Alzheimer’s Disease Prevention and Treatment 2014

Kathleen A. Welsh-Bohmer Ph.D.
Professor of Psychiatry & Director
Joseph and Kathleen Bryan
Alzheimer’s Disease Research Center (Bryan ADRC)
Department of Neurology

January 30, 2014
Disclosures

National Institute on Aging- P30-AG028377, R01- AG11380, P50-AG05128
Takeda, Merck, GSK, and Zinfandel Pharmaceutical Company Support

Duke University-
Bryan Neurobiology Building
Objectives

- Review the progress and challenges in developing effective treatments and preventive therapies for the chronic, neurodegenerative disease, Alzheimer’s disease (AD)

- Discuss the new diagnostic criteria for AD and the role of biomarkers in this context for enhancing diagnostic reliability and speeding drug discovery;

- Consider the major efforts underway to develop effective treatments for preventing or delaying symptom onset in AD and the implications of what we will learn from this work for future patient care.
Alzheimer’s Disease
Current projections & Economic Impact

5.3 million Americans with Alzheimer’s

170,000 North Carolinians

200 billion dollars in US annual costs

>15 million unpaid caregivers
Without a cure....

13.8 million + Americans affected by 2050 (Alz Assoc 2013)

1.1 Trillion annually (Alz Assoc, 2013)

Brief History of AD Therapeutics

- 1901: Alzheimer describes index case
- 1976: Alzheimer’s disease (AD) recognized as a common condition of late life (Katzman 1976)
- 1970's: Cholinergic hypothesis suggests treatment strategy
  - 1993: Tacrine is approved & similar drugs follow
    - 1995 Donepezil
    - 1996 Galantamine
    - 1997 Rivastigmine
- 2003: Second therapeutic class for AD
  - Memantine
- No new FDA approved medications since 2003

Auguste D: Index case described by Alois Alzheimer circa 1901

Aisen et al., 2013
Limitations to Current Treatments Options

- Effects are modest with no effect on underlying disease progression
- Cholinesterase inhibitors: Donepezil, rivastigmine, and galantamine
  - Mild to Moderate AD
  - No evidence that prevent or delay AD
  - Tolerability is limited by gastrointestinal side effects (nausea, vomiting, diarrhea, weight loss)
- NMDA receptor antagonist: Memantine
  - Improved tolerability profile but hallucinations, delusions, and agitation can occur & indicated only for moderate-to-severe AD
- Need for well tolerated AD therapies with broad & enduring clinical benefits across multiple domains including cognition, function, & behavior
Disease Modification: Altering the Hallmark Brain Pathology of Alzheimer Disease: Amyloid Plaques & Neurofibrillary Tangles

*Beta amyloid* “plaques” → Neurofibrillary Tangles (*p*-Tau protein) → Atrophy
Disease-Modifying Strategies

APP $\xrightarrow{\beta$-secretase} \alpha\beta \xrightarrow{\gamma$-secretase} Neuron death

secretase modulators

anti-inflammatories
oxidative stress
neuroprotectants

immunotherapy
amyloid binders

Courtesy Paul Aisen MD, UCSD
Recent AD Trials

- Negative Phase III:
  - Xaliproden (neuroprotection)
  - Tramiprosate (amyloid anti-aggregation)
  - Tarenflurbil (gamma secretase inhibitor)
  - Rosiglitazone (metabolic, anti-inflammatory)
  - Leuprolide (endocrine)
  - Dimebon (modulate Aβ metabolism)
  - Semagacestat (gamma secretase inhibitor)
  - Bapineuzumab, solanezumab (monoclonal anti-amyloid antibodies)
  - Intravenous Immunoglobulin IVIg (antibodies to oligomeric & fibrillar AB)
BACKGROUND: Alzheimer’s Treatment

Australian Imaging, Biomarker & Lifestyle Study (AIBL): Amyloid deposition by PIB and by autopsy precedes AD dementia by 15 years

CC Rowe et al, Neurobiol Aging, 2010
Alzheimer’s Disease - Treatment Challenges

Failure of treatment trials to date
(symptomatic treatment and/or disease modification)

**Stage** - AD dementia may be too late for effective intervention

**Underlying biology:** Failure to effectively address the underlying pathophysiology

**Outcomes & Measurement approaches**
Detectable change may be very small at late stage of disease

New research dimensions
(focus on ‘pre-symptom & early symptom stages of AD’)

- Search for new biomarkers to facilitate early diagnosis and evaluate efficacy in different stages of drug development
- Search for new ‘early diagnostic criteria’ and their validation
- Development of new validated clinical assessment tools sensitive to change in different dimensions in early AD
- Drug development for prevention, early intervention and disease modification in pre-symptomatic/ early symptomatic stages of AD
Treatment to Delay/Prevent AD Onset

- **Latent Stage** ("1° prevention")
- **Prodromal AD/MCI** ("2° prevention")
- **Threshold**
- **Symptomatic Stage** (Treatment)

Combines advances in clinical medicine & AD biomarkers
CSF Biomarkers of AD

- Optimal biomarker is a chemical or structural indicator that can be objectively measured and tracks a normal biological process or response to therapy
- AD characteristic changes
  - $\text{A}^\beta_{1-42}$ peptide,
  - total tau protein & phosphorylated tau
- Biochemical changes in brain reflected in the cerebrospinal fluid (CSF)

$^1$proteins found in plaques and tangles
CSF Biomarkers and Incipient Alzheimer Disease in Patients With Mild Cognitive Impairment

Niklas Mattsson, MD
Henrik Zetterberg, MD, PhD
Oskar Hansson, MD, PhD
Niels Andreasen, MD, PhD
Lucilla Parnetti, MD, PhD
Michael Jonsson, MD
Sanna-Kaisa Hernukko, PhD
Wiebe J. van der Flier, PhD
Marina A. Blankenstein, PhD
Michael Ewers, PhD
Kenneth Rich, MD
Einar Kaiser, MD
Marcel Verbeek, PhD
Magda Tsofaki, MD, PhD

Context: Small single-center studies have shown that cerebrospinal fluid (CSF) biomarkers may be useful to identify incipient Alzheimer disease (AD) in patients with mild cognitive impairment (MCI). However, large-scale multicenter studies have not been conducted.

Objective: To determine the diagnostic accuracy of CSF β-amyloid1-42 (Aβ42), total tau protein (T-tau), and tau phosphorylated at position threonine 181 (p-tau) for predicting incipient AD in patients with MCI.

Design, Setting, and Participants: The study had 2 parts: a cross-sectional study involving patients with MCI and controls to identify cut points, followed by a prospective cohort study involving patients with MCI, conducted 1990-2007. A total of 750 individuals with MCI, 529 with AD, and 304 controls were recruited from 12 centers in Europe and the United States. Individuals with MCI were followed up for at least 2 years or until symptoms had progressed to clinical dementia.

Main Outcome Measures: Sensitivity, specificity, positive and negative likelihood ratios (LRs) of CSF Aβ42, T-tau, and p-tau for identifying incipient AD.

Results: During follow-up, 271 participants with MCI were diagnosed with AD and 59 with other dementia. The Aβ42 assay in particular had considerable inter-rater variability. Patients who developed AD had lower median Aβ42 (356, range, 96-1075)

Prevalence and prognostic value of CSF markers of Alzheimer’s disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study


Mattson et al., 2009. JAMA 302, 385-93; Visser et al., 2009 Lancet Neurology 8: 619-27
## CSF Biomarkers in MCI & Incipient AD

### Diagnostic Accuracy of the Individual & Combined Biomarkers Applied to Patients With MCI Who Developed AD

<table>
<thead>
<tr>
<th>Biomarker Test</th>
<th>Sensitivity% (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>Positive LR (95% CI)</th>
<th>Negative LR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ42</td>
<td>79 (74-84)</td>
<td>65 (61-69)</td>
<td>2.3 (2.0-2.6)</td>
<td>0.32 (0.28-0.36)</td>
</tr>
<tr>
<td>P-tau</td>
<td>84 (80-88)</td>
<td>47 (42-52)</td>
<td>1.6 (1.4-1.8)</td>
<td>0.34 (0.31-0.37)</td>
</tr>
<tr>
<td>T-tau</td>
<td>86 (82-90)</td>
<td>56 (51-61)</td>
<td>1.9 (1.7-2.2)</td>
<td>0.26 (0.23-0.29)</td>
</tr>
<tr>
<td>Aβ42+ P-tau+ T-tau(^a)</td>
<td>83 (78-88)</td>
<td>86 (84-92)</td>
<td>7.0 (5.7-8.5)</td>
<td>0.17 (0.14-0.21)</td>
</tr>
</tbody>
</table>

Moderate increase in risk of disease with all three markers. Absence of markers leads to moderate decreased likelihood of disease. 12 Centers. Sample 750 MCI; 529 AD; 304 controls

\(^a\) Equation applied for all other MCI specificity 72%. Positive L-R=3.0, negative LR= 0.24, ppv 62%, npv 88%

Hypothetical Model of AD Biomarkers

- Amyloid-β accumulation (CSF/PET)
- Synaptic dysfunction (FDG-PET/fMRI)
- Tau-mediated neuronal injury (CSF)
- Brain structure (volumetric MRI)
- Cognition
- Clinical function

Clinical Disease Stage

Normal
Preclinical
MCI
Dementia

Staging Framework for Pre-Clinical AD

Stage 1
Asymptomatic amyloidosis
- High PET amyloid tracer retention
- Low CSF Aβ1-42

Stage 2
Amyloidosis + Neurodegeneration
- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/Hippocampal atrophy on sMRI

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

MCI → AD dementia
2013 Launching Alzheimer’s Disease Prevention Studies

- Dominantly Inherited Alzheimers Network (DIAN) Trial Unit (DIAN-TU), and
- Alzheimer’s Prevention Initiative (API) examine compounds to prevent AD onset and cognitive decline in genetic forms of the disease (young age of onset)

- Alzheimer’s Disease Cooperative Study Anti-Amyloid Treatment in Asymptomatic AD (ADCS-A4 Study) will examine treatments in individuals who show increased amyloid accumulation in their brains on amyloid imaging studies
- TOMMORROW Study examines individuals at high and low genetic risk (algorithm: age, APOE, TOMM40)
Dominantly Inherited Alzheimer’s Disease Network Study

- 2007 DIAN Cohort developed
- 2011 transitioned to the DIAN Trials Unit (TU)
- Mission: design and manage interventional trials in DIAN participants
Genetic enrichment for risk of AD (DIAN)

- Rare families with mutations in the presenillin gene
  - $PS1\ E280A$
- Inevitable early onset AD (age<45) in all individuals who inherit the gene mutation
- < 1% of all AD cases

DIAN-TU Biomarker Trial Design

- Placebo controlled, double-blinded, biomarker outcome trial
- 15 to +10 years of parental age of onset; asymptomatic (>50%) to mild dementia (CDR 0.5-1)
- 3-arm trial:
  - 2 active drugs vs. 1 pooled placebo
  - 3:1 Active:Placebo
- 120 mutation carriers
  - 90 Active drug
  - 30 placebo
- Estimated 90 non-carriers (placebo)

Drug treatment duration = 2 years
Initial Compound Selection

- **Solanezumab (Lilly)**
  - Humanized monoclonal antibody to Aβ
  - Good Phase III safety profile (little Amyloid Related Imaging Abnormalities ARIA)
  - Affect clearance
  - Evidence for Aβ binding in CSF and plasma

- **Gantenerumab (Roche)**
  - Totally human monoclonal antibody to Aβ;
  - Presumably lower ARIA profile, less immunogenicity; good Phase II safety data
  - Targets soluble and fibrillar forms of amyloid
  - Evidence of Aβ binding via PIB imaging (Ostrowitzki et al, Arch Neurol 2012)
### Study Drugs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>TYPE</th>
<th>Biomarker Outcomes</th>
<th>Downstream Biomarkers</th>
<th>EXPLORATORY Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solanezumab</td>
<td>Anti-Aβ antibody (soluble Aβ)</td>
<td>CSF total and free Aβ40 and Aβ42</td>
<td>CSF tau, ptau181 vMRI</td>
<td>FDG PET and fcMRI</td>
</tr>
<tr>
<td>(LILLY)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gantenerumab</td>
<td>Anti-Aβ antibody (aggregated Aβ)</td>
<td>PET PiB</td>
<td>CSF tau, ptau181 vMRI</td>
<td>FDG PET and fcMRI</td>
</tr>
<tr>
<td>(ROCHE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2 y biomarker outcome, then 3 y cognitive outcome for most promising drug(s) Announced October 10, 2013 will study a BACE inhibitor (Lilly) as well.
1. Preclinical AD treatment/biomarker development trials in people who, based on their age & genetic background, are at the highest imminent risk of AD symptoms
   - Autosomal dominant AD mutation carriers close to their estimated age at clinical onset (age 30+)
   - \( APOE \varepsilon 4 \) carriers close to their estimated age at clinical onset
2. Prevention registries to support these & other trials
   - Goal: ~3,300 \( E280A \ PSEN1 \) mutation kindred members in Antioquia, Colombia
   - Goal: ~250,000 persons, outreach efforts starting in North America [www.endALZnow.org](http://www.endALZnow.org)

1. To evaluate an anti-amyloid therapy in the preclinical treatment of autosomal dominant AD
2. To provide a better test of the amyloid hypothesis
3. To help qualify biomarkers for use as reasonably likely surrogate endpoints in preclinical AD trials
4. To provide a foundation for other preclinical AD trials
5. To complement, support & benefit from other prevention initiatives (including the TOMMORROW study & planned DIAN, A4 trials)
6. To provide a resource of data & samples to the scientific community after the trial is over
7. To give persons at highest imminent risk for AD access to investigational treatments
8. Set a platform for more trials to come- rapid turn key to test promising compounds
API Preclinical ADAD Treatment/Biomarker Development Trial

Double-blind, placebo-controlled trial for up to 60 months
Humanized monoclonal antibody to Aβ 1-40 and 1-42: crenezumab 300 mg SC q 2 weeks

Primary endpoint: change in the API composite cognitive score
24-month interim analysis using several cognitive/clinical endpoints, & florbetapir PET, FDG PET, MRI, CSF

300 PSEN1 E280A kindred participants from Colombia, plus
a small number of other autosomal dominant EOAD kindred participants from the US
Anticipated start date: second half of 2013/ early 2014
API APOE4 Trial Aims

1. To evaluate an anti-amyloid therapy in unimpaired APOE ε4 homozygotes using cognitive (primary) and biomarker (secondary) endpoints
2. To provide a better test of the amyloid hypothesis
3. To help qualify biomarkers for use as reasonably likely surrogate endpoints in preclinical AD trials
4. To determine the initial and longer-term impact of disclosing a person’s APOE genotype in the emerging era of AD prevention research
5. To provide a resource of data & samples to the scientific community after the trial is over
6. To give persons at increased risk for AD access to investigational treatments
7. Develop guidelines for genetic enrichment for AD in asymptomatic individuals
8. To complement, support & benefit from other initiatives

- Anti-amyloid treatment and industry partner TBD
- Expected start: ~2015
Anti-Amyloid Treatment in Asymptomatic AD (A4 Trial)-
Alzheimer’s Disease Cooperative Study (ADCS)

- Enrichment based on biomarkers associated with AD
  - 30% of clinically “normal” individuals over age 65 harbor amyloid plaque pathology
- Clinically normal older individuals with Aβ accumulation demonstrate
  - functional and structural neuroimaging abnormalities,
  - subtle cognitive deficits, and
  - increased likelihood of cognitive decline similar to MCI
- Unlike autosomal dominant AD, there is a nearly unlimited pool of potential older subjects at risk of AD but much less certainty about progression to dementia

Sperling R et al NeuroMolecular Medicine 2010
**A4 Trial- Alzheimer’s Disease Cooperative Study (ADCS)**

- Prevention trial in clinically normal older individuals (> age 70) Aβ+ on PET imaging
- Goal: treat with biologically active compound for 3 years randomized, double-blind, placebo-controlled trial
  - Lilly’s monoclonal antibody solanezumab as the first therapeutic drug
- Total N=1000 (N=500 per treatment arm)
- At least 2 year additional clinical follow-up
- Include Aβ- arm (N = 500) for natural history study
- Ethics substudy: Disclosure of Aβ (J. Karlawish)
- Novel outcome development substudies:
  - computerized cognitive test battery
  - task-free functional connectivity MRI
A4 Trial- Alzheimer’s Disease Cooperative Study (ADCS)
A4 Trial- Primary Outcomes

- Primary outcome – Rate of decline on Cognitive Composite
  - Episodic memory – Free and Cued Selective Reminding delayed recall and LM paragraph recall
  - Timed executive function test – Digit Symbol
  - Overall cognition- MMSE

- Secondary clinical outcomes –
  - Novel computerized battery – face-name memory, object pattern separation, attentional measures CogState

- Patient reported outcomes – e-COG, others

- CDR Sum of Boxes
PET amyloid imaging
decrease in mean cortical standard uptake ratio (SUVr)

CSF phospho-tau and tau
(in subset)

Volumetric MRI
Cortical thinning
Hippocampal atrophy

Functional MRI
Default network connectivity

Considering FDG in subset
Zinfandel/Takeda Pharmaceuticals and Duke University:

Delay of Alzheimer’s disease onset examined in individuals at risk of imminent AD symptom expression based on 2 genetic risk factors (APOE and TOMM40)
The gene TOMM40 (translocase of the outer mitochondrial membrane) is adjacent to, and in linkage disequilibrium with, the APOE gene.

Length variation of a poly T tract in the TOMM40 gene is associated with age of onset of cognitive impairment or AD.

- Only APOE4/4 (2%) informative for prediction
- Consideration of the two genes >97% informative for individual prediction
TOMMORRROW Study

- Phase III multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to pursue two primary objectives independently yet simultaneously:
  - To qualify a biomarker risk algorithm, composed of TOMM40 genotype, APOE genotype, and age, for prognosis of the risk of developing MCI due to AD within a 5-year timeframe; and
  - To evaluate the efficacy of low dose pioglitazone (PPAR agonist) to delay the onset of MCI due to AD in cognitively normal subjects who are predicted to be at high risk of developing MCI due to AD within 5 years.
Rationale for the Use of Pioglitazone

- Peroxisome proliferator-activated receptor gamma (PPARγ) agonists regulate multiple pathogenic pathways implicated in AD, including amyloid β homeostasis, insulin sensitivity, energy metabolism, lipid metabolism, and inflammation [Landreth G et al. 2008].

- PPARγ agonists also play crucial roles in energy metabolism due to their direct effects on mitochondrial function, biogenesis and, ultimately, ATP production and neuronal glucose utilization.

- Pioglitazone appears to be safe and well tolerated based on available information from healthy volunteers and subjects with AD [Geldmacher et al. 2011; Sato et al. 2011]

- Pioglitazone has an estimated 22 million patient-years of post-marketing experience for much higher doses than used in trial
TOMMORROW Study
Phase 3 Study Overview

Single, multicenter, double-blind, randomized, placebo-controlled study of low-dose pioglitazone to delay the clinical onset of MCI due to AD

• Single global registration trial
  • 50 sites across United States, Europe (Italy, United Kingdom, Switzerland, Germany, and Russia), & Australia
• 5,800 cognitively normal subjects (65-83 years)
  • Enriched for AD risk using an algorithm comprised of APOE/TOMM40 genotype information and age (4,622 subjects in the high-risk group)
• The duration of study approximately 4 years
  • Time to achieve 410 events in the high-risk group
Key secondary endpoints specified include:

- Cognitive decline: defined as a change from baseline on a composite score on the cognitive battery
- Functional change: defined as change from baseline on instrumental activities of daily living between treated and placebo groups
Methodological Challenges

- Determining appropriate neuropsychological outcome battery for the global clinical trial
- Operationalizing the recent NIA/AA core clinical criteria for Mild Cognitive Impairment due to AD (MCI-AD)
- Securing appropriate normative data to inform diagnostic decisions
- Ensuring that the neuropsychological measures and other questionnaires are linguistically and culturally validated and are performing in an equivalent manner across sites
Chair, Kathleen Welsh-Bohmer, Ph.D.

Responsible for Phase III Program neuropsychology study design & ongoing scientific oversight and support

- Brenda Plassman, Ph.D.
  - Multicenter population based studies
- Kathleen Hayden, Ph.D.
  - Statistical analysis/ Epidemiology
- Heather Romero, Ph.D.
  - Cross-cultural Neuropsychology
- Cassandra Germain, Ph.D.
  - Coordinator – NLO
AD4833 TOMMORROW Study
Neuropsychology Advisory Board (NPAB)

Advisors

Kathleen Welsh-Bohmer, PhD (Chair)
Professor Psychiatry/Medical Psychology & Medicine/Neurology
Director, Bryan Alzheimer’s Disease Research Center
Duke University

Mark A Espeland, PhD, FASA
Department Chair
Department of Biostatistical Sciences
Wake Forest University

Mary Sano, PhD
Professor, Psychiatry
Director - Alzheimer’s Disease Research Center
Mount Sinai Medical Center

Suzanne Craft, PhD
Professor of Gerontology and Geriatric Medicine
Director, Kulynych Center for Memory & Cognition Research
Wake Forest School of Medicine

Andreas Monsch, PhD
Professor, Psychology
Director of the Memory Clinic
University Hospital Basel, Switzerland

Lon S Schneider, MD
Professor of Psychiatry, Neurology, and Gerontology
Keck School of Medicine
University of Southern California
NPAB Deliberative Process

2011

NPAB Live Kickoff
Paris, FR
7/21/2011

NPAB Live Meeting
Chicago, IL
12/01/2011

Endpoints
determined

2012

Clinical trial design

NPAB TC Update
2/2/2012

NPAB TC Update
3/22/2012

NPAB TC Update
4/26/2012

NPAB TC Update
5/31/2012

NPAB TC Update
8/15/2012

NPAB TC Update
9/27/2012

2013

International validation design

NPAB Live Meeting
Vancouver, CA
7/19/2012

NPAB Final TC
1/24/2013
NPAB Objectives

- Determine appropriate neuropsychological outcome battery for the global trial
- Operationalize the recent NIA/AA core clinical criteria for Mild Cognitive Impairment due to AD (MCI-AD)
- Consider methods for securing appropriate normative data to inform diagnostic decisions
- Develop recommendations for linguistic and cultural validation as well as measure equivalence across sites
# Measuring Outcomes in Preclinical AD Cognitive Test Battery

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Tests</th>
</tr>
</thead>
</table>
| Episodic Memory        | California Verbal Learning Test – 2\textsuperscript{nd} Edition (CVLT-II)  
|                        | Brief Visuospatial Memory Test – Revised (BVMT-R)                     |
| Executive Function     | Trail Making Test (Part B)                                            |
|                        | WAIS-III Digit Span Test – backwards span                             |
| Language               | Multilingual Naming Test (MINT)                                      |
|                        | Semantic Fluency (animals)                                            |
|                        | Lexical / Phonemic Fluency (FAS)                                      |
| Attention              | WAIS-III Digit Span Test – forward span                               |
|                        | Trail Making Test (Part A)                                            |
| Visuospatial           | Clock Drawing Test                                                   |
|                        | Copy of BVMT figures                                                  |
### Core Clinical Criteria (Albert 2011)

- Cognitive concern reflecting a change in cognition reported by subject or informant or clinician \((i.e.,\) historical or observed evidence of decline over time)  
- Objective evidence of impairment in one or more cognitive domains, typically including memory \((i.e.,\) formal or bedside testing to establish level of cognitive function in multiple domains)  
- Preservation of independence in functional abilities - not demented  
- Etiology of MCI consistent with AD pathophysiological process

### Core Clinical Criteria (Operationalized)

- Clinical dementia rating scale score of 0.5  
  AND one of the following  
  - Fails at least one of the two memory tests in the cognitive test battery  
  - Fails 2 or more of the 12 measures in the cognitive test battery, representing separate cognitive domain  
  AND  
  - Fulfillment of the following criteria on two consecutive examinations, 6 months apart  
  - Other potential medical causes are ruled out as proximal cause of the cognitive disorder

### Core Clinical Criteria (Albert 2011)

- Cognitive concern reflecting a change in cognition reported by subject or informant or clinician (*i.e.*, historical or observed evidence of decline over time)
- Objective evidence of impairment in one or more cognitive domains, typically including memory (*i.e.*, formal or bedside testing to establish level of cognitive function in multiple domains)
- Preservation of independence in functional abilities - not demented
- Etiology of MCI consistent with AD pathophysiological process

### Clinical dementia rating scale score of 0.5 AND one of the following

- Fails at least one of the two memory tests in the cognitive test battery
- Fails 2 or more of the 12 measures in the cognitive test battery, representing separate cognitive domain AND
- Fulfillment of the following criteria on two consecutive examinations, 6 months apart
- Other potential medical causes are ruled out as proximal cause of the cognitive disorder

---

NPAB Objectives

- Determine appropriate neuropsychological outcome battery for the global trial
- Operationalize the recent NIA/AA core clinical criteria for Mild Cognitive Impairment due to AD (MCI-AD)
- Consider methods for securing appropriate normative data to inform diagnostic decisions
- Develop recommendations for linguistic and cultural validation as well as measure equivalence across sites
Requirements in Global Trial
International Validation Study
(Germany/Switzerland/Russia/Italy)

Harmonizing methods across languages and cultures for:
• Clinical diagnosis
• Measuring cognitive change
• Response to treatment

Diane Wild, MSc, Alyson Grove, MSc, Mona Martin, MPA, Sonya Eremenco, MA, Sandra McElroy, BA, Aneesa Verjee-Lorenz, MSc, Penniffer Erikson, PhD

1Oxford Outcomes Ltd., Oxford, UK; 2Health Research Associates, Seattle, WA, USA; 3Center on Outcomes, Research, and Education (CORE), Evanston, IL, USA; 4Pfizer Inc., Kalamazoo, MI, USA; 5Pennsylvania State University, State College, PA, USA

ABSTRACT

In 1999, ISPOR formed the Quality of Life Special Interest group (QoL-SIG)—Translation and Cultural Adaptation group (TCA group) to stimulate discussion on and create guidelines and standards for the translation and cultural adaptation of patient-reported outcome (PRO) measures. After identifying a general lack of consistency in current methods and published guidelines, the TCA group saw a need to develop a holistic perspective that synthesized the full spectrum of published methods. This process resulted in the development of Translation and Cultural Adaptation of Patient Reported Outcomes Measures—Principles of Good Practice (PGP), a report on current methods, and an appraisal of their strengths and weaknesses. The TCA Group undertook a review of evidence from current practice, a review of the literature and existing guidelines, and consideration of the issues facing the pharmaceutical industry, regulators, and the broader outcomes research community. Each approach to translation and cultural adaptation was considered systematically in terms of rationale, components, key actors, and the potential benefits and risks associated with each approach and step. The results of this review were subjected to discussion and challenge within the TCA group, as well as consultation with the outcomes research community at large. Through this review, a consensus emerged on a broad approach, along with a detailed critique of the strengths and weaknesses of the differing methodologies. The results of this review are set out as “Translation and Cultural Adaptation of Patient Reported Outcomes Measures—Principles of Good Practice” and are reported in this document.

Keywords: cultural adaptation, good practice, guidelines, linguistic validation, patient reported outcomes measures, translation.
Global Challenges – Cultural Validation

- English-speaking countries use published norms from the commercial supplier of the instruments (e.g. CVLT-II, BVMT-R, Wechsler -Digit Span)
- Non-English countries (Russia, Italy, Germany, Switzerland) regional normative information is not available nor are the tests validated for the purpose used in this study
- Development of normative standards and validating the neuropsychological measures used in the trial across countries and languages are necessary
An international validation study is underway in Switzerland, Russia, & Italy. Determine psychometrics, performance characteristics, and normative values

- Aid in clinical detection of mild cognitive impairments in these countries
- Establish measure equivalence across countries
- Facilitate future clinical trials and clinical practice
International Validation Study Design

For each country:

- Age: 65 – 88, inclusive
- 200 cognitively normal subjects (male and female) in the normative sample
  - 50 per group; 65-69, 70-74, 75-79, 80-88
- 25 mild to moderate Alzheimer’s disease patients for validation purposes
  - n= ~ 8 >78 years of age
  - n= ~ 17 <78 years of age
- 2 visits (Visit 1, Visit 2) for normal subjects – test/retest & alternative form reliability
  - Expected duration: ~6 months
Cognitively normal subjects will be randomly assigned to receive alternative forms of the two memory tests, the CVLT-II and BVMT-R.

The sample size is stratified to include 50 cognitively normal subjects per each age interval (65-69; 70-74; 75-79; 80-88).

At most 35 males or females per age group and at least 5 individuals with low education per strata to ensure adequate representation of gender and education.
Instrument Validation and Normative Study

Validation analyses

**Participants**

Normal Subjects

Mild to Moderate AD

Alt-Form Randomization

(n=200)

(n=25)

- Performance on the neurocognitive measures contrasted between Mild to Moderate AD patients and clinically verified cognitively normal subjects
- Establish test validity, construct validity, and diagnostic/criterion validity
- Comparisons of factor structures across countries and examination of findings relative to published US standards allow inferences of overall measure equivalence across countries
Lessons from Design of AD Prevention Studies: Expediting drug development

- FDA and EMA now amenable to the idea of pre-dementia AD,iving more options in trial design to explore promising compounds and CNS signals
  - Work in progress to operationalize new criteria, harmonize methods for measuring early clinical outcomes/composites, and establishing cut-points on CSF or imaging biomarkers
- Validation of the biomarkers as possible surrogate outcome - Necessity for illustrating not just lowering the marker but effecting a positive functional change/slowing progression of disease
  - Primary outcome: continuous measure such as CDR-SB (to capture effect on primary manifestations of disease and establish clinical relevance)
- Offer more expeditious “prevention” or “slowed progression” and an option to the lengthier and more expensive traditional MCI trial design
## Expected Impact Of Positive Findings

### Valid Biomarkers of AD

- Potential of geriatric population stratification in high/low risk at pre-symptomatic stage
- High risk patients can be monitored at pre-planned intervals to proactively identify any deterioration

- Potential of early diagnosis in high risk subjects

- Early diagnosis can lead to early intervention

- Potential to retain quality of life in remaining years and not merely extend lifespan
  - Can enable patients and carers to plan appropriately

- Potential for significant savings in healthcare costs

### Delaying the onset of MCI due to AD

- Pre-symptomatic treatment (if effective) can provide greater potential to impact disease process compared to providing treatment after symptoms appear

- Delaying onset of MCI due to AD can in turn delay onset of AD

- Potential to change the clinical practice for AD treatment

- More meaningful quality of life
  - Longer independence of elderly subjects
  - Less burden on relative/care provider

- Potential for significant savings in healthcare costs
Lifestyle to Enhance Brain Health

Slide compliments Dr Patrick Smith: Enlighten Study 2013
Preventable Lifestyle Factors in AD

- Sedentary lifestyle
- Obesity
- Dietary habits
- Hypertension and heart disease
- Diabetes
- Lack of cognitive engagement/stimulation
- Stress/depression
- Other medical conditions (e.g. sleep, pain)
Non-pharmacological Interventions Underway
Diet & Exercise- The ENLIGHTEN Study
Blumenthal et al: Contemporary Clinical Trials 34 (2013) 60–69

- Normal adults with memory complaints and cardiovascular risk conditions (55 yrs+)
- Targeting 160 participants randomized to 26 week aerobic exercise program, Dash diet, or both compared to usual care
- Change in neuropsychological function over 18 months
- Previous work in Australia (Lautenschlager et al (2008) JAMA 1027-1037) has found modest improvement (usual care deteriorated 1.04 pts on ADAS-cog; Intervention improved 0.26 pts; Overall difference was 1.3 points)
Nonpharmacological Interventions
Cognitive Training
ACTIVE Study- Rebok et al., JAGS 2014

Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study

N=2832 Cognitively healthy older adults (age 74; 26% AfAm)

Three training groups—memory, reasoning and speed-of-processing—and a control group.

Ten sessions (60 minutes) over five to six weeks, with some randomly selected for later booster sessions.

Outcomes: effects on ADLs, general function, QoL, & specific cognitive abilities (immediately, and at one, two, three, five and 10 years after the training)

• 6 Sites: Baltimore, Birmingham, Ala.; Boston; Detroit; State College, Pa.; & Indianapolis.
• The 10-year follow-up was conducted with 44 percent of the original sample between April 1998 and October 2010.
Nonpharmacological Interventions
Cognitive Training
ACTIVE Study- Rebok et al., JAGS 2014

- At 10 years- all participants reported less difficulty in IADLs
  - Memory (effect size=0.48)
  - Reasoning (ES=0.38)
  - Speed of Processing (ES=.36)
- Cognitive function tests showed
  - 73.6% reasoning-trained still performing above pre-trial baseline level –vs- 61.7% controls receiving no training (effect size 0.23; CI=.09-.38)
  - 70.7% speed-trained above their baseline level –vs- 48.8% controls (effect size 0.66 CI= .43-.88)
  - No difference in memory performance between the memory and control group after 10 years
  - Booster training additional durable effect for reasoning and speed of performance

- Mean age at follow-up = 82.
Observational studies suggest that maintaining heart-smart, healthy diet and engaging in regular exercise has a protective effect on later life outcomes

- Randomized clinical trials are the ultimate test of this assumption
- Enlighten study and other large RCT (e.g. European Dementia Prevention Initiative; Richard et al 2012) underway to explore effects of lifestyle modifications on cognitive health in single site and at population level

Cognitive training results are encouraging and suggest that it may prevent functional decline

- Finding consistent with very recent observational finding suggesting that cognitive engagement and physical exercise have persistent positive effects on cognition 5 years, 10 years later, respectively. (Jedrziewski et al 2014 Am J AD & Other Dementias)
Summary & Future Directions

- Clinical trials with promising disease modifying drugs have been disappointing in AD, despite evidence of target engagement.
  - Likely related to implementing therapy too late in disease course
  - Need to start earlier in the MCI or preclinical phase to have chance at effects
  - We will learn a tremendous amount from current trials-methods, surrogate measures and risks- assist in speeding AD drug development in future work and informing approaches in clinical practice

- Targeting amyloid **may not** be the optimal approach
  - Other targets focus on other mechanisms including upstream events:
    - Tau/ tangle formation
    - Mitochondrial function
    - Energy metabolism
    - Insulin sensitivity
    - Inflammation
    - Lipid metabolism
  - May need drugs with broad spectrum of action or combined therapies (e.g. AB reducing therapies with anti-inflammatory properties or other biologic)
Summary & Future Directions

- Non-pharmacological approaches (diet and exercise) also appear promising and important for brain health
  - Effect sizes similar to current memory medications for AD
  - Relatively safe &
  - Additional health benefits – cardiac and emotional health

- Future treatment likely person specific and will involve combination of approaches, which may vary as function of individuals disease severity
  - At any point in disease likely to involve both drug compounds and sensible life-style modifications
What to when patients and families need assistance?

- Useful resources:
  - NC Alz-Inc
    - [www.alznc.org](http://www.alznc.org)
    - 919.832.3732 or 800.228.8738
  - Alzheimer’s Association
    - [www.alz.org](http://www.alz.org)
    - 800.272.3900
  - Family Support Program at Duke University
    - 800 672 4213
  - Bryan Alzheimer’s Disease Research Center
    - [adrc.mc.duke.edu](http://adrc.mc.duke.edu)
Alzheimer’s Disease Prevention Registry

**Discovery, Prevention, Treatment**

- Goal is to mobilize the community to help in Alzheimer’s disease research
- The *ADPR* is a registry (*N* > 2500) of community members in the triangle who:
  - Are 55+
  - Do **not** have a diagnosis of Alzheimer’s disease
  - Are interested in possibly being involved in research in the future
  - And are registering to be informed of studies in the Bryan ADRC as they become available
Bryan ADRC
AD Prevention Registry

Be a part of the solution!
Every participant makes a difference!

ADRC (866-444-ADRC) or visit our website:
http://adrc.mc.duke.edu/
Work of the Bryan ADRC Team-Past & Present
THANK YOU