - serial MRI helpful as state marker
  - can be used as endpoint in dose finding
  - proof of concept studies
  - as secondary endpoint in pivotal studies
- Brain imaging (e.g. PET-amyloid imaging or regional glucose metabolism)
  - helpful as trait marker
  - yet no value as state marker

„Disease Modification“

For regulatory purposes a disease modifying effect will be considered when the pharmacologic treatment **delays the underlying pathological or pathophysiological disease processes and when this is accompanied by an improvement of clinical signs and symptoms of the dementing condition**. Consequently a true disease modifying effect cannot be established solely based on clinical outcome data, such a clinical effect must be accompanied by strong supportive evidence from a biomarker programme.

„Two step approach“

If in a **first step delay in the natural course of progression of the disease based on clinical signs and symptoms** of the dementing condition can be established, this may be acceptable for a limited claim, e.g. delay of disability. If these results are supported by a **convincing package of biological and/or neuroimaging data**, e.g. showing delay in the progression of brain atrophy, a full claim for disease modification could be considered.

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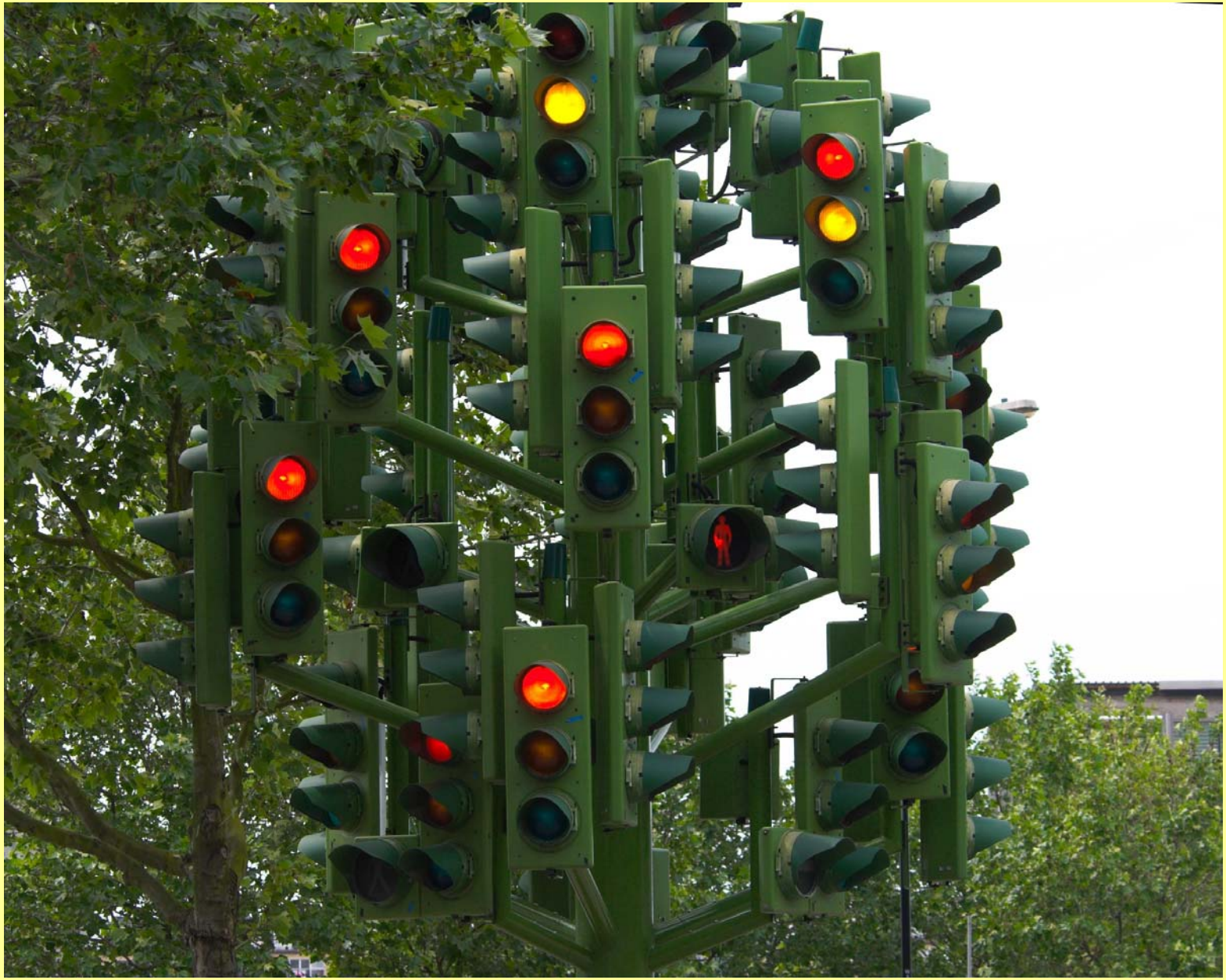
„Early and Ongoing Dialogue“

- **National:**
  - **Contact with Learned Societies**
  - **Scientific Advice**
  - **Ad Hoc-Expert-Meetings**
- **European/CHMP:**
  - **Efficacy Working Group**
  - **Scientific Advice Working Group**
  - **Scientific Advisory Groups (SAG‘s)**
  - **Ad Hoc Expert Working Groups**
  - **Ad Hoc Expert Groups**
- **Dialogue between EMEA-FDA**



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