Endpoints

in Alzheimer's disease clinical trials

An educational overview of clinical trial endpoints currently used in Alzheimer's disease

Co-created with the clinical and research community in mind

Prepared March 2021
M-XX-00004188

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by cognitive, functional, and behavioral deficits. Our understanding of the causes and potential treatments for AD is continually evolving. The goal of this interactive brochure is to provide greater recognition of what clinical trials measure (endpoints) in AD. We also aim to describe the relevance of common AD endpoints from the perspective of clinical teams managing people with AD.

Those who may find this guide useful include neurologists, psychiatrists, primary care physicians, early-career clinicians, and other health care professionals who want to understand the endpoints used in AD clinical trials. It is also suitable for trial investigators and staff involved in the design, management, and administration of clinical trials in AD. Information about regulatory guidance, statistical considerations, and biomarkers has been included in an interactive and approachable way.

We have supplemented this information with our years of research and clinical experience, adding our commentary and insights about the value and utility of the methods that investigators use to measure and understand AD research. *Where you see a speech bubble, this indicates where we have added our perspective*.

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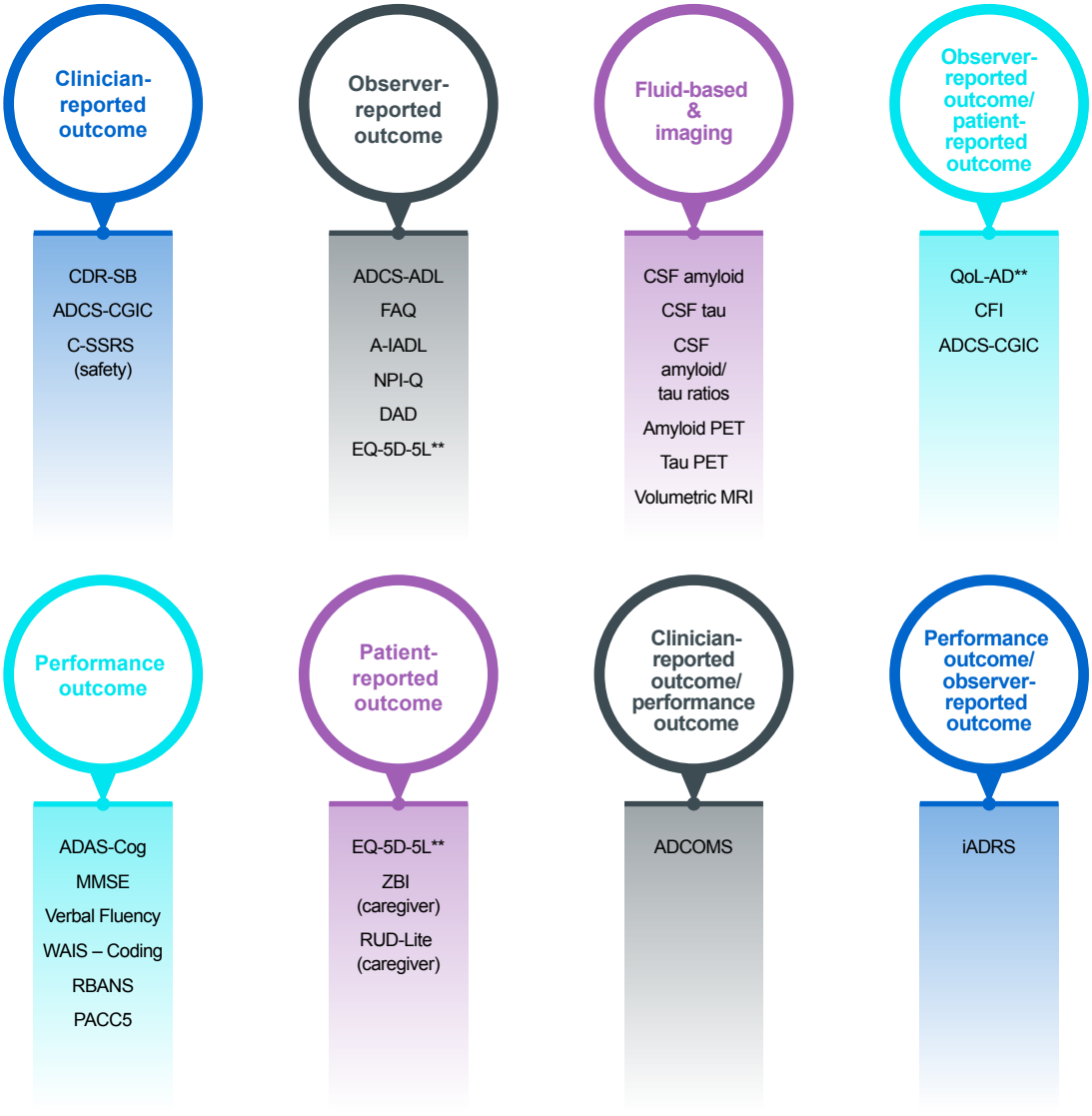
This booklet is for educational purposes only and is not intended to be a comprehensive assessment of clinical trial endpoints in Alzheimer's disease. The information included here along with commentary and input from members of the scientific community does not represent an endorsement or recommendation of any endpoints.

Contents

Index of clinical outcome assessments (COAs) and endpoints included in this booklet,* by category

Several types of COAs and endpoints are used in AD



*This is not a comprehensive list of AD endpoints

Also considered as a **Proxy-reported outcome, which is an assessment in which someone other than the patient reports on patient symptoms.[1]

ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS-ADL, Alzheimer's Disease Cooperative Study - Activities of Daily Living; ADCS-CGIC, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; A-IADL, Amsterdam - Instrumental Activities of Daily Living; CDR-SB, Clinical Dementia Rating-Sum of Boxes; CFI, Cognitive Function Instrument; CSF, cerebrospinal fluid; C-SSRS, Columbia-Suicide Severity Rating Scale; DAD, Disability Assessment for Dementia; EQ-5D-5L, 5-Level EuroQoL-5D; FAQ, Functional Activities Questionnaire; iADRS, Integrated Alzheimer's Disease Rating Scale; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NPI-Q, Neuropsychiatric Inventory-Questionnaire; PACC5; Preclinical Alzheimer Cognitive Composite 5; PET, positron emission tomography; QoL-AD, Quality of Life in Alzheimer's Disease; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RUD-Lite, Resource Utilization in Dementia – Lite Version; WAIS-IV, Wechsler Adult Intelligence Scale – Fourth Edition; ZBI, Zarit Burden Interview.

Endpoints in AD clinical trials

Introduction

Endpoints are precisely defined variables that are intended to reflect an outcome of interest that will address a specific research question.[2] In clinical trials, endpoints are used to evaluate treatment efficacy and/or safety.

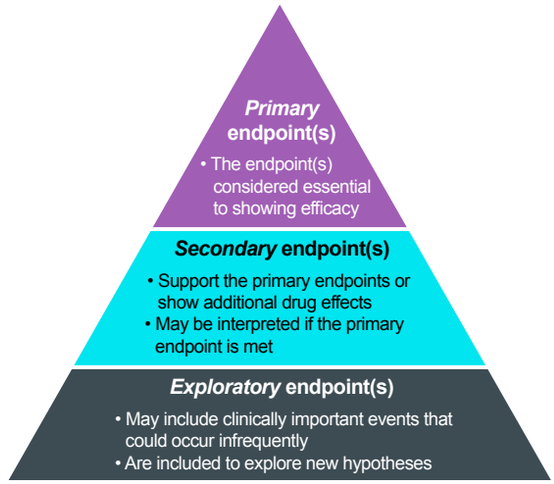
COAs differ from endpoints, in that they are the instruments used to evaluate the intended outcome. They can be made through reports by patients, clinicians, or non-clinician observers.[2] There are four main types of COA (**Figure 1**).[2]

Figure 1: Types of COA[2]

PRO	ClinRO	ObsRO	PerfRO
Patient-reported outcome	**Clinician-reported outcome**	**Observer-reported outcome**	**Performance outcome**
Reported directly by the patient	*Reported by a trained healthcare professional*	*Reported by observers other than the patient or healthcare professional*	*Reported by patients, administered by a trained individual*

Clinical trials employ a hierarchy of predefined endpoints (**Figure 2**).[3] In AD clinical trials, it is common to look at multiple endpoints. However, in statistical terms, a greater number of endpoints contribute to a potential reduction in study power, i.e. the likelihood or ability of a study to detect a true treatment effect.[3] Therefore, determining which endpoints to include in an AD trial requires a balance between trying to best capture the disease manifestations and ensuring the study is adequately powered.

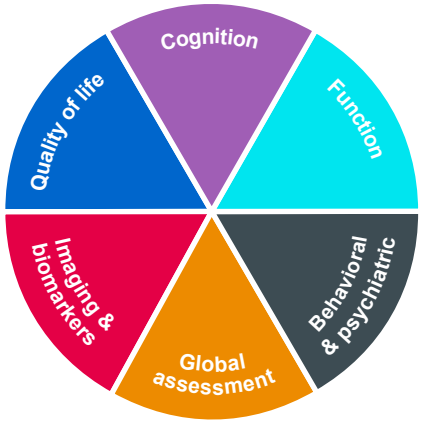
Figure 2: The hierarchy of predefined endpoints in clinical trials[3]



AD is a multifactorial disease with an evolving understanding of pathogenesis and treatment

AD is characterized by a progressive decline in cognitive function and impaired activities of daily living, leading to diminished quality of life.[4,5] Endpoints in AD are specific COAs of cognition, function, overall clinical response (i.e. global assessment), behavior and psychiatric symptoms, or quality of life (**Figure 3**).[6] Endpoints contribute to the interpretation of clinical efficacy of treatments in AD,[7] and they must be sensitive to change (to detect treatment effects) and clinically meaningful.[8]

Figure 3: Domains of AD outcome assessment[6]



AD, Alzheimer's Disease

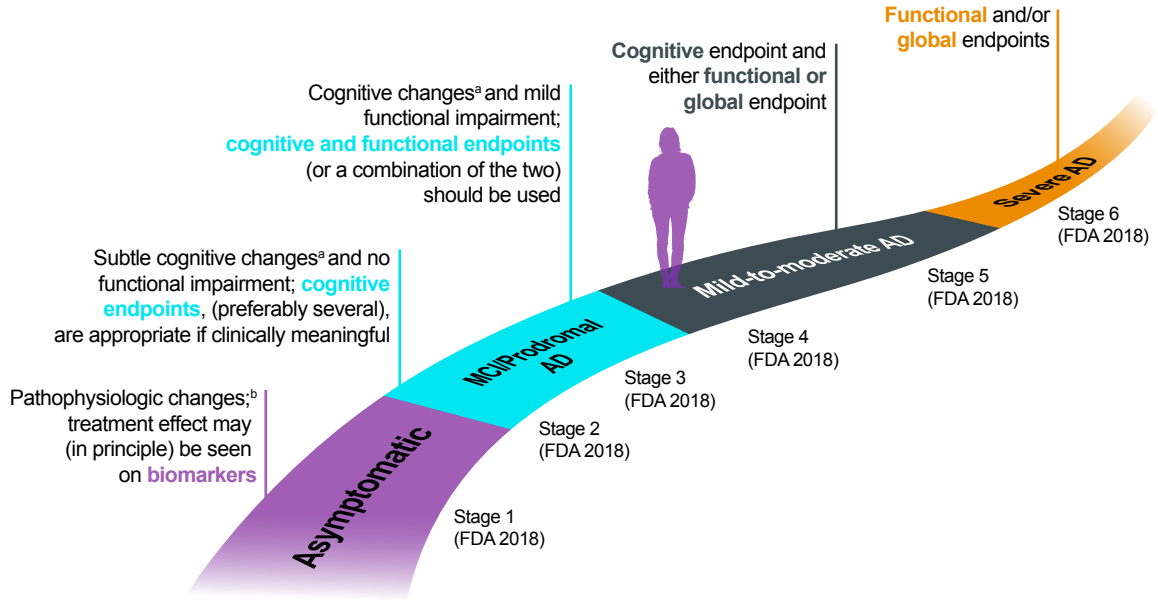
People with dementia and family caregivers have stated that:[8]

- *Questionnaire content for endpoints should be clear and limited in volume*
- *Cognition should be a core endpoint but should be used in conjunction with others to provide contextual, qualitative information*

Regulatory guidance on primary endpoints in AD clinical trials

Regulatory agencies have provided guidance on the use of AD endpoints by disease stage (**Figure 4**).[6,9] The US Food and Drug Administration (FDA) guidance states that a composite (combined cognitive and functional) outcome may serve as a primary endpoint in prodromal AD.[10] Both the FDA and European Medicines Agency (EMA) guidelines emphasize the importance of incorporating the patient voice in developing acceptable measures that are clinically meaningful.[11]

Figure 4: Regulatory guidance on disease stage applicability of endpoints in AD[6,9]



[a]Assessed by sensitive neuropsychological measures; [b]However, cognitive testing will likely be included in future regulatory guidance, for use in the preclinical stage.
AD, Alzheimer's Disease; MCI, mild cognitive impairment.

Table 1. Selected primary and secondary endpoints used in AD clinical trials (marked by X)
Note: This is not a complete list of all endpoints used in these trials, and biomarker/imaging endpoints are not included in this table.

	GRADUATE I & II[12,13]	LAURIET[14]	TAURIEL[15]	EMERGE & ENGAGE[16,17]	AHEAD 3-45[18]	Clarity AD[19]	ALZ-801*[,20]	TRAILBLAZER -ALZ2[21]
CDR-SB	X (primary)	X	X (primary)	X (primary)		X (primary)		X (primary)
ADCOMS						X		
ADAS-Cog	X	X (primary)	X	X		X	X (primary)	X
MMSE	X	X		X				X
Verbal Fluency Task	X							
WAIS-IV – Coding	X							
RBANS			X					
PACC5					X (primary)			
iADRS								X
ADCS-ADL	X	X (primary)	X	X				X
DAD								
FAQ	X							
A-IADL			X					
QoL-AD								
EQ-5D-5L								
CFI					X			
ADCS-CGIC								
NPI-Q								
C-SSRS	X							
ZBI								
RUD-Lite								

*Secondary endpoints for the planned ALZ-801 phase 3 trial are noted to be function, activities of daily living, and behavior[20]

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Table 2. Selected COAs/endpoints, by applicability across the spectrum of disease severity*

PRECLINICAL AD	MCI/PRODROMAL AD, MILD AD, MODERATE AD	SEVERE AD
Disease progression →		
CSF amyloid beta & tau	CDR-SB	CDR-SB
PET amyloid beta & tau	ADAS-Cog	MMSE
Volumetric MRI	MMSE	ADCS-ADL
PACC5	Verbal Fluency	DAD
CFI	WAIS-IV – Coding	FAQ
	RBANS	A-IADL
	PACC5	QoL-AD
	ADCS-ADL	EQ-5D-5L
	DAD	ADCOMS
	FAQ	ADCS-CGIC
	A-IADL	NPI-Q
	QoL-AD	C-SSRS
	EQ-5D-5L	ZBI & RUD-Lite
	ADCOMS	
	iADRS	
	ADCS-CGIC	
	NPI-Q	
	C-SSRS	
	ZBI & RUD-Lite	

*Categorization includes conclusions based on type of endpoint (i.e. domain).

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Individual endpoints summarized

In this section, we summarize several COAs/endpoints used in AD clinical trials, highlighting their focus, use in clinical practice and research, components, and scoring.

Table 3. COAs/endpoints that encompass both cognitive and functional domains

COA/endpoint	What is assessed	What is not assessed/limitations
Clinical Dementia Rating-Sum of Boxes (CDR-SB)	• Memory, judgement, problem solving, home and hobbies, orientation, and personal care[22]	• Dependent on the accuracy and consistent availability of the patient's informant; time-intensive[23]
Alzheimer's Disease Composite Score (ADCOMS)	• Composite of ADAS-Cog, CDR-SB, and MMSE[24]	• Not used in clinical practice because of complexity – measures must be statistically combined; time-intensive
Cognitive Function Instrument (CFI)	• Questionnaire (i.e. subjective assessment) of memory decline, cognitive difficulties, and functional decline[25–27]	• Lacks the sensitivity required for clinical trials
Integrated Alzheimer's Disease Rating Scale (iADRS)	• Combines cognition and daily function scores from the ADAS-Cog and the ADCS-IADL[28,29]	• Recently developed, thus limited evidence/evaluation of the endpoint to date
Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC)	• General performance, mental cognitive state, activities of daily living, and behavior[30,31]	• Not designed for use in the clinical practice setting

AD, Alzheimer's Disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-IADL, Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

Table 4. COAs/endpoints evaluating cognition

COA/endpoint	What is assessed	What is not assessed/limitations
Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)	• Memory, praxis, planning, and executive function[32,33]	• Too lengthy for clinical practice,[8,33] can be influenced by education/IQ, floor effects for MCI and early AD, may be insensitive to treatment effects
Mini-Mental State Examination (MMSE)	• Severity of cognitive impairment in two sections: memory, orientation, and attention; and name, follow instructions, copy, and write.[34] Can be completed quickly and frequently	• No measure of executive function. Can be affected by sociocultural factors, age etc.[35] Most sensitive for moderate stages of dementia, less so for MCI[5,35]
Verbal Fluency Task (VFT)	• Semantic (e.g. name as many animals as you can) and phonemic fluency (e.g. name words beginning with F). Correlates with severity and risk of progression in AD[36]	• Premorbid IQ and socioeconomic factors impact results. Differences in language use between cultures limit applicability of findings to some populations
Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV – Coding)	• Executive function, processing speed, attention, short-term memory, and cognitive flexibility[37]	• Limited utility in patients with lower levels of cognition[38]
Repeatable Battery for the Assessment of Neuropsychology Status (RBANS)	• Short-term and delayed memory, visuospatial ability, language, and attention[39]	• Insensitive to later-stage clinical progress; time-intensive
Preclinical Alzheimer Cognitive Composite 5 (PACC5)	• Composite of subscales from several measures designed for asymptomatic AD. Includes executive function and general cognition[40]	• Not used in clinical practice. As a combination of other measures, it may be time consuming

AD, Alzheimer's Disease; IQ, intelligence quotient; MCI, mild cognitive impairment.

Table 5. COAs/endpoints assessing function

COA/endpoint	What is assessed	What is not assessed/limitations
Disability Assessment for Dementia (DAD)	• The ability to perform everyday activities, tasks, and behaviors. Basic and instrumental ADLs, and leisure activities are included[41]	• Limited utility in early-stage AD
Functional Activities Questionnaire (FAQ)	• Used to measure ADLs for the previous 4 weeks. A total score of ≥ 6 may be used to discern MCI from mild AD[42]	• If patient has not performed an activity it cannot be assessed, leaving the questionnaire incomplete[42]
Amsterdam - Instrumental Activities of Daily Living (A-IADL)	• Aimed at detecting early-stage and early-onset dementia. Items cover household, personal finance, and leisure activities[43]	• The 70-item version is lengthy[43]
Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)	• Basic and instrumental ADL items (eating, walking, reading, cooking, etc.)[44]	• Functional impairment may not be detected in MCI,[45] relies on caregiver view and may be prone to bias,[44] time-intensive

AD, Alzheimer's Disease; ADL, activities of daily living; MCI, mild cognitive impairment.

Table 6. COA/endpoints measuring quality of life

COAs/endpoint	What is assessed	What is not assessed/limitations
Quality of Life in Alzheimer's Disease (QoL-AD)	• QoL, physical condition, mood, interpersonal relationships, ability to participate in meaningful activity, and financial situation[4,46]	• Caregiver-rated QoL-AD score is typically lower than self-rated QoL-AD.[47,48] Self-assessed QoL-AD may have limited response and correlation to changes in clinical outcomes[47]
5-Level EuroQoL-5D (EQ-5D-5L)	• QoL of 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/ depression[49]	• The self-completed EQ-5D-5L may not accurately reflect clinically important changes (e.g. functional assessment and CDR)[50]

CDR, clinical dementia rating; QoL, quality of life.

Table 7. Psychiatric COAs/endpoints		
COA/endpoint	**What is assessed**	**What is not assessed/limitations**
Neuropsychiatric Inventory–Questionnaire (NPI-Q)	• Neuropsychiatric symptoms across 12 domains[51]	• Does not include clinician rating
Columbia-Suicide Severity Rating Scale (C-SSRS)	• Suicidal ideation and suicidal behavior: severity of ideation, intensity of ideation, behavior subscale, and lethality subscale[52]	• Concerns regarding the appropriateness of use in patients with dementia; not specifically validated in the elderly population[53,54]

Table 8. COAs/endpoints on caregiving burden		
COA/endpoint	**What is assessed**	**What is not assessed/limitations**
Zarit Burden Interview (ZBI)	• Caregiver burden (29 items including caregiver health, psychological well-being, relationship with the patient, social life, and finances)[55]	• Reflects caregiver burden but not directly related to severity of patient's disease[55]
Resource Utilization in Dementia – Lite Version (RUD-Lite)	• Cost-effectiveness, resource use for dementia care[56,57]	• May not necessarily reflect resource use during clinical trials; resource use tends to be delayed

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

The CDR-SB is a clinician-reported assessment of cognition and function via a semi-structured interview with the patient and informant (e.g. a caregiver or family member).[22,58,59] It is suitable for assessment across the disease spectrum, from prodromal to moderate AD stages.[23] Limitations include length of assessment; dependency on accuracy and consistent availability of the patient's informant;[23] and risk of disease stage misclassification with moderate stage AD.[5]

Unlike the CDR-SB, the CDR-global scale (CDR-GS), is typically used for staging purposes, and characterizes a participant's level of impairment according to the following categories: 0 (normal), 0.5 (very mild/prodromal dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia).[60]

Domains:[22]

Memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care

Each domain is assessed for degree of impairment on a 5-point scale:
0 = none; 0.5 = questionable; 1 = mild;
2 = moderate; 3 = severe

Sum of boxes:[58] sum of the ratings for each domain (maximum score of 18)

Proposed meaningful change threshold* by disease stage:[61] MCI: +1; mild AD: +2; moderate-severe: +2

*A meaningful change threshold is the level of score change on an outcome that is perceived as meaningful in the target population. Proposed thresholds provided throughout this brochure are based on limited evidence from the literature, with individual studies adopting a variety of approaches/methodologies. Please refer to the specific references for details on the methods used and see the PFDD guidance 3 for recommended gold standard approaches[62]

Insights on use in clinical practice and research settings**

- *Rarely used in a day-to-day clinical setting*
- *Relies heavily on caregivers and requires the same rater for every measurement*
- *Unlikely to provide a continuous measure for each domain; informants usually provide information that covers only 1–2 weeks of changes, not 3 months*

**This is the experience and thoughts of our expert authors

Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog)

ADAS-Cog is a performance outcome and the most frequently used cognitive outcome in AD clinical trials. ADAS-Cog-11 assesses memory, praxis, concentration, planning, and executive function.[32,33] Expanded versions include: ADAS-Cog-12: + delayed word recall; ADAS-Cog-13: + number cancellation; and ADAS-Cog-14: + maze completion.[63] Key limitations include duration of assessment (not routinely used in clinical practice)[8,33] and its potentially limited ability to detect treatment effects as a single endpoint.[64]

ADAS-Cog consists of the following subtests:[65]

• Word recall	• Comprehension
• Following commands	• Word-finding ability
• Constructional praxis	• Spoken language ability
• Naming objects	• Remembering test instructions
• Ideational praxis	• Delayed word recall (ADAS-Cog-12)
• Orientation	• Number cancellation (ADAS-Cog-13)
• Word recognition	• Maze completion (ADAS-Cog-14)

The maximum score is 70 points; higher scores indicate more severe impairment

Proposed meaningful change threshold* in early AD: 3-point decline

*A meaningful change threshold is the level of score change on an outcome that is perceived as meaningful in the target population. Proposed thresholds provided throughout this brochure are based on limited evidence from the literature, with individual studies adopting a variety of approaches/methodologies. Please refer to the specific references for details on the methods used and see the PFDD guidance 3 for recommended gold standard approaches[62]

Insights on use in clinical practice and research settings**

- *A common outcome for cognition in clinical trials but not used in clinical settings*
- *Lengthy, time-dependent, and requires the scale box*
- *Premorbid IQ/education may impact the assessment*
- *Score is not meaningful if it remains unchanged but there is a decline in daily function*
- *Best suited to mild/moderate disease – floor effects for MCI and early AD*

**This is the experience and thoughts of our expert authors

Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)

The ADCS-ADL is an observer-reported outcome that assesses basic and instrumental activities of daily living items.[44] The scale was designed specifically for use in AD clinical trials, and caregivers or other informants complete the questionnaire.[44] However, impairment in functioning may not be detected in patients with mild cognitive impairment (MCI).[45]

ADCS-ADL consists of the following subtests:[44]

• Eating	• Handles mail
• Walking	• Hobbies or games
• Toileting	• Watching television
• Bathing	• Uses telephone
• Grooming	• Conversation
• Dressing	• Turns off lights
• Chooses clothes	• Clears the table
• Travel outside home	• Uses household appliances
• Shopping	• Puts away belongings
• Keeping appointments	• Finds belongings
• Able to be left alone	• Disposes of litter
• Discuss current events	• Obtains a beverage
• Reading	• Preparing a meal/snack
• Writing	

Total score ranges from 0 to 78; higher scores represent better functional level; lower scores indicate greater impairment

Insights on use in clinical practice and research settings*

- *Not used in clinical setting but may have value as a 'one-off' measure*
- *Provides a meaningful measure of cognitive change and translational impact*
- *Time-intensive*
- *Relies on caregiver view and is prone to bias*
- *Some questions cover topics that may not have occurred between ratings*
- *Insensitive to changes at the beginning of the disease; not sensitive enough for short clinical trials*

*This is the experience and thoughts of our expert authors

Mini-Mental State Examination (MMSE)

The Folstein MMSE is a performance outcome that quantitatively assesses the severity of cognitive impairment.[34] The MMSE is commonly used for inclusion criteria in AD clinical trials. It is considered to be most accurate for classifying moderate stages of dementia.[5] Limitations include potential impact by sociocultural variables, age, and education and it is less sensitive to subtle cognitive changes in patients with MCI.[35]

The **MMSE** consists of 2 sections:[35]

- ***Section 1****: covers orientation, memory, and attention (21 points maximum)*
- ***Section 2****: tests ability to name, follow verbal and written commands, write a sentence spontaneously, and copy a complex polygon (9 points)*

Lower scores indicate increasing cognitive impairment; a score of 23 or 24 is indicative of cognitive impairment or dementia[66,67]

Thresholds for a clinically meaningful decline increase with AD severity[61]

Insights on use in clinical practice and research settings*

- *Used by most clinical trials and commonly used in clinical practice*
- *Premorbid IQ and age affect score, and cut-off points vary*
- *Quick to use and can be completed more frequently than other scales*
- *SMMSE is better standardized and has been used in various settings*
- *Not related to the outcome of patients in the clinical setting*
- *No assessment of executive function*
- *Use has decreased due to licensing/copyright requirements*

*This is the experience and thoughts of our expert authors

Verbal Fluency Task Score

Semantic and phonemic fluency tests are performance outcomes that may be used to assess cognitive function in AD.[36] Verbal fluency, particularly semantic fluency, has been shown to correlate with severity of AD.[36] Semantic memory, and therefore fluency, is impaired in patients with amnestic MCI.[68] In addition, verbal fluency is associated with risk of progression to clinical dementia.[36]

Examples of verbal fluency tests:[36,68]

- **Semantic (or category) fluency**: *name as many animals as possible in 60 seconds*
- **Phonemic fluency**: *name as many words as possible beginning with the letter F, in 60 seconds*

Insights on use in clinical practice and research settings*

- *Used widely in the clinical setting*
- *Only takes 2 minutes and no special training required*
- *Helpful in clinical trials and for patient outcomes*
- *Education and premorbid IQ impact the results*
- *The influence of socioeconomic factors and language must be considered when used clinically or in global/other cultural contexts*

*This is the experience and thoughts of our expert authors

Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV) – Coding Subtest

The WAIS is a common and broadly used human intelligence test. The digit symbol substitution test (DSST, i.e. coding test) of the WAIS-R instrument assesses executive function (via processing speed).[37,69] The WAIS coding test has been shown to be highly predictive of time to conversion to AD in patients with MCI.[37,69] Its main limitation is that its utility is limited in patients with lower levels of cognition.[38]

The **WAIS-IV – Coding subtest evaluates**:[37]

- *Visuomotor processing speed*
- *Short-term visual memory*
- *Cognitive flexibility*
- *Ability to absorb new material*
- *Attention, concentration, and motivation*

Using a key that matches numbers to simple symbols, the patient copies symbols as quickly as possible, during a 2-minute period[37]

A higher score represents better performance;[37] in a study of patients with MCI, the mean score was 40.8 (SD 12.7)[69]

Insights on use in clinical practice and research settings*

- *Used for cases that require detailed memory assessment to differentiate MCI from AD*
- *Helpful for clinical trials*
- *Shows the patient's stage of disease*
- *Used in LD services*
- *Provides an SD, which is helpful*
- *It is not helpful as cognitive score drops to the medium level*

*This is the experience and thoughts of our expert authors

Repeatable Battery for the Assessment of Neuropsychology Status (RBANS)

The RBANS assesses cognition through a variety of tests.[39] Alternate versions of the test exist, to counteract practice effects (i.e. improved performance due to familiarity with the test). The measure was designed for use over a wide range of cognitive status, from normal to moderate AD.[39] The RBANS is for use in both clinical practice and research settings. Diagnostic accuracy for both clinical AD and MCI due to AD have been demonstrated.[70,71]

The RBANS consists of 12 subtests, which yield 5 index scores:[39]

- ***Immediate memory:***
  - *List learning*
  - *Story memory*
- ***Visuospatial constructional:***
  - *Figure copy*
  - *Line orientation*
- ***Language:***
  - *Picture naming*
  - *Semantic fluency*
- ***Attention:***
  - *Digit span*
  - *Coding*
- ***Delayed memory:***
  - *List recall*
  - *List recognition*
  - *Story recall*
  - *Figure recall*

Scores are scaled within each index and for a total score; a higher score indicates better performance[39]

Insights on use in clinical practice and research settings*

- *Used for small samples of patients referred to a neuropsychologist for detailed memory testing*
- *Useful in clinical trials where later-stage clinical progress is not pertinent*
- *Takes much longer than normal memory assessment*

*This is the experience and thoughts of our expert authors

Preclinical Alzheimer Cognitive Composite 5 (PACC5)

The Alzheimer's Disease Cooperative Study PACC is a composite performance outcome assessing cognition.[40] Components of 4 cognition endpoints are included, evaluating memory, executive function, and general cognition. The PACC was designed specifically for use as a primary endpoint for clinical trials in asymptomatic AD.[40] The PACC5 includes a fifth domain, category fluency (semantic memory).[72]

The **PACC5** consists of:[40,72]

- ***Total Recall*** *score from the FCSRT*
- ***Delayed Recall score*** *on the Logical Memory IIa subtest of the WAIS*
- ***Digit Symbol Substitution Test*** *score on the WAIS*
- *Total* ***MMSE*** *score*
- ***Category fluency***

Scores are combined into a single composite total score[40]

Insights on use in clinical practice and research settings*

- *Covers a few different areas and helpful in clinical trials*
- *Helpful to differentiate MCI and AD*
- *May have a good correlation with PET and CSF measures*
- *Not used in the clinical setting and limited clinical relevance*

*This is the experience and thoughts of our expert authors

Disability Assessment for Dementia (DAD)

The DAD is a clinical and functional observer-reported outcome measure used to assess the ability to perform activities, tasks, and behaviors of everyday life in people with dementia.[41] Activities are organized such that the ability to initiate, plan, and execute each is evaluated, therefore, informing on cognitive ability as well. Caregivers or other informants complete the questionnaire.It is designed to be free of gender bias and is performance-based.[41]

40 items on basic self-care, instrumental ADLs, and leisure:[41]

Basic ADLs (activities important for self-care), including dressing, hygiene, continence, and eating

Instrumental ADLs (activities important for maintenance in a specific environment), including meal preparation, telephoning, housework, taking care of finance and correspondence, going on an outing, taking medications, and the ability to stay safely at home

Leisure activities (activities beyond self-maintenance that are for the purpose of recreation), in terms of the interest that is shown toward these activities

A higher global score represents less disability

Insights on use in clinical practice and research settings*

- *Reflects patient outcomes in relation to day-to-day function*
- *Some parts of the test are used by occupational therapists in memory clinics*
- *Not reflecting the clinical trials at early stages*

*This is the experience and thoughts of our expert authors

Functional Activities Questionnaire (FAQ)

The FAQ is an observer-reported outcome used across many diseases. It is a clinical and functional measure of instrumental activities of daily living as assessed by an informant (e.g. a caregiver or family member) over 4 weeks.[42] A total FAQ score ≥ 6 may be used to distinguish mild AD from MCI.[42] The FAQ has been shown to predict progression from MCI to AD.[73] However, if the patient has not performed a certain activity, the questionnaire will be incomplete.[42]

Instrumental ADLs assessed on the FAQ:[42]

• Writing checks, paying bills, and keeping financial records	• Keeping track of current events
• Assembling tax or business records	• Attending to and understanding a television program, book, or magazine
• Shopping alone	• Remembering appointments, family occasions, and medications
• Playing a game of skill	• Traveling out of the neighborhood
• Making coffee or tea	
• Preparing a balanced meal	

Performance in each category is rated as:[42]

- *0 = normal*
- *1 = has difficulty, but does by self*
- *2 = requires assistance*
- *3 = dependent*

Score ranges from 0 to 30; higher scores on each of the categories indicate greater functional impairment[42]

Insights on use in clinical practice and research settings*

- *Used in some clinics, mainly by occupational therapists*
- *Shows patient decline as a set of standards better than general questioning*
- *Highly translational and measures of ADL provide meaningful measures and pragmatic assessment of clinical change*

*This is the experience and thoughts of our expert authors

Amsterdam - Instrumental Activities of Daily Living (A-IADL)

The A-IADL is a 70-item observer-reported questionnaire aimed at detecting early dementia and early-onset dementia.[43] It is a registered trademark of Alzheimer Center VU University Medical Center (Amsterdam, The Netherlands).[43,74] There is also a short version, with 30 items, which still covers the range of functional domains and takes 10–15 minutes to complete.[75] An informant of the patient (e.g. a caregiver or family member) completes the questionnaire.[43,74] IADL are complex activities that require multiple cognitive processes and involve minimal automated skills.[43]

70 items or 30 items (short-version), pertaining to, e.g. the following:[43,75]

• Household duties	• Paperwork and computer use
• Shopping	• Operating devices
• Cooking	• Driving and transportation
• Domestic appliances	• Games and books
• Finances and paying bills	

Each item has a 5-point scale response option:[43]

- *0 = no difficulty*
- *1 = slightly more difficulty*
- *2 = more difficulty*
- *3 = much more difficulty*
- *4 = no longer able to perform this task*

Higher scores indicate poorer functioning[74]

Insights on use in clinical practice and research settings*

- *Becoming a preferred measure in trials due to its sensitivity and contemporary activities/questions*
- *Not used in clinical practice*

*This is the experience and thoughts of our expert authors

Quality of Life in Alzheimer's Disease (QoL-AD)

The QoL-AD assesses quality of life, physical condition, mood, interpersonal relationships, ability to participate in meaningful activity, and financial situation.[4,46] Both self-assessment and informant interview versions exist; each can be completed in under 10 minutes.[6] Proxy-rated QoL-AD is typically found to be lower than self-rated QoL-AD;[47,48] and self-assessed QoL-AD may have limited correlation with changes in clinical outcomes.[47]

Domains:[47]

• Physical health	• Friends
• Energy	• Self as a whole
• Mood	• Ability to do chores around the house
• Living situation	• Ability to do things for fun
• Memory	• Money
• Family	• Life as a whole
• Marriage	

Each domain is assessed on a 4-point scale:[46,48]

- *1 = poor*
- *2 = fair*
- *3 = good*
- *4 = excellent*

Total score ranges from 13 to 52; a higher score represents better quality of life[46]

Insights on use in clinical practice and research settings*

- *Wide range of scoring/testing is helpful for clinical trials*
- *Short and quick*
- *Not routinely used in clinical care*

*This is the experience and thoughts of our expert authors

5-Level EuroQoL-5D (EQ-5D-5L)

The EQ-5D-5L is a proxy-rated outcome measure used across many diseases to measure the immediate health of the patient, i.e. “health today”.[49,50,76] It is designed for self-completion but may be used by a caregiver or family member instead. As a self-completed measure, it may not accurately reflect clinically important changes.[50]

The **EQ-5D-5L** assesses **5 dimensions:**[49]

- *Mobility*
- *Self-care*
- *Usual activities*
- *Pain/discomfort*
- *Anxiety/depression*

Each dimension has 5 response categories:[76]

- *No problems*
- *Slight problems*
- *Moderate problems*
- *Severe problems*
- *Unable to complete task*

An index score is calculated from –0.281 to 1[76]

Higher scores indicate better quality of life[76]

Insights on use in clinical practice and research settings*

- *Used mostly in the research setting*

*This is the experience and thoughts of our expert authors

Alzheimer's Disease Composite Score (ADCOMS)

The ADCOMS is a composite cognitive and functional endpoint that combines elements of 3 common endpoints (CDR-SB, ADAS-Cog, and MMSE) with the total score ranging from 0 to 1.97.[24] As such it is both a performance outcome and an observer-reported outcome. ADCOMS is intended for use in the clinical research setting. Sensitivity to clinical change in MCI/prodromal AD has been reported to be improved with the ADCOMS compared with the CDR-SB, ADAS-Cog, and MMSE individually.[24]

Scale and item[24]	PLS coefficient (weight)
ADAS-Cog	
Delayed word recall	0.008
Orientation	0.017
Word recognition	0.004
Word finding difficulty	0.016
MMSE	
Orientation time	0.042
Drawing	0.038
CDR-SB	
Personal care	0.054
Community affairs	0.109
Home and hobbies	0.089
Judgement and problem solving	0.069
Memory	0.059
Orientation	0.078

Insights on use in clinical practice and research settings*

- *Not used in everyday practice as measures must be statistically combined*
- *ADAS-Cog (the key component) is not commonly done in clinical practice*
- *Heavily weighted towards orientation (from all 3 tests)*

*This is the experience and thoughts of our expert authors

Cognitive Function Instrument (CFI)

The CFI is an assessment of early changes in cognitive status and functional abilities.[25] The CFI is a questionnaire completed by patients and/or an informant (e.g. a caregiver or family member).[26,27] Examples of questions are:[26] Do others tell you that you tend to repeat questions over and over? And do you need more help from others to remember appointments, family occasions, or holidays? The index was originally developed to determine whether a self-assessed measure of change in cognition is reliable and may serve as a trial endpoint.[25]

14 questions including items on the following (over the previous year):[26,27]

- *Memory decline*
- *Cognitive difficulties*
- *Functional decline*

Responses are recorded as:[26,27]

- *Yes = 1*
- *No = 0*
- *Maybe = 0.5*
- *Not applicable (an option for questions regarding driving, handling finances, and word performance)*

Responses are summed to create a total score, ranging from 0 to 14; a higher score reflects greater impairment[26,27]

Insights on use in clinical practice and research settings*

- *Helpful as a self-assessment for patient outcome measures in primary care*
- *Sensitive in early disease*
- *Minimal use in the clinical setting*
- *Lacks the sensitivity required for clinical trials*

*This is the experience and thoughts of our expert authors

Integrated Alzheimer's Disease Rating Scale (iADRS)

The iADRS combines scores from the ADAS-Cog and the ADCS-iADL.[29] Scores range from 0 to 146 with higher scores indicating better performance.[29] This composite score was designed to be more sensitive to MCI and to reduce variability in data.[29] Its sensitivity to progression from MCI to moderate AD has been reported as superior to several other composites and equal to or better than individual scales in detecting treatment differences.[28] The iADRS can be divided into 2 principal components: cognitive items and instrumental ADL.[28]

Items:[28]

Cognition
Word recognition
Delayed word recall
Word recall
Orientation
Daily function
Making a meal
Telephone
Going shopping
Household appliance
Current events
Obtaining beverage
Writing
Getting around
Being alone
Television
Keeping appointments
Clearing dishes

Insights on use in clinical practice and research settings*

- *Rarely used in clinical practice*
- *Degree to which it reflects clinical trial results and patient outcomes is not yet known*

**This is the experience and thoughts of our expert authors*

Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC)

The ADCS-CGIC is designed to assess clinically meaningful change over time in cognition, function, and behavior, in the research setting.[30,31] Unlike a targeted symptom scale, ADCS-CGIC takes into account the patient's overall function in these 3 domains.[30] The ADCS-CGIC is completed by a clinician who performs direct interviews with both the patient and the informant/caregiver.[31]

Domains:[30,31]

- *General*
- *Mental cognitive state*
- *Activities of daily living*
- *Behavior*

ADCS-CGIC uses a **7-point** scale:[30,31]

- *1 = marked improvement*
- *2 = moderate improvement*
- *3 = minimal improvement*
- *4 = no change*
- *5 = minimal worsening*
- *6 = moderate worsening*
- *7 = marked worsening*

Insights on use in clinical practice and research settings*

- *Not used in clinical practice, but easily understandable, meaningful endpoint*
- *Reflects patient outcomes, as it incorporates both patient and caregiver interview performed (and interpreted) by physician*
- *Used in clinical trials in several disease stages, from preclinical to mild AD*

*This is the experience and thoughts of our expert authors

Neuropsychiatric Inventory Questionnaire (NPI-Q)

The NPI is an interview of the caregiver or other informant assessing neuropsychiatric symptoms in the past 4 weeks, across 12 domains.[51] The NPI-Q is a condensed version of the NPI, completed by the caregiver/informant.[51] Symptom severity is assessed, but unlike the NPI, frequency is not assessed. Neuropsychiatric symptom severity on the NPI-Q has been shown to be associated with cognitive and functional impairment.[77] The NPI-Q is intended for use in clinical practice and is typically completed in under 5 minutes.[51]

Domains:[51]

• Delusions	• Disinhibition
• Hallucinations	• Irritability/lability
• Agitation/ aggression	• Aberrant motor behavior
• Dysphoria/ depression	• Nighttime disturbances
• Euphoria/elation	• Appetite/eating disturbances
• Apathy/ indifference	

Each domain is assessed for severity on a 3-point scale:

- *1 = mild*
- *2 = moderate*
- *3 = severe*

Total severity score ranges from 0 to 36; a higher score represents greater symptom burden

Insights on use in clinical practice and research settings*

- *Occasionally used in the clinical setting*
- *Considered useful in clinical practice and clinical trials for BPSD*

*This is the experience and thoughts of our expert authors

Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a safety outcome used across the field of psychiatry to prospectively measure the severity and frequency of suicidal ideation and suicidal behavior.[52,53] It is an observer-reported outcome in the form of a clinical interview intended to aid clinicians in assessing patient suicide risk.[53] Four constructs of suicide ideation and behavior are measured.[52] However, it should be noted that the C-SSRS is not specifically validated in the elderly population;[53] and concerns have been raised regarding the appropriateness of the C-SSRS for use in patients with dementia.[54]

C-SSRS components:[52]

- ***Severity of ideation*** *(yes/no):*
  1. *Wish to be dead*
  2. *Non-specific active suicidal thoughts*
  3. *Suicidal thoughts with methods*
  4. *Suicidal intent*
  5. *Suicidal intent with plan*
- ***Intensity of ideation:***
  - *Frequency, duration, controllability, deterrents, and reason for ideation*
  - *Each rated on a 5-point scale (1 being the least severe and 5 being the most severe)*
- ***Behavior subscale*** *(yes/no):*
  - *Actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior*
- ***Lethality subscale:***
  - *Actual lethality/medical damage*
  - *6-point scale (0 being no/minor physical damage and 5 being death)*
  - *If actual lethality is 0, potential lethality of attempts is assessed*
  - *3-point ordinal scale (0 being least likely lethal and 2 being most likely lethal)*

Insights on use in clinical practice and research settings*

- *Important safety assessment that can be done by trained raters, including non-experts in behavioral health; therefore, more useful in daily practice*
- *A safety measure in clinical trials but not used in clinical settings*
- *Does not adequately reflect patient outcomes and is inferior to a standard risk assessment*

*This is the experience and thoughts of our expert authors

Zarit Burden Interview (ZBI)

The ZBI evaluates caregiver burden in dementia.[55] The following domains are addressed through a series of statements: caregiver health, psychological well-being, relationship with the patient, social life, and finances.[55]

The original **ZBI** has 29 items[55]

Examples of items assessed:

- *I feel embarrassed over my spouse's behavior*
- *I feel strained in my interactions with my spouse*
- *I feel that my health has suffered because of my involvement with my spouse*
- *I feel that my spouse doesn't appreciate what I do for him/her as much as I would like*

Insights on use in clinical practice and research settings*

- *Used in some clinics and useful as a secondary outcome in clinical trials*
- *Reflects caregiver burden but not directly related to severity of patient's disease*

*This is the experience and thoughts of our expert authors

Resource Utilization in Dementia (RUD)

The RUD, developed for use in cost-effectiveness studies, captures resource use for dementia care.[56] The tool was designed for multinational use and to capture costs from the societal perspective. Both formal and informal care are assessed.[56] The RUD-Lite is an abbreviated version of the RUD and focuses on patient resource use (rather than both patient and caregiver resource use).[57]

The **RUD** tool measures assesses:[56,57]

- *Time spent assisting the patient with ADLs and instrumental ADLs*
- *Time spent supervising the patient*
- *Patient living accommodations*
- *Patient healthcare resource utilization*
- *Caregiver work status/impact, days missed*
- *Caregiver sleep*
- *Caregiver healthcare resource utilization*

Insights on use in clinical practice and research settings

- *Not used in the clinical setting, used in some service evaluation programs*
- *Helpful in clinical trials but may not necessarily reflect resource use during the trial itself; resource use tends to be delayed*

*This is the experience and thoughts of our expert authors

Fluid-based and imaging biomarkers in AD clinical trials

The FDA-NIH Biomarker Working Group defines a biomarker as:[78] "A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives."

In AD clinical trials, biomarkers can be classified as either diagnostic or endpoint biomarkers.[79]

- ***Diagnostic biomarkers*** *may be used for inclusion/exclusion criteria, sample size determination, or increasing statistical power (e.g. via stratification)*
- ***Endpoint biomarkers****, as trial outcomes, measure disease progression and detect treatment effects*

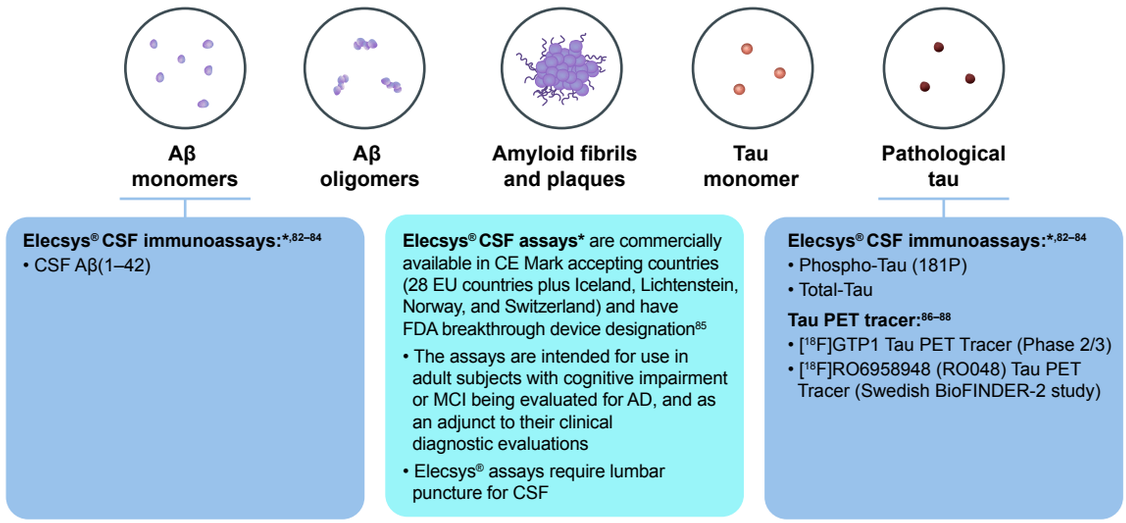
The evolving characterization of AD as a clinico-biological diagnosis requires biomarkers that detect preclinical and prodromal AD.[80] In addition to the early detection of AD pathophysiology for the inclusion of patients in clinical trials, biomarkers may be used for enrichment of the patient population by identifying those potentially most likely to experience treatment benefit.[80] Amyloid positron emission tomography (PET) and tau PET tracers are increasingly used as endpoints in AD clinical trials and play an important role in this setting.[81]

AD biomarkers may be biochemical- or imaging-based. Biochemical markers such as Aβ42, total Tau (tTau), phosphorylated Tau (pTau), Aβ42:40 ratio, and pTau:Aβ42 ratio are quantitative. Imaging biomarkers are qualitative (continuous) or quantitative (positive/negative) and include structural imaging such as magnetic resonance imaging (MRI) or computed tomography (CT); functional imaging such as fluorodeoxyglucose (FDG)-PET, functional MRI (fMRI), or single photon emission computed tomography (SPECT); or molecular imaging such as amyloid-PET or Tau-PET.

Biomarkers are essential for the detection of AD and the measurement of biological progression, and assays exist to measure both amyloid and tau progression (**Figure 5**).[82–88] Elecsys® cerebrospinal fluid (CSF) assays are commercially available in CE Mark accepting countries (28 EU countries plus Iceland, Lichtenstein, Norway, and Switzerland) and have FDA breakthrough device designation.[85] The assays are intended for use in adult subjects with cognitive impairment or MCI being evaluated for AD, and as an adjunct to their clinical diagnostic evaluations.

Figure 5: Assays that detect amyloid and tau progression

Note: the figure below shows Roche assays and is not intended to be comprehensive.



*Elecsys® CSF assays are not approved or cleared for clinical use in the US.

Aβ, amyloid beta; AD, Alzheimer's Disease; CSF, cerebrospinal fluid; FDA, Food and Drug Administration; MCI, mild cognitive impairment.

Individual biomarkers summarized

In this section, we summarize biomarkers used in AD, including the scientific rationale for their use in clinical trials to diagnose MCI and AD.

CSF – amyloid beta (Aβ)

Low CSF levels of Aβ42 is a key feature of AD.[89] Aβ is sequestered into amyloid plaques, reducing the amount in the CSF, and Aβ is predictive of AD pathology – CSF Aβ42 is highly sensitive for identification of prodromal AD cases in MCI cohorts.[89,90]

Insights on use in clinical practice and research settings*

- *Use in clinical practice depends on cost (of test), reimbursement rates (for lumbar puncture), and regional differences in patient willingness to undergo procedure*
- *Large variability in use depending on practice patterns in that area / expertise*
- *Strongly reflects clinical trial outcomes and key features of AD; pre vs post change could be useful*
- *Reflection of patient outcomes is likely delayed*

*This is the experience and thoughts of our expert authors

CSF – tau

High levels of pTau are characteristic of prodromal AD and AD dementia.[89,91,92] pTau is a measure of the amount of tau that is phosphorylated, the variant of tau found in tangles.[91] pTau predicts progression from MCI to AD dementia.[92]

Increased levels of tTau is characteristic of prodromal AD and AD dementia, reflecting axonal (neuronal) degeneration.[89,91] tTau gives a measure of the intensity of neurodegeneration in AD, but it is not a disease-specific marker.[89]

Insights on use in clinical practice and research settings*

- *Use in clinical practice depends on cost (of test), reimbursement rates (for lumbar puncture), and regional differences in patient willingness to undergo procedure*
- *Large variability in use depending on practice patterns in that area / expertise*
- *Strongly reflects clinical trial outcomes and key features of AD; pre vs post change could be useful*
- *As it is measurable, it can show the level of decline, but it must be combined with amyloid biomarkers*
- *Reflective of patient outcomes (assuming correct diagnosis of AD)*

*This is the experience and thoughts of our expert authors

CSF – amyloid beta and tau ratios

Aβ ratios are predictive of AD pathology:[89,91] a decreased Aβ42:Aβ40 ratio in MCI is predictive of progression to dementia.[89] Aβ40 is the most prevalent form of Aβ in CSF – the Aβ42:40 ratio accounts for between-individual differences in Aβ isoforms.[91]

High tTau:Aβ42 and pTau:Aβ42 ratios predict future cognitive decline.[93,94] A combined CSF biomarker test using Aβ42 and tTau has been reported to have 95% sensitivity and 83% specificity for the prediction of progression to AD.[93]

In the BioFINDER cohort, Elecsys® CSF assays were used to analyze a variety of CSF biomarkers.[84] pTau/Aβ42 and tTau/Aβ42 had ≈ 90% concordance with amyloid PET imaging, outperforming Aβ42 concordance (80%). Specificity and area under the curve were also improved with pTau/Aβ42 and tTau/Aβ42 ratios compared with Aβ42.[84]

Insights on use in clinical practice and research settings*

- *Ratios add substantial value for clinical trials when obtaining longitudinal assessments; these are good clinical outcome measures*
- *Use in the clinic is increasing but still in early stages of adoption*

*This is the experience and thoughts of our expert authors

Amyloid PET

Amyloid tracer binds to fibrillar Aβ and amyloid retention can be estimated by PET signal.[95] Types of tracers include Pittsburgh compound-B, florbetapir [18F] [AmyvidTM], florbetaben [18F] [NeuraceqTM], and flutemetamol [18F] [VizamylTM]. There are 3 FDA-approved tracers.

Insights on use in clinical practice and research settings*

- *Mixed opinion on utility for clinical trials: thought to be useful for baseline and longitudinal measures but also noted to be difficult to measure change*
- *In early stages of adoption in clinical practice*
- *Whether reflective of patient outcomes is a key question but believed by some to reflect outcomes in most cases*
- *Cost and exposure to radiation are potential limitations*

*This is the experience and thoughts of our expert authors

Tau PET

Tau PET tracers have been designed to bind neurofibrillary tangles, tau aggregates, and neuropil threads.[96] Flortaucipir [TauvidTM] is the only ligand which is FDA approved for tau PET in those with suspected AD.[97,98] [18F]GTP1 is a novel tau PET tracer in development that binds to tau pathology, enabling study of tau propagation.[86,99] GTP1 detects change in tau pathology over time in untreated patients.[100] Uptake of [18F]GTP1 has also been shown to correlate with the degree of cognitive impairment in AD.[101,102]

Insights on use in clinical practice and research settings*

- *In early stages of adoption in clinical practice, and use in clinical trials and whether reflective of patient outcomes are to be determined*
- *Likely helpful for optimal timing of targeted therapies: anti-amyloid (e.g. low to moderate amyloid and no or minimal tau), and for anti-tau therapies and anti-neuroinflammation therapies*

*This is the experience and thoughts of our expert authors

Volumetric MRI

Structural brain changes that occur with AD can be observed even prior to appearance of clinical symptoms.[103] Hippocampal volume is reduced prior to AD diagnosis. In dementia due to AD, entorhinal cortex volume is decreased by ≈ 30%–40% and hippocampal volume by ≈ 15%–25% compared with controls.[104] Structural features on MRI can predict progression from MCI to AD.[105]

Insights on use in clinical practice and research settings*

- *Widely used in clinical practice, and often underutilized by both neurologists and primary care physicians*
- *Hippocampal atrophy in setting of progressive short-term memory loss and family history of AD is highly predictive and cost-effective*
- *Radiologists can be asked to comment on hippocampal and other regional atrophy, saving time for other clinicians*
- *Often used in trials at baseline and post-intervention; reflective of clinical trial results but with a 6–12-month delay compared with CSF biomarkers*
- *Not linearly/directly reflective of patient outcomes*

*This is the experience and thoughts of our expert authors

Potential digital biomarkers

Prior to the onset of AD symptoms, biomarkers have the potential to predict AD progression.[106] Changes in olfaction, hearing, and walking speed can occur 5–15 years prior to the onset of cognitive impairments, and are therefore strong indicators of dementia.[107] Sensory and motor manifestations of AD can occur up to 15 years prior to an effective diagnosis; however, cognitive tests take a long time to administer, are limited by cultural bias, and are rater dependent.[108] In addition, stigma around AD may limit the use of cognitive testing and/or lead to delayed diagnosis.[109,110]

Digital biomarkers may have the potential to accelerate AD diagnosis and may improve prognosis.[108] Adoption of increasingly sophisticated mobile and wearable technologies (e.g. smart phones and smart watches) offers the opportunity to use “digital biomarkers” to measure the early changes in sensory and motor signs of AD. These measures can be passive/acquired (heart rate variability; gait speed; GPS) or active/prompted (memory tests; tapping tests; voice tests; eye movements).[108]

Summary

- *A variety of endpoints have been developed and used in AD clinical trials to assess potential therapeutic effect*
- *These outcome measures include cognitive, functional, quality of life, psychiatric, and caregiver burden scales, as well as imaging and biomarkers*
- *Utility of individual endpoints in clinical practice varies considerably, as does the extent to which they reflect clinical trial results and patient outcomes*

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M-XX-00004188