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Perceptions of Meaningful Change and the Clinical Dementia Rating Scale: Design of a Lived Experience Evaluation

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OBJECTIVE

Through in-depth, vignette-guided interviews, this research aims to define and differentiate clinically meaningful thresholds of change that reflect treatment benefit from both the patient and caregiver perspectives, supporting consistent interpretation of the Clinical Dementia Rating (CDR) across the continuum of early Alzheimer's disease (AD) from cognitively unimpaired (preclinical) AD to mild cognitive impairment (MCI).

- Explore changes in the CDR Global (CDR-G) score and CDR Sum of Boxes (CDR-SB) scores that are considered meaningful by individuals with cognitively unimpaired AD, individuals with MCI due to AD, and individuals representing potential care partners.
- Compare perceptions of meaningful change across individuals living with cognitively unimpaired AD or MCI due to AD and across care partners.
- Define clinically meaningful thresholds of change that reflect a treatment benefit from the perspective of persons living with AD and care partners to inform other decision-makers, including healthcare professionals, regulators, and payers.

CONCLUSION

- This work extends previous literature on the evaluation of meaningful change in CDR scores to include the lived experience of individuals with cognitively unimpaired AD or MCI due to AD.
- Understanding patient-centered and observer-reported metrics of meaningful change is key to supporting the interpretation of clinical meaningfulness in trials of the early stages of AD.
- Insights from this work will help ensure that endpoints used in clinical trials, such as score differences in the CDR, reflect changes that matter to individuals living with cognitively unimpaired (preclinical) AD or MCI due to AD, thereby supporting more effective evaluation of emerging therapies.

Alzheimer's Association International Conference 2026; London, United Kingdom; 12-15 July 2026

Background

- Early stages of AD are defined by the US Food and Drug Association (FDA)[1] through biological and clinical findings:
  - **Stage 1:** Pathophysiologic changes of AD (positive biomarkers), but **no evidence of clinical impact**
  - **Stage 2:** Pathophysiologic changes of AD (positive biomarkers) and **subjective cognitive decline** or **subtle decline on sensitive neuropsychological measures,** but **no functional decline**
  - **Stage 3:** Pathophysiologic changes of AD (positive biomarkers), **subtle or more apparent decline on sensitive neuropsychological measures, and mild functional decline**
- Stage 1 and Stage 2 reflect cognitively unimpaired (preclinical) AD and is a target for interventions to delay clinical progression.
- Incorporating the patient- and study partner-informed definitions of meaningful change across the early disease continuum (cognitively unimpaired AD and MCI due to AD) is critical to ensure that endpoints and interventions reflect meaningful, real-world experiences and priorities before observable cognitive or functional decline emerges.
- As the **CDR-G** and **CDR-SB** are widely used in AD clinical trials, understanding how patients and care partners interpret meaningful change on the CDR in early disease will inform relevant differences in real-world functioning and outcome decisions.

Methods

- A cross-sectional, single-visit, observational study will be conducted including qualitative interviews with 90 individuals: 30 with cognitively unimpaired AD, 30 with a diagnosis of MCI due to AD, and 30 study partners. Cognitively unimpaired AD will be characterized by the presence of AD biomarkers (plasma P-tau217) with self-reported cognitively unimpaired status.
- A standardized set of vignettes representing variations of CDR-G scores 0.0 and 0.5 and CDR-SB scores was created:
  - A team of experts, including trainers skilled in rating clinical trials, clinicians, and qualitative researchers constructed clinical narratives that reflect the lived experience of individuals with specific CDR profiles using real-world cases (Table 1).

Table 1. Distribution of Clinical Dementia Rating Domain Scores Across Vignettes

	Memory	Orientation	Judgment/ Problem solving	Community Affairs	Homes/ Hobbies	Personal Care	CDR-SB	CDR-G
John	0	0.5	0	0	0	0	0.5	0
Roger	0	0	0.5	0	0	0	0.5	0
Joanne	0.5	0.5	0	0	0	0	1	0.5
Brenda	0.5	0	0	0	0	0	0.5	0.5
Sandy	0	0.5	0.5	0	0	0	1	0.5
Randall	1.0	0.5	0.5	0.5	0.5	0	3.0	0.5
Frank	0.5	0.5	0.5	0.5	0.5	0	2.5	0.5

  - Narratives included detailed information typically elicited by a clinician while administering the CDR, which was:
    - Reviewed and refined by expert clinicians and study team members with specific experience administering and scoring the CDR
    - Abbreviated and adapted for presentation to participants by study team members with experience interviewing older adults with and without cognitive impairment
  - Study team members reviewed the participant-facing vignettes to ensure consistency with the original clinical narrative and CDR profile, readability for participants, and brevity.
- Each participant will review 3 of 7 vignettes (counterbalanced across participants) and respond to structured probes to capture perceptions of real-world impairments.

Figure 1. Scoring and Interpretation

CLINICAL DEMENTIA RATING (CDR):	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment and problem solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

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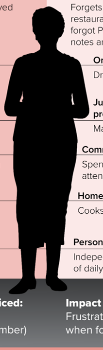
Brenda, 74-year-old woman; retired educator



Clinical presentation
CDR-G: 0.5; CDR-SB: 0.5

Memory: Tip-of-tongue failures; delayed recall of names
Orientation: Able to recite date, day of week, time of day
Judgment/ problem solving: Able to reason logically
Community affairs: Independent in functioning outside home
Home/hobbies: Home activities and hobbies well maintained
Personal care: Fully capable of self-care

Patient experience
CDR-G: 0.5; CDR-SB: 0.5

Memory: Forgets names of people, stores, restaurants in conversations; forgot PIN at ATM; keeps detailed notes and reminders
Orientation: Drives without issues
Judgment/ problem solving: Manages personal finances
Community affairs: Spends time with friends; attends concerts
Home/hobbies: Cooks, gardens
Personal care: Independent in activities of daily living

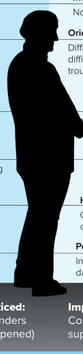
What others have noticed: Relies on husband for reminders (e.g., PIN number)

Impact in daily life: Frustrated and embarrassed when forgetting names

EXAMPLE PROBES

What health-related changes is Brenda experiencing?
Are these changes impactful to her? If so, how?
How much change would she have to experience for this to be a meaningful shift from her previous health?

John, 73-year-old man; retired plumber



Clinical presentation
CDR-G: 0; CDR-SB: 0.5

Memory: No memory loss
Orientation: Difficulty with time relationships
Judgment/ problem solving: Able to reason logically
Community affairs: Independent in functioning outside home
Home/hobbies: Home activities and hobbies well maintained
Personal care: Fully capable of self-care

Patient experience
CDR-G: 0; CDR-SB: 0.5

Memory: No noticeable changes
Orientation: Difficulty keeping track of days; difficulty with timelines of events; no trouble with finding his way around
Judgment/ problem solving: Manages personal finances and other activities
Community affairs: Active in local community
Home/hobbies: Carries out household chores
Personal care: Independent in activities of daily living

What others have noticed: Relies on wife for reminders (e.g., when events happened)

Impact in daily life: Confused and needs more support aids (e.g., calendar)

EXAMPLE PROBES

What health-related changes is John experiencing?
Are these changes impactful to him? If so, how?
How much change would he have to experience for this to be a meaningful shift from his previous health?

Sandy, 66-year-old woman, retired office manager

Clinical presentation
CDR-G: 0.5; CDR-SB: 1.0

Memory: No memory loss
Orientation: Difficulty with time relationships
Judgment/ problem solving: Slight impairment in solving problems
Community affairs: Independent in functioning outside home
Home/hobbies: Home activities and hobbies well maintained
Personal care: Fully capable of self-care

Patient experience
CDR-G: 0.5; CDR-SB: 1.0

Memory: Able to remember and discuss recent events
Orientation: Wrote event on wrong date in calendar; trouble with day of week
Judgment/ problem solving: Paid same utility bill twice
Community affairs: Active in local community
Home/hobbies: Carries out household chores
Personal care: Independent in activities of daily living

What others have noticed: Disorganized compared to previous functioning

Impact in daily life: Needs new support aids (e.g., calendar)

EXAMPLE PROBES

What health-related changes is Sandy experiencing?
Are these changes impactful to her? If so, how?
How much change would she have to experience for this to be a meaningful shift from her previous health?

Planned Analysis/Discussion

Interview data will be coded and analyzed using a directed content analysis approach, guided by an a priori coding framework informed by the interview guide and refined iteratively based on the data.[2]

A definition of meaningful change in the early AD disease continuum is necessary to ensure outcome assessments capture impacts that are relevant, including those living in the early stages of cognitively unimpaired AD as well as study partners. Results will be published in the future to inform clinical research.

References

1. FDA. Early Alzheimer's disease: Developing drugs for treatment. March 2024.
2. Hsieh H, Shannon SE. Qual Health Res. 2005;15:1277-1288.

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