Results from the Cognition Working Group of the PRO Consortium

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Agenda

- Qualitative data collection and results
  - Procedures
  - Concept elicitation
  - Conceptual framework
  - Insight interviews
- Conclusions

Qualitative Study Overview

- Cross-sectional qualitative study design, 11 US sites (VA, VT, CA, GA, TX, KS for controls only)
  - Focus group discussions
  - Recruited by sites from clinic population

- Inclusion/exclusion criteria
  - aMCI: MMSE 24-30, CDR = 0.5
  - probable AD: NINCDS-ADRDA or DSM-IV criteria; MMSE 20-26; CDR> 1.0.
  - Informants: sees and/or speaks with an eligible participant a minimum of 3 days per week with a minimum of 6 hours per week of in-person interaction;
  - controls: MMSE $\geq$28, CDR = 0
  - exclude MDD

Qualitative Study Overview (cont)

- Discussion elements selected from literature, expert input:
  - Symptoms
  - Daily Functioning
  - Social Interactions
  - Mood
  - Executive Functioning and Other Symptoms
  - Impact on Informant

- Subsequent Insight interviews, 2 US sites (Texas, VT)
  - Simultaneous, parallel interviews with patients and informants
  - Scenario checking for insight

Demographics of Participants by Diagnosis

	aMCI Patient (N=26)	AD Patient (N=39)
Age		
Mean (SD)	78.6 (7.7)	77.6 (7.4)
Gender (n, %)		
Male	18 (69.2%)	21 (53.8%)
Ethnicity (n, %)		
Hispanic or Latino	2 (7.7%)	2 (5.1%)
Not Hispanic or Latino	24 (92.3%)	36 (92.3%)
Missing	0 (0.0%)	1 (2.6%)
Race[1] (n, %)		
American Indian or Alaska Native	1 (3.8%)	0 (0.0%)
Asian	0 (0.0%)	1 (2.6%)
Black or African American	1 (3.8%)	1 (2.6%)
Native Hawaiian or other Pacific Islander	0 (0.0%)	0 (0.0%)
White	23 (88.5%)	36 (92.3%)
Other	2 (7.7%)	1 (2.6%)
Native English Speaker (n, %)	26 (100%)	37 (94.9%)

[1] Not mutually exclusive

Demographics of Participants by Diagnosis (cont'd)

	aMCI Patient (N=26)	AD Patient (N=39)
Employment Status[1] (n, %)		
Employed, full-time	1 (3.8%)	0 (0.0%)
Employed, part-time	1 (3.8%)	0 (0.0%)
Unemployed	1 (3.8%)	4 (10.3%)
Retired	22 (84.6%)	33 (84.6%)
Other	2 (7.7%)	0 (0.0%)
Highest Level of Education[1] (n, %)		
Elementary/primary school	0 (0.0%)	1 (2.6%)
Secondary/high school	5 (19.2%)	11 (28.2%)
Some college	6 (23.1%)	10 (25.6%)
College degree	10 (38.5%)	11 (28.2%)
Postgraduate degree	5 (19.2%)	6 (15.4%)
Other	0 (0.0%)	1 (2.6%)

[1] Not mutually exclusive

Results: Themes Emerging from Focus Groups

I. Symptoms

- Conversational skill (repetition, complexity, reduced participation)
- Word/name recall
- Delayed recall
- Attention
- Comprehension of written material
- Comprehension of spoken material
- Processing speed
- Concentration

Results: Themes Emerging from Focus Groups

II. Task Performance

- Hobby participation (decrease) /skill loss
- Navigation
- Gadget/Tool use
- Meal preparation

And a lot of the meals I used to make, um, I can't remember what they were...Uh, well, I used to—I used to take the regular tomatoes and do it like my grandmother did, she made, you know, regular, she never bought the stuff in jars or cans, so she used to make it and I used to make it like that, but then it got to be too much. You have to cook it for about 3 hours, so now I just buy the sauce in a bottle, [laughs] dump it in there… ***(MCI patient)***

Results: Themes Emerging from Focus Groups

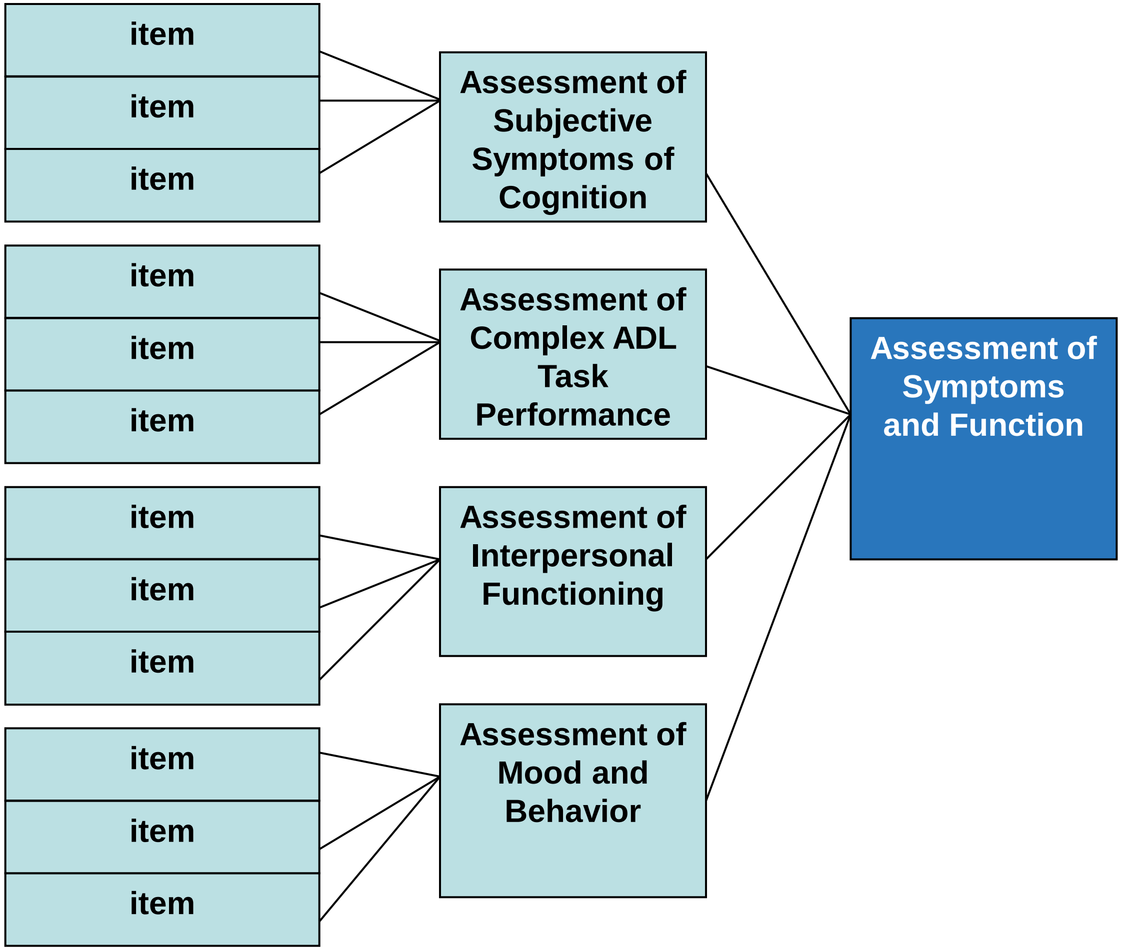
III. Interpersonal Functioning

- Conversational skill (repetition, complexity, reduced participation)
- Detachment from social situations

It's been about six or eight months…I notice it almost primarily when we were in—in company… 'Cause I used to be able to tell some great jokes. But now you cannot tell jokes if you don't know the names of the people that you're talking about… You don't uh communicate as well…with a fun crowd. ***(MCI patient)***

I find I'm silent more than I used to be because someone else beats me to it you know. I'm thinking about what I might say and somebody over there starts to talk about it and I'm listening instead of- instead of talking about it. ***(MCI patient)***

Conceptual Framework as a Guide to Measure Development



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Assessment of Subjective Symptoms of Cognition

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item
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Assessment of Complex ADL Task Performance

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Assessment of Interpersonal Functioning

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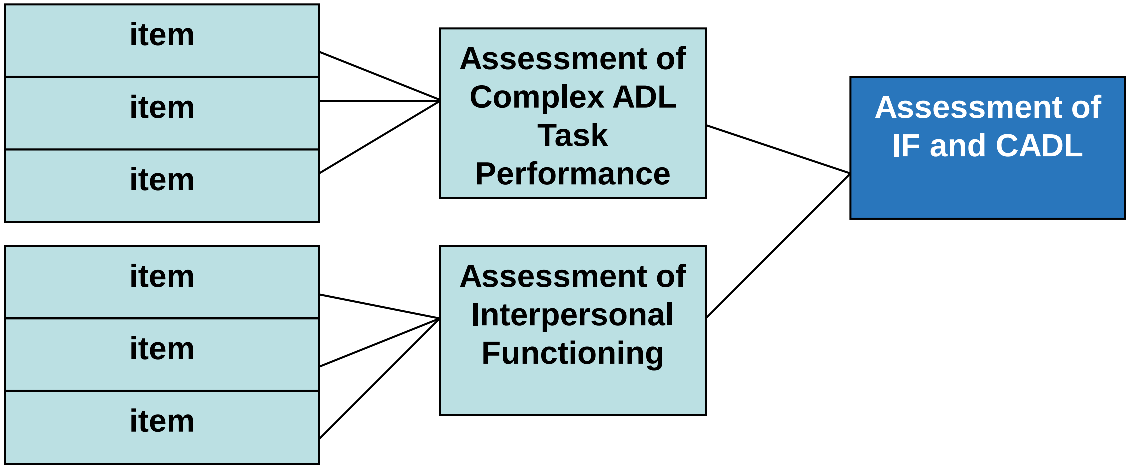
Assessment of Mood and Behavior

Assessment of Symptoms and Function

Revised Conceptual Framework



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Assessment of Complex ADL Task Performance

Assessment of Interpersonal Functioning

Assessment of IF and CADL

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

Conceptual Framework Core Concepts

- **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.)

Preliminary Feedback from FDA

- Complex ADLs and IF are potentially good targets for PRO development in MCI

- Patient insight and reliability of the informant could be problematic

- Avoid duplication across endpoints in labeling

  - Mood and behavior in patients with cognitive impairment needs to be shown to be distinct from depression in other types of patients

  - Concern about measurement of cognition through clinician reported outcomes vs PROs

Insight in MCI

- Several studies point to patient heightened awareness or unique knowledge regarding deficits in a stage prior to AD[1,2,3]

- Comparison across studies is hampered by different definitions of insight and differences in methods for assessing insight. Inconsistent findings on insight in MCI may relate to failure to view insight as domain-specific rather than a global construct

- The literature supports the conclusion that MCI patients demonstrate more intact insight than AD patients across different insight domains

1. Cook S, Marsiske M. Subjective memory beliefs and cognitive performance in normal and mildly impaired older adults. *Aging Ment Health. Jul 2006;10(4):413-423.; 2.* Doody RS, Ferris SH, Salloway S, et al. Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. *Neurology. May 5 2009;72(18):1555-1561; 3.* Reisberg B, Gauthier S. Current evidence for subjective cognitive impairment (SCI) as the pre-mild cognitive impairment (MCI) stage of subsequently manifest Alzheimer's disease. Int Psychogeriatr. Feb 2008;20(1):1-16.

Insight Interviews

- The Cognition WG conducted 22 1:1 interviews (11 pairs) to address the FDA Reviewers' concern that patients with MCI lacked sufficient insight to report on their own symptom experience accurately

- The insight literature review performed by UBC and the WG suggested that insight may be domain-specific

- Interviews were designed to simultaneously compare informant and patient reports about specific scenarios reflecting interpersonal functioning and complex ADLs, in both MCI and AD patients
  - Interviews were stopped at pre-specified timepoints, moderators compared notes and patients and informants were then interviewed about specific scenarios upon which they reported
  - 2 scenarios for each domain

- Patients and informants were also interviewed regarding relevance of item content for these two domains

Insight Interview Sample Description

Location	Site Specialty	Number of aMCI Dyads	Number of AD Dyads	Total Number of Participants
Austin, TX	Psychiatry	4	1	10
Bennington, VT	Neurology	3	3	12
	Total	***7***	***4***	***22***

Interview Sample—Patient Characteristics

	aMCI Patient (N=7)	AD Patient (N=4)
Age (years)		
Mean (SD)	76 (5.5)	68 (9.3)
Range	69-82	55-77
Gender (n, %)		
Male	4 (57.1%)	2 (50%)
Female	3 (42.9%)	2 (50%)
Ethnicity (n, %)		
Hispanic or Latino	1 (14.3%)	1 (25%)
Race (n, %)		
Caucasian	4 (57.1%)	4 (100%)
Black or African American	3 (42.9%)	-
Native English Speaker (n, % yes)	7 (100%)	4 (100%)

Interview Sample—Informant Characteristics

	aMCI Informant (N=7)	AD Informant (N=4)
Age (years)		
Mean (SD)	65.4 (16.3)	58.8 (12.1)
Range	45-84	47-72
Gender (n, %)		
Male	2 (28.6%)	1 (25%)
Female	5 (71.4%)	3 (75%)
Ethnicity (n, %)		
Hispanic or Latino	-	-
Race (n, %)		
Caucasian	4 (57.1%)	4 (100%)
Black or African American	3 (42.9%)	-
Native English Speaker (n, % yes)	7 (100%)	3 (75%)

Additional Characteristics

- 36.4% with college degree (none of the AD patients)
- 7 informants were spouses, 4 were children
- Mean time known patient = 49.2 years (11-69)
- Amount of time spent with patients in last week = 132.4 hrs (4 – 168)

Clinical Characteristics

Clinical Measure	aMCI Patients (N=7)	AD Patients (N=4)
MMSE Score[1]		
Mean (SD)	28.3 (1.7)	23.8 (1.5)
Median	28.0	23.0
Range	(25.0-30.0)	(23.0-26.0)
CDR Global Score[2]		
Mean (SD)	0.50 (0.00)	0.88 (0.25)
Median	0.50	1.00
Range	(0.5-0.5)	(0.5-1.0)

Example of Insight Scenario for Complex ADL

- INFORMANT: we just got a new alarm system in, and I set the alarm for the night. Yeah, so it was only like a day or so ago. And I told her you can’t go out either of the doors, mom, you know? Not, not that she’s wandering or anything. But just--you just don’t open the doors now or go feed anything to the birds because it’s nighttime, the alarm’s set, and let’s--we’re all going to bed. So, halfway into mid sleep I hear all the alarms going off. And I jump out of bed, like, mom, what’d you do? And I’m running downstairs, you know, and this wakes up the whole house, actually, because by the time I get down there the alarms are in full mode. And I’m like trying--she goes, remember the number? I says, yes, mom, I do, you know? So, we have it set to that number that she’s going to remember, as well, so--but she--it takes her a long tour to program these things. She doesn’t get to mechanics of, like, cell phones or stuff like that, so. . . (03-11-204)

Example of Insight Scenario for Complex ADL

- PATIENT: But the other night, um, I was—the kids left something that belongs to me put out on the front porch—I call it the front porch, they call it the back, but, um, I keep garbage, you know, where you throw—it was a bottle, a plastic bottle and they didn't put it out there, so I opened the door to put it out 'cause I didn't want it—it was empty, I didn't want it in the kitchen. So, the alarm system goes off and my daughter's up stairs asleep and I'm saying, oh, I don't know how to put this thing off, you know, I really didn't—well, I figured, you know, go decode it or something, but she came down and took it off and she says 'you can't open these doors,' which you can't open the door or window when that system is active. (01-11-204)

- Concept: Complex ADLs

- Related Items: How often do you have difficulty using devices like cell phones, remote controls, or computers? How often do you have difficulty following step-by-step instructions? How often do you have difficulty learning new information, tasks, or procedures?

Example of Insight Scenario for IF

- INFORMANT: --supposed to go in there [to sweetheart dance] happy and, and this kind of stuff, and not have to recover anything. So, it was at our church and, and, and, um--but all of that, I had to help her see that, [wife], if you started off by saying to me, we're going to take our grandson by his mom's job, she says that it's okay, then, one, we'd have left in time. Two, we'd have been directly there, and we wouldn't be having this conversation. …And, and, and it's not until we back things out and she can see that maybe I'm not the villain she thinks I am. (03-06-203)

Example of Insight Scenario for IF

- PATIENT: And I had called his mother, and told her that we would drop him at the hospital. That's where she works. And anyway, uh--and I had said 7:00, and I forgot to give that detail to [husband's name]. And so she was looking for us to drop him at the hospital at 7:00. And I told [husband's name], we're going to drop him off, you know? And [husband's name] started heading to church. So, it was around 7:30 when we got to, got to. . .But we had to go to the hospital, because I saw we were headed to church. I said, why are you going this? He said, well, you told me we were going to drop him off. I said, we're going to drop him off at the hospital. And it was just my not giving enough details, that's it. And I have a bad habit of doing that. I tell you part of it. Not going to tell you the whole, the whole--I, I know the whole thing. And I think I'm giving enough information. But, I didn't give enough information, so he was headed to church. (01-06-203)
- Concept: Interpersonal Functioning
- Relevant Item: How often do you have difficulty saying what you mean?

PROCOG Data

Clinical Measure	aMCI Patient[1] (N=7)	aMCI Informant[2] (N=7)	AD Patient[1] (N=4)	AD Informant[2] (N=4)
ADCS-ADL[3]	-	67.86 (8.95)	-	61.75 (11.47)
PROCOG Total Score[4]	72.71 (40.36)	63.29 (35.80)	59.25 (55.66)	82.00 (15.43)
PROCOG Subscales				
Affect	1.62 (1.04)	1.30 (0.85)	1.25 (1.31)	1.55 (0.65)
Skill Loss	0.91 (0.79)	0.74 (0.67)	0.93 (1.08)	1.52 (0.60)
Semantic Memory	1.77 (1.11)	1.63 (0.92)	1.70 (1.65)	1.80 (0.78)
Memory for Recent Events	1.39 (0.70)	1.20 (0.79)	1.22 (1.43)	1.53 (0.50)
Cognitive Functioning	1.48 (0.83)	1.39 (0.64)	1.15 (0.83)	1.48 (0.62)
Social Impact	0.89 (0.43)	0.87 (0.73)	0.56 (0.52)	1.33 (0.46)
Long Term Memory	2.00 (1.15)	1.43 (0.98)	0.50 (0.58)	0.25 (0.50)

For ADCS-ADL, higher scores indicate higher functioning; for PROCOG, higher scores indicate greater impairment. ADCS-ADL was completed by the informant

Is Self-report a Viable Strategy for Cognition Outcome Measures?

"Although informant reports of IADL performance are more accurate than self-reports for patients with dementia, it is possible that persons with MCI can self-report ADL."

Galasko D et al. ADCS Prevention Instrument Project Assessment of Instrumental Activities of Daily Living for Community-dwelling Elderly Individuals in Dementia Prevention Clinical Trials. *Alzheimer Dis Assoc Disord* 2006;20:S152–S169.

"These subjective complaints do not necessarily correlate with objective measures of memory impairment or cognitive performance but they may be an early indication of impairment at a state that is undetectable by standard testing instruments."

Coley N et al. Memory complaints to the general practitioner: data from the GuidAge Study. *J Nutr Health and Aging* 2008;12(8):66S-72S.

Conclusions

- Qualitative data indicate that patients with cognitive impairment of mild severity can provide insights into their deficits, reinforced by parallel descriptions of impairments from their informants
- Preliminary evidence from PROCOG data indicates that aMCI are aware of greater deficits than their informants, and that AD patients report less impairment than their informants (very small sample)
- Complex ADLs and Interpersonal Functioning remain promising domains for PRO assessment in aMCI

Backup Slides

Item Coverage

I. Symptoms

1. I forget names of people I know well
2. I have trouble remembering conversations
3. My thinking is slower than it once was
4. I find it difficult to focus

II. Complex ADLs

1. I put things away in the wrong place
2. I am slower at reading than I used to be
3. I find it hard to plan events like a party or vacation
4. I am not as organized as I used to be
5. I am doing less around the house then I used to
6. I rely on others to help me remember my appointments

Item Coverage (cont’d)

III. Social Interaction

1. I find it difficult to remember stories I want to tell when talking to others
2. I lose track when I am telling a story or joke
3. I find it hard to follow conversations
4. Others make my point in conversation before I can
5. I find it harder to keep up with conversations than it was in the past
6. I participate less in conversations because I can’t always keep up

IV. Mood and Behavior

1. I don’t want to do the things I used to like doing
2. I don’t like to be by myself
3. My emotions are affecting my relationships with the people I love
4. People say I don’t have patience
5. My memory problems frustrate the people I am closest to
6. Things upset me now more easily than they used to

Patient Inclusion Criteria

Patients must meet ALL of the following inclusion criteria to be enrolled in this research study:

1. Age ≥ 50 years;
2. Native English speaker;
3. Willing and able to travel to research site for focus group or one-on-one interviews;
4. Willing to provide written informed consent; and
5. Able to understand and comply with the requirements of the study, based on study investigator.

Patient Inclusion Criteria: Probable AD

1. Complaint of memory impairment;
2. MMSE scores between 20-26 within the last 3 months;
3. Diagnosis of mild to moderate probable AD based on NINCDS-ADRDA and/or DSM-IV criteria;
4. Clinical Dementia Rating (CDR) score ≥1.0.

Patient Inclusion Criteria: aMCI

1. Self or informant report of memory decline;
2. MMSE scores between 24-30 within the last 3 months;
3. Clinical Dementia Rating (CDR) score = 0.5;
4. Self or informant report of intact /basic functional abilities;
5. No diagnosis of dementia;
6. Meets protocol-defined criteria for MCI.

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2. MMSE scores between 24-30 within the last 3 months;
3. Clinical Dementia Rating (CDR) score = 0.5;
4. Self or informant report of intact /basic functional abilities;
5. No diagnosis of dementia;
6. Meets protocol-defined criteria for MCI.

Control Group Inclusion Criteria

1. No diagnosis of dementia or MCI;
2. Cognitively healthy with an MMSE ≥ 28 within the last 3 months;
3. Clinical Dementia Rating (CDR) score = 0.

Informant Inclusion Criteria

A family member/friend must meet ALL of the following criteria to be considered for enrollment into this study:

1. Family member or friend of patient meeting criteria above, who has familiarity with the patient’s basic and complex Activities of Daily Living; sees and/or speaks with an eligible participant a minimum of 3 days per week with a minimum of 6 hours per week of in-person interaction;
2. Has known participant for ≥1 year;
3. 21 years of age or older;
4. Native English speaker;
5. Willing to provide written informed consent;
6. Able to understand and comply with the requirements of the study, based on study investigator judgment.

The Measurement Need – What Are We Missing?

- Perceived Deficits: "…donepezil-treated amnestic MCI subjects subjectively rated themselves as better. Consistent with this observation, informants of untreated patients rated them as worse compared to the observations of informants of treated subjects. One hypothesis generated by the current study is that most of the standardized outcome measures were not sensitive enough to treatment benefits in this minimally impaired population."
- "Newer MCI-specific instruments may show greater sensitivity to change in MCI. Additionally, new instruments are needed that sensitively measure functional change in complex activities in subjects with MCI." (p. 1560)

Doody RS, Ferris SH, Salloway S et al. Donepezil treatment of patients with MCI. A 48-week randomized, placebo-controlled trial. *Neurology.* 2009; 72: 1555-1561.

FDA Required Elements per PRO Guidance

Instrument Rationale	Provided
Labeling Language	Provided
Endpoint Model	Provided
Conceptual Framework	Under revision
Content Validity Documentation	Ongoing
Qualitative study protocols and interview guides	Completed
Item tracking matrix showing items retained and items deleted	Ongoing
Qualitative study summary of results with evidence of saturation	Ongoing
Justification	
in relation to the desired claim(s) for response options, recall period, scoring	TBD

- Following measure finalization (in Phase III of the project): Assessment of Psychometric Properties, Instrument Scoring, Recall Period, Score Interpretation, Clinical Trial Results, Mode of Administration, Translation