

Capturing the Signal in Mild Cognitive Impairment of the Alzheimer's Type: Industry Partnerships in Pre-Competitive Measure Development

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Disclosure and Acknowledgements



- C. Leibman is an employee of Janssen AI
- Views and opinions are Leibman's, not Janssen AI's
- Acknowledgements – special thanks:
 - Core Advisors: Rachelle Doody, Serge Gauthier, Douglas Galasko
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 - UBC Team: Bill Lenderking, Kellee Howard, Leah Kleinman
 - Cognition Initiative working group members and respective organizations (on slide 17)

Outline



- How did we get here...
- Rising to the challenges: C-Path Institute, PRO Consortium
- The cognition working group
 - Does measuring still matter
- Working Status and next steps

Continued Challenges

	Antibiotics	CNS	Cardiovascular	Respiratory
Failure due to safety (phase I)	85-100	20-30	30-40	50
Failure due to efficacy	5-15	70	60	50

NEWS & ANALYSIS

TRIAL WATCH

Phase III and submission failures: 2007–2010

The Centre for Medicines Research International has noted that the average for the combined success rate at Phase III and submission has fallen to ~50% in recent years. To learn more about the causes for Phase III and submission failures, Thomson Reuters Life

primarily be due to the challenging science in these areas, but is perhaps also a result of the pressure on companies to replenish pipelines with drugs that have high potential for approval and reimbursement, particularly in a period during which patent expiries for major

Lack of Efficacy in Humans is the Most Common Reason for Drug Failure in CNS

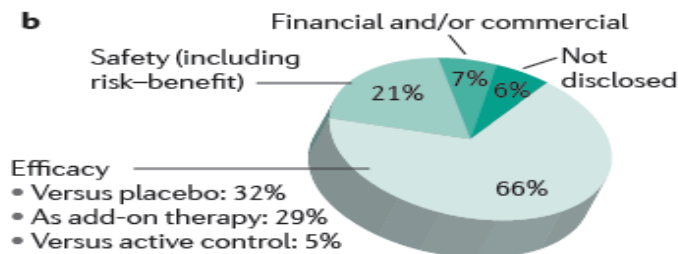
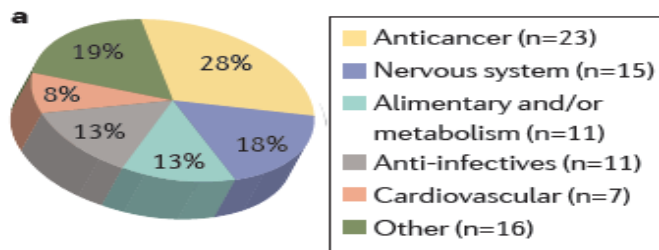
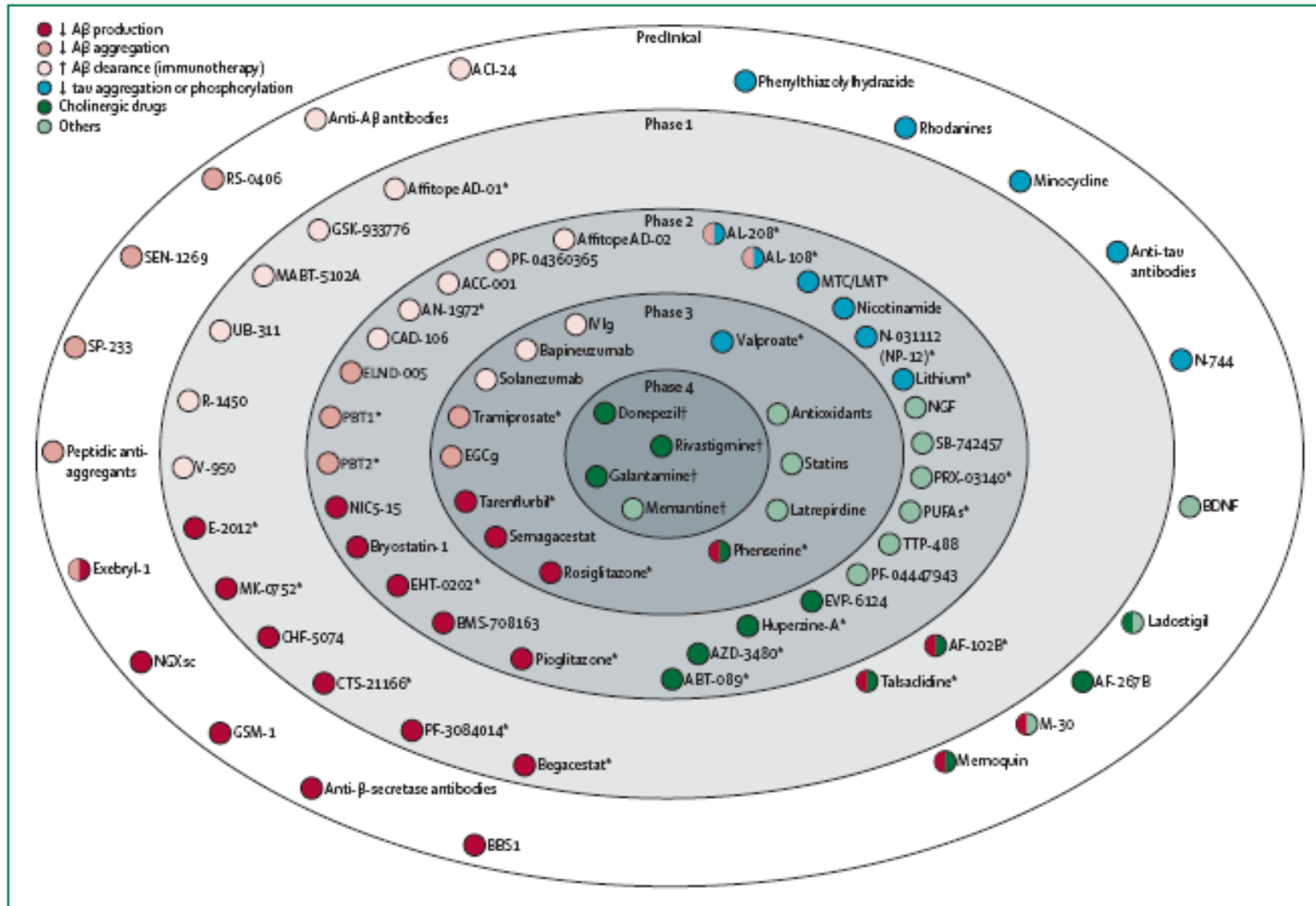


Figure 1 | **Phase III and submission failures: 2007–2010.** The 83 failures are divided according to therapeutic area (a) and reason for failure (b).

Has this deterred us...clinical trials in AD

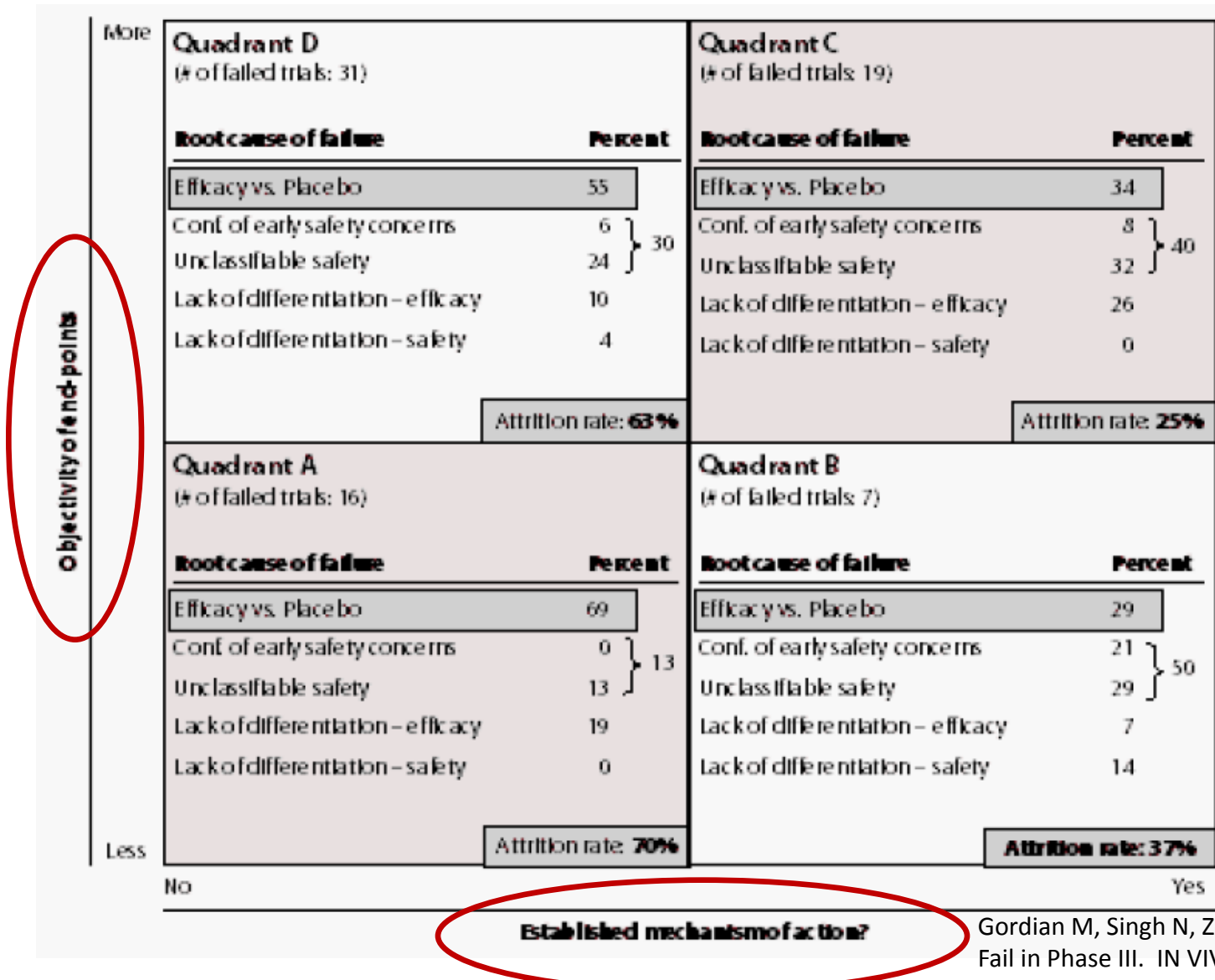


Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M. Alzheimer's disease: Clinical trials and drug development. *Lancet Neurol* 2010;9:702-16.

Root cause analysis – why do we fail?

Objectivity of endpoints	More	Quadrant D (# of failed trials: 31)	Quadrant C (# of failed trials: 19)																												
		<table border="1"> <thead> <tr> <th>Root cause of failure</th> <th>Percent</th> </tr> </thead> <tbody> <tr> <td>Efficacy vs. Placebo</td> <td>55</td> </tr> <tr> <td>Conf. of early safety concerns</td> <td>6</td> </tr> <tr> <td>Unclassifiable safety</td> <td>24</td> </tr> <tr> <td>Lack of differentiation – efficacy</td> <td>10</td> </tr> <tr> <td>Lack of differentiation – safety</td> <td>4</td> </tr> <tr> <td colspan="2" style="text-align: right;">Attrition rate: 63%</td> </tr> </tbody> </table>	Root cause of failure	Percent	Efficacy vs. Placebo	55	Conf. of early safety concerns	6	Unclassifiable safety	24	Lack of differentiation – efficacy	10	Lack of differentiation – safety	4	Attrition rate: 63%		<table border="1"> <thead> <tr> <th>Root cause of failure</th> <th>Percent</th> </tr> </thead> <tbody> <tr> <td>Efficacy vs. Placebo</td> <td>34</td> </tr> <tr> <td>Conf. of early safety concerns</td> <td>8</td> </tr> <tr> <td>Unclassifiable safety</td> <td>32</td> </tr> <tr> <td>Lack of differentiation – efficacy</td> <td>26</td> </tr> <tr> <td>Lack of differentiation – safety</td> <td>0</td> </tr> <tr> <td colspan="2" style="text-align: right;">Attrition rate: 25%</td> </tr> </tbody> </table>	Root cause of failure	Percent	Efficacy vs. Placebo	34	Conf. of early safety concerns	8	Unclassifiable safety	32	Lack of differentiation – efficacy	26	Lack of differentiation – safety	0	Attrition rate: 25%	
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Less	No	<table border="1"> <thead> <tr> <th>Root cause of failure</th> <th>Percent</th> </tr> </thead> <tbody> <tr> <td>Efficacy vs. Placebo</td> <td>69</td> </tr> <tr> <td>Conf. of early safety concerns</td> <td>0</td> </tr> <tr> <td>Unclassifiable safety</td> <td>13</td> </tr> <tr> <td>Lack of differentiation – efficacy</td> <td>19</td> </tr> <tr> <td>Lack of differentiation – safety</td> <td>0</td> </tr> <tr> <td colspan="2" style="text-align: right;">Attrition rate: 70%</td> </tr> </tbody> </table>	Root cause of failure	Percent	Efficacy vs. Placebo	69	Conf. of early safety concerns	0	Unclassifiable safety	13	Lack of differentiation – efficacy	19	Lack of differentiation – safety	0	Attrition rate: 70%		<table border="1"> <thead> <tr> <th>Root cause of failure</th> <th>Percent</th> </tr> </thead> <tbody> <tr> <td>Efficacy vs. Placebo</td> <td>29</td> </tr> <tr> <td>Conf. of early safety concerns</td> <td>21</td> </tr> <tr> <td>Unclassifiable safety</td> <td>29</td> </tr> <tr> <td>Lack of differentiation – efficacy</td> <td>7</td> </tr> <tr> <td>Lack of differentiation – safety</td> <td>14</td> </tr> <tr> <td colspan="2" style="text-align: right;">Attrition rate: 37%</td> </tr> </tbody> </table>	Root cause of failure	Percent	Efficacy vs. Placebo	29	Conf. of early safety concerns	21	Unclassifiable safety	29	Lack of differentiation – efficacy	7	Lack of differentiation – safety	14	Attrition rate: 37%	
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	Yes	Established mechanism of action?																													

pAD Clinical Development – Familiar Warnings?



Gordian M, Singh N, Zimmel R, Elias T. Why Products Fail in Phase III. IN VIVO, April 2006.

Challenges and Problems in RCTs for AD



- Patients
- Drugs
- Outcome Measurements
- Trial Protocol
- Optimization of Resources

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AD Challenges Provide Unique Pre-Competitive Collaborative Opportunities



- Historical challenges...outweighed by overwhelming benefits
- Leveraging the expertise of scientists across numerous disciplines and backgrounds
- Increased transparency around evidence expectations and requirements leading to more targeted activities
- Efficient allocation of scarce resources for researchers

Critical Path Institute (C-Path)



- Established in 2005 by the University of Arizona and the FDA
- An independent, non-profit organization
- Dedicated to implementing FDA's Critical Path Initiative (CPI) - A strategy for transforming the way FDA-regulated products are developed, evaluated, manufactured, and used
- Provides a neutral forum for collaboration aimed at accelerated development of safe and effective medical products

PRO Consortium



- Formed in late 2008 by C-Path, in cooperation with the FDA and the pharmaceutical industry
- **Membership**
 - Only available to medical product companies
- **Non-Voting Participants**
 - Representatives of governmental agencies
 - Clinical consultants, patient advocates, academic researchers, and CROs partnering in the development of the PRO instruments

Members



- **Abbott**
- **Actelion Pharmaceuticals**
- **Allergan**
- **Amgen**
- **Astellas Pharma**
- **AstraZeneca**
- **Boehringer Ingelheim**
- **Bristol-Myers Squibb**
- **Daiichi Sankyo**
- **Eisai**
- **Eli Lilly & Company**
- **Forest Laboratories**
- **GlaxoSmithKline**
- **Ironwood Pharmaceuticals**
- **Janssen Pharmaceuticals**
- **Merck**
- **Novartis**
- **Novo Nordisk**
- **Pfizer**
- **Roche**
- **Sanofi-Aventis**
- **Shire**
- **Sunovion**
- **Takeda Pharmaceuticals**
- **UCB**

Goals of PRO Consortium



- Enable pre-competitive collaboration that includes FDA input/expertise
- Avoid development of multiple PRO instruments for same purpose
- Share costs of developing new PRO instruments
- Develop qualified, publicly available PRO instruments
- Facilitate FDA's review of medical products by standardizing PRO endpoints

Objective of Working Groups



- To develop a PRO instrument that can be accepted by the FDA as 'qualified' for use as the measure of a primary or key secondary efficacy endpoint in clinical trials for the target disease/condition

Cognition Working Group - Background



- Increasing interest in mild cognitive impairment (MCI) due to AD presents an opportunity to advance outcomes measurement by expanding the range of measurement targets beyond neuropsychological assessments into the realm of patient-reported outcomes (PROs)
- Recent diagnostic clarification around MCI (Alpert et al, 2011) is an important step in making research results more replicable
- FDA has provided a general PRO Guidance on the processes and steps necessary to develop an instrument that is 'fit for purpose'
- FDA has encouraged consortiums to participate in developing PROs for single disease indications

Cognition Working Group – Current Aims



- Objective
 - To develop a reliable, valid and FDA-qualified PRO for use in clinical trials
- Disease (and stage[s] if appropriate)
 - MCI due to AD
- Target population
 - aMCI meeting Petersen criteria
- Role of PRO measure in endpoint hierarchy
 - Co-Primary

Cognition WG Participants



Company/Organization	Name
Abbott	Steven Hass, Nicholas Greco, Amy Duhig Co-Chair
AstraZeneca	Anna-Karin Berger, Daniel Eek, Lori Frank
Boehringer Ingelheim	Juergen Reess, Mark Gordon
Bristol-Myers Squibb	David Budd, Lucinda Orsini
Eisai	Lara Verdian
Janssen	Loretto Lacey, Christopher Leibman Co-Chair , Gary Romano
Merck	Julie Chandler, Yi Mo
Novartis	Ari Gnanasakthy, Jennifer Petrillo, Simu Thomas
Pfizer	Zoe S. Kopp, Joel Bobula
Roche	Nina Hill, Judith Dunn, Todd Paporello, Glenn Morrison

Progress and Current Status



- **October 2009:** UBC Cognition Initiative affiliated with C-Path to form Cognition Working Group
- **December 2009:** Created and submitted Scoping Stage Summary Document (SSSD) to FDA per FDA Qualification Review Process requirements
- **March 2010:** Finalized qualitative data collection protocol and obtained IRB approval
- **March-April 2010:** Trained data collection sites
- **April 2010:** Met with FDA to discuss feedback on SSSD
- **April 2010:** Collected qualitative data
- **April 2010:** Completed initial qualitative data analysis
- **May 2010:** Expert Panel Meeting, preliminary Conceptual Framework
- **November 2010:** PRO Scoping Stage Summary Document to FDA
- **March 2011:** Insight Interviews conducted, FDA feedback received, mini-Delphi Panel conducted on draft instrument
- **September-December 2011:** Cognitive Interviewing and Expert panel

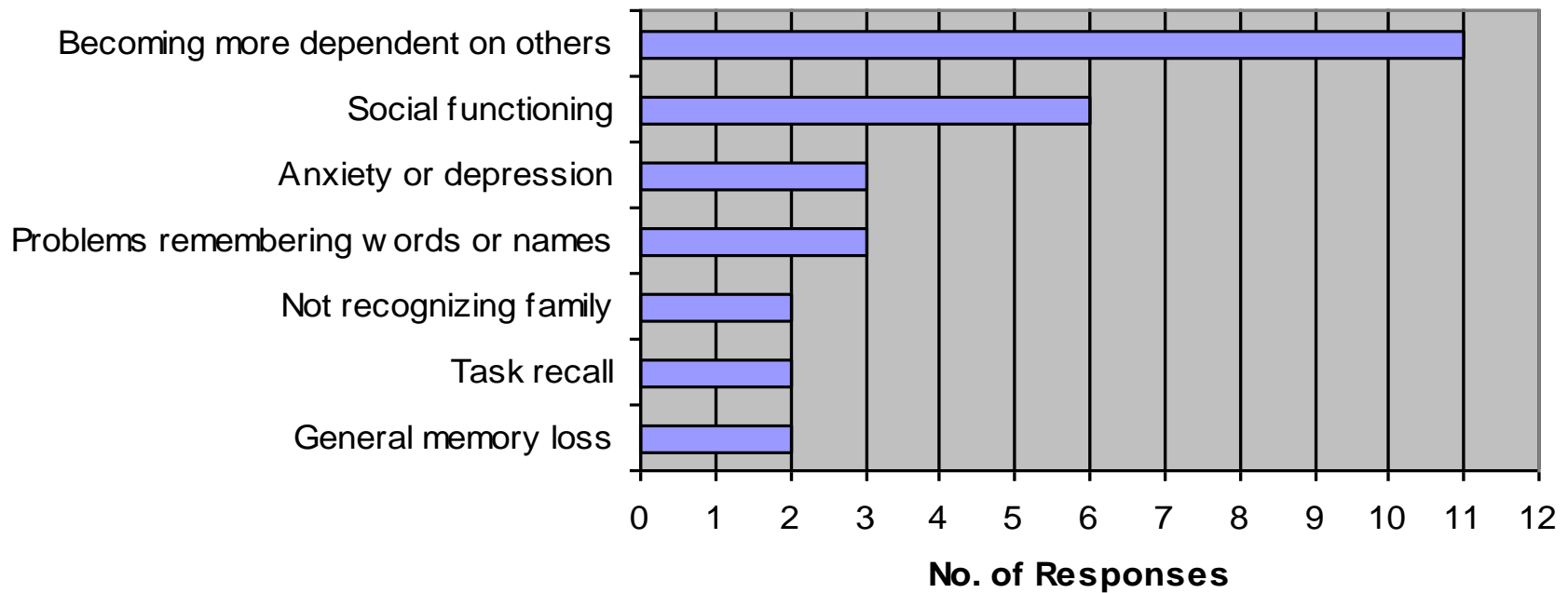
Where are we going...



- Phase I: COMPLETE
 - Expert panel meeting
 - Literature review of relevant outcome measures
 - Literature review of evidence for patient insight
 - Project bibliography
 - Communication forum via website
 - Focus group protocol for qualitative data collection
- Phase II: NEAR COMPLETION
 - Creation and submission of FDA Scoping Stage Summary Document – DONE – revise
 - Collection of qualitative data – focus groups -- done
 - Identification of domains to measure – done
 - Item pool, measure draft– done
 - Cognitive interviewing -- **ongoing**
- Phase III:
 - Psychometric evaluation of the new measure
 - Finalization of measure content and scoring
 - Preparation of the PRO Evidence Dossier

Why the patient's voice matters...

'What particular symptoms of early Alzheimer's disease worry you the most?'



Q11: What particular symptoms of Alzheimer's disease worry you the most? [if not mentioned ask about the following (1) memory loss; (2) task recall - not remembering why you went into a room; (3) increased reliance on lists; (4) problems remembering words or names; (5) feelings of anxiety or depression; (6) social functioning - keeping up with group discussions; (7) becoming more dependent on spouse or children]

Conclusions



- Alzheimer's disease is uniquely complex in its pathophysiology and clinical manifestations and there is substantial gap in the patient assessment tools necessary to conduct robust trials
- Increased collaboration in innovative and unique ways across industry, basic and clinical researchers will be required to develop solutions for the AD clinical trial challenges
- The C-Path - Cognition Working Group is developing a fit for purpose scale for use in clinical trials in patients with MCI due to AD following the FDA ***Guidance for Industry for Patient-Reported Outcome Measures***

Back-up Slides

Conceptual Framework

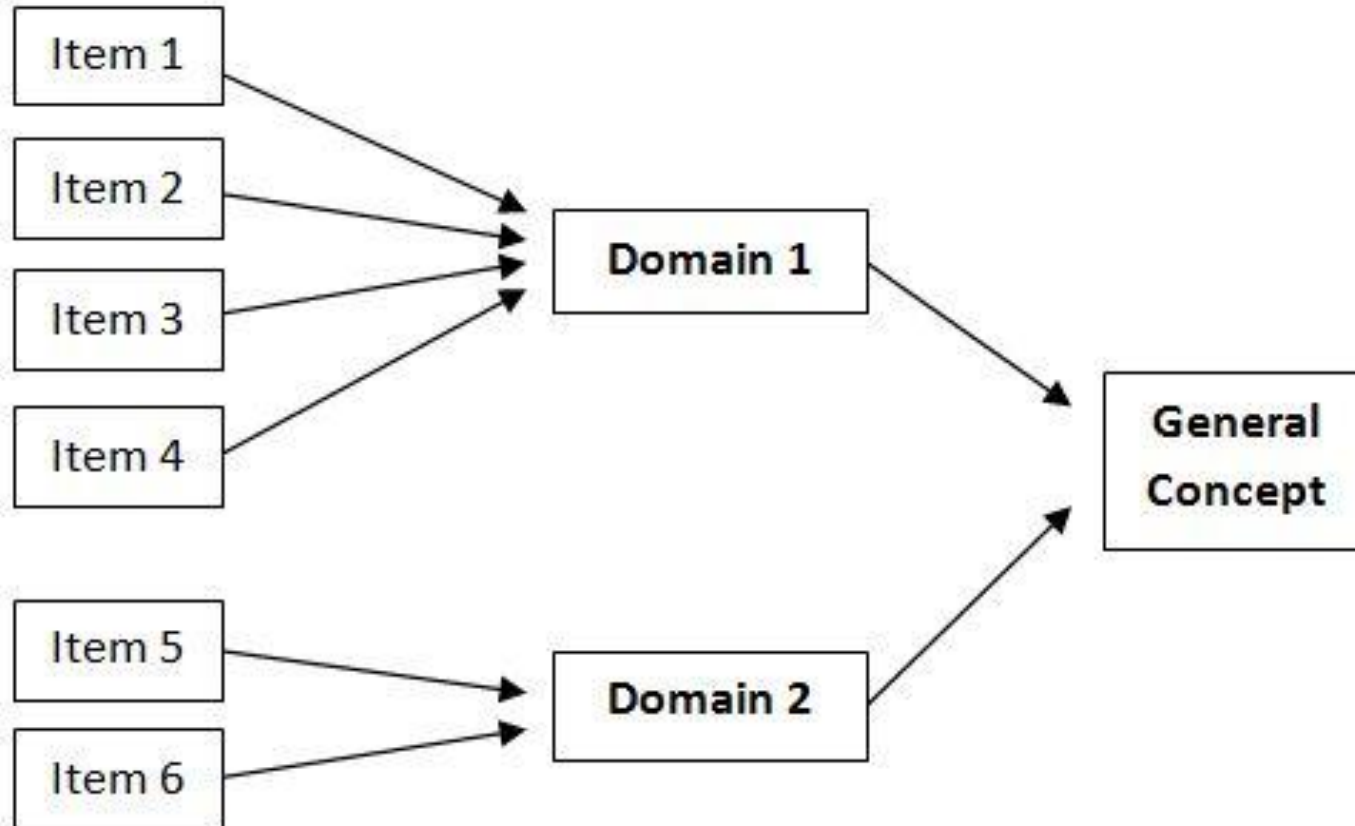
Core Concepts



- **Interpersonal functioning:** Interpersonal functioning is expressed as the ability to interact effectively and appropriately with other people across a wide range of relationships (e.g., as parent, spouse, employee). It also includes successful role functioning in a social context. Several skill sets are required including organization required to maintain social relationships, maintaining social roles in relation to others, managing emotions in social contexts, conversational skill, and social uses of language, especially humor.
- **Complex activities of daily living (ADL) task performance:** Everyday functioning is expressed by the ability to complete Complex Activities of Daily Living which are activities requiring cognitive skills beyond those required for Instrumental Activities of Daily Living. Examples include organizing information and materials for task completion, planning skills required for hobby and task completion, household management tasks, using memory in the process of task completion, managing finances, and accurately navigating in one's environment (e.g., walking or driving the way to the grocery store.).

- Mission
- **To establish and maintain a collaborative framework with appropriate stakeholders for the development of qualified, publicly available patient-reported outcome (PRO) instruments for use in clinical trials where PRO endpoints are used to support product labeling claims.**

Conceptual Framework



Challenges



- Field is evolving quickly
 - This group is developing information at the same time the field is struggling with lexicon and population characterization, i.e., diagnostic criteria and terminology are changing
- Sustained advocacy for current effort
 - We are one of many prodromal AD workstreams in the competition of ideas
- Measurement target is complex