“Enhancing Translational Research and Clinical Development in Alzheimer’s Disease and other Dementia: The Way Forward”

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US Regulatory Context and Challenges
• Current landscape
• 2013 Draft Guidance on Early Stage Alzheimer’s Disease
• Systemic Roadblocks: biomarker development
• Systemic Roadblocks: Outcome measure development
• Systemic Roadblocks: Clinical trial conduct
Current Challenges

• In face of impending epidemic, path to new treatments seems fraught
• Recent trials in patients with Alzheimer’s dementia have not been successful
• May reflect lack of correct target, or
• May reflect intervention too late in disease, or
• Both
Current Challenges

• Fear that Alzheimer’s drug development less attractive than more successful areas
  – Low success rate
  – High cost of studies
  – Uncertainty about diagnosis of subjects
  – Lack of response biomarkers
FDA’s 2013 Draft Guidance

• “Developing Drugs for the Treatment of Early Stage Disease”
• Previous trial methods for use in Alzheimer’s dementia still acceptable (co-primary endpoint)
• Draft Guidance responsive to potential need to study patients in early disease course
• Recognizes the need for diagnostic criteria—biomarker based—in pre-symptomatic AD
FDA’s 2013 Draft Guidance: Potential Outcome Measures

• For prodromal AD or MCI due to AD, suggests a composite scale that assesses both function and cognition in early patients

• For pre-symptomatic patients, suggests cognitive measures only, and FDA could use the accelerated approval mechanism

• Time-to-event analysis starting at any stage pre-dementia, suggests composite scale
Systemic Roadblocks: Biomarker Development

• Draft guidance indicates FDA’s willingness to approve a drug for AD under accelerated approval based on changes to a biomarker that are “reasonably likely to predict a clinical effect”

• Unfortunately, no such biomarker is currently recognized
Challenges: Biomarker Development

• How could Alzheimer’s Disease biomarkers be more rapidly developed?

• “Industrial” scale validation efforts
  – Substantial efforts to recruit and follow large numbers of patients through all phases of disease, as well as healthy people and individuals with other putative causes of dementia
  – Refine and standardize assays and imaging techniques
  – Use standard data collection
  – Evaluate use in dx as well as correlation with clinical condition
  – “Research” scale efforts currently ongoing in several regions
Challenges: Outcome Measure Development

• Most urgent: potential pharmacodynamic measures of drug effect—quantitative markers

• For pre-symptomatic disease:
  – Cognitive battery

• For early disease; time-to-event:
  – Composite scale
Could a Biomarker be an Outcome Measure?

• Anatomic images—e.g., atrophy, hippocampal volume, etc. have some face validity but I understand performance characteristics not established

• Need discussion about how a biomarker or composite of biomarkers would be developed (ie what evidence base) for this use
Systemic Roadblocks: Clinical Trial Conduct

- Trials are too slow, too expensive, don’t answer enough questions
- Propose “standing trial”, AKA “master protocol” or “clinical trial network” to help address these problems
- Multi-stakeholder supported ongoing trial program to develop biomarkers/endpoints and evaluate investigational interventions
- Use adaptive designs to allow forward momentum
- Incorporate new investigational agents as they become available
- Would need the help of patients and advocates to reach out into the community and enlist physicians and enrollees
- Such trials can be partly pragmatic and yet contain intensive sub-studies
- FDA has been working with stakeholders in oncology to initiate such trials
Summary

- FDA has issued draft guidance on trials in very early Alzheimer’s, working to issue a final
- Success of such a program requires good diagnostic criteria and outcome measures
- We do not have good pharmacodynamic measures for AD drug development
- The magnitude of the challenge really requires “industrial scale” natural history, biomarker validation and clinical trials infrastructure