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# Clinically Meaningful Outcomes in Early Alzheimer Disease: A Consortia-Driven Approach to Identifying What Matters to Patients

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## Abstract

*Background:* Numerous statistically derived composite measures have recently been proposed as clinical outcome assessments (COAs) for clinical trials in the early stages of Alzheimer disease. Critical Path Institute's Coalition Against Major Diseases (CAMD) advanced a proposed statistically derived composite measure to regulatory agencies with the goal of qualifying it as a COA for pre-dementia trials. In response to FDA's requirement to demonstrate that proposed COAs are meaningful to patients, this project aimed to identify the most important cognition-related concerns patients and informants report early in the disease and determine how this information maps to what is assessed by several statistically derived composite measures. *Methods:* Leveraging qualitative research completed by Critical Path Institute's Patient-Reported Outcome Consortium, CAMD utilized a summary report that included frequency grids of reported concerns of amnestic mild cognitive impairment patients and their informants, as well as the narrative transcripts from focus groups. Transcripts were reviewed and analyzed to identify which cognitive domains the patient- and informant-reported concerns mapped onto. The results were then compared to see how well these cognitive domains were represented in various statistically derived composite measures. *Results:* The patient- and informant-reported concerns primarily mapped to the cognitive domains of episodic memory and, secondarily, orientation and language. Depending on the specified composite, there were varying levels of alignment between their subcomponents and these cognitive domains. *Conclusion:* Through secondary analyses of existing qualitative data, this study examined several statistically derived composite measures and found that they generally capture cognitive domains that reflect aspects of day-to-day functioning that patients and informants consider meaningful.

## Keywords

cognition, predementia, clinical outcome assessments, clinical trials, Alzheimer disease

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## Introduction

More than a decade has passed since the last new drug for Alzheimer disease (AD) obtained regulatory approval, though hundreds of compounds have entered clinical trials but failed to achieve their primary endpoint(s) during this time.[1] One possible explanation for these disappointing clinical trials is that successful treatment may require intervening at a much earlier stage in the disease course, before significant neurodegeneration has occurred.[2] Clinical trials are therefore increasingly targeting patients at earlier stages of AD, including mild cognitive impairment (MCI) or early dementia (eg, studies NCT01953601, NCT01224106, NCT02245737, NCT02484547, and BAN2401 on www.clinicaltrials.gov). Some, however, argue that this may still be too late as biomarker and neuropathology studies suggest that the pathological processes that lead to dementia already begin decades before the initial clinical symptoms appear.[3-6]

In its recent draft guidance for industry titled "Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease,"[7] the United States Food and Drug Administration (FDA) recognized that the co-primary cognitive and functional or global assessment measures required for clinical trials of drugs for dementia would be more challenging to apply in early-stage disease. Nonetheless, they maintained that the principle of co-primary outcome measures prevails, citing the need to ensure that any cognitive benefit would be clinically meaningful.[7] The evaluation of a meaningful treatment benefit requires that the clinical outcome being measured is something that is clinically important and that matters to the patient, that is, that the treatment substantively affects how the patient feels, functions, or survives.[8] The meaningfulness of a treatment benefit is also a primary concern of payers. For example, while the amyloid positron emission tomography (PET) imaging ligand florbetapir was approved by the FDA, the Centers for Medicare and Medicaid Services determined that there was insufficient evidence to conclude that the technique would improve clinical diagnosis or improve outcomes for individuals with AD.[9]

The FDA draft guidance went on to cite the Clinical Dementia Rating–Sum of Boxes (CDR-SB)[10] scale as an example of a tool that assesses both cognitive and functional changes.[7] This outcome measure is also included in the recent European Medicines Agency (EMA) draft guidance on treatment of AD and other dementias.[11] Yet there remain some concerns both among regulators and investigators conducting clinical trials regarding the clinical meaningfulness of CDR-SB score changes and the ability of this measure to assess treatment-related outcomes.[12,13] In addition, there is concern with subjective bias of informant interviews and the vulnerability of this tool to intra- and interrater and informant variance across a multiyear clinical trial.[14]

The field has yet to reach consensus on which cognitive or functional measures should be used in the pre-dementia, MCI, stages.[1,13] Measures of cognition, such as the theoretically derived composite Alzheimer's Disease Assessment Scale–Cognitive (ADAS-Cog)[15] and the Mini-Mental State Examination (MMSE)[16] screening measure are traditionally used in trials of subjects with AD dementia but lack sensitivity in the pre-dementia stages (eg, MCI).[17,18] Chiefly because of ceiling effects (ie, the participant cannot do any better, they achieve full credit, on an outcome measure or subcomponent thereof) of many of the subcomponents, these measures are not optimal in demonstrating cognitive impairment or tracking disease progression in MCI and hence cannot be considered as clinically meaningful in the early stages of the disease.[13,19] Researchers have therefore sought to optimize existing measures by identifying and combining sensitive subcomponents and creating statistically derived and, hopefully, more meaningful composite measures.[20] A statistically derived composite measure differs from theoretically derived composite measures in that the former uses a statistical approach (vs a theoretical one) to selecting the components that comprise the measure.

The Critical Path Institute's (C-Path) Coalition Against Major Diseases (CAMD), whose mission is to qualify drug development tools to accelerate treatments for neurodegeneration,[21] advanced a proposed statistically derived composite measure to the EMA and FDA with the goal of qualifying it as a primary endpoint measure for pre-dementia trials. Qualification of a measure represents a formal conclusion that within the stated context of use, the measure's results can be relied on to assess a specific concept and have a specific interpretation and application in drug development and regulatory decision making.[8,22]

CAMD's measure, the AD COMposite Score (ADCOMS), consists of items taken from the ADAS-Cog, MMSE, and CDR-SB. ADCOMS was statistically designed to be sensitive to tracking the progression of cognitive decline in a population of individuals with amnestic MCI.[23] Member companies in CAMD's Predementia Cognitive Outcome Assessment (pCOA) Working Group, a number of which have independently developed other composite scales for use as clinical outcome assessments (COAs) for AD trials, came together precompetitively, to advance this statistically derived composite measure for regulatory qualification as a COA for use in early AD trials. In response to the initial filing, both agencies requested demonstration of the composite's clinical meaningfulness. The FDA specifically recommended that CAMD leverage qualitative research, such as that gathered by C-Path's Patient-Reported Outcome (PRO) Consortium,[24] to demonstrate that the concepts of interest assessed by the composite measure relate to concerns considered meaningful to the population for which the composite is intended.[25] The purpose of the project reported here was to identify the most important cognition-related concerns patients and informants report early in the disease and determine how this information maps to what is assessed by several statistically derived composite measures, including ADCOMS.

**Table 1.** Inclusion and Exclusion Criteria for Patients With Mild Cognitive Impairment (MCI) and Their Informants.

| MCI Patients Had to Meet the Following Criteria | Informants Had to Meet the Following Criteria |
|---|---|
| • Age ≥50 y<br>• Native English speaker<br>• Willing and able to travel to research site for focus group or one-on-one interviews<br>• Willing to provide written informed consent<br>• Able to understand and comply with the requirements of the study, based on study investigator<br>• Self- or informant report of memory decline<br>• MMSE scores between 24 and 30 within the last 3 mo<br>• Self- or informant report of intact basic functional abilities<br>• CDR global score = 0.5<br>• Meets protocol-defined criteria for MCI based on Winblad et al (2004)[26] | • Family member or friend of patient who had familiarity with the patient's basic and complex activities of daily living; sees and/or speaks with an eligible participant a minimum of 3 d/wk with a minimum of 6 h/wk of in-person interaction; has known participant for >1 y to be considered for enrollment into this study<br>• Aged ≥21 y<br>• Native English speaker<br>• Willing to provide written informed consent<br>• Able to understand and comply with the requirements of the study, based on study investigator judgment |
| **MCI patients were excluded based on the following criteria:** | **Informants were excluded based on the following criteria:** |
| • A diagnosis of dementia<br>• Patients diagnosed with major depressive disorder (MDD) as indicated by the Patient Health Questionnaire–9 Depression Scale (PHQ-9; score ≥10)<br>• Any clinically relevant condition that, in the opinion of the investigator/coordinator (based on recall or medical record review), would interfere with completing the study, including, but not limited to, severe hearing and/or vision impairment and severe mental illness<br>• Serious negative life event in the previous 3 mo that would negatively impact the participant's mood in the judgment of the investigator<br>• History of alcohol or substance abuse consistent with *DSM-IV* criteria within the past 2 y (*DSM-V* had not been published at the time this study was conducted.)<br>• Participants could be currently taking prescription or nonprescription medication for their memory problem. | • Currently providing care to numerous (≥3) individuals with cognitive impairment<br>• Current self-reported substance abuse<br>• Presence of any dementing illness, such as AD or MCI<br>• Any relevant condition that would interfere with the conduct of the study, including but not limited to severe hearing impairment that would interfere with participation in group or interview<br>• Severe vision impairment that would interfere with ability to self-complete written questionnaires<br>• A serious negative life event in the previous 3 mo that may negatively impact participant mood based on study investigator judgment |

Source: Table adapted from Gordon et al (2015).[25]
Abbreviations: AD, Alzheimer disease; CDR, Clinical Dementia Rating; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-V, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; MMSE, Mini-Mental State Examination.

## Materials and Methods

To address the concerns raised by regulators, CAMD worked with the PRO Consortium's Cognition Working Group to identify the cognition-related symptoms/concerns that patients and informants report early in the disease and compare how this information maps to the subcomponents of various composites, including the composite (ie, ADCOMS) advanced by CAMD for regulatory qualification. Specifically, CAMD utilized a comprehensive formal Briefing Document previously submitted to the FDA by the PRO Consortium's Cognition Working Group that included narrative transcripts from interviews and focus groups. The focus groups and interviews, conducted to obtain patient and informant perspectives of the experience of MCI, took place in March-April 2010. The inclusion and exclusion criteria for the amnestic MCI (aMCI) patients and their informants are listed in Table 1. Amnestic MCI is defined as "clinically significant memory impairment that does not meet criteria for dementia."[27] Table 2 provides key participant demographic information. (For further information, please refer to Gordon et al[25]) Institutional review board (Ethical Review Committee, Inc, Independence, MO) approval was obtained and all participants provided written informed consent before participating.

From the Briefing Document, the pCOA Working Group constructed frequency grids (Table 3) summarizing the concerns that emerged during 5 independent focus groups with a total of 25 patients diagnosed with aMCI (n = 25) and their collateral informants (n = 25); the 5 focus groups were conducted with patients interviewed separate from their collateral informants. These concerns were divided into 3 categories based on the frequency and concordance between participant and informant reports: (1) concerns that were endorsed more frequently by patients than informants (>15% discordance, with more endorsement by the patients); (2) concerns that were endorsed by a similar number of patients and informants (<15% discordance between patients and informants); and (3) concerns endorsed more frequently by informants than patients (>15% discordance with more endorsement by informants).

**Table 2.** Key Characteristics of MCI Patients and Their Informants.

| Characteristics | MCI Patient (n = 25) | Informant (n = 25)[a] |
|---|---|---|
| Mean age (SD) | 78.4 (7.7) | 71.5 (9.1) |
| Male gender, n (%) | 17 (68.0) | 4 (16.7) |
| Ethnicity, n (%) | | |
| Hispanic or Latino | 2 (8.0) | 2 (8.3) |
| Not Hispanic or Latino | 23 (92.0) | 22 (91.7) |
| Race,[a] n (%) | | |
| American Indian or Alaska Native | 1 (4.0) | 3 (12.5) |
| Asian | – | – |
| Black or African American | 1 (4.0) | 1 (4.2) |
| White | 22 (88.0) | 22 (91.7) |
| Other | 2 (8.0) | 1 (4.2) |
| Current living/domestic situation, n (%) | | |
| Living alone | 1 (4.0) | – |
| Living with partner/spouse/family/ friends | 24 (96.0) | – |
| Other | – | – |
| Employment status,[a] n (%) | | |
| Employed, full-time | 1 (4.0) | 5 (20.8) |
| Employed, part-time | – | 2 (8.3) |
| Homemaker | 2 (8.0) | 3 (12.5) |
| Unemployed | 1 (4.0) | – |
| Retired | 21 (84.0) | 16 (66.7) |
| Disabled | 1 (4.0) | – |
| Other | 2 (8.0) | – |
| Highest level of education,[a] n (%) | | |
| Elementary/primary school | – | – |
| Secondary/high school | 5 (20.0) | 6 (25.0) |
| Some college | 6 (24.0) | 7 (29.2) |
| College degree | 10 (40.0) | 7 (29.2) |
| Postgraduate degree | 4 (16.0) | 5 (20.8) |
| Other | – | – |
| Comorbid conditions,[a] n (%) yes | | |
| None | 4 (16.0) | – |
| Angina | 2 (8.0) | – |
| Arthritis | 10 (40.0) | – |
| Asthma | 1 (4.0) | – |
| Cancer | 3 (12.0) | – |
| Chronic obstructive pulmonary disease/emphysema | 1 (4.0) | – |
| Congestive heart failure | 1 (4.0) | – |
| Hypertension | 9 (36.0) | – |
| Other | 4 (16.0) | – |
| Relationship to patient | | |
| Spouse | – | 20 (83.3) |
| Child | – | 2 (8.3) |
| Other family relation | – | – |
| Friend | – | 2 (8.3) |
| Length of time known patient; y, mean (SD) | – | 46.0 (17.3) |
| Amount of contact patient with patient in last week; h, mean (SD) | – | 129.1 (57.9) |

Source: Table adapted from Gordon et al (2015).[25]
Abbreviations: MCI, mild cognitive impairment; SD, standard deviation.
[a]One informant had a missing demographic form.

Based on FDA's emphasis on incorporating the patient voice into the determination of clinical meaningfulness, the CAMD pCOA Clinical Meaningfulness Subteam focused on all concerns endorsed by at least 50% of patients and/or informants. Two independent expert reviewers (M.T.R. and K.H.) leveraged axial coding and reviewed the narrative transcripts (corresponding to all items) to identify onto which primary and secondary cognitive domains the concerns expressed within the narratives mapped, including the following cognitive and noncognitive domains: memory, executive functioning, attention, language, visuospatial/motor coordination, orientation, and neuropsychiatric. Items that appeared unrelated to cognitive or neuropsychiatric impairment were classified as "None" or "Non-AD age-related changes." The primary domain assigned was the one most frequently described by patients and/or informants, whereas the secondary domains were described less frequently.

After assigning primary and secondary domains, the two reviewers exchanged results and met to adjudicate their respective findings. Alignment on findings occurred >95% of the time. When the two reviewers differed in their domain assignments, they reviewed the transcript together and reached consensus. The entire exercise was independently completed twice by each rater, separated by approximately 2 months; then the results of the original and follow-up ratings were compared to ensure validity and replicability of the findings.

To assign the primary and secondary status of the domains, the two reviewers also calculated the frequency of endorsement by domain. The results of the narrative analysis were then compared to assess how well these cognitive domains were represented in various statistically derived composite measures, including ADCOMS (see Table 4).

Most statistically derived composite measures are primarily based on analysis of Alzheimer's Disease Neuroimaging Initiative (ADNI) data,[17,23,29-32] plus or minus clinical trial data. By design, ADNI contains measures commonly used in mild-to-moderate AD clinical trials to-date, such as the MMSE, ADAS-Cog, and/or CDR. Therefore, it is not surprising that the majority of the statistically derived composite measures are comprised from these same measures as noted in Table 4. The items incorporated into ADCOMS were selected based on their responsiveness to early AD clinical decline as determined by identifying the combination of items that achieved the largest mean to standard deviation ratio among all combinations tested. For information on the derivation methods and rationale of the other composite measures, please refer to the respective references.[29-33]

As noted above, the CAMD pCOA Clinical Meaningfulness Subteam ascertained the degree of overlap between the concerns most commonly reported by aMCI patients and informants. The subteam also compared the subcomponents of the various composite measures, including ADCOMS.

## Results

This research addressed the central question of whether the various statistically derived composites effectively assess the most meaningful concerns shared by aMCI patients and their

**Table 3.** Frequency of Specific Concerns Expressed by aMCI Patients and Informants (n = 25).

| | Patient Concern | | Informant Concern | |
|---|---|---|---|---|
| | n | % | n | % |
| Patient more concerned than informant (>15% difference) | | | | |
| Assistive devices for memory | 22 | 88 | 18 | 72 |
| Memory—forgets names | 20 | 80 | 9 | 36 |
| Social interaction | 19 | 76 | 12 | 48 |
| Impact—on social functioning | 14 | 56 | 10 | 40 |
| Irritation/irritated/irritating | 14 | 56 | 7 | 28 |
| Memory problems—affecting verbal expression | 13 | 52 | 6 | 24 |
| Communication-spoken | 11 | 44 | 6 | 24 |
| Assistance—physical | 9 | 36 | 3 | 12 |
| Shopping | 9 | 36 | 5 | 20 |
| Patient and informant have similar concern rate (within 15%) | | | | |
| Memory/recall | 25 | 100 | 25 | 100 |
| Leisure activities/hobbies | 20 | 80 | 18 | 72 |
| Impact—caregiver/informant | 18 | 72 | 17 | 68 |
| Insight (into problems) | 16 | 64 | 15 | 60 |
| Duration of memory problems/memory loss | 14 | 56 | 15 | 60 |
| Employment status | 14 | 56 | 11 | 44 |
| Sleep | 14 | 56 | 16 | 64 |
| Driving—changes in | 13 | 52 | 16 | 64 |
| Impact—on daily activities | 12 | 48 | 10 | 40 |
| Coping | 11 | 44 | 9 | 36 |
| Handling money | 11 | 44 | 14 | 56 |
| Emotional | 9 | 36 | 10 | 40 |
| Misplacing things | 9 | 36 | 8 | 32 |
| Organization/organize | 9 | 36 | 11 | 44 |
| Worry | 9 | 36 | 7 | 28 |
| Chores | 8 | 32 | 5 | 20 |
| Energy | 8 | 32 | 7 | 28 |
| Embarrass/embarrassment | 7 | 28 | 7 | 28 |
| Frequency of memory problems | 7 | 28 | 8 | 32 |
| Impact-on work functioning | 7 | 28 | 7 | 28 |
| Short-tempered (short-fused) | 7 | 28 | 4 | 16 |
| Denial | 6 | 24 | 8 | 32 |
| Dependence physical | 6 | 24 | 7 | 28 |
| Brain performance changes | 5 | 20 | 5 | 20 |
| Communication—written | 5 | 20 | 5 | 20 |
| Impact of memory problems | 5 | 20 | 7 | 28 |
| Living situation | 5 | 20 | 5 | 20 |
| Informant more concerned than patient (>15% difference) | | | | |
| Personality | 12 | 48 | 20 | 80 |
| Frustration | 11 | 44 | 16 | 64 |
| Interest/motivation | 10 | 40 | 15 | 60 |
| Cooking | 9 | 36 | 17 | 68 |
| Medicine | 8 | 32 | 12 | 48 |
| Memory problems—dates | 7 | 28 | 13 | 52 |
| Planning | 7 | 28 | 11 | 44 |
| Attention/focus/concentration | 6 | 24 | 10 | 40 |
| Directions—needs help in | 6 | 24 | 11 | 44 |
| Physical problems | 6 | 24 | 12 | 48 |
| Comprehension—written | 5 | 20 | 11 | 44 |
| Dependence—supervision | 5 | 20 | 10 | 40 |

Abbreviation: aMCI, amnestic MCI.

**Table 4.** Composite Measures Evaluated.

| Subscale | Instrument | AstraZeneca ProADAS | Pfizer | Janssen TriAD | Janssen TriAD-G | Eisai ADCOMS | Janssen ADCCS | Merck AD3D |
|---|---|---|---|---|---|---|---|---|
| Immediate Word Recall | ADAS-Cog | X | X | X | X | | X | X |
| Commands | ADAS-Cog | | | | | | | |
| Construction | ADAS-Cog | | | | | | | |
| Delayed Word Recall | ADAS-Cog | X | X | X | X | X | X | X |
| Naming | ADAS-Cog | | | | | | | |
| Ideational Praxis | ADAS-Cog | | | | | | | |
| Orientation | ADAS-Cog | X | X | X | X | X | X | X |
| Word Recognition | ADAS-Cog | | | | | X | X | X |
| Recall Instructions | ADAS-Cog | | | | | | | |
| Spoken Language | ADAS-Cog | | | | | | | |
| Word Finding | ADAS-Cog | X | | | | X | | |
| Comprehension | ADAS-Cog | | | | | | | |
| Number Cancellation | ADAS-Cog | X | | | | | | |
| CDR-SB | CDR | | X | | | X | X | |
| CDR-SB-Cog | CDR | | | X | X | | | |
| Functional Activities Questionnaire (FAQ) | FAQ (Pfeffer et al, 1982)[28] | | X | | X | | | |
| MMSE | MMSE | | | | | | | |
| MMSE–Orientation | MMSE | | | | | X | | |
| MMSE–Const Praxis | MMSE | | | | | X | | |
| Trail Making Test B | NTB | | | | | | | X |
| Digit Span Back | NTB | | | | | | | X |
| Category Fluency Test–Animals | NTB | | | | | | | X |
| Trail Making Test A | NTB | | | | | | | X |
| Digit Span Forward | NTB | | | | | | | X |
| Digit Symbol | NTB | | | | | | | X |

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; NTB, Neuropsychological Test Battery.

collateral informants. To answer this question, the verbatim narrative transcripts of aMCI patients and their collateral informants were reviewed and concerns mapped to primary and/or secondary cognitive and noncognitive domains. Table 5 reflects the results of this mapping exercise. Two examples illustrate the importance of this remapping effort. First, regarding the concerns about driving changes, the narratives revealed that the most frequently reported complaints mentioned difficulties remembering where to go rather than becoming disoriented when driving. Thus, for the item "driving changes," the primary domain was memory and the secondary domain, orientation. The second example relates to the concern of "embarrassment." While this frequently expressed concern might on first glance be assigned to a neuropsychiatric domain (ie, anxiety), a closer read of the narratives revealed that in many cases patients reported feeling embarrassed because they were unable to track a topic in conversation or forgot what they wanted to say. In these cases, embarrassment was described as resulting from memory impairment, and the item was therefore assigned to the cognitive domain of memory.

Some items did not map onto a cognitive or neuropsychiatric domain. Therefore, based on the two independent expert reviews, these items were designated "None" or "Non-AD Age-Related" because, for the most part, they appeared related to aging issues not specific to AD dementia or concomitant neuropsychiatric changes. Knowledge of, training in, and clinical experience with normal healthy aging and dementia populations allows one to decipher normal age-related concerns from those that reflect dementia. However, in some cases even the verbatim transcripts provided insufficient detail to assign a specific concern to advancing age or dementia. For example, one participant stated, "I spend a lot of time resting at the television set. . . . I watch a little; I just snooze a lot." While one might infer something AD-related as contributing to this concern—for example, the inability to follow a conversation on TV—this inference would go beyond what is stated in the transcript.

The reported concerns were calculated to determine the frequency of reported primary and secondary cognitive and noncognitive domains. Table 6 reflects that the most frequently reported concerns mapped onto one primary cognitive domain, episodic memory. Secondary patient and informant cognitive concerns most frequently mapped to the domains of orientation and language.

Table 4 reflects that all the composite measures examined objectively assess episodic memory via an immediate, delayed, and/or recognition subscale. In addition, all composites except the ProADAS and AD3D contain a subjective memory rating via the Clinical Dementia Rating scale. In terms of language, both the ProADAS and ADCOMS contain a subjective rating

**Table 5.** Mapping of Concerns Identified Through Qualitative Research to Relevant Cognitive Domains.

| Qualitative Research Item | 1. Primary Domain<br>2. Secondary Domain |
|---|---|
| Assistive Devices for Memory | Memory |
| Cooking | Memory |
| Driving—changes in | 1. Memory<br>2. Orientation |
| Duration of memory problems / memory loss | Memory |
| Employment status | None/Non-AD age-related |
| Frustration | 1. Memory<br>2. Neuropsychiatric |
| Handling money | Memory |
| Impact—caregiver/informant | 1. Memory<br>2. Neuropsychiatric |
| Impact on social functioning | 1. Memory<br>2. Language[a] |
| Insight (into problems) | Memory |
| Interest/motivation | Neuropsychiatric |
| Irritation/irritated/irritating | Neuropsychiatric |
| Leisure activities/hobbies | None/Non-AD age-related |
| Memory—forgets names | Memory |
| Memory problems—affecting verbal expression | 1. Memory<br>2. Language[a] |
| Memory problems—dates | 1. Memory<br>2. Orientation |
| Memory/recall | 1. Memory<br>2. Orientation |
| Personality | Neuropsychiatric |
| Sleep | None/Non-AD age-related |
| Social interaction | 1. Memory<br>2. Language[a] |

Abbreviation: AD, Alzheimer disease.
[a]Word Finding Difficulties.

**Table 6.** Frequency of Reported Primary and Secondary Cognitive Concerns Endorsed by ≥50% of Patients and/or Informants.

| All Concerns Endorsed by ≥50% of Patients and/or Informants | | | |
|---|---|---|---|
| Domain | Primary | Secondary | Total Frequency |
| Memory | 14 | 0 | 14 |
| Neuropsychiatric | 3 | 2 | 5 |
| Language (Word Finding) | 0 | 3 | 3 |
| Orientation | 0 | 3 | 3 |
| None/Non-AD Age-Related | 2 | 0 | 2 |
| Total | 19 | 8 | 27 |

of Language (Word Finding) as part of the ADAS-Cog. Orientation is objectively assessed in all the composites through the ADAS-Cog Orientation subtest. In addition, ADCOMS contains two objective memory measures (ie, ADAS-Cog Delayed Word Recall, Word Recognition), as well as one subjective memory rating (CDR Memory). In addition, it contains two objective measures of Orientation (ADAS-Cog Orientation and MMSE Orientation), as well as one subjective Orientation rating (CDR Orientation). Furthermore, ADCOMS is composed of an objective measure of visuospatial/motor coordination (ie, MMSE Constructional Praxis), a subjective rating of language (ADAS-Cog Word Finding Difficulty), and several subjective ratings of function (CDR Personal Care, Community Affairs, and Home and Hobbies).

However, it is worth keeping in mind that none of the objective subtests comprising ADCOMS (or any measure) is a pure measure of a discrete cognitive domain. Rather, most objective measures of cognition tap into and require various cognitive processes for successful completion. For example, drawing the overlapping pentagons from the MMSE (ie, Constructional Praxis) requires attention, as well as visuospatial abilities and motor coordination. Additionally, the 3 subjective CDR ratings of functioning (eg, personal care, community affairs, home, and hobbies) also rely on multiple aspects of cognition, including attention, memory, language, and/or executive function.

Once the aMCI patients and their collateral informants' concerns were mapped and frequencies calculated, the CAMD pCOA Clinical Meaningfulness Subteam explored each of the statistically derived composite's subcomponents to determine which cognitive and noncognitive domains each captures. Table 7 lists the various statistically derived composite's component measures, what domains each was determined to tap into, as well as their composition. The domains represented include both cognitive and noncognitive neuropsychiatric domains (ie, mood or behavioral changes secondary to the illness), although none of the statistically derived composites contains an assessment of neuropsychiatric symptoms.

## Discussion

The goal of this research was to determine whether the most meaningful concerns shared by aMCI patients and their collateral informants are captured by various statistically derived composites developed for use as exploratory outcome measures in early AD clinical trials. These composites were all derived using cohort data from ADNI, and in some cases clinical trial data as well. Items incorporated into these composites were selected using somewhat different statistical approaches, but all were based on their responsiveness to clinical decline at the predementia stage of the AD spectrum. Thus, although the composites were developed independently by several pharmaceutical companies, it is not surprising that they all reflect a common set of cognitive domains: memory, orientation, visuospatial/motor coordination, language, and executive function. There were some differences, however. While most of the composites contain both cognitive and functional measures, the ProADAS and AD3D include only cognitive measures. The AD3D also includes objective measures of executive function from the Neuropsychological Test Battery (NTB)[34] that were not included in the other composites. NTB measures were considered for ADCOMS but statistically determined to add nothing beyond what was already captured by subjective ratings of function in the CDR-SB.

**Table 7.** Domain Mapping and Comparison of Statistically Derived Composite Component Measures.

| Composite Component Measures | Composite Mapping |
|---|---|
| Objective Memory Measures: | All Composites |
| ADAS-Cog Immediate Word Recall | All but ADCOMS |
| ADAS-Cog Delayed Word Recall | All Composites |
| ADAS-Cog Word Recognition | ADCOMS, ADCCS; AD3D |
| Subjective Memory Rating: | All but ProADAS and AD3D |
| CDR Memory | All but ProADAS and AD3D |
| Objective Orientation Measures | ALL Composites |
| ADAS-Cog Orientation | All Composites |
| MMSE Orientation | ADCOMS |
| Subjective Orientation Rating | All but ProADAS and AD3D |
| CDR Orientation | All but ProADAS and AD3D |
| Objective Visuospatial/Motor | ADCOMS |
| Coordination (VSp/Motor Coord) | ADCOMS |
| MMSE Constructional Praxis | |
| Subjective Language Rating | ProADAS and ADCOMS |
| ADAS-Cog Word Finding Difficulty | ProADAS and ADCOMS |
| Objective Attention and/or Executive Function | Varied |
| Trail Making Test–Part B | AD3D |
| Digit Span | AD3D |
| Digit Symbol | AD3D |
| Category Fluency | AD3D |
| Number Cancellation | ProADAS |
| Subjective Attention and/or Executive Function | All but ProADAS and AD3D |
| CDR Judgment and Problem Solving | All but ProADAS and AD3D |
| Subjective Ratings of Function | Varied |
| CDR Personal Care | All but ProADAS and AD3D |
| CDR Community Affairs | All but ProADAS and AD3D |
| CDR Home and Hobbies | All but ProADAS and AD3D |
| FAQ | Pfizer and TriAD-G |
| None—not applicable | None—not applicable |

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive; ADCOMS, AD COMposite Score; CDR, Clinical Dementia Rating; FAQ, Functional Activities Questionnaire; MMSE, Mini-Mental State Examination; NTB, Neuropsychological Test Battery.

Analysis of transcripts from focus groups and interviews conducted by the PRO Consortium's Cognition Working Group with individuals diagnosed with aMCI as well as their collateral informants revealed that their primary concerns most frequently mapped to the cognitive domain of episodic memory. Secondary concerns mapped to the domains of orientation and language (word finding). Additional items from the narrative mapped onto noncognitive, neuropsychiatric, and non-AD age-related domains. Although neuropsychiatric symptoms were the second highest rated items, it should be noted that the verbatim transcripts were aimed at (ie, possibly biased towards) the respondents answering with a neuropsychiatric concern. For instance, if an interview question queried whether memory problems had made the patient more irritated or irritable, it seems logical that the responses would map onto/reflect neuropsychiatric symptoms. It should be noted that ADCOMS research showed that the addition of a formal neuropsychiatric measure (ie, Neuropsychiatric Inventory [NPI]) did not add anything to the model and was not as powerful a predictor as those measures that made it into the model.

An important limitation to this study is that it did not prospectively/directly test whether performance on each of the composite measures correlated with the reported concerns in daily life (ie, tested the ecological validity). Ecological validity studies of the ADAS-Cog are also unfortunately lacking despite this being the most frequently used clinical endpoint measure in AD clinical drug trials in MCI and mild-to-moderate AD. Some studies suggest poor correlation between the ADAS-Cog and clinician- and patient-reported outcomes. Other studies suggest that informant-reported functional impairment may follow cognitive decline on the ADAS-Cog and that correlation between the two measures may increase over time.[35]

While qualitative research is essential for capturing the voices and concerns of patients and informants and thus demonstrating meaningfulness, it is associated with a number of limitations arising from the subjective nature of the data. In this particular case, one factor that may affect the reliability of the data is that aMCI patients may not accurately self-report changes in cognition or function due to anosognosia.[36,37] Informant reports may also be of questionable reliability based on a number of factors including how much time the informant spends with the patient. Thus, for example, spouses may be more reliable than adult children, although spouses are also likely to be older adults and may have subtle cognitive impairments that affect the reliability of their reports. The nature of the relationship between dyads (eg, patient and spouse, patient and adult child, or patient and other caregiver) imposes an additional source of bias. For example, caregiver burden and depression may lead to more negative assessments of patient characteristics.[38] Notably, it has been demonstrated that there is a lack of correlation between self-reported vs caregiver-reported outcomes in cases with MCI due to AD from ADNI.[36] The aMCI patients interviewed were not evaluated using biomarkers, thus making it impossible to know if their aMCI was due to AD. Finally, these patient/informant interviews were conducted in independent focus groups, which can add additional biases, as patients and informants may be prompted to express concerns only after hearing these concerns from another participant in the group.

There are other ways to approach the topic of clinical meaningfulness. This study provided qualitative insights on the most meaningful outcomes in MCI from the patient and informant perspectives. It did not take into account clinician or payer perspectives or other potentially important factors such as the "ability to live without assistance." The approach taken in this study aligns with the FDA vision and focus on integrating patient voice into COA development.

It is important to keep in mind that in addition to being clinically meaningful, a good neuropsychological test or resulting composite measure should have good psychometric properties and evidence that it assesses something meaningful

for the particular patient group being studied. For example, a composite measure such as the original ADAS-Cog may cover clinically meaningful domains for mild AD (ie, episodic memory), but this measure has well-documented psychometric limitations[39] and is not suitable for use earlier in the AD spectrum.[40]

## Conclusions

Through prospective analyses of qualitative research data from the PRO Consortium's Cognition Working Group, the CAMD pCOA Clinical Meaningfulness Subteam evaluated how well the concerns of patients and informants map to statistically derived composite measures. This analysis showed that these composites do indeed capture the cognitive domains that reflect what patients and informants identify subjectively as their areas of greatest concern. While patients and informants do not typically use the vocabulary of neuropsychology in their complaints, independent review of their verbatim concerns by experts enabled translation of these voices into domains that are captured using neuropsychological tests and supported with scientific understanding of the functional consequences of brain disease.

The literature supports that two of the earliest and most sensitive neuropsychological tests from healthy older adults through patients with prodromal AD are measures of episodic memory and timed executive functioning.[41,42] In addition, it is well established that language/word finding and orientation difficulties are problems in individuals who progress from aMCI into mild dementia. Although executive functioning did not arise as a reported concern of individuals early in the AD disease process (ie, amnestic MCI), it is acknowledged that as the disease progresses these concerns become more prominent.

In closing, this is one of several approaches to address the meaningfulness of what is being assessed by statistically derived composite measures for early AD research. The approach was enabled by collaboration between two C-Path consortia (ie, CAMD and PRO Consortium) and is aligned with FDA's emphasis on patient-focused drug development.[43,44] Alignment across precompetitive consortia was a key factor in this project's success in identifying measures that assess outcomes that are most meaningful to patients. While CAMD has since discontinued advancing ADCOMS as a primary endpoint measure through the formal regulatory qualification path, work on other statistically derived composite outcome measures is being continued by others.

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### Declaration of Conflicting Interests

The following author(s) declare that they have no conflict of interest: DS, SJC, and SH. MTR: financial competing interest—Johnson & Johnson; nonfinancial competing interest—none. KH: financial competing interest—employed by AstraZeneca until 2014. KH is a paid consultant to AstraZeneca; nonfinancial competing interest—none. MFG: financial competing interest—Boerhinger Ingelheim; nonfinancial competing interest—none. RS: financial competing interest—paid consultant to Athena Diagnostics (Quest) and Janssen Research & Development; advisory board member for Biogen, Amarantus Bioscience, and Avanir Pharmaceuticals, and has been an expert panel member for Adelphi Values (as part of C-Path's PRO Consortium); receives research support from Avid Radiopharmaceuticals, Eli Lilly and Company, and Eisai Pharmaceuticals, as well as from the Alzheimer's Disease Cooperative Study (ADCS, funded by the National Institute on Aging), for which he is a steering committee member; receives royalties for published neuropsychological tests from Psychological Assessment Resources, Inc; nonfinancial competing interest—none.

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