Title

Outcome measures for Alzheimer's disease: A global inter-societal Delphi consensus

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Authors

Ellison, Tim S
Cappa, Stefano F
Garrett, Dawne
et al.

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Correspondence: Giovanni B. Frisoni, Centre de la Memoire, Batiment Louise Morier, Rue, Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland. giovanni.frisoni@hcuge.ch.

#@AgeMelbourne; @AgeAmsterdam; @AgeSingapore

AUTHOR CONTRIBUTIONS

The steering committee, comprising Giovanni B. Frisoni (Chair/non-voting member), Michael Weiner, and Pieter-Jelle Visser (voting members), defined the overall aims and scope of the consensus, assembled the expert panel, guided the development of the surveys for each voting round, reviewed the responses and critically evaluated the evidence. A professional medical writer (Tim Ellison, PhD, of PharmaGenesis London, London, UK) supported the steering committee by initiating and project managing the process, performing literature searches, drafting and distributing the questionnaires, and collating and analyzing the responses. The rest of the authors completed the surveys and critically reviewed the manuscript drafts.

CONFLICT OF INTEREST

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Hoffmann-La Roche Ltd., and payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events from Biogen, F. Hoffmann-La Roche Ltd. (all to his institution). G.B.F. reports no conflicts of interest for the current manuscript. D.G. is a former professional lead for older people and dementia care at the Royal College of Nursing, UK, and a board member of the International psychogeriatric Association. J.G. is the Executive Director of Alzheimer Europe, which receives grants and support for its activities from the EU health and research programs and from private and public organizations and institutions. T.I. has served as a consultant or advisory board member for Eisai, Biogen, and F. Hoffmann-La Roche Ltd., and is funded by the Japan Agency for Medical Research and Development. J.H.K. has served as a consultant for Biogen and has received royalties from Pearson, Inc. C.L. has served as a consultant or advisory board member for AstraZeneca, GlaxoSmithKline, Eisai, Novartis, Forest Laboratories, Supernus Pharmaceuticals, Adlyfe, Takeda, Wyeth, Lundbeck, Merz Pharma, Eli Lilly and Company, Pfizer, Genentech, Elan Corporation, NFL Players Association, NFL Benefits Office, Avanir Pharmaceuticals, Zinfandel Pharmaceuticals, Bristol Myers Squibb, Abbvie, Janssen Pharmaceuticals, Orion Pharma, Otsuka Pharmaceutical, Laboratoires Servier, Astellas Pharma, F. Hoffmann-La Roche Ltd., Karuna, SVB Leerink, Maplight Therapeutics, Axsome Therapeutics, Global Institute on Addictions, GW Research Limited, and Merck. A.B.M. has received fees from Abbott Laboratories and Nutricia for serving as a consultant and an advisory board member, and for teaching lessons. J.M. has been funded by National Institutes of Health (NIH) grants #5R0I AF062639, R01 AG0567152, and P01AG019724. 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M.L., M.P., L.R., P.S., and M.V. report no conflicts of interest. P.J.V. received a research grant from Biogen, which was paid to the University. C.J.W. is a full-time employee of the Alzheimer's Association. M.W. has served as a consultant for: Acumen Pharmaceuticals, Alzeca Biosciences, Alzheon, Inc., AlzPath, Anven Biosciences, Baird Equity Capital, BioClinica, Cerecin, Cytox, Dolby Family Ventures, Duke University, Eli Lilly and Company, FUJIFILM-Toyama Chemical Co., Garfield Weston Foundation, Genentech, Guidepoint Global, Indiana University, Japanese Organization for Medical Device Development, Inc. (JOMDD), NervGen Pharma, Nestle/Nestec, NIH, Merck Sharp & Dohme Ltd., PeerView Internal Medicine, Patient-Centered Outcomes Research Institute / Patient-Powered Research Network (PCORI/PPRN), F. Hoffmann-La Roche Ltd., T3D Therapeutics, University of Southern California (USC), Medscape, Eisai, and Vida Ventures. M.W. has acted as a speaker/lecturer for: The Buck Institute for Research on Aging, China Association for Alzheimer's Disease (CAAD), Japan Society for Dementia Research, and the Korean Dementia Society. M.W. has traveled with support from: the University of Southern California (USC), NervGen Pharma, The American Society of Functional Neuroradiology, and the Clinical Trials on Alzheimer's Disease conference. M.W. holds stock with Alzeca Biosciences, AlzPath, and Anven Biosciences, and has stock options with Alzheon, Inc. M.W. receives research support from the following sources: NIH; Department of Defense; PCORI; California Department of Public Health; University of Michigan; Siemens; Biogen; The Larry L. 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ENDORSEMENTS

Endorsed by the European Academy of Neurology.

Outcome measures for Alzheimer's disease: A global inter-societal Delphi consensus

Tim S. Ellison[1], **Stefano F. Cappa**[2,3], **Dawne Garrett**[4], **Jean Georges**[5], **Takeshi Iwatsubo**[6,7], **Joel H. Kramer**[8], **Maryna Lehmann**[9], **Constantine Lyketsos**[10], **Andrea B. Maier**[11,12,13,14,#], **Jennifer Merrilees**[8], **John C. Morris**[15], **Sharon L. Naismith**[16], **Flavio Nobili**[17,18], **Marco Pahor**[19], **Dimity Pond**[20], **Louise Robinson**[21], **Pinar Soysal**[22,23], **Mathieu Vandenbulcke**[24,25], **Christopher J. Weber**[26], **Pieter Jelle Visser**[27,28,29], **Michael Weiner**[30,31], **Giovanni B. Frisoni**[32,33]

[1]PharmaGenesis London, London, UK

[2]Scuola Universitaria Superiore IUSS Pavia, Pavia, Italy

[3]Dementia Research Center, IRCCS Mondino Foundation, Pavia, Italy

[4]Royal College of Nursing, London, UK

[5]Alzheimer Europe, Luxembourg, Luxembourg

[6]Unit for Early and Exploratory Clinical Development, The University of Tokyo Hospital, Tokyo, Japan

[7]Department of Neuropathology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[8]Department of Neurology, Memory and Aging Center, University of California, San Francisco, California, USA

[9]World Dementia Council, George, South Africa

[10]Richman Family Precision Medicine Center of Excellence in Alzheimer's Disease, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University and Medicine, Baltimore, USA

[11]Department of Medicine and Aged Care, The Royal Melbourne Hospital, The University of Melbourne, Melbourne, Victoria, Australia

[12]Faculty of Behavioural and Movement Sciences, Department of Human Movement Sciences, Vrije Universiteit, Amsterdam Movement Sciences, Amsterdam, Netherlands

[13]Healthy Longevity Translational Research Program, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

[14]Centre for Healthy Longevity, National University Health System, Singapore, Singapore

[15]Department of Neurology, Washington University, St. Louis, Missouri, USA

[16]School of Psychology, The University of Sydney, Sydney, New South Wales, Australia

SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

[17]UO Clinica Neurologica, Istituto di Ricovero e Cura a Carattere Scientifico Ospedale Policlinico San Martino, Genova, Italy

[18]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, and Child and Mother Health, University of Genoa, Genova, Italy

[19]Department of Aging and Geriatric Research, Institute on Aging, University of Florida College of Medicine, Gainesville, Florida, USA

[20]Faculty of Health and Medicine, School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia

[21]Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK

[22]Department of Geriatric Medicine, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey

[23]European Society of Geriatric Medicine, Dementia Special Interest Group

[24]Neuropsychiatry, Department of Neurosciences, Leuven Brain Institute, KU Leuven, Leuven, Belgium

[25]Geriatric Psychiatry, University Psychiatric Centre KU Leuven, Leuven, Belgium

[26]Alzheimer's Association, Chicago, Illinois, USA

[27]Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience (MHeNS), Maastricht University, Maastricht, Netherlands

[28]Alzheimer Center, Department of Neurology, Neuroscience Campus Amsterdam, Amsterdam University Medical Center, VU Medical Center, Amsterdam, Netherlands

[29]Department of Neurobiology, Care Sciences and Society, Division of Neurogeriatrics, Karolinska Institute, Stockholm, Sweden

[30]San Francisco Veterans Affairs Medical Center, San Francisco, California, USA

[31]Department of Radiology and Biomedical Imaging, University of California, San Francisco, California, USA

[32]Laboratory of Neuroimaging of Aging (LANVIE), University of Geneva, Geneva, Switzerland

[33]Memory Clinic, Department of Readaptation and Geriatrics, Geneva University and University Hospitals, Geneva, Switzerland

Abstract

Introduction: We aim to provide guidance on outcomes and measures for use in patients with Alzheimer's clinical syndrome.

Methods: A consensus group of 20 voting members nominated by 10 professional societies, and a non-voting chair, used a Delphi approach and modified GRADE criteria.

Results: Consensus was reached on priority outcomes ($n = 66$), measures ($n = 49$) and statements ($n = 37$) across nine domains. A number of outcomes and measurement instruments were ranked for: Cognitive abilities; Functional abilities/dependency; Behavioural and neuropsychiatric

symptoms; Patient quality of life (QoL); Caregiver QoL; Healthcare and treatment-related outcomes; Medical investigations; Disease-related life events; and Global outcomes.

Discussion: This work provides indications on the domains and ideal pertinent measurement instruments that clinicians may wish to use to follow patients with cognitive impairment. More work is needed to develop instruments that are more feasible in the context of the constraints of clinical routine.

Keywords

Alzheimer's disease; consensus; Delphi; dementia; measures; outcomes

1 | INTRODUCTION

There are currently estimated to be over 55 million people worldwide living with dementia, with the number of people affected expected to rise to 153 million by 2050.[1,2] Alzheimer's disease (AD), defined by impairment of cognitive function, particularly memory, and confirmed by the presence of amyloid plaques and tau tangles, is the most common cause of dementia, accounting for an estimated 60% to 80% of cases.[3] The etiology of AD remains poorly understood. Until recently, there were no pharmacological or non-pharmacological treatments that specifically acted on the disease pathology.[3,4] However, in 2021, the first new treatment for AD since 2003 went through an accelerated approval by the Food and Drug Administration (FDA) based on a surrogate endpoint (amyloid removal), that was considered "reasonably likely to predict a clinical benefit to patients".[5] Individuals with AD progress through pre-symptomatic to symptomatic stages, often termed preclinical prodromal (mild cognitive impairment [MCI]), mild, moderate, and severe dementia.[6] Patients with symptomatic AD typically have an amnestic presentation and demonstrate impairment in executive functions as well. These and other cognitive impairments progressively interfere with activities of daily living (ADLs) and eventually lead to loss of independence.[4,6] However, the range of symptoms and clinically relevant outcomes across the AD spectrum are diverse because variants may present non-amnestic symptoms, such as language, visual-perceptual, or executive/behavioral impairment, which are also likely to be caused by neuroplasticity dysfunction.[7]

AD-related outcomes are measurable consequences or issues that relate to the clinical, economic, and human impact of having the disease on patients with symptomatic AD and other key stakeholders such as their caregivers and families. Multiple outcomes and outcome measures are used in studies of patients with MCI and AD dementia. They are heterogeneous, often lack adequate sensitivity to measure change in disease progression, and may not reflect what patients and other key stakeholders in AD value.[8–12] A recent review of outcome measures used in randomized controlled trials ($n = 91$) of non-pharmacological interventions for patients with symptomatic AD found that only 22% of the outcome measures were used in more than one of the trials included in the review.[11] This inconsistency in the use of outcome measures makes it difficult to compare and interpret results across studies.[9,10] Furthermore, it is unclear which outcomes and outcome measures are most appropriate for use in real-world clinical practice from both the patient and professional perspective.[9,10] Outcomes are not just of importance for measuring disease

progression, but also for identifying social and medical needs as part of coordinating AD support services.

Several consensus initiatives have been undertaken to ensure agreement can be achieved on recommendations of outcomes and outcome measures for use in patients with symptomatic AD who are engaged in research studies as well as clinical care.[13–18] Previous consensus initiatives focused on outcomes in clinical trials for dementia in general, and therefore they may not all be applicable to AD in real-world settings. Moreover, the consensus initiatives did not necessarily involve the prioritization of outcomes from comprehensive lists. The aim of the current initiative was to achieve consensus among experts on priority outcomes and outcome measures for use in clinical practice when caring for patients who have symptomatic AD, with a focus on its MCI and mild and moderate dementia stages. Outcome measures for cognitively healthy individuals who have preclinical AD and for patients with severe AD dementia were not considered in this initiative, owing to the broad scope of such a proposal and because clinically meaningful outcomes in the initial and late stages of AD have their own specificities.

2 | METHODS

2.1 | Consensus group organization

A steering committee led the consensus initiative, comprising Giovanni B. Frisoni (Chair/non-voting member), Michael Weiner, and Pieter-Jelle Visser (voting members). The overall aims and scope of the consensus were defined by the steering committee. Under the guidance of the steering committee, PharmaGenesis London assembled an expert panel of participants representing diverse specialties by contacting pertinent international professional societies and asking for recommendations of specialists in AD with expertise in outcome measures. Specialists from different geographical regions of the world were invited to help ensure that the consensus initiative was international. In total, there were 18 panel members, consisting of a patient (n = 1), patient advocate representatives (n = 2), family physicians (n = 2), nurses (n = 2), psychiatrists (n = 2), neuropsychologists (n = 2), geriatricians (n = 3), and neurologists (n = 4). Panel members were from Europe (n = 7), North America (n = 6), the Asia-Pacific region (n = 4), and Africa (n = 1). Of the 18 panel members, 6 were recommended by the Steering Committee and 12 were recommended by, selected from, or represent 10 professional societies and relevant non-government organizations, including: Alzheimer’s Association (C.J.W., D.G., L.R.); Alzheimer Europe (J.G.); American Academy of Neurology (J.C.M.); European Association of Geriatric Psychiatry (M.V.); European Academy of Neurology (F.N.); Dementia SIG of the European Geriatric Medicine Society (P.S.); Federation of the European Societies of Neuropsychology (S.F.C.); Dementia SIG of the International Neuropsychological Society (S.L.N.); SIG on Ageing and Health at the World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians (D.P.); World Dementia Council (M.L.). F. Hoffmann-La Roche Ltd. funded the involvement of PharmaGenesis London; however, F. Hoffmann-La Roche Ltd. did not have any input into the process or content. No funds were provided to the steering committee members or expert panel.

PharmaGenesis London developed the statements and surveys and analyzed the results, guided by the steering committee. Questionnaires were completed by the consensus group, consisting of the voting members of the steering committee and the expert panel. All answers were anonymous to the steering committee and expert panel.

2.2 | Delphi process

Prioritized outcomes, outcome measures, and consensus statements were developed using a Delphi process consisting of three rounds of voting (Figure 1). The first two rounds were conducted via online surveys (SurveyMonkey, San Mateo, CA, USA) between April and July 2021. From extensive lists of outcomes and outcome measures identified via a systematic literature review, participants selected those and added additional ones not in the lists that they perceived to be of the highest priority, which were then brought forward to the second round of voting. In the second round, the group ranked these in order of priority. The group also voted on whether each outcome or measure was relevant to mild disease, moderate disease, or both. Statements were developed based on comments entered as free-text by consensus group members in response to the first questionnaire. In the second questionnaire, voting on statements proceeded anonymously using a five-point Likert scale: strongly agree, agree, neither agree nor disagree, disagree, or strongly disagree. Statements could be altered, and new statements, outcomes, and outcome measures could be added by the group throughout the voting stages. The threshold for consensus was predefined as at least 70% of the consensus group voting ‘agree’ or ‘strongly agree.’

A final voting round on the prioritized lists of outcomes and measures, and on statements that had not already reached consensus, took place during a virtual meeting in September 2021. The meeting was moderated by the non-voting member of the steering committee. The consensus group discussed the proposed statements, and the statement wording was updated before the group voted for the third time. Six members of the expert panel were unable to join the virtual meeting. They reviewed the final statements after the meeting and voted via the online survey.

2.3 | Systematic literature review

Lists of outcomes and supporting evidence were identified via a systematic literature review (Figure 2). The literature search strategy was based on a strategy employed by Tochel et al.[7] Studies identified by Tochel et al. during their literature review were consulted and searches were extended to literature published up until 1 October 2021, searching in PubMed and EMBASE. Details of the search strings are shown in Tables S1 and S2. For the extended search, studies were included regardless of language. Inclusion and exclusion criteria were the same as those used by Tochel et al. For example, we excluded studies that: did not allow information related to symptomatic AD across the spectrum to be distinguished from other conditions such as stroke; did not provide sufficient data to answer the research questions (e.g., commentaries or opinion pieces); did not use an explicit research methodology to gather the required research data. Review of publications was performed by one member of the research group (T.S.E.), and for each included publication, one member of the research group completed data extraction (T.S.E.), noting the number of participants, methodological approach, and results. Initial lists of outcome measures were obtained from the ROADMAP

project (roadmap-alzheimer.org), and panel members were given the opportunity to suggest additional measures. The evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system,[19] and the gradings were reviewed and agreed on by the steering committee and expert panel.

3 | CONSENSUS OUTPUTS

3.1 | Overview of outputs

Informed by the systematic literature review, outcomes, and outcome measures were organized into nine domains: (1) cognitive abilities; (2) functional ability and dependency; (3) behavioral and neuropsychiatric symptoms; (4) patient quality of life (QoL); (5) QoL of caregivers and families; (6) health, social care, and treatment-related outcomes; (7) medical investigations; (8) significant disease-related life events; and (9) global outcomes. During the voting stages, long lists of outcomes and outcome measures were filtered down to prioritized shortlists, as shown in Table 1. Studies identified from the systematic literature reviews that reported outcomes of importance to patients, caregivers, and healthcare professionals are detailed in Table S3. The consensus group ranked the prioritized outcomes and outcome measures in order of priority (Table 2) and indicated their relevance for mild and moderate disease (Table 3). General considerations and statements associated with each domain are shown in Table 4.

3.2 | General statements

AD is defined pathologically as amyloid plaques, tau tangles, and neurodegeneration, which lead to cognitive decline and dementia.[3] Alzheimer's clinical syndrome refers to patients who appear to have AD diagnosed clinically, but who do not have a biomarker-confirmed diagnosis.[20] The clinical diagnosis of AD can be supported by documentation of AD biomarkers obtained by positron emission tomography scans and cerebrospinal fluid; new plasma biomarkers may also be diagnostically meaningful. However, for the purposes of this Delphi process, we use the term Alzheimer's clinical syndrome, which is defined clinically as a progressive amnestic process that leads to dementia, which is believed to be caused by an underlying AD pathology. General statements that are applicable to all domains cover issues such as ease of use of outcome measures, choice of measures from the lists of prioritized measures, relevance to mild and moderate disease, and alternatives to outcome measures (Statements 0.1–0.9; Table 4). Wherever possible, outcomes and outcome measures should be suitable for measuring disease progression across multiple stages of disease. However, assessment of disease progression is more important in the early stages of symptomatic Alzheimer's clinical syndrome than in the later stages; consequently, measures that are more relevant to mild disease should be prioritized.

One challenge is that, in early symptomatic Alzheimer's clinical syndrome, changes in outcome measures can be subtle and therefore difficult to detect. For example, the AD Assessment Scale – Cognitive Subscale (ADAS-Cog) demonstrates a ceiling of performance effects in early symptomatic AD, and some of its subtests are unable to discriminate subtle changes in cognition.[21,22] Ceiling and floor effects limit accurate assessment using many outcome measures, and this may be related to educational background and socioeconomic

status.[23,24] Despite an association between low education and a higher risk of developing AD, few cognitive function outcome measures have been assessed in individuals with low educational levels.[23] From the prioritized list of outcome measures, cutoff scores for adults with low education have been established for the Mini-Mental State Examination (MMSE), Rey Auditory Verbal Learning Test, Trail Making Test – Trail A, and Trail Making Test – Trail B.[23] The challenge for immigrants of having to access outcome measures in a foreign language is also an important emerging issue.

This Delphi consensus provides recommendations for use of outcomes and measures focused on the context of a memory clinic with a multidisciplinary assessment team. In other settings (such as primary care), it may not be feasible to implement the measures at the frequency recommended. In addition, an overall limitation in this field is the lack of applicability of the measures to non-whites and non-European/American cultures and languages.[25]

3.3 | Domain 1: Cognitive abilities

Outcomes in the cognitive skills domain were selected from an original list of 14 and prioritized in the following order: memory, executive functions, language and communication, judgement and insight, orientation, and spatial cognition (Table 2). The impact of memory impairment in Alzheimer's clinical syndrome was a key theme in the literature and was rated as an important outcome by patients, caregivers, and healthcare professionals in 14 studies identified in the literature searches.

From a long list of measures of cognitive abilities ($n = 53$), the group shortlisted seven. The MMSE and the ADAS-Cog are the most widely used cognitive measures in disease-modifying trials.[15] However, for use in clinical practice, the group ranked the Montreal Cognitive Assessment (MoCA) highest. The MoCA is a brief global measure that is easily administered with little training and demonstrates good overall construct validity.[26] Additionally, the MoCA has been validated in AD, and has been shown to be an accurate cognitive tool for detecting and monitoring AD in clinical practice.[27] Although measures such as the MMSE and MoCA were prioritized, the group recognized their limitations and agreed that ideally these should be used in combination with more in-depth measures. Indeed, meta-analyses of the use of the MMSE and MoCA for the detection of dementia have found little evidence to support their use in isolation for diagnostic purposes.[28–30]

It is also important for clinicians to consider that outcome measures for cognitive abilities can be affected by other factors, such as hearing and visual impairment and poor motor skills. When using the standard orally administered MoCA, scores are significantly lower for individuals with hearing loss than in those with normal hearing.[31] Although some cognitive tests have been adapted for individuals with hearing or vision impairments, this may affect their validity, especially if the adaptation results in deletion of items.[32]

There is a need for a more comprehensive outcome measure to assess language and communication. Language and communication impairment was reported as an impactful outcome in eight studies and was prioritized by the consensus group.[33–40] However, measures to assess language in clinical practice only explore selected aspects, such as

picture naming and verbal fluency, and are therefore suboptimal. Moreover, they generally take a long time to administer and score and consequently are seldom used in clinical practice. Currently available measures to assess communication abilities are also suboptimal. There is therefore a need for brief but valid measures of language and communication abilities.

It should be noted that cognitive tests such as the MMSE and MoCA have limitations. For example, at initial assessment, these measures are unable to determine whether a person's performance represents a decline from prior function. Cognitive tests cannot capture decline (unless obtained serially, which is not possible when a person initially presents for diagnosis) but are able to show a comparison of a person's current performance on cognitive tests with the test performance of normative groups (inter-individual comparison). Because almost all normative groups are composed of mainly white people (and many are limited to English-speaking white people), cognitive test assessment of non-white people is further complicated by test bias.[25] Ideally, a measure would capture intra-individual change and use the patient as his or her own control, which would reduce the bias currently seen with norm-referenced tests.

3.4 | Domain 2: Functional ability and dependency

Selected outcomes in the functional ability and dependency domain (in order of priority) were ADLs and instrumental ADLs (IADLs), independence and autonomy, social engagement, cognitive engagement, and physical health and mobility (reported in 21 studies; Tables 2 and 3). Prioritized measures (in order of priority) were the Functional Activities Questionnaire (FAQ), Lawton IADL, Amsterdam IADL – Short Version, Barthel Index, Amsterdam IADL, and the Katz ADL. The FAQ is a commonly used IADL scale that has been shown in one study to offer adequate sensitivity to distinguish between MCI and mild AD dementia.[41] However, this study has not yet been replicated and according to current diagnostic guidelines, people with MCI often have functional impairment.[42] The choice of measure for this domain depends on the setting. More detailed scales such as the Amsterdam IADL may be more difficult to use in a primary care setting but may, however, be useful in specialist secondary care centers. Therefore, simpler scales such as the Lawton IADL or the short form of the Amsterdam IADL may be more appropriate in primary care. The group discussed the paucity of appropriate outcome measures to assess physical frailty in Alzheimer's clinical syndrome and drafted a statement on this topic, but consensus was not reached in the final vote with only 63% in agreement (70% was required for consensus). The group agreed on the importance of assessing not only ADLs and IADLs but also motor function, as assessed by means of walking speed or other standardized performance measures, such as the Short Physical Performance Battery.[43,44] It should be noted again that a major caveat for the use of these scales is that they were developed, validated, and standardized in groups of Western white people and may not apply to other groups and cultures. In addition, some scales require caregiver / informant input, but this may not always available in primary care, which might influence the choice of outcome measure.

3.5 | Domain 3: Behavioural and neuropsychiatric symptoms

Twelve outcomes were prioritized for this domain, and these outcomes were reported in 21 studies (Tables 2 and 3). The highest priority outcomes were: behavior that is aggressive, challenging and unpredictable; agitation; depression; personality changes; and apathy. Among outcomes for this domain, depression, anxiety, and pain management should be prioritized by clinicians because of their impact on physical, psychological and social function and their potential to be treated. All outcomes are arguably important, but certain priority outcomes have the potential to be very disruptive, even if mild, as detailed in Table 4. As well as being valuable for assessing disease progression, assessment of behavioral and neuropsychiatric symptoms is crucial for management planning and differentiating the diagnosis from other neurodegenerative diseases.

The prioritized measures (in order of priority) were: the Neuropsychiatric Inventory (NPI), NPI-Questionnaire (a brief questionnaire form of the NPI), Geriatric Depression Scale, NPI-12 item version, Cornell Scale for Depression in Dementia, Hamilton Depression Rating Scale (HDRS), and the Dimensional Apathy Scale. Measures in this domain may be most valuable if administered when a specific behavioral or neuropsychiatric symptom is identified that impacts QoL and then repeated to assess the impact of therapy.

3.6 | Domain 4: Patient QoL

Fifteen studies reported impacts on patient QoL. Overall patient QoL was the most highly prioritized outcome in this domain, followed by impact on relationships, social contact, remaining active, maintaining the ability to participate in hobbies, access to dementia-friendly environments, treatment side effects, and sexual health (Tables 2 and 3). These outcomes are important for the well-being of the patient but are less relevant for the assessment of disease progression. Assessment of dementia often focuses on losses and deficits. In contrast, an assessment of QoL has the potential to identify and reframe meaningful aspects of the patient's life. An assessment of QoL provides a structure for examining variables, such as physical, social, and emotional function, that can be used to maintain care or as an avenue for change. The group selected and recorded, in order of priority, the most important patient QoL measures for use in clinical practice: Quality of Life in Alzheimer's disease, Dementia Quality of Life, Dementia Quality of Life-Proxy, EQ-5D-5L, EQ-5D-3L, and World Health Organization Quality of Life. Additionally, the consensus group noted that a semi-structured interview with the patient and a reliable career is a good alternative to structured questionnaire tools for this domain.

3.7 | Domain 5: QoL of caregivers and families

The prioritized outcomes in this domain, in order of priority, were: caregiver support, overall impact on caregiver, caregiver/family mental and physical health, caregiver self-efficacy, relationship between caregiver and patient, family involvement in care, other caregiver commitments/loss of free time, and spouses' 'duty' to care (Tables 2 and 3). These outcomes were reported in 22 studies. Prioritized outcome measures were voted for in the following order: Zarit Burden Interview, CarerQoL-7D, Neuropsychiatric Inventory Caregiver Distress Scale, Caregiver Activity Survey, General Health Questionnaire, HDRS, and Center for Epidemiological studies – Depression scale.

In real clinical practice, few outcome measures are used to assess the quality of caregivers' and families' lives. For some measures, such as the HDRS, specific training should ideally be provided. Another challenge is that, in some countries, clinicians are not reimbursed by the government to attend to a caregiver's needs unless they are counted as the primary patient, which they are frequently not.

3.8 | Domain 6: Health, social care, and treatment-related outcomes

Thirteen outcomes related to health, social care, and treatment were prioritized; the top five outcomes were: access to and use of health services and disease information, delaying entry into institutionalized care, delirium, falls, and hospitalization (Tables 2 and 3). These outcomes were reported in 21 studies. Nine measures were selected; the top five measures were direct non-medical costs, long-term institutional care costs, hospital inpatient costs, resource use inventory, and accident and emergency costs. In this domain, the differences between different countries and regions may be huge and highly dependent on the nature of national health systems.

3.9 | Domain 7: Medical investigations

Outcomes and outcome measures in the medical investigations' domain were collated, but the group voted not to recommend these for assessment of the progression of AD. Instead, statements were drafted and voted on, reflecting the group's view that many biomarkers currently offer little value in assessing disease progression beyond diagnosis (Table 4).[45,46] Cognitive and functional decline are more important measures of disease progression and impact. There is some evidence that regional brain volume loss may aid in assessing disease progression before diagnosis,[47,48] and a statement was drafted on this topic. However, the statement did not reach consensus in the final vote, with only 63% of the group in agreement (70% was required for consensus).

3.10 | Domain 8: Significant disease-related life events

Eleven outcomes were prioritized, which were reported in six studies; the highest priority outcomes were losing the ability to function at work, losing decision-making responsibility, needing help with basic ADLs, impact on family and losing the ability to drive/loss of license.

3.11 | Domain 9: Global outcomes

Three outcomes were prioritized: identifying individuals' needs and wants, global improvement and staging severity of dementia (Tables 2 and 3). Global outcomes were reported as being important to patients and caregivers in one study.[49] Nine measures were prioritized in the following order: Clinical Dementia Rating (CDR) and its derivative, the CDR scale – Sum of Boxes, Clinical Global Impression scale, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change, Clinician's Interview-Based Impression of Change (CIBIC) plus caregiver interview, CIBIC, Global Deterioration Scale, and Nutritional status with BMI computation.

The CDR is based on semi-structured interviews in which the patient and caregiver or family member are interviewed separately. The CDR is widely used[50] and has been translated into

84 languages. Moreover, ~12, 000 clinicians in 113 countries worldwide have been certified in its use, and it has functioned as the primary endpoint in clinical trials of early AD and as a co-primary endpoint in trials of mild–moderate AD.[50,51] Although comprehensive in terms of yielding a global 'sum of boxes' score based on cognitive and functional domains, it takes over 30 min to administer and must be administered and scored by a trained clinician; therefore, it is not feasible in all clinical settings. An electronic version (eCDR) has been developed, is being validated, and may be available in the future.[52] The seven-item Global Deterioration Scale[53] is used to stage cognitive and functional abilities of patients with dementia, does not require a separate interview with either the patient or informant and does not require extensive training. However, ease of use may translate into lower precision and a less informative tool. Currently, these global outcome measures are used primarily in research rather than in real-world clinical practice.[54] The group, therefore, identified an unmet need for global outcome measures to be used by clinicians in real-world settings.

4 | CONCLUSIONS

Through an iterative voting and feedback process, this Delphi consensus generated priority lists of outcomes and measures in symptomatic Alzheimer's clinical syndrome. Lists and statements of recommendations were supported by the results of a systematic literature search and evidence level gradings. Clearly, there was strong consensus that the MoCA and MMSE are recommended for assessment of memory and overall cognitive functioning in mild and moderate disease, respectively, and that CDR is recommended to stage dementia severity at both disease stages. Consensus was also strong on the Barthel index to measure dependency in moderate stages, geriatric depression scale and NPI to measure depression in mild and aggressive/unpredictable behavior in moderate disease. Consensus was very strong on prescriptions to measure access and use of health services in mild stages and long-term institutional care costs to measure hospitalizations in moderate stages. However, the relatively lower level of concordance on scales to measure functional ability in the mild stages; patient QoL; caregiver and family QoL; and significant disease-related life events supports the need for more research on measurement tools to be used in the clinical routine.

Consensus was reached on priority lists of outcomes and outcome measures and 37 statements across nine domains in symptomatic Alzheimer's clinical syndrome: (1) cognitive abilities; (2) functional ability and dependency; (3) behavioral and neuropsychiatric symptoms; (4) patient QoL; (5) caregiver and family QoL; (6) health, social care, and treatment-related outcomes; (7) medical investigations; (8) significant disease-related life events; and (9) global outcomes. Exploring clinical outcomes in Alzheimer's clinical syndrome has various purposes other than simply monitoring disease progression. For patients with Alzheimer's clinical syndrome, outcomes are also important in identifying social and medical needs and in guiding appropriate and individualized support. Some of the domains identified are likely to be more important to patients, some more relevant to caregivers and families, and others more pertinent to healthcare professionals.

The Delphi method has both advantages and disadvantages. It is generally suitable for initiatives such as ours that require subjective expertise and judgmental inputs regarding

complex, large multidisciplinary problems, for which opinions are required from a large group and anonymity is considered to be beneficial.[2] However, bias may enter unintentionally, such as in the manner of how questions are formulated and who is invited to participate.[55] In addition, one limitation of consensus approaches in general is that there is a tendency to recommend the most familiar and widely used measures, rather than address the problems with current measures and develop novel ideas. Our inclusion of consensus statements as well as prioritized outcomes and measures seeks to address this potential challenge by highlighting some of the shortcomings of current outcomes and measures.

The authors of this paper are aware that expert opinion can be useful when evidence is insufficient to make informed decisions, but empirical evidence should always be the ground truth. Future efforts will need to study head-to-head and in the intended patient population the feasibility and accuracy of the outcome measures that we have prioritized. Sensitivity analyses should address the question of when over the time course of the disease they most robustly distinguish between levels of impairment. Computerized testing is now readily available and efficient and should be used for future disease tracking of cognitive abilities.[56]

A limitation of the present Delphi study was the limited input from patients', caregivers', and family members' perspectives. Further studies may wish to develop a separate process to obtain their views in the future. Future studies should also ensure that domains of relevance to all stakeholder groups are considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT

1. **Systematic review**: PubMed searches of the literature extended a previous systematic review that assessed outcomes of importance to patients with Alzheimer's clinical syndrome, their caregivers and healthcare professionals involved in their care.
2. **Interpretation**: This Delphi consensus identified priority outcomes in symptomatic Alzheimer's clinical syndrome and key outcome measures that are most applicable for use in clinical practice.
3. **Future directions**: More work is needed to develop instruments that are more feasible in the context of the constraints of clinical routine. Future studies should ensure that domains of relevance to all stakeholder groups are considered. Further research could also explore key stakeholder views on the domains, especially the views of patients, caregivers and family members.

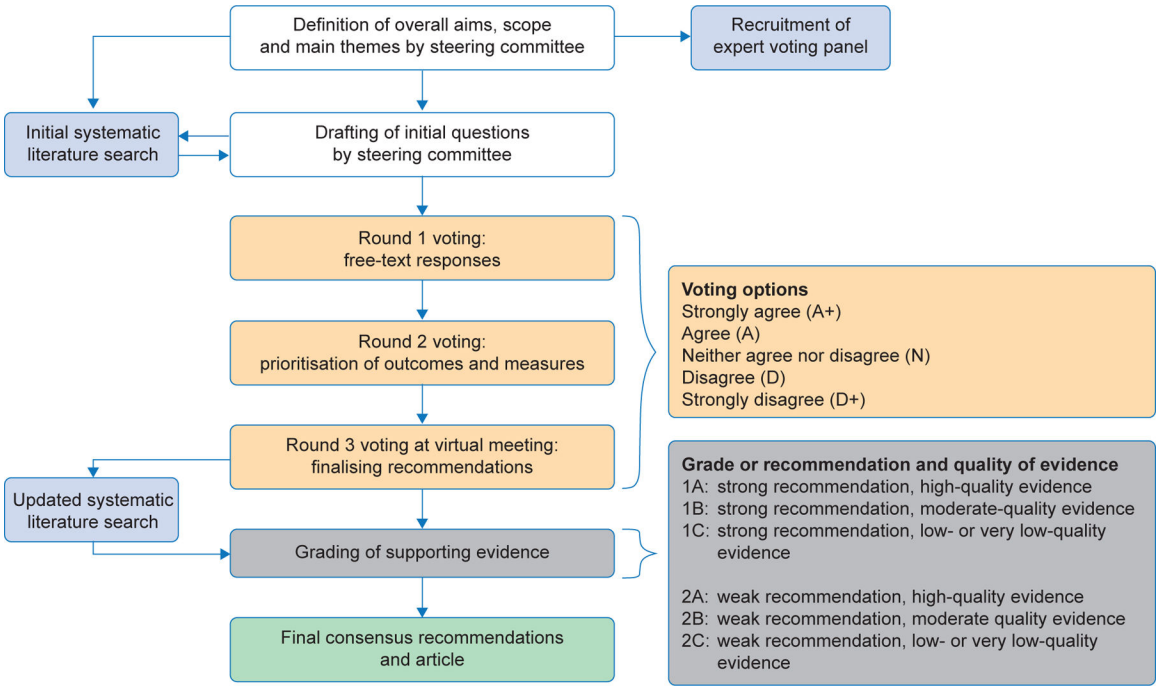

FIGURE 1.

Delphi consensus process. The steps outlined by Rosenfeld et al.[124] were followed and the GRADE approach was used.[19] The consensus group (n = 18) completed online surveys between April and July 2021 (rounds 1 and 2) and voted anonymously at a live virtual meeting in September 2021 (round 3). Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation system

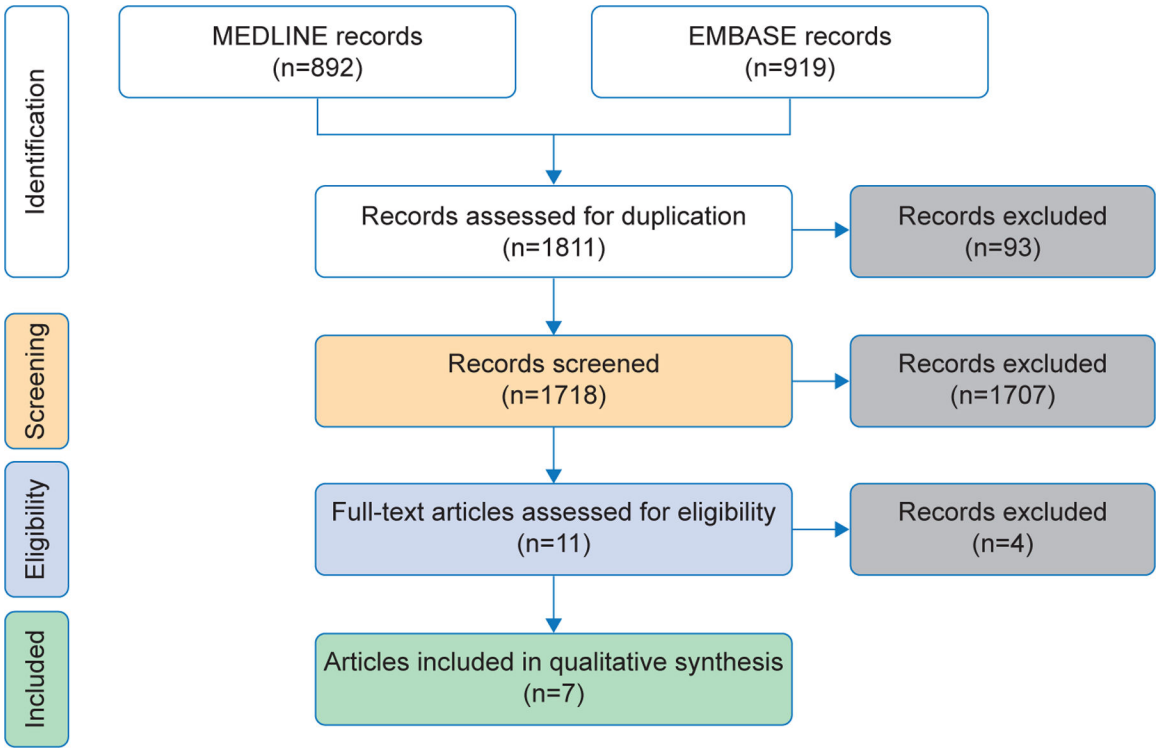

FIGURE 2.

Systematic literature search strategy for studies reporting outcomes of importance for assessing disease progression in symptomatic Alzheimer's clinical syndrome published between 26 July 2019 and 1 October 2021 (an update to the searches performed by Tochel et al. 2019[7]). The exclusion criteria were non-English language, review article, editorial, protocol, no human participants (i.e., in vitro or animal studies), not about Alzheimer's clinical syndrome or mild cognitive impairment, not reporting outcomes of importance to patients, caregivers, or healthcare professionals

TABLE 1

Numbers of outcomes and corresponding measures for symptomatic Alzheimer's clinical syndrome that were: Initially selected for voting, prioritized from the initial list during the voting rounds, added during the voting rounds, and in the final prioritized shortlist for the final Delphi consensus voting round

	Outcomes				Measures			
Domain	**Initial list**	**Prioritized from list**	**Additional**	**Final list**	**Initial list**	**Prioritized from list**	**Additional**	**Final list**
1. Cognitive abilities	14	6	0	6	53	7	0	7
2. Functional ability and dependency	4	4	1	5	21	6	0	6
3. Behavioural and neuropsychiatric symptoms	18	9	3	12	13	7	0	7
4. Patient QoL	6	8	0	8	30	5	0	5
5. Caregivers and family QoL	6	6	2	8	19	7	0	7
6. Health, social care, and treatment-related outcomes	8	8	5	13	11	7	2	9
7. Medical investigations[a]	7	0	0	0	5	0	0	0
8. Significant disease-related Events	3	3	8	11	0	0	0	0
9. Global outcomes	2	2	1	3	8	8	2	8
Total	**68**	**46**	**21**	**66**	**160**	**47**	**4**	**49**

Note: The initial list was developed from extensive lists of outcomes and measures identified via a systematic literature review. The outcomes and measures that were "prioritized" from the initial list were those that the consensus group perceived to be "of the highest priority". Additional outcomes and measures that were considered by the consensus group to be of the highest priority but not in the original list were added to the final list. Informed by the systematic literature review, the outcomes and measures were organized into nine domains.

Abbreviation: QoL, quality of life.

[a]Outcomes and outcome measures in the medical investigations' domain were collated, but the group voted not to recommend these for assessment of the progression of AD. Instead, statements were drafted and voted on, reflecting the group's view that many biomarkers currently offer little value in assessing disease progression beyond diagnosis (Table 4).

TABLE 2

Outcomes and outcome measures for symptomatic Alzheimer's clinical syndrome ranked by the Delphi consensus group in order of priority for each domain

Domains	Outcomes	Outcome measures	
1. Cognitive abilities	1. Memory 2. Executive functions 3. Language and communication 4. Judgement and insight 5. Orientation 6. Spatial cognition	1. MoCA[26,27]	Montreal Cognitive Assessment
		2. MMSE[57,58]	Mini-Mental State Examination
		3. ADAS-Cog-11[59]	Alzheimer's Disease Assessment Scale – Cognitive subscale version 11
		4. RAVLT[60]	Rey Auditory Verbal Learning Test
		5. TMT-B[61,62]	Trail Making Test – trail B
		6. ACE-R[63–65]	Addenbrooke's Cognitive Examination-Revised
		7. TMT-A[62]	Trail Making Test – trail A
2. Functional ability and dependency	1. ADLs and IADLs 2. Independence and autonomy 3. Social engagement 4. Cognitive engagement 5. Physical health and mobility	1. FAQ (IADL)[41]	Functional Activities Questionnaire
		2. Lawton IADL[66–68]	Lawton Instrumental Activities of Daily Living
		3. A-IADL-Q-SV	Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version
		4. BI[69]	Barthel Index
		5. A-IADL-Q[70–73]	Amsterdam Instrumental Activities of Daily Living Questionnaire
		6. Katz ADL[74]	Katz Activities of Daily Living questionnaire
3. Behavioural and neuropsychiatric symptoms	1. Aggressive, challenging and unpredictable behavior 2. Agitation 3. Depression 4. Personality changes 5. Apathy 6. Anxiety and insecurity 7. Sleep patterns 8. Mood 9. Hallucinations 10. Wandering 11. Delusions/other psychotic behavior 12. Disinhibition	1. NPI[75]	Neuropsychiatric Inventory
		2. NPI-Q[76]	Neuropsychiatric Inventory Questionnaire
		3. GDS[a] 77	Geriatric Depression Scale
		4. NPI-12	Neuropsychiatric Inventory-12-item version
		5. CSDD[78]	Cornell Scale for Depression in Dementia
		6. HDRS[79]	Hamilton Rating Scale for Depression
		7. DAS[80]	Dimensional Apathy Scale
4. Patient QoL	1. Patient QoL 2. Impact on relationships 3. Social contact 4. Remaining active 5. Maintaining ability to participate in hobbies 6. Access to dementia-friendly environments 7. Treatment side effects 8. Sexual health	1. QoL-AD[81,82]	Quality of Life in Alzheimer's Disease
		2. DEMQoL and DEMQoL-Proxy[83–85]	Dementia Quality of Life
		3. EQ-5D-5L[85,86]	EuroQoL – 5 dimensions, 5 levels
		4. EQ-5D-3L[86]	EuroQoL – 5 dimensions, 3 levels World
		5. WHOQoL[87]	Health Organization Quality of Life

Domains	Outcomes	Outcome measures	
5. QoL of caregivers and families	1. Caregiver support 2. Overall impact on caregiver 3. Caregiver/family mental and physical health 4. Caregiver self-efficacy 5. Relationship between caregiver and patient 6. Family involvement in care 7. Other caregiver commitments/loss of free time 8. Spouse's 'duty' to care	1. ZBI[88–90]	Zarit Burden Interview
		2. CarerQoL-7D[91]	
		3. NPI-D[87]	Neuropsychiatric Inventory with Caregiver Distress scale
		4. CAS[92]	Caregiver Activity Survey
		5. GHQ[93]	General Health Questionnaire
		6. HDRS[94]	Hamilton Rating Scale for Depression
		7. CES-D[95]	Center for Epidemiological Studies – Depression scale
6. Health, social care, and treatment-related outcomes	1. Access and use of health services and disease information 2. Delaying entry into institutional care 3. Delirium 4. Falls 5. Hospitalization 6. Assessment of decision to treat disease-related symptoms 7. Stability of symptoms 8. Frailty 9. Medication side effects 10. Frequent infections 11. Malnutrition 12. Dysphagia 13. Time to mortality	1. Direct non-medical costs 2. Long-term institutional care costs 3. Hospital inpatient costs 4. Resource use inventory 5. Accident and emergency costs 6. Prescriptions 7. Hospital outpatient costs 8. Out of pocket costs 9. Cost to caregiver/family in terms of 'time out of role'/time spent caring	
7. Medical investigations[b]			
8. Significant disease-related events	1. Losing ability to function at work 2. Losing decision-making responsibility 3. Needing help with basic ADLs 4. Impact on family 5. Losing ability to drive/loss of license 6. Entering institutional care 7. Losing ability to participate in leisure/social activities 8. Need for at-home care 9. Losing ability to use phone and computer 10. Relationship problems 11. Incontinence		
9. Global outcomes	1. Identifying individuals' needs and wants 2. Global improvement 3. Staging severity of dementia	1. CDR (including eCDR)[96]	Clinical Dementia Rating
		2. CDR-SB[96]	CDR scale – Sum of Boxes
		3. CGI[97]	Clinical Global Impression
		4. ADCS-CGIC[98]	Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change
		5. CIBIC + caregiver's interview[99]	Clinician's interview-based impression of change plus caregiver's interview
		6. CIBIC	Clinician's Interview-Based Impression of Change

Domains	Outcomes	Outcome measures	
		7. GDS[a] 53	Global Deterioration Scale
		8. Nutritional status with BMI computation[100,101]	

Note: The consensus group was not asked to list the domains in order of priority.

Abbreviations: ADL, activities of daily living; BMI, body mass index; IADLs, instrumental activities of daily living.

[a] *Note* that the Geriatric Depression Scale and the Global Deterioration Scale both use the same abbreviation (GDS); for clarity, these scales are referred to by their full names in the text and Table 3.

[b] Outcomes and outcome measures in the medical investigations' domain were collated, but the group voted not to recommend these for assessment of the progression of AD. Instead, statements were drafted and voted on, reflecting the group's view that many biomarkers currently offer little value in assessing disease progression beyond diagnosis (Table 4).

TABLE 3

Consensus on: The priority outcomes and outcome measures for symptomatic Alzheimer's clinical syndrome generated from the Delphi process (listed in order of relevance to mild and moderate disease); and the frequency at which each of the nine domains should be measured

Domain 1: Cognitive abilities

Outcomes[a]		**Measures**[a]	
Mild disease	**Moderate disease**	**Mild disease**	**Moderate disease**
Memory	Judgement and insight	MoCA	MMSE
Executive functions	Orientation	ADAS-Cog-11	ADAS-Cog-11
Spatial cognition	Executive functions	TMT-B	MoCA
Language and communication	Language and communication	RAVLT	ACE-R
Judgement and insight	Spatial cognition	ACE-R	TMT-A
Orientation	Memory	TMT-A	TMT-B
		MMSE	RAVLT
Assessment frequency	**Consensus vote** [b]	**GRADE score** [c]	**Key supporting evidence**
Every 6 months	**Strongly agree/agree 85%** Neutral/don't know 10% Disagree/strongly disagree 5%	1C	7,26,27,39,40,57–65,102–104

Domain 2: Functional ability and dependency

Outcomes [a]		**Measures** [a]	
Mild disease	**Moderate disease**	**Mild disease**	**Moderate disease**
Cognitive engagement	ADLs and IADLs	FAQ(IADL)	FAQ (IADL)
Social engagement	Physical health and mobility	Lawton IADL	Katz ADL
Independence and autonomy	Independence and autonomy	Amsterdam IADL Short Version	Lawton IADL
ADLs and IADLs	Social engagement	Amsterdam IADL	Amsterdam IADL – Short Version
Physical health and mobility	Cognitive engagement	Barthel Index	Amsterdam IADL
		Katz ADL	FAQ (IADL)
Assessment frequency	**Consensus vote** [b]	**GRADE score** [c]	**Key supporting evidence**
Every 6 months	**Strongly agree/agree 95%** Neutral/don't know 5%	1C	7,39,41,43,49,66–74,102,103,105–111

Domain 3: Behavioural and neuropsychiatric symptoms

Outcomes [a]		**Measures** [a]	
Mild disease	**Moderate disease**	**Mild disease**	**Moderate disease**

Domain 1: Cognitive abilities

Outcomes[a]		Measures[a]	
Mild disease	**Moderate disease**	**Mild disease**	**Moderate disease**
Depression	Aggressive, challenging and unpredictable behavior	Geriatric Depression Scale	NPI
Anxiety and insecurity	Hallucinations	NPI	NPI-Q
Personality changes	Wandering	NPI-Q	NPI-12
Mood	Sleep patterns	NPI-12	Geriatric Depression Scale
Apathy	Delusions/other psychotic behavior	HDRS	CSDD
Sleep patterns	Agitation	CSDD	DAS
Agitation	Disinhibition	DAS	HDRS
Delusions/other psychotic behavior	Apathy		
Disinhibition	Depression		
Aggressive, challenging and unpredictable behavior	Personality changes		
Hallucinations	Anxiety and insecurity		
Wandering	Mood		
Assessment frequency	**Consensus vote** [b]	**GRADE score** [c]	**Key supporting evidence**
Every 3–6 months	**Strongly agree/agree 90%** Neutral/don't know 10%	1C	7,39,49,75–80,103,112,113

Domain 4: PatientQoL

Outcomes [a]		Measures [a]	
Mild disease	**Moderate disease**	**Mild disease**	**Moderate disease**
Patient QoL	Patient QoL	QoL-AD	QoL-AD
Impact on relationships	Impact on relationships	DEMQoL and DEMQo-Proxy	DEMQoL and DEMQoL-Proxy
Social contact	Social contact	WHOQoL	EQ-5D-5L
Remaining active	Treatment side effects	EQ-5D-5L	EQ-5D-3L
Maintaining ability to participate in hobbies	Access to dementia-friendly environments	EQ-5D-3L	WHOQoL
Treatment side effects	Remaining active		
Sexual health	Maintaining ability to participate in hobbies		
Access to dementia-friendly environments	Sexual health		
Mild disease	**Moderate disease**	**Mild disease**	**Moderate disease**
Assessment frequency	**Consensus vote** [b]	**GRADE score** [c]	**Key supporting evidence**

Domain 1: Cognitive abilities

Outcomes[a]		Measures[a]	
Mild disease	**Moderate disease**	**Mild disease**	**Moderate disease**
Every 6–12months	**Strongly agree/agree 86%** Neutral/don't know 14%	1C	7,39,49,81–87,102,103,105,114

Domain 5: QoL of caregivers and families

Outcomes [a]		Measures [a]	
Mild disease	**Moderate disease**	**Mild disease**	**Moderate disease**
Relationship between caregiver and patient	Caregiver support	ZBI	ZBI
Spouse's 'duty' to care	Overall impact on caregiver	NPI-D	NPI-D
Caregiver self-efficacy	Caregiver/family mental and physical health	HDRS	HDRS
Overall impact on caregiver	Family involvement in care	CES-D	CES-D
Caregiver/family mental and physical health	Other caregiver commitments/loss of free time	CarerQoL-7D	GHQ
Caregiver support	Caregiver self-efficacy	GHQ	CarerQoL-7D
Family involvement in care	Relationship between caregiver and patient	CAS	CAS
Other caregiver commitments/loss of free time	Spouse's 'duty' to care		
Assessment frequency	**Consensus vote** [b]	**GRADE score** [c]	**Key supporting evidence**
Every 6 months	**Strongly agree/agree 90%** Neutral/don't know 10%	1C	7,40,49,87–95,102,105,112

Domain 6: Health, social care, and treatment-related outcomes

Outcomes [a]		Measures [a]	
Mild disease	**Moderate disease**	**Mild disease**	**Moderate disease**
Access and use of health services and disease information	Hospitalization	Prescriptions	Long-term institutional care costs
Stability of symptoms	Medication side effects	Out of pocket costs	Accident and emergency costs
Medication side effects	Dysphagia	Direct non-medical costs	Hospital inpatient costs
Hospitalization	Time to mortality	Hospital outpatient costs	Hospital outpatient costs
Assessment of decision to treat disease-related symptoms	Delirium	Cost to caregiver /family in terms of 'time out of role'/time spent caring	Prescriptions
Frailty	Falls	Hospital inpatient costs	Out of pocket costs
Time to mortality	Frequent infections	Resource use inventory	Cost to caregiver /family in terms of 'time out of role'/time spent caring
Delirium	Malnutrition	Accident and emergency costs	Direct non-medical costs

Domain 1: Cognitive abilities

Outcomes[a]		Measures[a]	
Mild disease	**Moderate disease**	**Mild disease**	**Moderate disease**
Falls	Delaying entry into institutional care	Long-term institutional care costs	Resource use inventory
Malnutrition	Stability of symptoms		
Dysphagia	Frailty		
Frequent infections	Access and use of health services and disease information		
Delaying entry into institutional care	Assessment of decision to treat disease-related symptoms		
Assessment frequency	**Consensus vote** [b]	**GRADE score** [c]	**Key supporting evidence**
Every 12months	**Strongly agree/agree 100%**	1C	7,39,40,49,103,105

Domain 8: Significant disease-related life events

Outcomes [a]		Measures [a]	
Mild disease	**Moderate disease**	N/A	
Losing ability to participate in leisure/social activities	Entering institutional care		
Losing ability to function at work	Needing help with basic ADLs		
Losing ability to drive/loss of license	Incontinence		
Relationship problems	Need for at-home care		
Losing decision-making responsibility	Losing decision-making responsibility		
Impact on family	Impact on family		
Losing ability to use phone and computer	Relationship problems		
Needing help with basic ADLs	Losing ability to participate in leisure/social activities		
Incontinence	Losing ability drive/loss of licence		
Need for at-home care	Losing ability to use phone and computer		
Entering institutional care	Losing ability to function at work		
Assessment frequency	**Consensus vote** [b]	**GRADE score** [c]	**Key supporting evidence**
N/A	**Strongly agree/agree 90%** Neutral/don't know 10%	1C	7,39,49,103

Domain 9: Global outcomes

Outcomes [a]		Measures [a]	
Mild disease	**Moderate disease**	**Mild disease**	**Moderate disease**
Staging severity of dementia	Staging severity of dementia	CDR, including eCDR	CDR, including eCDR

Domain 1: Cognitive abilities

Outcomes[a]		Measures[a]	
Mild disease	**Moderate disease**	**Mild disease**	**Moderate disease**
Global improvement	Global improvement	CDR-SB	CDR-SB
Identifying individuals' needs and wants	Identifying individuals' needs and wants	CGI	CGI
		CIBIC + caregiver's interview	CIBIC + caregiver's interview
		CIBIC	CIBIC
		ADCS-CGIC	Global Deterioration Scale
		Global Deterioration Scale	Nutritional status with BMI computation
		Nutritional status with BMI computation	ADCS-CGIC
Assessment frequency	**Consensus vote** [b]	**GRADE score** [c]	**Key supporting evidence**
Every 6–12months	**Strongly agree/agree 80%** Neutral/don't know 20%	1C	49–51,53,97,98,100,101

Note: The level of consensus, key supporting evidence, and GRADE score, which was used to grade the evidence, are indicated.

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation system; N/A, not applicable.

[a]The group voted on the relevance of each outcome or measure to disease stage. Options were mild, moderate, both mild and moderate, neither and don't know. Outcomes and measures are listed in order of relevance (from most to least), based on totals of votes for mild and both (designated "mild" in the table) and moderate and both (designated "moderate " in the table).

[b]The threshold for consensus was predefined as at least 70% of the consensus group voting "agree" or "strongly agree".

[c]Grade of recommendation: 1A, strong recommendation, high-quality evidence; 1B, strong recommendation, moderate-quality evidence; 1C, strong recommendation, low-quality or very low-quality evidence; 2A, weak recommendation, high-quality evidence; 2B, weak recommendation, moderate-quality evidence; 2C, weak recommendation, low-quality or very low-quality evidence. See Table 2 for an explanation of the acronyms for the listed measures.

TABLE 4

Consensus statements and recommendations for the use of outcomes and outcome measures in symptomatic Alzheimer's clinical syndrome

Number	Statement	Consensus vote[a]			GRADE score[b]	Key supporting Evidence
		Strongly agree / agree	Neutral / don't know	Disagree / Strongly disagree		
	General considerations					
0.1	Assessing disease progression is more important in the early stages of Alzheimer's clinical syndrome than in the late stages; therefore, outcome subdomains and measures that are more relevant to mild AD than moderate AD should be prioritized	70%	10%	20%	1C	Expert opinion
0.2	Whenever possible, prioritized outcome subdomains and measures should be suitable for measuring disease progression over multiple stages of the disease, rather than specific disease stages only	95%	5%		1C	Expert opinion
0.3	In mild Alzheimer's clinical syndrome, changes in outcome measures can be subtle and therefore difficult to detect	85%	10%	5%	1C	22
0.4	Outcome measure tests should be easy and relatively quick to perform	85%	15%		1C	Expert opinion
0.5	Outcome measure tests should be familiar to a wide range of healthcare professionals across the world and available in different languages	100%			1C	Expert opinion
0.6	There should ideally be a small number of robust and validated outcome measure tests used for longitudinal assessment	100%			1C	Expert opinion
0.7	In some cases, scales for some domains should be customized and personalized	70%	25%	5%	1C	Expert opinion
0.8	In some cases, a well-conducted or semi-structured interview is more informative than using structured scale outcome measures	70%	30%		1C	Expert opinion
0.9	The choice of outcome measure for some domains (e.g. cognitive abilities) should be based on disease stage, educational status and social status	75%	20%	5%	1C	23,24
	Domain 1: Cognitive abilities					
1.1	Outcome measures for cognitive abilities in mild and moderate Alzheimer's clinical syndrome are important for assessing medication requirements and for advance planning, respectively	70%	30%		1C	Expert opinion
1.2	There is a need for a more comprehensive outcome measure to assess language and communication in Alzheimer's clinical syndrome	95%	5%		1C	Expert opinion
1.3	Screening measures (e.g. the MMSE and MoCA) should ideally be used in combination with more in-depth measures for relevant domains	70%	20%	10%	1C	Expert opinion
1.4	The performance of outcome measure tests for cognitive abilities can be affected by other factors (e.g. hearing impairments and loss of language ability in many elderly patients)	100%			1C	31,32,115
	Domain 2: Functional ability and dependency					
2.1	Functional ability should include an assessment of motor function and not just instrumental activities of daily living and activities of daily living	70%	30%		1C	Expert opinion
2.2	Social engagement and physical health and mobility are important for both detection and progression of Alzheimer's clinical syndrome, but they may be affected by other conditions, such as frailty, sarcopenia and geriatric depression in older adults	80%	20%		1C	Expert opinion

Number	Statement	Consensus vote[a]			GRADE score[b]	Key supporting Evidence
		Strongly agree / agree	Neutral / don't know	Disagree / Strongly disagree		
	General considerations					
2.3	More detailed scales (e.g. Amsterdam IADL) are useful in tertiary centers, but are more difficult to apply in peripheral centers where simpler scales (e.g. Lawton IADL) may be more useful	70%	30%		1C	Expert opinion
	Domain 3: Behavioural and neuropsychiatric symptoms					
3.1	Depression, anxiety and pain should be prioritized because they should be detected and treated, and can impact function, rather than because they are measures of disease progression	96%	4%		1C	
3.2	The following subdomains have the potential to be very disruptive to the patient and their caregiver/ family, even if mild: personality changes; aggressive, challenging and unpredictable behavior; sleep patterns; depression; agitation	100%			1C	
3.3	Behavioural and neuropsychiatric symptoms are crucial for management planning and for differential diagnosis compared with other neurodegenerative diseases	75%	15%	10%	1C	
	Domain 4: Patient QoL					
4.1	The Patient QoL domain should be used to demonstrate 'positive', as well as negative, outcomes (e.g. those that the patient performs well on)	95%	5%		1C	
4.2	A semi-structured interview with the patient and a reliable caregiver is a good alternative to structured questionnaire tools	80%	20%		1C	
4.3	Both a patient QoL measure and a patient QoL measure completed by a caregiver on the patient's behalf should be considered as QoL outcome measures	100%			1C	
4.4	The values of patients and/or caregivers should be considered in the assessment of QoL outcomes	100%			1C	
	Domain 5: QoL of caregivers and families					
5.1	Few of the listed outcome measures for quality of the caregivers' and families' lives are widely used	90%	10%		1C	
5.2	Quality of the patient–caregiver relationship and caregiver personality may be important factors in assessing future treatment decisions	90%	10%		1C	
5.3	Ideally, both the objective and subjective impact on the caregiver should be measured	100%			1C	
5.4	Self-efficacy is an important subdomain for both the patient and caregiver to identify learning/educational and resource needs and to identify situations in which the caregiver is not able to manage caregiving responsibilities	85%	15%		1C	
	Domain 6: Health, social care, and treatment-related outcomes					
6.1	Health, social care and treatment-related outcomes are of most importance in moderate Alzheimer's clinical syndrome, but are also relevant in mild Alzheimer's clinical syndrome	84%	16%		1C	
6.2	It is challenging to generalize the impact of healthcare costs across different countries; it is important to identify the services and resources used to account for what is available in different countries or regions within countries	100%			1C	
	Domain 7: Medical investigations					

Number	Statement	Consensus vote[a]			GRADE score[b]	Key supporting Evidence
		Strongly agree / agree	Neutral / don't know	Disagree / Strongly disagree		
	General considerations					
7.1	Many biomarkers offer little value for assessing progress after diagnosis; cognitive and functional decline are more important measures	85%	15%		1B	45,46
7.2	Wealthier countries (and regions) have a big advantage in obtaining testing – a situation that lacks equity	90%	10%		1C	Expert opinion
7.3	Some measures (e.g. brain scans, amyloid-PET and CSF biomarkers such as amyloid beta) have little value as outcome measures, but are crucial for diagnosis	78%	11%	11%	1B	45,46
	Domain 8: Significant disease-related life events					
8.1	The need for more at-home care in society is likely to become more important in the future	100%			1C	122,123
8.2	Frequent clinical and neuropsychological monitoring is crucial for patients who are still driving or working	85%	15%		1C	Expert opinion
	Domain 9: Global outcomes					
9.1	The listed outcome measures are tools primarily used for research rather than in real-world clinical practice	75%	25%		1C	54
9.2	Global outcome assessments should also measure what the person can do rather than only focusing on deficits	100%			1C	Expert opinion
9.3	There is an unmet need for global outcome measures to be used by clinicians in a real-world setting	95%	5%		1C	54

Note: Statements were generated from the Delphi process for each of the nine domains and for general considerations. The level of consensus, key supporting evidence, and GRADE score, which was used to grade the evidence, are indicated.

Abbreviations: AD, Alzheimer's disease; ADL, activities of daily living; GRADE, Grading of Recommendations Assessment, Development and Evaluation system; IADLs, instrumental activities of daily living; MMSE, Mini-Mental State Examination; MoCA Montreal Cognitive Assessment; QoL, quality of life.

[a]The threshold for consensus was predefined as at least 70% of the consensus group voting 'agree' or 'strongly agree'.

[b]Grade of recommendation: 1A, strong recommendation, high-quality evidence; 1B, strong recommendation, moderate-quality evidence; 1C, strong recommendation, low-quality or very low-quality evidence; 2A,