Evaluation of What Matters Most in Existing Clinical Outcomes Assessments in Alzheimer's Disease

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Background

The Alzheimer's Disease Patient and Caregiver Engagement (AD PACE) initiative was designed as a series of projects aimed at incorporating the understanding and assessment of treatment-related needs, preferences, and priorities among individuals with or at risk for AD and their care partners, across the continuum of disease.

One of AD PACE initiatives, the What Matters Most (WMM) study, was conducted to assess and better understand treatment-related needs (i.e., what matters) and the preferences and priorities (i.e., what matters most) of individuals with or at risk for AD and their care partners. The WMM Study identified treatment-related outcomes that matter (are important, meaningful) to people with or at risk for AD and their caregivers, and then assessed how much each treatment-related outcome matters to those individuals, and which outcomes matter most.

The study presented here extends this work by comparing the concepts identified in the WMM studies to the concepts that are included in existing clinical outcome assessments (COAs) and selected neurocognitive measures commonly used in AD clinical trials and divided into three parts **(Part 1 & 2 Reported in this poster)**.

Part 1- Identify Existing Measures: Review literature and ClinicalTrials.gov to identify COAs and neurocognitive measures commonly used in target populations (preclinical, MCI and mild AD, moderate AD, severe AD)

Part 2- Conduct Concept Mapping: Select a subset of COAs meeting defined criteria and map content of these to the most important concepts from WMM Qualitative Study

Part 3- Conduct a Detailed Instrument Review and Gap Analysis (ongoing): Critically review available evidence for each COA (up to 20) to determine how existing measures meet (or can meet, with modification) needs for assessing the concepts of greatest importance to individuals at risk for or with AD or their care partners

Methods

Part 1- Identify Existing Measures:
PubMed and Embase searches were conducted using a preapproved search strategy limited to studies published in English within the last 5 years (2014-2019) meeting inclusion and exclusion criteria. Studies with populations across the continuum of AD (preclinical to severe) or caregivers of individuals the aforementioned stages. Studies included any pharmacological intervention. No intervention needed to be reported in the case of registry or observational/real-world studies. Included studies needed to report at least one type of outcome of interest: clinician-reported outcome (ClinRO), observer-reported outcome (ObsRO) , Neurocognitive/performance outcome (PerfO) or patient-reported outcome (PRO). Studies where the majority of the data came from the US or Canada of the following types were included: clinical trials, observational or registry studies, consensus reports, and guidelines or position statements regarding COA selection for interventional studies. Seminal articles published before this period were also included. Additionally, a search of ClinicalTrials.gov identified COAs and neurocognitive measures used as primary and secondary endpoints in registries and interventional studies within the past 5 years.

Data collected included information regarding the study type (i.e., clinical trial or real-world observational or registry study), sample (preclinical AD, MCI, mild, moderate, or severe AD), and COAs used as outcome measures. The type of COA was assigned by a licensed clinical psychologist, and verified by an external researcher with previous experience in AD. Measures were implemented to ensure COA measures were only counted once. COAs recommended for Part 2 were those used in 4 or 5 of the AD populations, those used in only 3 AD populations (including preclinical), and expert recommendation.

Part 2- Conduct Concept Mapping:
The content of each COA identified in Part 1 **(Table 1)** were compared with the 42 items/concepts from the WMM Study survey (Vradenburg et al., 2019). Each WMM item/concept was mapped to items on the individual COAs using copies of the instrument or its manual (where available), publicly available information (literature, websites), and researcher's internal COA repository. The mapping exercise considered all versions of individual measures available to them at the time of this review (e.g., ACAS-Cog and ADAS-Cog 13).

The COA mapping was done by 3 individuals: 2 who conducted the WMM qualitative interviews and 1 outcomes researcher with research experience in persons with dementia and care partners.

Results

Part 1- Identify Existing Measures: Included records from the database search and Clinicaltrials.gov search were combined for total of 107 unique studies in 109 records. The majority of studies were clinical trials (n = 99), with the remainder consisting of real-world observational and registry studies (n = 10). No consensus reports, guidelines or position statements were included in the review as they did not meet inclusion criteria.

Neurocognitive/PerfO measures were the most common type of COA identified in the combined searches. COAs and unnamed composite COAs were most frequently used in MCI, mild and moderate AD populations; COAs were used less often among preclinical (n = 22) and severe AD populations (n = 13). Twenty COAs **(Table 1)** were recommended for Part 2 mapping exercise based both on the type of COA instrument, the populations in which they have been used, and the general content of each measure (e.g., cognitive functioning, mood, behavioral symptoms).

Table 1: COAs Reported in the Literature Retained and for Part 2 Mapping Exercise

COAs used in 4-5 AD Populations	COAs used in 3 AD Populations (including Pre-clinical AD)	Composite COAs	Others
▪ Alzheimer's Disease Assessment Scale **(ADAS)** cognitive subscale **(ADAS-Cog)** ▪ Alzheimer's Disease Cooperative Study - Activities of Daily living Inventory **(ADCS-ADL)** ▪ Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change **(ADCS-CGIC)** ▪ Cornell Scale for Depression in Dementia **(C-SDD)** ▪ Clinical Dementia Rating Scale- including CDR Sum of Boxes **(CDR/CDR-SB)** ▪ Free and Cued Selective Reminding Test **(FCSRT)** ▪ EuroQol 5-Dimensional Health-Related Quality of Life Scale **(EQ 5D)** ▪ Mini-Mental State Examination **(MMSE)** ▪ Montreal Cognitive Assessment **(MoCA)** ▪ Neuropsychiatric Inventory **(NPI/NPI-Q)** ▪ Quality of Life in Alzheimer's Disease Scale **(QoL-AD)** by Proxy ▪ Zarit Burden Interview **(ZBI)**	▪ [Pfeffer] Functional Activities Questionnaire **(FAQ)** ▪ Alzheimer's Disease Cooperative Study - Activities of Daily living Inventory - MCI (specific) **(ADCS-ADL-MCI)** ▪ Rey Auditory Verbal Learning Test **(RAVLT)**	▪ AD COMposite Scores **(ADCOMs)** ▪ Integrated Alzheimer's Disease Rating Scale **(iADRS)** ▪ Preclinical Alzheimer Cognitive Composite **(PACC)**	▪ Digit Symbol Substitution Test **(DSST)** ▪ Wechsler Memory Scale **(WMS)**

The six most frequently reported COAs included the ADAS-Cog (n = 65), MMSE (n = 52), NPI (n = 45), ADCS-ADL (n = 36), CDR/CDR Sum of Boxes (n = 33), and ADCS-CGIC (n = 19). Of these, only three COA measures were used in all 5 AD stages: MMSE, ADCS-ADL, and NPI.

Part 2- Conduct Concept Mapping:
Table 2 presents the results of the mapping exercise. The WMM concepts that most closely matched items in the COAs reviewed (as defined by 6 or more red codes) included:

- **10 COAs -** Not have difficulty doing hobbies or leisure activities; Learns new information, tasks, or procedures
- **8 COAs -** Completes basic household chores
- **7 COAs -** Remembers things on a list or reminder; Remembers what someone just told you/them; Remembers words or names of familiar objects; Orientation to date and time; Manages money or pays bills correctly
- **6 COAs -** Socializes with family and friends

The COAs that directly mapped (indicated by cells in red) to the most WMM concepts (defined as 10 or more) included ADCS-ADL (17 concepts), iADRS (15 concepts), ADCS-ADL-MCI (14 concepts), ADCOMs (13 concepts), and CDR/CDR-SB (12 concepts). Two COAs (ADCS-CGIC and ZBI) did not directly map (i.e., had no red cells) to any of the individual WMM concepts.

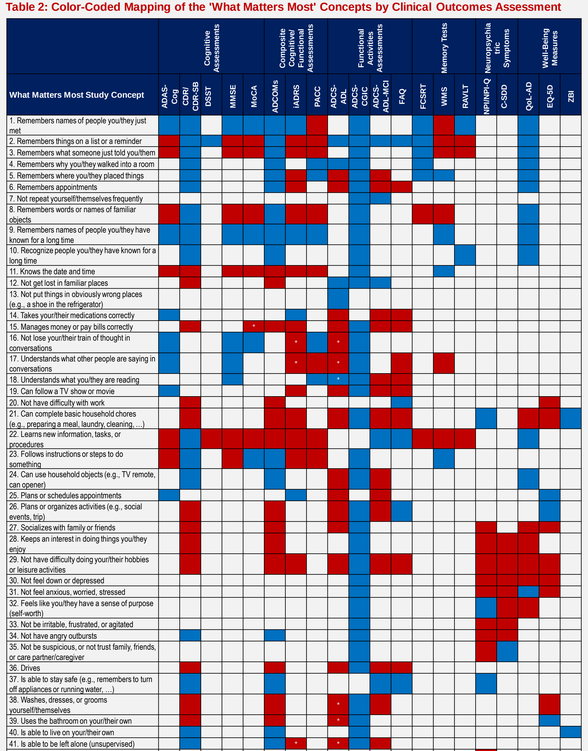
Concepts were included in the 20 COAs that were not identified in the WMM studies list of 42 Concepts. The most common additional concepts (defined as included in 3 or more COAs) include:

- **7 COAs -** Constructional praxis
- **3 COAs -** Orientation to place, Quality of patient's spoken language, Visual spatial/visuoperception, Writing a sentence that includes a subject and verb and makes sense, Making phone calls/using a phone, Walking

The COAs that had the most non-WMM concepts (defined as 10 or more) included the iADRS (12 concepts) and the ADCS-ADL (10 concepts), and covered concepts, such as difficulty with using a telephone, smartphone, or electronic device; difficulty handling mail; obtaining a beverage; disposing of litter; and difficulties walking. Based on study methodology these items did not map to the narrowed down list of 42 items from the WMM study.

Results (Continued)

Table 2: Color-Coded Mapping of the 'What Matters Most' Concepts by Clinical Outcomes Assessment



* Item appears on one or more references but not in the primary instrument reviewed.
RED cells indicate an exact match between the WMM concept and an item in the COA.
BLUE cells indicate a close but not exact match between the WMM concept and an item in the COA.
Any WMM concepts that contained both red and blue codes for a COA were ultimately coded red in this table.

Results (Continued)

Results from this mapping exercise indicate that every WMM concept is represented in one or more of the 20 COAs reviewed, even if not always an exact or perfect conceptual equivalent. These results provide additional evidence for the importance of the 42 WMM concepts as they are either directly or indirectly included in existing measures, many of which are considered to be gold standards in AD. Not surprisingly, no single instrument covered all of the 42 WMM concepts.

Nine of the 42 WMM concepts matched well (coded red) to multiple COAs (defined as 6 or more).

Limitations

- Instrument selection (i.e., creation of the set of COAs to be reviewed) was based on stringent and well-described inclusion criteria. Other criteria could have yielded different measures for assessment.
- Concepts beyond the final 42 from the WMM studies that are included in the assessed COAs were not assessed for patient/care partner importance in this work.
- While the concept mapping was rigorously conducted, it was not completely objective, and some subjectivity was required in the mapping decisions. Determinations on whether an item was an exact conceptual match and inherently captured a WMM concept (even if the language differed) was debated by the mapping team and only direct matches to qualitative interviews were coded red. For example, the CDR/CDR-SB instrument documents the clinician's report on the "memory" of the patient, which may be based on the clinician's interview with the patient or an informant. The CDR/CDR-SB worksheets do not inquire about all aspects of memory, such as "remembers words or names of familiar objects;" therefore this concept was marked as "blue" or not an exact (but close) match for the CDR/CDR-SB. It is possible that other researchers would have made different decisions.
- Mapping of WMM concepts to existing instruments was dependent on materials available to researchers at the time of this work. In some cases, researchers did not have actual copies of instruments, manuals, and other testing materials. Some mapping (and blue/red coding) may change with review of additional materials.

Conclusions

Performance outcome measures (e.g., MMSE, MoCA, and DSST) were the most common type of COA identified, followed by clinician-reported and observer-reported measures. Only three COAs were used in all 5 AD populations: MMSE, ADCS-ADL, NPI. Very few patient-reported measures were identified; the most frequently being the EQ5D (used in 4/5 AD populations).

Some of the most important and meaningful symptoms and impacts of AD identified by patients and care partners in the WMM Studies are not captured by the most widely used COAs. The lack of alignment between the WMM concepts and content of the COAs may be, in part, due to the COAs identified and the fact most of the COAs are designed to measure observations in the clinic. The things that matter to patients and caregivers may be difficult to measure this way.

Overall, these results support that many of the most used COAs in AD do capture concepts identified as important to AD populations and their care partners. Use of companion tools should be considered to fully demonstrate meaningful disease and treatment-related impacts/benefits across multiple domains. Such tools can be used to supplement existing neurocognitive or other COA measures to more fully capture concepts of interest for those living with Alzheimer's Disease and their care partners.

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About AD PACE: UsAgainstAlzheimer's AD PACE initiative, is a pre-competitive collaboration that brings together nonprofit entities, people living with AD, care partners supporting for those living with AD, academic leaders, healthcare and biopharmaceutical industry, and government advisors to identify and quantify treatment-related needs, preferences, and priorities among individuals representing different stages of the AD continuum and their care partners to inform drug development, regulatory and reimbursement decision-making. If you are interested in partnering with AD PACE, please contact Allison.Martin@faegredrinker.com

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