Development of a patient-reported outcome (PRO) instrument to assess complex activities of daily living and interpersonal functioning in patients with mild cognitive impairment due to suspected Alzheimer's disease: the qualitative research phase

Mark Forrest Gordon, MD, FAAN, Amy Duhig, PhD, Julie Chandler, PhD, Elisabeth Piault, PharmD, Lori Frank, PhD, and William Lenderking, PhD
on behalf of the Cognition Working Group of the Critical Path Institute's Patient-Reported Outcome Consortium
Ridgefield, CT, North Chicago, IL, Whitehouse Station, NJ, Genentech, CA, Washington, DC, Lexington, MA

PRO CONSORTIUM CRITICAL PATH INSTITUTE

Background

Most existing outcome measures for patients on the Alzheimer's disease (AD) spectrum were developed to assess impairment in Alzheimer's dementia and exhibit poor performance when administered in patients with amnestic mild cognitive impairment (herein referred to as "MCI"). The Cognition Working Group (WG) of the Critical Path Institute's Patient-Reported Outcome (PRO) Consortium is developing a Patient-Reported Outcomes instrument for qualification by FDA as a "fit for purpose" endpoint in clinical trials of patients with MCI. This tool will capture patients' perspectives regarding their condition and its impact on their lives and is intended to be used as a secondary endpoint in drug development programs. The measure is being developed within a public-private partnership with industry, academia, and regulators through the qualification process for drug development tools [FDA draft guidance, 2010]. This process fosters a pre-competitive environment and permits interactions with the FDA through the Consultation and Advice phase.

Objectives

- Document that patients with MCI can provide reliable and valid self-reports regarding symptoms and functioning.
- Complete the qualitative work to support the development of a measure that, alongside measures of cognitive function, will document treatment benefit that is sensitive to change in patients with MCI.

Methods

Three qualitative data collection efforts were completed from 2010 to 2012:
1)focus groups and interviews to obtain patient language for the experience of cognitive impairment (n=25 patients with MCI);
2)insight interviews of 7 dyads {1 informant (caregiver): 1 patient} to address the extent to which MCI patients can self-report; and
3)cognitive interviews on the draft measure based on data gathered in the prior steps.

The **inclusion criteria** were revised during the course of the study to reflect the updated definition of MCI, as outlined in Fig. 1.
The inclusion criteria common to all three interviews were:

- Age ≥50 years
- Self or informant report of memory decline
- MMSE scores between 24-30 within the last 3 months
- Self or informant report of intact basic functional abilities
- No diagnosis of dementia

Fig 1: The inclusion criteria that differed between the interview.

Concept elicitation interviews (2010)	Insight interviews (2011)	Cognitive debriefing interviews (2012)
Clinical Dementia Rating (CDR) score = 0.5	CDR was not required as an inclusion criterion	CDR was not required as an inclusion criterion
Meet protocol-defined criteria for MCI based on Winblad, et al., 2004	Meets protocol-defined criteria for MCI based on Winblad, et al., 2004.	Objective evidence of MCI diagnosis based on neuropsychological testing that meets criteria for MCI as outlined in Albert et al. 2011. The neuropsychological testing criteria include cognitive performance one and a half standard deviations below normal for age and educational level on any one of the following tests: a. Immediate and Delayed Recall of the Wechsler Memory Scale (revised) Logical memory Test I and II, b. Free and Cued Selective Reminding Test, c. California Verbal Learning Test, d. Rey Auditory Verbal Learning Test, e. Other accepted test with prior approval from investigator

- Institutional Review Board approval was obtained.
- The conceptual framework was iteratively modified based on the comments of three core experts during the mini-Delphi and of eight advisors during the second advisory panel.

Conceptual framework development, item generation and refinement

- Concepts that patients considered to be important and that clinical experts (n=8) deemed to reflect patients' functioning in Complex Activities of Daily Living (CADLs) and Interpersonal Functioning (IF) were organized in a conceptual framework.
- Items were generated to measure these two concept domains based on the patients' own words.
- Draft questionnaire was modified based on patients' feedback and recommendations from clinical experts.

Insight Interviews

- Concordant reports from the MCI patients and informants were considered evidence of patient insight for the domains of interest.

Results

Patient Populations (see Table 1)

Concept Elicitation

The early qualitative data collection along with input from expert panelists led to a list of potential domains representing the patient experience of having MCI. Following review of potential domains, the WG determined that functioning in Complex Activities of Daily Living (CADLs) and Interpersonal Functioning (IF) represented critical and unique aspects of the patient experience of MCI, that impairments in these two domains were likely to be noticed by the majority of MCI patients, and that these domains were not well measured by existing instruments. The WG therefore pursued item development for these two domains.

Complex activities of daily living (CADL)
Activities requiring cognitive skills beyond those required for Instrumental ADLs, e.g. 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.

Interpersonal Functioning (IF)
Behaviors that reflect 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 (e.g. person with primary responsibility for household maintenance). Successful IF requires several skill sets, such as the executive functioning skill of organization required to maintain social relationships (e.g. maintaining social calendar), maintaining social roles in relation to others, managing emotions in social contexts, conversational skill for appropriate interactions, and understanding and employing social uses of language, especially humor.

- Patients with MCI self-reported the following issues with interpersonal functioning among other issues: difficulty with spoken communication (44%), difficulty with written communication (20%), difficulty with social interactions (76%), memory problems where they forgot the names of others (80%), and memory problems that affected their ability to express things verbally (52%).
- Patients with MCI self-reported the following issues with complex ADLs among others: cognitive issues impacted their daily activities (48%) or impacted their work functioning (28%), issues around chores (32%), cooking (36%), planning (28%), handling money (44%), and difficulty with completing a multistep process (12%).

Insight Interviews
•All of the MCI dyads showed scenario concordance based on qualitative review.

Cognitive debriefing interviews
•Findings from these interviews were used to ensure that patients with MCI understood the meaning of the draft items, identified them as relevant to their lives, and were able to justify their response selection. Clarifying verbiage was added for items poorly worded or that had been misinterpreted by patients. Items were removed when multiple patients did not find them to be relevant.

Table 1: Subject demographics and clinical characteristics

	Concept elicitation interviews (n=25)	Insight interviews (n=7)	Cognitive Debriefing (n=28)
Age Mean (SD)	78.4 (7.7)	76 (5.5)	74.7 (8.5)
Gender (n Male, %)	17 (68.0%)	4 (57.1%)	14 (50.0%)
Ethnicity (n Hispanic or Latino, %)	2 (8.0%)	1 (14.3%)	3 (10.7%)
Race[1] (n, %)			
American Indian or Alaska Native	1 (4.0%)		-
Asian	-		2 (7.1%)
Black or African American	1 (4.0%)	3 (42.9%)	8 (28.6%)
White	22 (88.0%)	4 (57.1%)	18 (64.3%)
Other	2 (8.0%)		
Native English Speaker (n, %)	25 (100%)	7 (100%)	27 (96.4%)
Current Living/Domestic Situation (n, %)			
Living alone	1 (4.0%)		6 (21.4%)
Living with partner/spouse/family/friends	24 (96.0%)	7 (100%)	22 (78.6%)
Highest Level of Education[1] (n, %)			
Elementary/primary school	-		1 (3.6%)
Secondary/high school	5 (20.0%)	1 (14.3%)	5 (17.9%)
Some college	6 (24.0%)	1 (14.3%)	8 (28.6%)
College degree	10 (40.0%)	4 (57.1%)	8 (28.6%)
Postgraduate degree	4 (16.0%)	1 (14.3%)	6 (21.4%)
Other	-		-
Time since diagnosis in years Mean (SD)			2.0 (2.4)
Time since first reported memory symptoms in years Mean (SD)			3.7 (2.4)
MMSE Score Mean (SD)	27.9 (1.5)	28.3 (1.7)	26.9 (1.8)
CDR Global Score	0.50 (0.14)	0.64 (0.23)	
Depression Medication (n, % yes)			7 (25.0%)
Medication for Cognition (n, % yes)			5 (17.9%)

Fig 2. Conceptual Framework Revised Based on Qualitative Research Results And Expert Panel Feedback

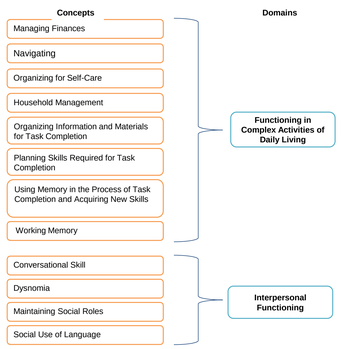

Fig. 3. Example of the similarity between patient and informant reports that suggested presence of insight

Patient	Informant
Uh, yeah, I did forget my granddaughter's birthday, yeah I did, and, uh, I, I have to look at things, like I say, I've got it written down and I still don't remember, you know, I, I think it's [month], but I, you know, I have to stop and think what the dates they were. And when she was born my husband and I, we went to [country], she was born in [city] and, um, we flew up there to [country] when she was born and I think I would remember that [laughs] but, you know, I, I didn't and, you know—	Um, but sometimes she'll--she goes, do you remember what date this person was on, like, you know, a birthday or something. Sometimes she forgets that. Um, she actually forgot one of my niece's birthdays, you know? And my older brother was furious about that. I'm like, you know, you know, it's not--because she doesn't live with them, you know? She hardly sees these kids, you know? So how is she going to remember that, oh, today's the seventh and it's going to be, you know, so-and-so's birthday? So, she had to call up and, you know, wish the child a happy birthday, who's now [age] and stuff like that, you know, and that. I mean, she remembers my kids' birthdays because we live with her, you know? I mean, it's not, you know--I think if it's--she calls it out-of-sight, out-of-mind type deal, you know?

Discussion

- Through focus groups and interviews, items were generated reflecting the patient's perspective, providing sufficient evidence of patient participation in item development.
- CADLs and IF were selected as the conceptual framework's two domains with the highest utility for a self-reported measure of the impact of MCI.
- During the interviews, MCI patients and informants showed concordance in describing specific concerns relevant to CADLs and IF, suggesting both the reliability and validity of the patients' reports and their retained insight within these domains.
- The dyad interviews demonstrated that MCI patients retain insight regarding their deficits, based on agreement between narratives from the MCI patient and the non-cognitively impaired informant.
- Limitations: Based on the small number of insight interview dyads, we suggest caution in interpreting these results.
- The inclusion criteria were based on the prevailing and evolving diagnostic research criteria during the course of the study.
- The current draft instrument consists of 26 items rated on a 5-point, frequency-based, verbal rating scale ("Never" to "Always"). Currently there is no recall period for the instrument, due to the nature of the items, some of which might occur weekly or even daily as MCI progresses, whereas other items such as remembering appointments and managing finances might be a problem monthly or might occur less frequently.

Conclusions

- The Cognition Working Group (WG) of the Critical Path Institute's Patient-Reported Outcome (PRO) Consortium is developing a PRO instrument for qualification by FDA as a "fit for purpose" endpoint in clinical trials of patients with MCI.
- The Cognition WG's draft PRO instrument incorporates the patient's perspective.
- These interviews suggest that patients with MCI retain insight of their CADLs and IF.
- Insight will be further evaluated in the quantitative analysis.
- Following demonstration of its content validity, the instrument will undergo quantitative testing to evaluate its psychometric properties.

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- Dr. Frank was an employee of UBC when portions of this work were completed. She subsequently participated in the WG as a non-member participant. She does not report any conflict of interest. The views expressed here are those of Dr. Frank and do not necessarily reflect those of the Patient Centered Outcomes Research Institute (PCORI), where she is employed.
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Expert Panel Members	Affiliation
Paul Aisen, MD	University of California, San Diego, School of Medicine
Jeffrey Cummings, MD	Lou Ruvo Brain Institute, Las Vegas
Rachelle S. Doody, MD, PhD	Baylor College of Medicine
Steven H. Ferris, PhD	New York University School of Medicine
Douglas Galasko, MD	University of California, San Diego, School of Medicine
Serge Gauthier, MD, FRCPC	McGill Centre for Studies in Aging
Mary Sano, PhD	Mount Sinai School of Medicine
Bruno Vellas, MD	University of Toulouse
Gordon Wilcock, FRCP	University of Oxford, Nuffield Department of Medicine
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