D2.1 First list of priority Real World Evidence relevant outcomes for AD

116020 - ROADMAP

Real world Outcomes across the AD spectrum for better care: Multi-modal data Access Platform

WP2 – Outcome Definition

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Document History

Version	Date	Description
V0.1	23/01/2017	Outline
V1.0	03/02/2017	First Draft by UEDIN team
V1.0	03/02/2017	Consortium review: feedback from NICE (Jacoline Bouvy), GE (Emilse Roncancio-Díaz)
V2.0	15/03/2017	Integration of comments from the UEDIN team and production of the final version.

Definitions

- **Dementia, Alzheimer's disease and other dementia subtypes.** Please refer to Dr. Tim Wilkinson's summary of dementia diagnostic criteria in Annex 1.
- **Outcomes.** Alzheimer's disease (AD) related outcomes are consequences or issues that relate to the clinical, economic and humanistic impact of having the disease on patients, carers and other parties; we consider them pertinent to AD research when using real world data. Real world data sources include, but are not limited to: pragmatic clinical trials, registry studies, claims databases/administrative data and electronic health records. We have differentiated between conceptually-defined outcomes and tools and instruments that have been developed to measure them in the tabulated lists of outcomes in this document.

- Partners of the ROADMAP Consortium are referred to herein according to the following codes:
  - **UOXF**. The Chancellor, Masters and Scholars of the University of Oxford (United Kingdom) – **Coordinator**
  - **NICE**. National Institute for Health and Care Excellence (United Kingdom)
  - **EMC**. Erasmus University Rotterdam (Netherlands)
  - **UM**. Universiteit Maastricht (Netherlands)
  - **SYNAPSE**. Synapse Research Management Partners (Spain)
  - **IDIAP JORDI GOL**. Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (Spain)
  - **UCPH**. Københavns Universitet (Denmark)
  - **AE**. Alzheimer Europe (Luxembourg)
  - **UEDIN**. University of Edinburgh (United Kingdom)
  - **UGOT**. Goeteborgs Universitet (Sweden)
  - **AU**. Aarhus Universitet (Denmark)
  - **LSE**. London School of Economics and Political Science (United Kingdom)
  - **CBG/MEB**. Aagentschap College ter Beoordeling van Geneesmiddelen (Netherlands)
  - **IXICO**. IXICO Technologies Ltd (United Kingdom)
  - **RUG**. Rijksuniversiteit Groningen (Netherlands)
  - **Novartis**. Novartis Pharma AG (Switzerland) **– Project leader**
  - **Eli Lilly**. Eli Lilly and Company Ltd (United Kingdom)
  - **BIOGEN**. Biogen Idec Limited (United Kingdom)
  - **ROCHE**. F. Hoffmann-La Roche Ltd (Switzerland)
  - **JPNV**. Janssen Pharmaceutica NV (Belgium)
  - **GE**. GE Healthcare Ltd (United Kingdom)
  - **AC Immune**. AC Immune SA (Switzerland)
- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the ROADMAP project (116020).
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The ROADMAP Consortium, comprising the above-mentioned legal entities.
- **Consortium Agreement.** Agreement concluded amongst ROADMAP participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

Publishable Summary

We have produced a first list of Real World Evidence (RWE) outcomes for Alzheimer's disease across the spectrum, having drawn upon findings from literature and following consultation with some of our partners within the Consortium who are leading experts in their fields in both academia and industry.

In the next stages of our work, we will prioritize outcomes and agree on criteria for meaningful delay in disease progression through synthesizing our findings from systematic reviews, stakeholder surveys, priority setting workshops and on-going collaboration within the Consortium.

1. Introduction

We have produced a preliminary outcomes list following a focussed review of published and unpublished literature. We then revised it after considering suggestions from WP2 contributors. Given the tight timeline in which this task was conducted, the list is by no means exhaustive. It represents an attempt at creating the 'universe' of outcomes across the spectrum of Alzheimer's disease and relevant to a wide range of stakeholders, including patients, carers, clinicians, scientists, policy makers and others.

Some of the reports reviewed comprise multiple systematic reviews or outcomes identified as pertinent in Alzheimer's disease research by international expert working groups. Over the lifespan of ROADMAP WP2's research activities we will add, remove and rank the outcomes as we prioritise outcomes recognised as significant to different, relevant stakeholder groups. The criteria for what makes an outcome or outcome measure will be clarified in due course. These priority outcomes will be further investigated in relation to validity, reliability and ability to detect meaningful change in Alzheimer's disease progression.

2. Outcome categories

We have compiled tabulated lists of:

(1) outcome entities (including domains and subdomains); and

(2) tools or instruments that have been developed to measure these

Under some outcome categories, where appropriate, outcome entities only are listed. We also acknowledge that there is overlap in these outcome categories and they are not necessarily mutually exclusive.

Outcomes categories included are:

- Clinical diagnosis endpoints specific to dementia/Alzheimer's disease across the spectrum
- Global outcomes
- Cognition
- Functioning/Dependency
- Behaviour/Neuropsychiatric symptoms
- Impact on the caregiver
- Resource utilisation and costs
- Patient quality of life
- Alzheimer's disease biomarkers
- Clinical outcomes (not a diagnosis of Alzheimer's disease or other dementia subtype)
    - Mortality
    - Comorbidities
- Significant events across the disease course

At this point, we have chosen not to subcategorise outcome measures by different stages of AD because many tools were not designed for use during a particular stage between preclinical and severe AD. With many outcome measures, there may be self- vs proxy- rating versions as well as versions of different lengths. E.g. SF6, 12 and 36. This will be elaborated upon in future iterations of this list.

The outcome category 'significant events across the disease course' was purposively added to give patients and carers a platform to specify what outcomes are most relevant to them at this early stage of identifying priority outcomes on the ROADMAP project. The outcome entities listed in this category are mostly derived from the International Consortium for Health Outcomes Measurement (ICHOM) Standard Set for dementia, a list compiled by an international group of physicians, measurement experts and patients. Representatives of Alzheimer Europe have also made contributions to the contents of this category.

Outcome category and entities
CLINICAL DIAGNOSIS ENDPOINTS SPECIFIC TO DEMENTIA/ALZHEIMER'S DISEASE ACROSS THE SPECTRUM[1]
Mild Cognitive Impairment (MCI)
MCI due to AD
Amnestic MCI (aMCI)
Non-amnestic MCI (naMCI)
Subjective Cognitive Impairment (SCI)
Subjective Memory Complaint (SMC)
Subjective Cognitive Decline (SCD)
Prodromal AD (pAD)
Dementia
Alzheimer's disease
Alzheimer's dementia (dementia phase of AD)
Mild/moderate/severe AD
Other dementia subtypes (not AD)
Vascular dementia
Mixed dementia
Frontotemporal dementia
Lewy bodies dementia
Dementia in other diseases classified elsewhere

[1] For further details, please see Dr. Tim Wilkinson's dementia diagnostic criteria summary in Annex I.

Outcome categories and entities	Outcome measures[2]
GLOBAL OUTCOMES	
Staging severity of dementia	Clinical Dementia Rating (CDR)
Global improvement	Clinical Dementia Rating Scale - sum of boxes (CDR-SB)
Therapeutic index (drug effect only)[3]	Clinical Dementia Rating- Global scoring (CDR-G)
Domains of Global CDR	Clinical Global Impression (CGI)
Memory	FDA Clinician's Interview Based Impression of Change (CIBIC)
Orientation	Clinician's Interview Based Impression of Change (CIBIC) + Caregiver's interview
Judgment	Clinician's Interview Based Impression of Change Plus (CIBIC+)
Problem-solving	Reisberg's Global Deterioration Scale (GDS)
Community affairs	
Home and hobbies	
Personal care	

[2] This list is not intended to map to the entities/domains/subdomains shown in the left-hand column but is simply a list of many of the instruments in use.

[3] Therapeutic index (TI), also known as the therapeutic ratio and margin of safety, is assessed using the Clinical Global Impression measurement tool. It describes the dosage at which the clinician thinks a drug will be of maximum therapeutic benefit to the patient without posing a serious risk to or very adverse side effects. It is terminology specific to Pharmacology.

Outcome categories and entities	Outcome measures[4]
COGNITION	
Cognitive impairment	Mini Mental State Examination (MMSE)
Cognitive decline	Montreal Cognitive Assessment (MoCA)
Cognitive trajectories	Modified Mini Mental Examination (mMMS)
Change in cognition	Modified Mini-Mental State Examination (3MS)
Attention	Paired-associate learning: Favourites (NIH examiner/toolbox)
Concentration	Mini-Cog
Level of consciousness	Addenbrooke's Clinical Examination (ACE)
Registration	Addenbrooke's Clinical Examination – Revised (ACE- R)
Language and communication	ADAS-Cog-11[5]
Immediate word recall	ADAS-Cog-13
Delayed word recall	ADAS-Cog14
Semantic verbal fluency	The Repeatable Battery for the Assessment of Neuropsychological status (RBANS)
Categorical verbal fluency	The Eriksen Flanker test (NIH examiner/toolbox)
Phonemic verbal fluency	Severe impairment battery (SIB)
Word recognition	Trail Making Test – Trail A
Naming	Trail Making Test – Trial B
Visuospatial ability	Boston Naming Test (BNT)
Visual memory	Everyday cognition (Ecog), Mail-In Cognitive Function Screening Instrument (MCFSI) – caregiver & patient versions
Visual construction	Informant Questionnaire on Cognition Decline in the Elderly (IQCODE)

[4] This list is not intended to map to the entities/domains/subdomains shown in the left hand column but is simply a list of many of the wide range of cognitive measurement instruments in use.
[5] Alzheimer's Disease Assessment Scale – Cognitive subscale version 11.

Visual discrimination	Dot counting (NIH examiner/toolbox)
Allocentric space	Four Mountains Task
Egocentric space	Free and Cued Selective Reminding Test (FCSRT)
Executive functions	Virtual reality supermarket trolley
Working memory	PACC scale
Processing speed	UK Biobank cognitive assessment battery [6]
Calculation	CANTAB computerized tests
Visual attention	COGSTATE computerised tests
Visual search and scanning	CDR computerised assessments
Mental flexibility	Modified Perceived Deficit Questionnaire
Sequencing and shifting	Wechsler Memory Scale
Abstraction	Wechsler Memory Scale Revised
Social cognition	Consortium to Establish a Registry for Alzheimer's disease Neuropsychological Assessment Battery (CERAD-NAB)
Memory	Rey Auditory Verbal Learning Test (RAVLT)
Learning	California Verbal Learning Test (CAVLT)
Spatial memory	Memory Function Questionnaire (MFQ)
Verbal memory	Cognitive Complaints Inventory (CCI)
Conceptual knowledge	Memory Assessment Clinic-Q) (MAC-Q)
Verbal episodic memory	Cognitive Functioning Index
Subjective memory complaints	Memory Impairment Screen (MIS)
Others	General Practitioner Assessment of Cognition (GPcog)
Ideational praxis	Allen cognitive level screening tool

[6] Administered via touchscreen during initial baseline assessment and then re-implemented as web-based questionnaires during follow-up, the UK Biobank cognitive assessment battery includes: fluid intelligence, trail making, symbol digit substitution, pairs matching and numeric memory tests.

Constructional praxis	Allen cognitive performance test
Following commands	Arizona battery for communication disorders of dementia
Perception	Information-memory-concentration test
Perceptual-motor skills	Middlesex elderly assessment of mental state (MEAMS)
Fluid intelligence	Neurobehavioral cognitive status examination
Crystallised intelligence	Rivermead behavioural memory test (RBMT)
	Williams memory assessment scales
	Kendrick battery for detection of dementia in the elderly
	Kendrick cognitive tests for the elderly (same as the above?)
	Lowenstein OT cognitive assessment (LOTCA)
	Language disorder of dementia
	Modified Perceived Deficit Questionnaire

Outcome categories and entities	Outcome measures[7]
FUNCTIONING/DEPENDENCY	
Global functionality	Alzheimer's Disease Cooperative Study/Activities of Daily Living for MCI(ADCS-MCI-ADL)
Communication and engagement with the environment	Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale (ADSC-ADL)
Outside activities	Day-Out Task (Performance based)
Instrumental Activities of Daily Living (IADLs)	Cambridge Behavioural Inventory Revised (CBI-R)
Ability to use telephone	Katz ADL
Shopping capacity	Physical Self-Maintenance Scale (PSMS)
Food preparation	Disability Assessment in Dementia (DAD)
Housekeeping	Functional Activities Questionnaire (FAQ)
Laundry	Barthel Index
Transportation/Driving capacity	Functional Assessment Staging (FAS)
Responsibility for own medications	Lawton IADL Scale
Financial capacity	Blessed Dementia Rating Scale (BDRS)
Management of everyday technology	Brody's IADL Scale
Supervision (preventing dangerous events)	Bristol Activities of Daily Living Scale (BADLs)
Communication	Dependency Scale (DS)
Activities of Daily Living (ADLs)	Every day Problems Test (EPT)
Hygiene/bathing	Amsterdam ADL Questionnaire
Dressing	Functional Capacity Index
Toileting	Financial Capacity Index (FCI)
Transferring	University of California San Diego Performance-Based Skills Assessment (UCSD-UPSA)

[7] This list is not intended to map to the entities/domains/subdomains shown in the left hand column but is simply a list of many of the wide range of function/dependency scales in use.

Walking	Management of Everyday Technology Assessment
Mobility	Driving Habits Questionnaire
Eating	

Outcome categories and entities	Outcome measures[8]
BEHAVIOUR AND NEUROPSYCHIATRIC SYMPTOMS	
Aggression	Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD)
Agitation	Dimension Apathy Scale (DAS)
Irritability	Columbia University Scale for Psychopathology in AD (CUSPAD)
Disinhibition	Neuropsychiatric Inventory (NPI)
Motor disturbances	NPI-12 (original +sleep +appetite change +caregiver stress)
Sleep patterns/ night time behaviours	Neuropsychiatric Inventory Questionnaire (NPI-Q) (informant)
Appetite/ eating disorders	Neuropsychiatric Inventory (Nursing home) (NPI-NH)
Euphoria	Hamilton Rating Scale for Depression (HAD)
Delusions	Cohen-Mansfield Agitation Inventory (CMAI)
Hallucinations	Cornell Scale for Depression in Dementia (CSDD)
Depression	Geriatric Depression Scale (GDS)
Anxiety	Rating Anxiety in Dementia (RAID)
Dysphoria	Brief Psychiatric Rating Scale (BPRS)
Motor disturbance	
Apathy/indifference	

[8] This list is not intended to map to the entities/domains/subdomains shown in the left hand column but is simply a list of many of the scales in use.

Outcome categories and entities	Outcome measures[9]
IMPACT ON THE CAREGIVER	
Caregiver objective burden	Zarit Burden Interview (ZBI)
Caregiver perceived burden	Sense of Competence Scale – SCQ (27) and short sense of competence scale SSCQ (7)
Caregiver stress	Relative Stress Scale (RSS)
Caregiver mood	Neuropsychiatric Inventory with Caregiver Distress Scale (NPI-D)
Caregiver co-morbidities	Neuropsychiatric Inventory in Nursing homes (NPI- NH) Occupational Disruption Domain
Staff Carer Morale	Brief Symptom Inventory (BSI)
Caregiver time	General Health Questionnaire (GHQ)
Financial toll	Centre for Epidemiological Studies – Depression Scale (CES-D)
Carer Quality of Life	Sense of Coherence Scale (SOC-13)
	Locus of Control of Behaviour Scale
	Hamilton Depression Rating Scale (HADS)
	Maslach Burnout Inventory (MBI)
	Caregiver Activity Survey (CAS)
	Caregiver Activities Time Survey (CATS)
	Resource Utilisation in Dementia(RUD)
	RUD Lite
	Caregiver specific QoL measures
	Carer Quality of Life (two parts: the CarerQoL-7D and the CarerQoL-VAS)
	Generic QoL measures[10]

[9] This list is not intended to map to the entities/domains/subdomains shown in the left hand column but is simply a list of many of the measurement instruments assessing impact on the caregiver in use.

[10] Any of the generic QoL measures listed in patient QoL section below might be used as measures here.

Outcome categories and entities	Outcome measures[11]
RESOURCE UTILISATION AND COSTS[12]	
Patient-related items	RUD
Living accommodation	RUD Lite
Patient health care resource utilisation (HCRU)	Resource Use Inventory (RUI)
Medication/medical device use	Client Service Receipt Inventory (CSRI)
Caregiver-related items	***Direct medical costs***
Formal caregiver time	Hospital inpatient costs
Informal caregiver time	Hospital outpatient costs
Time assisting with ADLs	A&E costs
Time assisting with IADLs	Ambulance costs
Time supervising	Prescriptions
Caregiver work status, impact, work days missed	Direct non-medical costs
Caregiver sleep	Long term/ institutional care costs
Caregiver HCRU	***Indirect costs***

[11] This list is not intended to map to the entities/domains/subdomains shown in the left hand column but is simply a list of some of the measurement instruments or costs that are taken into account when assessing resource utilisation and costs in Alzheimer's disease treatment and care
[12] These are subdomains covered in one (or more) of the relevant measurement tools listed on the right

Outcome categories and entities	Outcome measures[13]
PATIENT QUALITY OF LIFE	
General health	***Dementia specific QoL measures***
Physical health	Quality of Life in Alzheimer's Disease (QoL-AD) (informant- and self-report versions)
Energy	Dementia Quality of Life (DEMQoL and DEMQoL Proxy)
Usual activities	The Dementia Quality of Life Instrument (DQoL)
Mood	Bath Assessment of Subjective Quality of Life in Dementia (BASQID)
Living situation	Alzheimer's Disease Related Quality of Life (ADRQL)
Memory	Modified COOP/WONCA charts
Family	Progressive Deterioration Scale (PDS)
Marriage	Patient Activity Scale -AD plus the Modified Apparent Emotion Scale (PES+AD+AES)
Friends	Activity and Affect Indicators of QoL (AAIQoL)
Self as a whole	Community Dementia Quality of Life Profile (CDQLP)
Ability to do chores around the house	Cornell-Brown Scale for Quality of Life in Dementia (CBS)
Ability to do things for fun	Psychological Well-Being in Cognitively Impaired Persons (PWB-CIP)
Money	***Generic QoL measures***
Life as a whole	EuroQoL - 5 dimensions, 3 levels (EQ-5D-3L) (previously known as EQ-5D)
Pain/Discomfort	EuroQoL – 5 dimensions, 5 levels (EQ-5D-5L)
Well-being	Health Utility Index 1 (HUI 1)
Role Functioning (physical)	Health Utility Index 2 (HUI 2)
Role Functioning (emotional)	Health Utility Index 3 (HUI 3)
Vitality	Short form 36 (SF36)

[13] This list is not intended to map to the entities/domains/subdomains shown in the left hand column but is simply a list of many of the wide range of QoL scales in use.

Mental health	Short form 12 (SF12)
Social functioning	Short Form 6 (SF6)
Self-care	World Health Organisation Quality of Life – Brief version (WHOQoL –Brief)
Role Functioning (physical)	Visual analogue scale (EQ-VAS)
Role Functioning (emotional)	Quality of life in late-stage dementia (QUALID)
Vitality	A dementia specific quality of life questionnaire by professionals (QUALIDEM)
	Quality of Well-being Scale (QWB-SA)
	ICEpop CAPability instrument for Older people (ICECAP-O)
	Duke Health Profile (DHP)
	The Recovering Quality of Life – 10 items (ReQoL-10)
	The Recovering Quality of Life – 20 items (ReQoL-20)
	The CORE Outcome Measure (CORE-OM)

Outcome categories and entities

ALZHEIMERS'S DISEASE BIOMARKERS

Genetic biomarkers, *e.g.,*

APOE e4

APP

PSEN1

PSEN2

Functional neuroimaging biomarkers (PET), *e.g.,*

Amyloid beta

Tau

Structural neuroimaging biomarkers (MRI/CT), *e.g.,*

Hippocampal atrophy

Medial temporal lobe atrophy

Entorhinal atrophy

Whole brain volume

CSF biomarkers, *e.g.,*

CSF amyloid beta

CSF total tau

CSF phosphorylated tau (p-tau)

And others, including: blood, plasma & serum biomarkers, MRS and SPECT scans

Outcome categories and entities	Outcome measures[14]
OTHER CLINICAL OUTCOMES (NOT A DIAGNOSIS OF ALZHEIMER'S DISEASE OR OTHER DEMENTIA SUBTYPE)	
Mortality	Charlson Comorbidity Index
Comorbidities	Frailty Index
Stroke	
Cerebrovascular disease	
Coronary heart disease	
Diabetes	
Other vascular diseases	
Obesity	
Parkinson's Disease	
Epilepsy	
Other neurological disorders	
Cancer	
Musculoskeletal diseases	
Respiratory diseases	
Genitourinary diseases	
Renal diseases	
Eye-related impairments	
Hearing impairments	
Fractures and other trauma	
Delirium	

[14] This list is not intended to map to the entities/domains/subdomains shown in the left hand column but is simply a list of some of the instruments used to assess comorbidities.

Outcome categories and entities
SIGNIFICANT EVENTS ACROSS THE DISEASE COURSE
Ability to drive
Hospitalisation
Institutionalisation
Need for assistance at home
Need for full time care
Safety
Starting medication for symptomatic AD
Starting antipsychotic medication
Premature loss of paid employment
Respite care take up
Sick leave
Welfare support (monetary support)
Guardianship measures

3. List of resources

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Gothenburg, IDIAP Research Institute, University of Maastricht, University of Copenhagen, University of Oxford, Aarhus University, NICE, Novartis and the Medicines Evaluation Board.

4. Conclusion and next steps

There is a plethora of Alzheimer's disease related outcomes that could be considered important in research; we have compiled a comprehensive list of these under the categories outcome entities, and where appropriate, outcome measures. It is not an attempt at a complete list but it covers great breadth – from different clinical aspects of AD to quality of life and significant patient-centred events across the disease course.

Feedback from WP2 partners following submission of this deliverable, a first list of priority RWE outcomes for AD across the spectrum, for review suggests that there is a wish for a reconfiguration of these tabulated lists of outcome entities and outcome measures. Future iterations of this deliverable may include simplification of the outcome categories and mapping of measurement tools to outcome entity domains and subdomains. Using different nomenclature with respect to the outcome categories will also be considered.

Our next steps will necessitate adding, removing and ranking the outcomes as we prioritise outcomes recognised as significant to different, relevant stakeholder groups. This process will be informed by conducting systematic reviews, surveys, priority setting workshops and other stakeholder engagement activities to assess and determine priority outcomes and agree on criteria for meaningful delay in disease progression. How this deliverable will relate or evolve into D2.3, stakeholder lists of priority outcomes, and D2.4, a progression marker and outcomes classification matrix, will be clarified in due course.

On-going collaborative efforts within the Consortium will be key in moving this Work Package forward and feeding into the work of other Work Packages.

ANNEXES

ANNEX I. Diagnostic criteria for dementia and its subtypes

Tim Wilkinson, updated Dec 2016.

Dementia

Criteria	Details	Comments
ICD-10(1) 1992	A syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation	• Requires ≥2 of any higher cortical functions to be impaired • Does not specify the requirement for objective cognitive testing
DSM-IV(2) 2000	Multiple cognitive deficits, which include memory impairment and at least one of the following: aphasia, apraxia, agnosia or disturbance in executive functioning. Social or occupational function is also impaired. A diagnosis of dementia should not be made during delirium	• Requires memory impairment along with another cognitive domain involved • Does not specify the requirement for objective cognitive testing
DSM-V(3) 2013	1. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains. These domains include: complex attention, executive function, learning, memory, language, perceptual-motor and social cognition 2. The evidence for these deficits should consist of concern of the individual, a knowledgeable informant or a clinician accompanied with substantial cognitive impairment, preferably documented by formal neuropsychological testing 3. The cognitive deficits must interfere with independence in everyday activities and cannot occur exclusively in the context of a delirium or be better explained by another mental disorder	• DSM-V calls the syndrome ‘major neurocognitive impairment’ rather than ‘dementia’ • Formal neuropsychological testing preferable
NIA-AA(4) 2011	1. Cognitive impairment must interfere with the ability to function at work or at usual activities, to represent a decline from a previous level and not be explained by delirium or a major psychiatric disorder	• Requires ≥2 of any higher cortical functions to be impaired

	2. Cognitive impairment is diagnosed through a combination of history taking from the patient and an informant and an objective cognitive assessment 3. A minimum of two of the following domains should be impaired: ability to acquire and remember new information, reasoning and handling of complex tasks, visuospatial abilities, language functions or changes in personality or behaviour	• Requires objective cognitive testing

Alzheimer's disease

Criteria	Details	Comments
NINCDS-ADRDA(5) 1984	Two step process: 1. Identify dementia syndrome 2. Alzheimer's disease phenotype identified based on clinical features and neuropsychological testing o Probable AD – deficits in ≥2 areas, progressive worsening of memory and other cognitive functions, onset between age 40-90, absence of systemic disorders or other brain diseases that could account for the dementia o Possible AD – presence of second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of dementia and a single, gradually progressive severe cognitive deficit in the absence of other identifiable causes o Definite AD – clinical criteria for probable AD plus with histopathological evidence from biopsy or autopsy	• Requires dementia to be present for Alzheimer's disease to be diagnosed • Does not account for use of biomarkers or overlap with other aetiologies such as vascular disease
DSM-IV(2) 2000	Presence of a gradually progressive memory disorder which included deficits in at least one additional cognitive domain which is sufficiently severe to cause impairment of functioning	• Requires dementia to be present for Alzheimer's disease to be diagnosed • Does not account for use of biomarkers or overlap with other aetiologies such as vascular disease
NIA-AA(4,6) 2011	AD is a continuum with three broad stages: 1. Asymptomatic or preclinical phase 2. Symptomatic predementia or mild cognitive impairment phase with no impairment of every day functioning 3. Fully symptomatic or dementia phase	• Revision of 1984 NINCDS-ADRDA criteria • Preclinical AD phase intended for research purposes only, not clinical use

	Probable AD Meets criteria for dementia (see above) and in addition: 1. Insidious onset 2. Clear-cut history of worsening cognition 3. The initial and most prominent deficits are in one of the following categories: a. Amnestic –impairment in learning and recall b. Non-amnestic – language, visuospatial or executive dysfunction 4. Diagnosis of probable AD should not be applied if there is: a. Substantial concomitant cerebrovascular disease b. Features of Dementia with Lewy bodies c. Prominent features of behavioural variant frontotemporal dementia d. Prominent features of primary progressive aphasia e. Evidence of another cause that could have a substantial effect on cognition **Possible AD dementia** • Core criteria are met however the course of the disease is atypical • Mixed presentation such as concomitant cerebrovascular disease or there are features of other diseases that may contribute to a decline in cognitive function Biomarkers (CSF Aß42 and tau, structural changes on MR imaging, functional brain) are complimentary to, but not a prerequisite for a diagnosis. **Preclinical AD phase** – biomarker changes only, without any symptoms	• Supports diagnosis of AD in absence of dementia • 'AD" refers to pathological process, regardless of whether patient is symptomatic • No requirement for *objective* memory impairment (subjective or objective would suffice) • Biomarkers not necessary for diagnosis • Validity - specificity 70% and sensitivity of 80% compared to original NINCDS-ADRDA criteria(7), specificity 95% and sensitivity 66% in cohort of patients with early-onset AD and FTD(8)
IWG-2(9–11) 2007 - updated 2010 & 2014	**Defines three types/stages of AD:** 1. Asymptomatic at risk for AD - positive biomarker evidence of AD but no symptoms 2. Presymptomatic AD - carry a proven AD autosomal dominant mutation (e.g. PSEN1, PSEN2, APP) 3. AD (either typical or atypical) – Need 1 plus 2 1. Early and significant episodic memory impairment that includes: a. Gradual and progressive change in memory function over more than 6 months b. Objective evidence of an amnestic syndrome of the hippocampal type 2. In vivo evidence of Alzheimer's pathology. One of: a. Decreased $Aß_{42}$ together with increased t-tau or p-tau in CSF b. Increased tracer retention on amyloid PET	• AD category includes patients across the breadth of the symptomatic spectrum from mild memory impairment through to severe dementia • Unlike NIA-AA criteria, they do not delineate an MCI or predementia phase • Biomarker evidence is prerequisite to make AD diagnosis

c. AD autosomal dominant mutation present (in PSEN1, PSEN2, or APP) **Exclusion criteria:** 1. Sudden-onset 2. Early occurrence of gait disturbance, seizures, major behavioural changes 3. Focal neurological features 4. Early extrapyramidal signs 5. Early hallucinations 6. Cognitive fluctuations 7. Evidence of other conditions to account for memory and related symptoms	• Supports diagnosis of AD in absence of dementia • 'AD' refers to symptomatic patients only • Requires presence of *objective* memory impairment • Validity – when compared to post-mortem diagnosis, specificity of 73% and sensitivity of 54% (although no functional imaging and used CT not MR in this cohort)(12)

Vascular dementia

Criteria	Details	Comments
NINDS-AIREN(13) 1993	Need to (1) identify dementia syndrome, then (2) identify evidence of cerebrovascular disease and (3) establish a relationship between the two **Step 1. Dementia** 1. Cognitive decline from a previously higher level of functioning 2. Manifested by impairment of memory and two or more cognitive domains a. Orientation b. Attention c. Language d. Visuospatial functions e. Executive functions f. Motor control g. Praxis 3. Deficits preferably established by clinical examination and neuropsychological testing 4. Deficits severe enough to interfere with activities of daily living not due to physical effects of stroke alone **Step 2. Cerebrovascular disease** 1. Presence of focal signs on neurological examination 2. Evidence of cerebrovascular disease on brain imaging as evidenced by any or all of: a. Large vessel infarcts b. Single strategically placed infarct c. Multiple basal ganglia and white matter lacunes d. Extensive periventricular white matter lesions **Step 3. A relationship between the two above disorders** One or more of: 1. Onset of dementia within three months following a stroke 2. Abrupt deterioration in cognitive functions or stepwise progression of cognitive deficits	• Requires memory impairment (although there is evidence that disturbance in frontal executive functions rather than memory are more prominent features of VaD, with relatively preserved memory impairment) (14) • Requires memory deficit and ≥2 other cognitive domains • Requires neuroimaging confirmation of cerebrovascular disease

ADDTC(15) 1992	• Dementia - a deterioration in intellectual function sufficient to interfere with daily activities which is not isolated to a single category of intellectual performance. • Probable VaD - requires a diagnosis of dementia and evidence of two or more strokes by history, neurological examination or brain imaging, or the identification of a single stroke with a clear temporal relationship to the onset of dementia. There should be evidence of at least one infarct outside the cerebellum on neuroimaging • Possible VaD - requires evidence of dementia along with evidence of a single stroke without a clear temporal relationship to the onset of dementia or a diagnosis of Binswanger's disease (subcortical leukoencephalopathy) that includes early onset of urinary incontinence or gait disturbance, extensive white matter disease on brain imaging and vascular risk factors	• ≥2 cognitive domains must be affected but no specific requirement for memory impairment • Requires neuroimaging confirmation of cerebrovascular disease • Specifies at least one infarct must be outwith the cerebellum
DSM-IV(2) 2000	1. Meets DSM-IV criteria for dementia (above) 2. Evidence of focal neurological signs or laboratory evidence of cerebrovascular disease	• No requirement for neuroimaging evidence of cerebrovascular disease
DSM-V(3) 2013	1. Evidence of significant cognitive decline from a previous level of performance in one or more of: a. Learning and memory b. Language c. Executive function d. Complex attention e. Perceptual-motor f. Social cognition 2. Cognitive deficits interfere with independence in everyday activities. 3. Cognitive deficits do not occur exclusively in the context of delirium 4. Cognitive deficits are not better explained by another mental disorder 5. The clinical features are consistent with a vascular aetiology as suggested by either: a. Onset of deficits is temporally related to one or more cerebrovascular events b. Evidence for decline is prominent in complex attention and frontal-executive function 6. Evidence of the presence of cerebrovascular disease from history, examination and/or neuroimaging considered sufficient to account for cognitive deficits 7. Deficits not better explained by another brain disease or systemic disorder	• No absolute requirement for neuroimaging evidence of cerebrovascular disease

ICD-10(1) 1992	1. Meets ICD-10 criteria for dementia (above) 2. An unequal distribution of deficits in higher cognitive functions and clinical evidence of focal brain damage manifested by at least one of: a. unilateral spastic weakness of the limbs b. unilaterally increased tendon reflexes c. an extensor plantar response d. pseudobulbar palsy 3. Evidence from the history, examination or investigations of significant cerebrovascular disease which is judged to be aetiologically related to the dementia	• No absolute requirement for neuroimaging evidence of cerebrovascular disease
Summary of validity studies for VaD	The differences between the sets of criteria means that they do not appear to identify the same patients(16–18). In particular concordance between the ADDTC and NINDS-AIREN criteria is poor at around 33%(19). In one study the ADDTC criteria for possible vascular dementia were found to be the most sensitive whereas the DSM-IV and NINDS-AIREN criteria for possible vascular dementia were considered better at excluding mixed dementia from the 'pure' vascular type(17). The NINDS-AIREN criteria show high specificity but at the cost of low sensitivity (around 20%)(13). The newer DSM-V criteria are yet to be compared directly to the more established sets of criteria.	

Dementia with Lewy Bodies

Criteria	Details	Comments
McKeith criteria(20–22) 1996, updated in 1999 & 2005	1. Central feature (essential for a diagnosis): a. Dementia- progressive decline of sufficient magnitude to interfere with normal social or occupational function b. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression c. Deficits on tests of attention, executive function and visuospatial ability may be especially prominent 2. Core features (two core features for diagnosis of probable DLB, one for possible DLB): a. Fluctuating cognition b. Recurrent visual hallucinations that are typically well formed and detailed c. Spontaneous features of parkinsonism 3. Suggestive features (if one or more are present along with one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features a diagnosis of possible DLB can be made if there are one or more suggestive features) a. REM sleep behaviour disorder b. Severe neuroleptic sensitivity c. Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging 4. Supportive features a. Repeated falls and syncope b. Transient, unexplained loss of consciousness c. Severe autonomic dysfunction d. Hallucinations in other modalities e. Systematised delusions f. Depression g. Relative preservation of medial temporal lobes on brain imaging h. Generalised low uptake on SPECT/PET perfusion scan with reduced occipital activity i. Abnormal (low uptake) MIBG myocardial scintigraphy j. Prominent slow wave activity on EEG with temporal lobe transient sharp waves 5. A diagnosis is less likely if: a. Presence of cerebrovascular disease evident as focal neurological signs or on brain imaging	• Validity - Several studies have evaluated the sensitivity and specificity of the DLB criteria (23–26). All the studies have shown that the specificity of the criteria is high 84-100%, indicating few false positive results. The sensitivity reported in the studies is much lower however 22-83%. The sensitivity was shown to be higher when the criteria were applied prospectively rather than retrospectively however(25). The updated 2005 criteria sought to improve the sensitivity compared to previous versions(21)

b. Presence of any other physical illness or brain disorder sufficient to account for clinical picture
c. If parkinsonism only appears for the first time at a stage of severe dementia

6. Temporal sequence of symptoms:
   DLB should only be diagnosed when dementia occurs before or concurrently with parkinsonism (if present)

Frontotemporal dementia – behavioural variant

Criteria	Details	Comments
FTDC(27) 2011	1. Evidence of a neurodegenerative disease a. Progressive deterioration of behaviour and/or cognition 2. Possible bvFTD (three or more of the following) a. Early behavioural disinhibition b. Early apathy or inertia c. Early loss of sympathy or empathy d. Early perseverative, stereotyped or compulsive/ritualistic behaviour e. Hyperorality and dietary changes f. Neuropsychological profile of executive/generation deficits with relative sparing of memory and visuospatial functions 3. Probable bvFTD (all of the following must be met) a. Meets criteria for possible bvFTD b. Exhibits significant functional decline c. Imaging results consistent with bvFTD (one or more of the following) i. Frontal and/or anterior temporal atrophy on CT or MRI ii. Frontal hypometabolism on SPECT or PET 4. Exclusion criteria (if (a) or (b) present than a diagnosis of bvFTD cannot be made. If (c) present then possible bvFTD can still be diagnosed but probably bvFTD cannot) a. Pattern of deficits is better accounted for by other disorder b. Behavioural disturbance is better accounted for by a psychiatric diagnosis c. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process	• Validity - when compared to pathologically confirmed FTD cases, the FTDC criteria for possible bvFTD have a high reported sensitivity of 85-93% and specificity of 82% (27–29). When the criteria for probable FTD are employed the specificity rises to 95% however this comes at a cost to sensitivity which falls to 80-85% (28,29).

Frontotemporal dementia – primary progressive aphasia

Criteria	Details	Comments
Mesulam criteria for PPA(30) 2001 PPA subtype criteria(31) 2011	Two-step process in which first the criteria for a diagnosis of PPA must be met, as previously described by Mesulam in 2001 (30). **Criteria for the diagnosis of PPA based on criteria by Mesulam 2001** 1. Most prominent clinical feature is difficulty with language 2. These deficits are the principal cause of impaired daily living activities 3. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease Exclusion criteria 1. Pattern of deficits is better accounted for by other disorder 2. Cognitive disturbance is better accounted for by a psychiatric diagnosis 3. Prominent initial episodic memory, visual memory and visuoperceptual impairments 4. Prominent, initial behaviour disturbance If these criteria are met, a subtype diagnosis of PPA (either PNFA, SD or lvPPA can be made based on the criteria below: **Diagnostic criteria for NFPA** 1. At least one of the following core features must be present a. Agrammatism in language production b. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech) 2. At least two of the following other features must be present a. Impaired comprehension of syntactically complex sentences b. Spared single-word comprehension c. Spared object knowledge 3. Imaging must show at least one of the following a. Predominant left posterior fronto-insular atrophy on MRI b. Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET **Diagnostic criteria for SD** 1. Both of the following core features must be present a. Impaired confrontation naming	• Validity - there are no published data for the sensitivity and specificity of the 2011 diagnostic criteria for PPA and its subtypes

   b. Impaired single-word comprehension
2. At least three of the following other diagnostic features must be present:
   a. Impaired object knowledge, particularly for low-frequency or low familiarity items
   b. Surface dyslexia or dysgraphia
   c. Spared repetition
   d. Spared speech production (grammar and motor speech)
3. Imaging must show at least one of the following
   a. Predominant anterior temporal lobe atrophy
   b. Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET

Diagnostic criteria for lvPPA

1. Both of the following core features must be present
   a. Impaired single-word retrieval in spontaneous speech and naming
   b. Impaired repetition of sentences and phrases
2. At least three of the following of features must be present
   a. Speech errors in spontaneous speech and naming
   b. Spared single-word comprehension and object knowledge
   c. Spared motor speech
   d. Absence of frank agrammatism
3. Imaging must show at least one of the following
   a. Predominant left posterior perisylvian or parietal atrophy on MRI
   b. Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET

Abbreviations

AD – Alzheimer's diseases

NINCDS-ARDRA - National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer Disease and Related Disorders

NIA-AA - National Institute of Ageing and Alzheimer's Association

IWG - International Working Group

VaD – vascular dementia

NINDS-AIREN - National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences

ADDTC - The State of California Alzheimer's Disease Diagnostic and Treatment Centres

DLB – dementia with Lewy Bodies

FTD – frontotemporal dementia

FTDC - Frontotemporal Dementia Consortium

PPA – primary progressive aphasia

PNFA – progressive non-fluent aphasia

SD – semantic dementia

lvPPA – logopenic variant primary progressive aphasia

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