Stratified Medicine and Targeted Clinical Trials for AD Drug Development in Light of Recent Phase III Trial Results

Chairs: Lon Schneider,

Terry Goldberg, Larry Ereshefsky

ISCTM's Involvement in AD Clinical Trials and Methodology

1st Annual Meeting: Montreal 2005: Long-Term Treatment Trials in MCI/ AD (moderator, M Farlow)

ISCTM 2008 Autumn Conference: Focus on Alzheimer's Disease

- Understanding of Disease Progression (R Mohs, G Grossberg)
- Imaging, CSF and Plasma Biomarkers (S Potkin, G Small)
- Trial Designs Likely to Meet Valid Long-Term Disease Progression Effect: Learning from the Past, Preparing tor the Future (R Anand, S Romano)
- Clinical Endpoints in Alzheimer's Disease Progression (G Gharabawi, P Tariot)
- Regulatory Views on Trial Designs Likely to Meet Valid Long-Term Disease Progression Effect (R Anand, H Feldman)

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ISCTM 2010 6th Annual Meeting

- Clinical Trials in the Prodromal Phase of Alzheimer's Disease - Methodological Challenges and Clinical Outcomes
  - Chairs: G Garibaldi, M Davidson

ISCTM 2011 7th Annual Meeting

- Do Clinical Results to Date Suggest that Drug Development Based on the Amyloid Hypothesis of Alzheimer's Disease Is Dead?
  - Chairs: R Anand, L Ereshefsky, D Feltner

ISCTM 2012 8th Annual Scientific Meeting: Research-to-Policy Forum

- Are Clinical Trials of New Treatments for Chronic CNS Diseases Early Enough and Long Enough?
  - Chairs: R Ferziger, R Manderscheid ,L Ereshefsky

*National Alzheimer's Project Act (*NAPA) and AAIC

- **Comment on NAPA's Scientific Agenda for a National Initiative on Alzheimer's Disease**
  ISCTM Comment document: Submitted March 2012
- Meeting/TCs with William Thies and staff
- ISCTM will be submitting a methodological session at the AAIC Boston 2013 meeting

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Talking Points from ISCTM's Comments on NAPA

Given the tremendous costs and time frames necessary for the fulfillment of a 'traditional' regulatory path, we suggest further exploration of novel strategies to accelerate and improve trials design including:

a. Stratified enrollment such as 'banding' different ages/stages of illness in a disease course modification/prevention trial including treatment arms for pre-clinical, MCI, mild, and moderate patients.

b. Selection of high risk volunteers/patients with potential accelerated course to demonstrate proof of concept (familial Alzheimer's disease, or APOE4 genotype)

c. Interim analyses to satisfy a modified regulatory approval process that incentivizes investment in long-term trials, including provision for study continuation to occur as a post-marketing commitment.

d. Incorporation of naturalistic designs where all subjects are given the opportunity to remain in the protocol whether or not 'dropped from treatment'

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Other Issues to Consider

i. Development and validation of more sensitive neuropsychological testing and improved measures to assess long-term treatment effects

ii. Use of prodromal /pre-clinical biomarkers, cognitive and/or behavioral symptoms to reliably identify ‘at risk’ subjects.

iii. Multi-factorial approaches to risk identification and patient selection. What is the most appropriate patient population (severity and course) for distinctly unique treatments?

iv. How long should patients be followed?

v. Disease progression trials in Alzheimer’s Disease might need to be ‘targeted’ to improve the probabilities of success, and better identify multiple pathological processes, e.g., tau-opathy vs. amyloid burden, or both.