

Clinical Dementia Rating – Sum of Boxes (CDR-SB)

A clinical endpoint to measure cognitive changes
in the early stages of Alzheimer's disease

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The design of clinical studies in Alzheimer's disease (AD) largely depends on the clinical stage

Cognitive decline impacts all cognitive domains to a variable extent and is associated with increasing functional impairment over time. In the early stages of AD, patients often exhibit slow and variable progression, warranting a study design of longer duration with sensitive and valid endpoints that can measure subtle changes over time¹

	Preclinical AD	Mild cognitive impairment (MCI) due to AD	Mild AD dementia	Moderate AD dementia	Severe AD dementia
	Stage 1 & 2	Stage 3	Stage 4	Stage 5	Stage 6
FDA and NIA-AA¹	Pathological features of AD but asymptomatic (stage 1), or subtly impaired cognitive performance	Pathological features of AD and subtly impaired performance on neuropsychological measures and mild functional deficits	Clinically diagnosed mild dementia	Clinically diagnosed moderate dementia	Clinically diagnosed severe dementia
Objectives of intervention: Slow progression and/or delay onset of AD dementia ^{2,3} Features:		<ul style="list-style-type: none"> Biomarker abnormalities (amyloid, tau and neurodegeneration) Objective evidence of impairment in one or more cognitive domains; no significant impairment in activities of daily living (MCI)² Affects multiple cognitive domains with functional impact on daily life: no longer fully independent (mild AD dementia)^{3,4} 			
Duration	Longitudinal study: ~3–5 years	Longitudinal study; ~18–24 months		Shorter study duration; ~3–12 months	
Outcomes	Sensitive and valid clinical endpoints to measure subtle changes to cognitive decline	Sensitive and valid clinical endpoints to measure subtle changes to cognitive and functional decline		Measure progression in cognitive and functional abilities	

Table adapted from Cohen S, et al. 2022

The challenge in establishing clinical endpoints to measure cognitive changes in the early stages of AD

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Clinical endpoints for early stage AD

Historical context

- Historically, studies measuring efficacy of symptomatic treatments for the treatment of AD dementia were validated for overt dementia, not the early stages of AD⁶
- In the early stages of AD, spanning mild cognitive impairment (MCI) due to AD and mild AD dementia, measurement may be more challenging; the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) both called for novel approaches to assess efficacy of treatments in these early stages, recognizing the limitations of those validated for overt dementia⁶
- The FDA guidance and EMA guidelines stated that a treatment should demonstrate efficacy on both a cognitive measure and a functional measure i.e., determine “that a clinically meaningful effect was established by a demonstration of benefit on the functional measure and that the observed functional benefit was accompanied by an effect on the core symptoms of the disease as measured by the cognitive assessment”⁶
- It was suggested that integrated cognitive and functional endpoints, such as the Clinical Dementia Rating — Sum of Boxes (CDR-SB) score, could fulfil the requirement

Key considerations for choosing clinical endpoints for early stages of AD^{7,8}



Do they have acceptable levels of reliability and validity, as well as sensitivity to change over time?



Do the functional skill assessments feature instrumental activities of daily living, which are prone to early cognitive decline, or items indexing contemporary everyday activities?



To what extent does any change in cognitive or functional scores reflect meaningful changes?

What is the Clinical Dementia Rating scale (CDR) and what does it measure?

- CDR is a global measure of cognition and function obtained by interviewing both patient and care partner¹⁻³
- It is a commonly used staging tool for AD in research settings, requires training, and takes ~30 minutes to administer^{1,4}
- The CDR is intended to measure “the influence of cognitive loss on the ability to conduct everyday activities”³
- It measures six domains covering cognition and function; there are up to 10 questions per domain
- The **sum of boxes of the CDR (CDR-SB)** is the sum score of the six domains – it has been emphasized and applied to interventional clinical trials to **track progression** in the early stages¹



CDR is mostly used in research settings; it requires a trained clinician to administer, interpret and score the CDR and requires an extended period of time with both a care partner and the patient^{1,4}

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1. Tzeng, RC, et al. Front. Aging Neurosci. 2022;14:1021792;
2. O'Bryant S, et al. Arch Neurol. 2008; 65(8): 1091–1095;
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Scoring of domains of cognition and function

Rating scale for each domain ⁵	0	0.5	1	2	3	
	None	Questionable	Mild	Moderate	Severe	
Cognition	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 relationship; 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
	Judgement/ Problem-solving	Solves everyday problems, handles business and financial affairs well; judgment good in relation to past performance	Slight impairment in these activities	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
Function	Community affairs	Independent function at usual level in job, shopping, volunteer and social groups	Life at home, hobbies and intellectual interests slightly impaired.	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 the home	Appears well enough to be taken to functions outside the 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 the 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	

Scoring and interpretation

- CDR yields two scores: Global CDR score and CDR-SB scores (table)¹
- The global CDR score ranges from 0 to 3 and requires computation into an algorithm to **stage dementia severity**^{1,2}
- CDR-SB scores, with total scores ranging from 0 to 18, can **track changes** within and between stages of dementia severity over time. It also provides more information than the global CDR score in patients with very mild and mild AD dementia^{1,2}
- In the very early stages of AD (CDR 0.5), the annual rate of change in CDR-SB scores is around 1–2. This gives a narrow window, over an 18-month study period, to measure meaningful benefit³

CDR-SB Total Score	Disease Severity	Global CDR score
0	Normal	0 (normal)
0.5–4.0 0.5–2.5 3.0–4.0	Questionable cognitive impairment to very mild dementia Questionable impairment Very mild dementia	0.5 (very mild)
4.5–9.0	Suggests mild dementia	1 (mild)
9.5–15.5	Suggests moderate dementia	2 (moderate)
16.0–18.0	Suggests severe dementia	3 (severe)

References:

1. O'Bryant S, et al. Arch Neurol. 2008; 65(8): 1091–1095;
2. Tzeng, RC, et al. Front. Aging Neurosci. 2022;14:1021792;
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What does a change in CDR score from 0.5 to 1 mean?

	Memory	Community Affairs	Home/Hobbies
CDR Domain Score 0.5 (Very mild impairment)	Consistent slight forgetfulness; partial recollection of events; “benign” forgetfulness	Slight impairment in these activities	Life at home, hobbies, and intellectual interests slightly impaired
CDR Domain Score 1 (Mild impairment)	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned

A change in CDR score from 0.5 to 1 in the domains measured is the difference between slight impairment and loss of independence. Such losses in cognition and function are likely to be meaningfully felt by most patients, care partners, and families⁴

How does CDR compare with other commonly used clinical tools?



Memory, executive function, visuospatial function, and language are among the most affected cognitive domains in the early stages of AD. Therefore, a brief assessment tool that is able to assess impairment in these domains will be optimal.¹

	Definition	Assessment and evaluation		Cognitive domain							Functioning and daily living
	Purpose and description	Study clinical sample level of functioning	Evaluation scale	Orientation	Attention and working memory		Memory	Visuospatial	Language	Executive function	Activities of daily living
MMSE Mini-Mental State Examination ²⁻⁵	To screen people for cognitive impairment Time: ~5–10 minutes Training required: Minimal	Assesses all stages (not sensitive for MCI)	Lower score = greater impairment /30	<ul style="list-style-type: none"> ✓ Know and state the current date and place ✓ Keep track of time and place in everyday living 	<ul style="list-style-type: none"> ✓ Follow examiner's instructions with focus ✓ Manipulate information in one's head 		<ul style="list-style-type: none"> ✓ Learn and recall new information during exam 	<ul style="list-style-type: none"> ✓ Copy 2D geometric shapes 	<ul style="list-style-type: none"> ✓ Name common objects ✓ Repeat sentences and phrases ✓ Follow written and oral commands 	<ul style="list-style-type: none"> ✗ NOT ASSESSED 	<ul style="list-style-type: none"> ✗ NOT ASSESSED
MoCA Montreal Cognitive Assessment ^{5,6}	To screen people for cognitive impairment Time: ~10 minutes Training required: Minimal	Assesses MCI to mild	Lower score = greater impairment /30	<ul style="list-style-type: none"> ✓ Know and state the current date and place 	<ul style="list-style-type: none"> ✓ Repeat series of digits ✓ Sustain attention ✓ Manipulate information in one's head 		<ul style="list-style-type: none"> ✓ Learn new info and recall it later in the exam 	<ul style="list-style-type: none"> ✓ Draw a clock without copying ✓ Copy a drawing of a cube ✓ Copy 3D geometric shapes 	<ul style="list-style-type: none"> ✓ Name common objects ✓ Repeat sentences and phrases ✓ Generate words from a specific category 	<ul style="list-style-type: none"> ✓ Correct alternating numbers and letters ✓ Generate words starting with a specific letter ✓ Think abstractly ✓ Plan clock drawing 	<ul style="list-style-type: none"> ✗ NOT ASSESSED
CDR Clinical Dementia Rating ^{7,8}	To stage, based on interview with patient and informant, the severity of cognitive impairment Time: >30 minutes Training required: Yes	Assesses all stages	Higher score = greater impairment /18	<ul style="list-style-type: none"> ✓ Know and state the current date and place ✓ Keep track of time and place in everyday living 	<ul style="list-style-type: none"> ✓ Manipulate information in one's head ✓ Concentrate on everyday activities 		<ul style="list-style-type: none"> ✓ Learn and recall new information during exam ✓ Learn and recall information in daily activities 	<ul style="list-style-type: none"> ✗ NOT ASSESSED 	<ul style="list-style-type: none"> ✓ Repeat sentences and phrases 	<ul style="list-style-type: none"> ✓ Think abstractly ✓ Solve problems and make decisions ✓ Demonstrate appropriate judgement ✓ Plan and organize 	<ul style="list-style-type: none"> ✓ Capable of personal hygiene, dressing, feeding ✓ Continence ✓ Perform usual social and occupational functions ✓ Carry out household chores and use tools ✓ Interest in and ability to carry out hobbies ✓ Solve everyday problems and financial affairs

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