Best-Fit Clinical Outcomes Assessment Measures to Evaluate What Matters Most in Alzheimer's Disease: **Identifying a Core Outcomes Set From Existing Measures**

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BACKGROUND

- The What Matters Most (WMM) in Alzheimer's disease (AD) research program seeks to identify and measure disease- and treatment-related needs, preferences, and priorities of diverse populations of people at risk for or living with Alzheimer's disease (PLWAD) and their care partners across the AD continuum (Supplemental Figure S-1). Previous WMM research:
  - Identified an initial 42 WMM concepts endorsed as important and developed a conceptual model of disease, ultimately comprising 50 concepts across 6 domains (Figure 1).[1-3]
  - Assessed selected psychometric properties of the conceptual model and quantified the prioritization and impact of WMM concepts in a large (n=640) observational survey-based study.[4-5]
  - Mapped COAs most frequently used in AD studies to WMM concepts (i.e., "legacy" measures).[6]
- As AD treatments emerge, it is critical to select robust, patient-centric outcome measures with a demonstrated link to priorities among those living with cognitive impairment and their care partners.

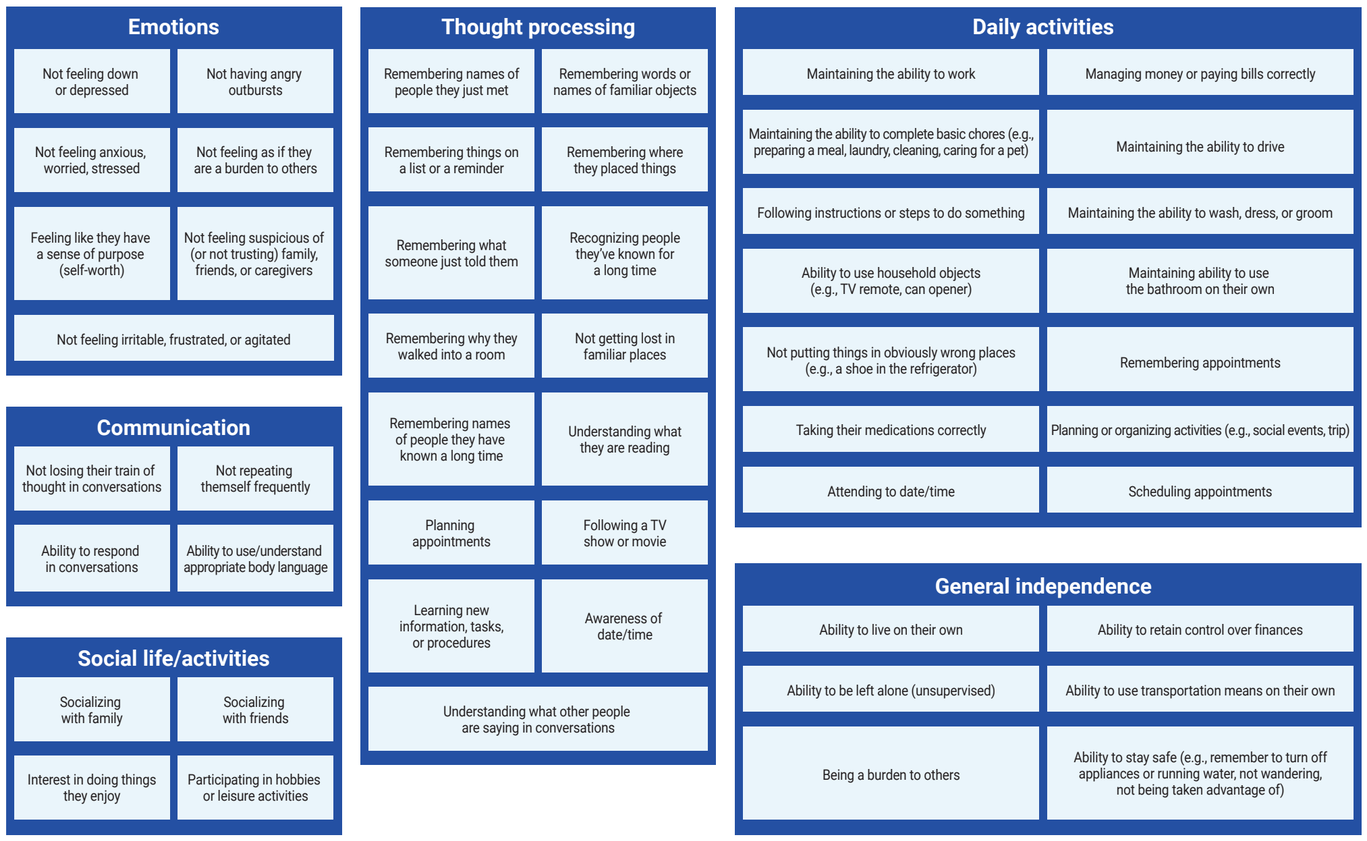
OBJECTIVE

- To identify measures that directly and specifically capture WMM patient-centric outcomes ("best-fit" COAs) and create a Core Outcomes Assessment set for use across the AD continuum.

METHODS

- Consistent with previous concept mapping,[6] items from both frequently used, legacy COAs and newly identified, additional ("supplemental") COAs were reviewed and matched either directly (item content explicitly maps to content/intent of WMM concept) or indirectly (content/intent of WMM concept is assumed based on item content) to WMM concepts.
  - Evidence for each best-fit COA was reviewed to determine how existing measures meet or could be modified to meet needs for assessing WMM concepts.
  - Measurement gaps, where WMM concepts lack a corresponding measure, were identified.
- A targeted literature review identified candidate COAs (i.e., measures with appropriate development and established measurement properties specific for use across the spectrum of AD severity that may capture the WMM concepts).
  - ClinicalTrials.gov was searched to identify COAs and neurocognitive measures that have been used in registries, interventional studies, and recent drug approvals in the US within the past 5 years (2012-2022 primary completion dates).
  - Desktop research was conducted based on the expertise of the investigation team to supplement searches.
  - Subject-, care partner-, and clinician-reported versions of tools were included.

Figure 1. Domains of the **WMM Conceptual Model of Disease**



CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; PET = positron emission tomography.

Note: The conceptual model of disease was previously presented at the Clinical Trials on Alzheimer's disease (CTAD) meeting held 24-27 October 2023 in Boston, MA, and at the Alzheimer's Association International Conference (AAIC) held 28 July-1 August 2024 in Philadelphia, PA.

RESULTS

- Among 20 candidate legacy COAs, 8 tools were selected for mapping (Table 1): ADCOMS, ADCS-ADL-MCI, CDR, FAQ, iADRS, NPI/NPI-Q, PACC, and QoL-AD (Supplemental Tables S-1 and S-2).
- Searches for supplemental measures identified an additional 20 measures, 11 of which were selected for mapping (Table 2): A-IADL-Q, ADRQL, AES, BADLS, CMAI, CFIa, CogState C3, daily diary assessments, ECog, NIH Toolbox, and PROMIS/Neuro-QoL Short Forms (Supplemental Tables S-3 and S-4).
- The selected best-fit measures offered the broadest direct or indirect alignment with the WMM model (Tables 1 and 2).
  - As expected, no single measure was identified that provided complete, direct coverage of WMM concepts and important measurement gaps were identified, especially regarding relevant concepts/domains from prioritization and impact evaluations (Table 3).

Table 1. **WMM Domain Coverage for Legacy Measures Best-Fit Set**

Domain (number of concepts)		CDR/ CDR-SB	ADCS-ADL-MCI	FAQ	ADCOMS	iADRS	PACC	NPI/ NPI-Q	QoL-AD
Emotions (7 concepts)	Direct	0	0	0	0	0	0	6	2
	Indirect	1	0	0	1	0	0	1	2
Communication (4 concepts)	Direct	0	0	0	0	1	0	0	0
	Indirect	1	2	0	0	0	3	1	0
Social Life/Activities (4 concepts)	Direct	3	1	1	4	1	0	4	4
	Indirect	1	1	0	0	0	0	0	0
Thought Processing (15 concepts)	Direct	2	4	3	3	8	6	0	0
	Indirect	8	3	2	9	2	3	0	9
Daily Activities (14 concepts)	Direct	8	7	5	7	4	2	0	1
	Indirect	4	1	2	3	2	0	1	1
General Independence (6 concepts)	Direct	1	3	2	0	1	0	1	0
	Indirect	4	1	1	2	0	0	1	1

ADCOMS = Alzheimer's Disease Composite Score; ADCS-ADL-MCI = Alzheimer's Disease Cooperative Study–Activities of Daily Living–Mild Cognitive Impairment (specific); CDR-SB = Clinical Dementia Rating–Sum of Boxes; FAQ = (Pfeffer) Functional Activities Questionnaire; iADRS = Integrated Alzheimer's Disease Rating Scale; NPI = Neuropsychiatric Inventory; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PACC = Preclinical Alzheimer's Cognitive Composite; QoL-AD = Quality of Life scale.

Table 2. **WMM Domain Coverage for Supplemental Measures Best-Fit Set**

Domain (number of concepts)		NIH Toolbox	ECog-12	PROMIS/ Neuro-QoL	Daily Diary	CMAI	CFIa	BADLS	A-IADL-Q	ADRQL	AES	CogState C3
Emotions (7 concepts)	Direct	4	0	4	4	2	0	0	0	3	0	0
	Indirect	0	0	2	1	1	0	0	0	0	1	0
Communication (4 concepts)	Direct	0	2	2	0	0	1	1	0	0	0	0
	Indirect	0	0	0	2	1	2	0	1	2	0	0
Social Life/Activities (4 concepts)	Direct	1	0	4	2	0	1	1	0	1	3	0
	Indirect	0	0	0	2	0	2	1	1	3	0	0
Thought Processing (15 concepts)	Direct	4	6	9	7	0	2	2	0	0	0	1
	Indirect	4	3	4	4	0	6	1	2	0	1	5
Daily Activities (14 concepts)	Direct	0	3	12	3	0	5	5	7	0	0	0
	Indirect	1	4	2	4	0	1	1	3	3	2	1
General Independence (6 concepts)	Direct	0	2	5	0	0	1	2	2	0	0	0
	Indirect	0	0	0	0	0	1	0	0	1	0	0

A-IADL-Q = Amsterdam–Independent Activities of Daily Living Questionnaire; ADRQL = Alzheimer's Disease-related Quality of Life; AES = Apathy Evaluation Scale; BADLS = Bristol Activities of Daily Living Scale; CFIa = Cognitive Functioning Index–Acute; CMAI = Cohen-Mansfield Agitation Inventory; CogState C3 = Computerized Cognitive Composite; ECog-12 = Everyday Cognition Scales–12 item; Neuro-QoL = Neurological Quality of Life; NIH = National Institutes of Health; PROMIS = Patient-Reported Outcomes Measurement Information System.

Note: Number in each cell indicates number of concepts covered by a particular measure in each domain. Measures with at least one concept covered directly. Measures with coverage of concepts indirectly.

Table 3. **WMM Domain Coverage for Best-Fit Core Measure Set**

Domain (number of concepts)	ADCOMS*	ADCS-ADL-MCI*	ADRQL	A-IADL-Q	AES	BADLS	CDR/ CDR-SB*	CFIa	CMAI	CogState C3	Daily Diary	ECog	ECog-12	FAQ*	iADRS*	NIH Toolbox	NPI/NPI-Q*	PACC*	PROMIS/ Neuro-QoL	QoL-AD*
Emotions (7 concepts)	■		■				■		■		■					■	■		■	■
Communication (4 concepts)		■	■			■		■			■	■	■	■	■			■	■	
Social Life/Activities (4 concepts)	■	■	■	■	■	■	■	■	■		■			■	■	■	■		■	■
Thought Processing (15 concepts)	■	■		■		■	■	■		■	■	■	■	■	■	■		■	■	■
Daily Activities (14 concepts)	■	■		■		■	■	■		■	■	■	■	■	■	■	■	■	■	■
General Independence (6 concepts)	■	■		■			■	■				■	■	■	■		■		■	

* indicates a Legacy Measure.

Note: Green shading indicates WMM domain coverage (direct or indirect) for best-fit core measure set.

CONCLUSIONS

- The WMM conceptual model of disease domains reflect the disease and treatment-related needs, preferences, and priorities of individuals at risk for or living with AD.
  - Best-Fit Core Measure Set is a roadmap for selecting measures that target the outcomes most relevant to PLWAD.
- Although legacy measures may map to some of the WMM domains, they do not do so completely and are often not based on the PLWAD dementia.
- Supplemental measures connect future clinical trials to previous work, increase relevance of clinical trials to patients, and expand impact of future clinical trials.

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