Evaluation of clinical benefits of treatments for Alzheimer's disease

Kathy Y Liu, Sebastian Walsh, Carol Brayne, Richard Merrick, Edo Richard, Robert Howard

The need for regulatory approval of new therapies for the treatment of Alzheimer's disease—a progressive neurodegenerative condition—has made the assessment of treatment efficacy an urgent priority for discussion and investigation in the field. In the first part of this Personal View, we summarise current views on what constitutes a clinically meaningful benefit from treatment for Alzheimer's disease, including the concept of a minimum treatment effect against which to compare trial outcomes and its limitations. Considering existing and divergent definitions of clinically meaningful change, we define this concept in the second part of the Personal View by proposing a new approach that consecutively considers whether a treatment benefit for Alzheimer's disease is noticeable, valuable, and worthwhile in the context of costs and risks. This approach could be a useful foundation from which the field can move forwards on this issue and address existing gaps in understanding.

Lancet Healthy Longev 2023; 4: e645–51

Division of Psychiatry, University College London, London, UK (K Y Liu MRCPsych, Prof R Howard MD)**; Cambridge Public Health, University of Cambridge, Cambridge, UK** (S Walsh MPhil, Prof C Brayne MD, R Merrick MSc)**; Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Nijmegen, Netherlands** (Prof E Richard MD)**; Department of Public and Occupational Health, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands** (Prof E Richard)

Correspondence to: Dr Kathy Liu, Division of Psychiatry, University College London, London W1T 7NF, UK **kathy.liu@ucl.ac.uk**

Introduction

The progressive nature of dementia due to Alzheimer's disease can challenge the conclusions of trials that are not long enough to capture definitive clinical outcomes, such as dementia diagnosis or institutionalisation. For older individuals who do not have a rare, autosomal dominant, monogenic mutation causative of Alzheimer's disease, the condition is multifactorial and Alzheimer's disease biomarker positivity has uncertain clinical predictive value.[1] Drug trial designs have aligned with regulators' requirements for marketing approval, which do not include demonstration of a minimum difference in outcome. Clinicians widely recognise that a statistically significant difference favouring treatment on any trial endpoint does not necessarily represent a clinically meaningful benefit.[2] US Food and Drug Administration (FDA) approvals of two anti-amyloid monoclonal antibodies for the treatment of early Alzheimer's disease have been accompanied by disagreement on the relevance of empirically determined minimal clinically important difference thresholds, and by ambiguity as to what constitutes a clinically meaningful benefit for Alzheimer's disease therapies. The appraisal of clinical benefit has implications for interactions between patients, caregivers, and clinicians when discussing prescribing options and delivery of cost-effective interventions in health-care systems increasingly strained by an ageing population. In this Personal View, we summarise current views on the concept of a minimum treatment effect to measure clinical benefit, and we propose how future research could approach this fundamental issue.

Minimal clinically important difference thresholds to evaluate Alzheimer's disease therapies

Minimal clinically important differences are important in many health specialties, and are defined as the smallest difference in the outcome of interest that patients or their proxies perceive as important and that would indicate the need for a change in the patient's management,[3,4] conceptualising a distinction between statistical significance and clinical meaningfulness of any treatment effects observed in clinical trials. No gold-standard method exists to calculate minimal clinically important differences, and all current approaches have methodological issues that limit their potential applicability.[5] Although a combination of different approaches might be preferred, anchor-based methods that link changes in clinical outcome assessment score to clinical perspectives have been prioritised over distribution-based methods, which compare changes in clinical outcome assessment score to a statistical measure of variability.[6]

For Alzheimer's disease specifically, the FDA considers demonstration of a statistically significant change (in one well controlled trial with confirmatory evidence) on the Clinical Dementia Rating–Sum of Boxes score (CDR-SB) in early Alzheimer's disease as substantial evidence of effectiveness for traditional regulatory approval.[2,7–9] The CDR-SB, an 18-point composite measure of cognition and function, wherein higher scores reflect greater impairment, has correspondingly been used as a primary outcome measure in anti-amyloid therapy trials in early Alzheimer's disease (ie, mild cognitive impairment and mild dementia associated with characteristic pathophysiological changes of Alzheimer's disease). Two studies using anchor-based methods derived clinician-rated, within-patient, minimal clinically important difference estimates for the CDR-SB in early Alzheimer's disease,[10,11] and subsequent studies have used the CDR-SB change as an anchor to estimate minimal clinically important differences for other scales in individuals who are cognitively unimpaired and individuals with early Alzheimer's disease.[12,13] The mean CDR-SB score change after 1 year in patients with mild cognitive impairment due to Alzheimer's disease, investigated in two studies using three different anchors, was approximately 1 point. These studies anchored CDR-SB score change to clinician-rated meaningful decline in any domain,[11] a minimal worsening on the Mild Cognitive Impairment-Clinical Global Impression of Change,[10] or a 1-point worsening from any category on the Global Deterioration Scale,[10] and minimal clinically

important difference thresholds increased with worsening Alzheimer's disease severity.[11] We have previously compared the reported minimal clinically important differences for early Alzheimer's disease to reported phase 3 trial primary outcomes (ie, between-group CDR-SB differences) and concluded that average differences between drug and placebo at 18-month endpoints for high-dose aducanumab (drug *vs* placebo mean changes from baseline in CDR-SB score were 0·03 and –0·39 in two identically designed studies)[14] and lecanemab (drug *vs* placebo mean change from baseline in CDR-SB score was –0·45)[5] were unlikely to represent a clinically meaningful difference.[2,15]

The reported minimal clinically important difference estimates for early Alzheimer's disease represent mean clinical outcome assessment score changes within individuals who had (minimal) clinically meaningful decline,[10,11] whereas primary outcomes from randomised controlled trials—which represent the gold standard for assessment of treatment efficacy—are conventionally expressed as mean differences between active and placebo groups in change from baseline on a clinical outcome assessment score. Although the appropriateness of applying mean minimal clinically important difference estimates calculated from individual change scores to between-group differences is debated,[16] between-group differences in randomised controlled trials represent the mean change (decline) from baseline in the drug-treated group after accounting for the effects of placebo. The interpretation that the mean CDR-SB change from baseline associated with a true treatment effect (ie, the reduction in decline observed in the trials) is smaller than the mean CDR-SB change corresponding to a (minimal) meaningful clinical decline is, therefore, both valid and useful.

The specific application of available minimal clinically important difference thresholds to evaluate within-individual change in trials is subject to statistical and conceptual considerations. As the empirically derived minimal clinically important difference estimates are themselves group means, they might not be an appropriate threshold to define meaningful change for any single individual[17] because individual thresholds for clinically meaningful change can also vary.[10,11] Group means might underestimate the amount of change needed to be meaningful at an individual level due to larger measurement error around individual change scores.[18] Thus, analyses that depend on the dichotomisation of a continuous clinical outcome assessment scale, based on a minimal clinically important difference threshold derived from a group mean, might not actually provide a valid evaluation of within-individual change. Comparing the proportion of patients in drug and placebo groups who meet a prespecified minimal clinically important difference threshold (ie, a responder analysis) is also associated with loss of power and could be erroneously interpreted as the chance that a drug will help a patient to have a clinically important treatment effect. Because how the treatment group would have responded to a placebo is unknown, a higher so-called response rate in the active treatment group could still be due to a marginal (and clinically trivial) average drug response that pushes some individuals slightly past the cutoff to be classified as responding to the drug.[19,20] Crossover, or n-of-1, trials are designed to examine within-individual treatment effects, but these are not feasible for Alzheimer's disease, in which baseline symptom status will progressively worsen and effective washout could not be expected after swap of treatment group if the drug alters the neuropathological disease course.

Alternatives to minimal clinically important difference thresholds to evaluate Alzheimer's disease therapies

Other approaches to evaluate the clinical benefit of therapies for Alzheimer's disease bypass minimal clinically important differences altogether. Some of these relate specifically to disease-modifying therapies, which are assumed to affect underlying disease pathophysiology and therefore confer predictive and cumulative benefit beyond the end of the trial period.[21,22] The FDA's designation of amyloid plaque reduction as a surrogate marker, judged as reasonably likely to predict clinical benefit in Alzheimer's disease clinical trials,[23] exemplifies the concept of predictive benefit. Cumulative benefit refers to the anticipated accrual of clinical benefits with increasing duration of disease-modifying therapeutic treatment, so that the difference in outcomes between drug and placebo groups is expected to increase over time. The implication is that any statistically significant improvement on a surrogate marker or cognitive scale relative to placebo is sufficiently meaningful as larger clinical gains are anticipated to appear and accrue with time. The main limitations with this approach are that even if amyloid plaque reduction is predictive of a small cognitive benefit,[24,25] the question of whether this benefit is clinically meaningful still applies; the evidence to support the hypothesis that drug and placebo outcomes will continue to diverge beyond the end of completed clinical trials is still insufficient.

The so-called time saved with treatment is another approach to contextualise the clinical benefit of small differences on cognitive scales, whereby between-group treatment effects are assessed against time instead of clinical outcome assessment score change.[26] Using this approach, the time difference between the intervention and placebo groups to reach a specified point of outcome measure decline can be framed as, for example, the equivalent of 5 months of time saved with treatment. However, it is important to recognise that, in contrast to a clear binary outcome such as loss of a specific function or ability, or nursing home admission, any amount of so-called time saved is simply a re-engineering of an

arbitrary relative change in score on the continuous clinical outcome assessment scale compared with the placebo group. Thus, the difficulty in defining whether the time saved translates to a clinically relevant difference persists. The time saved approach is therefore potentially misleading and obvious risks exist for this concept to be emotively and inaccurately communicated to both lay and expert audiences. For example, lecanemab has been credited by the Alzheimer's Association as giving "more months of recognizing their spouse, children and grandchildren",[27] without any good evidence to support this emotive and appealing claim. The evaluation of binary outcomes, such as reaching a minimal clinically important difference level of decline on an outcome measure,[26] would require specific statistical methods that reduce bias by incorporating censored data from individuals for whom the event is not observed when comparing the two groups.[28]

A further issue is that the perspectives of patients and caregivers have not been incorporated into existing empirical estimates of minimal clinically important differences in Alzheimer's disease, which are instead based on clinician-rated anchors and do not necessarily reflect clinical meaningfulness to patients and their families.[22] Patient and caregiver views are important, particularly for dementia. However, it is crucial to acknowledge the specific challenges associated with collecting and interpreting patient-reported (and proxy) outcome measures in cognitively impaired individuals,[29] especially as their condition progresses. Partly because of the irreversible and terminal nature of the condition, patients, their families, and clinicians will be particularly sensitive to exaggerated or selectively reported interpretations of trial findings,[30] as well as to clinical trial experiences that can lead to functional unblinding and increase the risk of bias on subjectively rated functional and quality-of-life outcomes.[19] Further study is needed on how patient and caregiver perspectives can be integrated into clinical trials, including between-group and within-group reliability of ratings from clinicians, patients, and caregivers in clinical trial settings.

Approaches that bypass minimal clinically important differences can lead to the conclusion that any, however small, statistically significant difference in a progressive neurodegenerative disease is meaningful. Given the substantial limitations of the approaches that we have discussed, the lack of distinction between statistical and clinical significance serves to emphasise the importance and validity of having an a priori conceptual standard against which to measure clinical meaningfulness. On the other hand, a single minimal clinically important difference (leading to the binary conclusion that a treatment is meaningful or not meaningful) is also unlikely to apply or be acceptable to all individuals or groups. Thus, there is a need to review, clarify, and gain consensus on what is meant by a minimum clinically meaningful effect in Alzheimer's disease.

A proposed approach to evaluate the clinical benefit of Alzheimer's disease therapies

Defining the term meaningful change to provide a foundation for quantitative assessment and the incorporation of patient and caregiver perspectives is important. We build on Weinfurt's suggested approach for the evaluation of clinical meaningfulness,[31] which proposes first establishing whether a change is noticeable (ie, clear, perceptible, and can easily be communicated) and, if so, then establishing whether it represents a worthwhile change after consideration of the treatment-associated costs, adverse effects, and burden (eg, of fortnightly, clinic-based infusions).

Applying this model to Alzheimer's disease involves specific considerations and adaptations. First, we apply the term change to differences between treatment and placebo groups at trial endpoint, as we will consider these to represent the best available estimate of the expected change associated with the true treatment effect. Between-group differences favouring active treatment translate to a mean reduction in cognitive decline experienced by the treatment group, but we do not claim or expect this change to be noticeable on an individual level.

Second, given the distinction between cognitive and functional impairment in the clinical diagnosis of Alzheimer's disease stages (the absence of functional impairment defines mild cognitive impairment, whereas both cognitive and functional impairment are required for a dementia diagnosis) and in the evaluation of Alzheimer's disease therapies, we propose a further modification to Weinfurt's model to account for the possibility that a noticeable change in a so-called core symptom (eg, cognition) might not be associated with a functional change; thus, in certain cases, a core symptom change might not be judged to be clinically valuable. We therefore separate Weinfurt's first step into an intermediate consideration of whether a change is valuable for the individual, irrespective of any costs or risks, followed by a final step in which this value is weighed against specific risks and costs to ascertain whether the benefit is worthwhile (ie, net beneficial) in the individual-specific context (figure). Consideration of

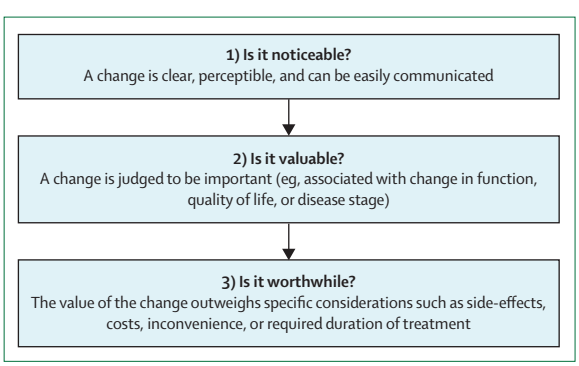

Figure: **Three-step approach for the evaluation of clinical benefit from Alzheimer's disease therapies (an expansion from Weinfurt's approach[31])**

whether a change is valuable is relevant to Alzheimer's disease because this judgement is likely to vary across individuals and contexts, such as disease severity, independently of a consideration process that balances risks versus costs. The separate consideration of an effect's actual value also makes the consideration process more explicit, because whether a change is worthwhile depends on whether the value is sufficiently high and the risks and costs are sufficiently low, which will also vary across individuals, groups, and contexts.

Third, considering therapies that could potentially be shown to modify disease course, early treatment (or, for asymptomatic individuals, preventive treatment) effects might not represent noticeable changes at trial endpoint, but could nonetheless be shown to be valuable and worthwhile with ongoing treatment. Thus, we propose that, if and when evidence of disease-course modification has been convincingly shown with longer-term data and novel trial designs, whether the treatment effects are valuable and worthwhile can be considered independently of whether they are noticeable.

This three-step approach could therefore be adopted to assess clinical benefit by individuals, groups (patients, caregivers, and clinicians), and systems (regulators and those who pay for health care). This approach could be useful to structure individual clinical discussions regarding whether treatments are likely to be worthwhile across the different stages of Alzheimer's disease and to identify knowledge gaps for future studies. Using donepezil and lecanemab as examples, we discuss how this approach can potentially be used at the individual, group, and system levels.

Compared with placebo, 24–26 weeks of treatment with donepezil 10 mg was associated with a 0·53 (95% CI –0·73 to –0·33) CDR-SB point difference change from baseline scores (ie, reduced cognitive decline) in patients with moderate to severe Alzheimer's disease.[32] In a single trial, lecanemab administered at 10 mg/kg was associated with a 0·45 (95% CI –0·67 to –0·23) CDR-SB point benefit after 18 months of treatment in early Alzheimer's disease.[5] No study has specifically investigated what magnitude of between-group mean differences might constitute a noticeable effect in participants with different severity stages of Alzheimer's disease. On the basis of the scarce available data from early Alzheimer's disease, the smallest mean change on the CDR-SB scale corresponding to a minimal worsening on the Mild Cognitive Impairment-Clinical Global Impression of Change was 0·34 points at 6 months (or 0·64 points at 12 months, when the correlation between the two variables was stronger).[10] No equivalent data exist for patients with moderate to severe Alzheimer's disease, and most individuals who are cognitively unimpaired (with or without amyloid positivity) do not show cognitive decline (equivalent to a 0·5 CDR-SB point) over the course of a 2–3-year trial.[12] The CDR-SB, which increases in 0·5–1·0 point increments, might not be sufficiently sensitive to fully capture the smallest change that would be noticeable in all individuals with early Alzheimer's disease. Furthermore, between-group mean differences of less than 0·5 CDR-SB points are not easy to communicate to patients and their families. Patients and caregivers need to be informed that noticeable change on an individual level occurs against a background of ongoing cognitive decline, and that the average treatment effect, represented by a reduction in cognitive decline between treatment and placebo groups, is not likely to be noticeable within an individual.

Assuming these differences did represent a noticeable change, could they represent a valuable change? This assessment is likely to depend on the context and on who is being asked. For example, individuals with mild cognitive impairment—but not individuals with Alzheimer's disease dementia—might judge that a noticeable change (ie, reduction in cognitive decline) is valuable, even if it did not alter their functional ability or quality of life. Again, no study has specifically investigated the magnitude of effects that individuals or groups might consider to represent a valuable change in Alzheimer's disease. On the basis of the data currently available, the smallest mean CDR-SB change anchored to a 1-point change on the Global Deterioration Scale (which measures the clinical stage of Alzheimer's disease) was reported to be 0·67 points (SD 0·96) over 6 months in early Alzheimer's disease (or 1·91 points [SD 1·87] at 36 months, at which timepoint the correlation between the two variables was strongest).[10] The CDR-SB score change in those judged to have a meaningful decline was reported to be 0·98 for patients with mild cognitive impairment, 1·63 for patients with early Alzheimer's disease, and 2·30 points for patients with moderate to severe Alzheimer's disease over 1 year.[11] Considering the available evidence, uncertainty exists as to whether the reported primary outcomes of donepezil and lecanemab represent actually valuable differences that meaningfully affect function or represent a different stage of illness. Although lecanemab was associated with 2·0 points less decline on a secondary functional outcome (the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment; range 0–53), compared with placebo,[5] the strength of the correlation between CDR-SB and this scale is unknown, so this finding does not shed light on the functional relevance of CDR-SB changes. Functional and quality-of-life outcomes should be considered together with core symptomatic scales when evaluating a treatment's clinical benefit because interventions could exert a beneficial but non-specific effect (eg, on sleep or appetite),[7] which could improve function or quality of life without addressing specific symptoms of the indicated neurodegenerative disease. Other outcome measures might be relevant to ascertain how valuable a change is at different disease stages, including caregiver burden, behavioural and psychological symptoms, and

longer-term outcomes such as life expectancy and nursing home admission.[21] For example, donepezil treatment in patients with mild to moderate Alzheimer's disease over 3 years was not associated with improvements in disability, caregiver burden, or delay in institutionalisation,[33] but continued donepezil treatment in patients with moderate to severe Alzheimer's disease was associated with cognitive and functional benefits[34,35] and reduced nursing home admission.[36] The challenge of showing valuable change would be magnified if future attempts were made to study individuals with Alzheimer's disease biomarker positivity who are currently cognitively unimpaired, as the clinical predictive value of a reduction in Alzheimer's disease biomarkers alone is not clear, and longer follow-up would be needed to detect changes in functional and quality-of-life outcomes.[37]

The final consideration is whether the treatment effect is worthwhile after considering side-effects, costs, duration of treatment, etc. Individuals will need to consider whether any potentially valuable cognitive and functional benefits associated with treatment are outweighed by personal costs and risks. Organisations that judge value for money for health systems, such as the National Institute for Health and Care Excellence in England, might convert differences on quality-of-life scales to quality-adjusted life-years, which combine life expectancy and quality of life in a single index and are used to compare the value of medical interventions. These are personally, politically, and commercially influenced decisions that are less suited to empirical assessment, but are relevant for the evaluation of the clinical benefit of any treatment and of whether the benefits outweigh the costs (in relation to resources and harms) at a population level. Donepezil is generally cheap, easy to administer, and well tolerated, so assuming that the observed benefit is potentially valuable as judged by specific individuals, groups, or systems, it is more likely (but not guaranteed[38]) to be judged to represent a worthwhile benefit compared with 18 months of treatment with lecanemab. Lecanemab requires fortnightly intravenous administration and additional clinical and radiological monitoring,[39] is associated with more serious side-effects than donepezil (eg, severe infusion reactions; dizziness, falls, or stroke associated with amyloid-related imaging abnormalities; and death), and costs approximately US $26 500 (€24 766) per patient per year,[40] in addition to its large system-level infrastructure and workforce resource implications. The explicit consideration of costs and risks in the evaluation of whether a clinical benefit is worthwhile also raises the question of whether drug effects could possibly be assessed against treatment as usual in future trials, which could incorporate the value of non-specific therapeutic benefits.[41]

The examples of lecanemab and donepezil show knowledge gaps within the three-step approach to evaluate clinical benefit, highlighting where further research is needed. For example, it would be useful to ascertain, compare, and incorporate clinician-based, patient-based, and caregiver-based findings and opinion-based methods for a range of relevant scales to broaden understanding of what might constitute noticeable and valuable treatment effects in Alzheimer's disease. Earlier studies reported relevant scales targeting specific outcome domains across Alzheimer's disease stages,[21,42] which could be used to assess noticeable (eg, via cognition or composite measures using anchor-based methods) and valuable change (eg, via associated functional, health, economic, and neuropsychiatric symptom outcomes). Further investigation of how baseline disease severity, sex and gender, or physical conditions and frailty could affect these judgements would also be important. Alternative trial designs, such as delayed-start studies[43] or longer trials, are needed to address the valid assessment of disease-modifying therapies' cumulative and predictive benefits. Further studying how best to communicate trial findings accurately and honestly to patients and caregivers is also necessary so that they can be better supported to make informed decisions about treatment. The clinical outcome assessment scales need to be reliable, valid, and responsive to change.[44] Although focusing on these elements would be beyond the scope of this Personal View, these measurement properties are important criteria that warrant specific consideration for future clinical trials. A straightforward method to validly assess minimal clinically important differences for within-individual change in Alzheimer's disease is unlikely to exist, and although the comparison between mean within-individual changes and between-group differences in Alzheimer's disease is subject to limitations, the application still represents the best available approach to evaluate the clinical benefits of treatment.

Conclusions

The fundamental concept of assessing whether a treatment effect represents a meaningful clinical benefit is not unique to the field of Alzheimer's disease. However, the progressive nature of the disease, the critical need for breakthroughs, the market potential, and the emergence of new Alzheimer's disease treatments with small effect sizes and substantial adverse effects and costs has made establishing clinical benefit an urgent priority for discussion and investigation. As new therapies for the treatment of Alzheimer's disease receive regulatory and marketing approvals, considering how to assess the clinical relevance of treatment effects reported in trial data is now especially important. We propose that consecutively considering whether a benefit is noticeable, valuable, and worthwhile in the context of specific costs and risks represents a useful base from which to approach this issue and to address existing gaps in understanding.

Contributors
SW, KYL, and RH conceived the idea for this Personal View. KYL wrote an initial draft which all authors then contributed to. All authors had final responsibility for the decision to submit for publication.

Declaration of interests
We declare no competing interests.

Acknowledgments
KYL is supported by the UK Medical Research Council (MR/S021418/1). SW is funded by a National Institute for Health and Care Research Doctoral Fellowship. RM is funded by Alzheimer's Research UK (doctoral studentship ARUK-PhD2017–34). RH is supported by the University College London Hospitals NHS Foundation Trust National Institute for Health Research Biomedical Research Centre. The authors' funding sources were not involved in the writing of the manuscript or the decision to submit it for publication.

References

1 Dubois B, Villian N, Frisoni GB, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. *Lancet Neurol* 2021; **20:** 484–96.
2 Liu KY, Schneider LS, Howard R. The need to show minimum clinically important differences in Alzheimer's disease trials. *Lancet Psychiatry* 2021; **8:** 1013–16.
3 Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989; **10:** 407–15.
4 Schünemann HJ, Guyatt GH. Commentary—goodbye M(C)ID! Hello MID, where do you come from? *Health Serv Res* 2005; **40:** 593–97.
5 van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med* 2022; **388:** 9–21.
6 Watt JA, Veroniki AA, Tricco AC, Straus SE. Using a distribution-based approach and systematic review methods to derive minimum clinically important differences. *BMC Med Res Methodol* 2021; **21:** 41.
7 Leber P, Millson D, Jolley D, Ward H, Qizilbash N, Schneider LS. What is the evidence that a dementia treatment works? In: Qizilbash NSL, Chui H, Tariot P, Brodaty H, Kaye J, Erkinjuntti T, eds. Evidence-based dementia practice. Oxford: Blackwell Science, 2003: 376–427.
8 Schneider LS, Goldberg TE. Composite cognitive and functional measures for early stage Alzheimer's disease trials. *Alzheimers Dement (Amst)* 2020; **12:** e12017.
9 US Food and Drug Administration. Demonstrating substantial evidence of effectiveness for human drug and biological products guidance for industry. December, 2019. https://www.fda.gov/media/133660/download (accessed Oct 13, 2023).
10 Lansdall CJ, McDougall F, Butler LM, et al. Establishing clinically meaningful change on outcome assessments frequently used in trials of mild cognitive impairment due to Alzheimer's disease. *J Prev Alzheimers Dis* 2022; **10:** 9–18.
11 Andrews JS, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimers Dement (N Y)* 2019; **5:** 354–63.
12 Borland E, Edgar C, Stomrud E, Cullen N, Hansson O, Palmqvist S. Clinically relevant changes for cognitive outcomes in preclinical and prodromal cognitive stages: implications for clinical Alzheimer trials. *Neurology* 2022; **99:** e1142–53.
13 Wessels AM, Rentz DM, Case M, Lauzon S, Sims JR. Integrated Alzheimer's disease rating scale: clinically meaningful change estimates. *Alzheimers Dement (N Y)* 2022; **8:** e12312.
14 Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. *J Prev Alzheimers Dis* 2022; **9:** 197–210.
15 Walsh S, Merrick R, Richard E, Nurock S, Brayne C. Lecanemab for Alzheimer's disease. *BMJ* 2022; **379:** o3010.
16 Van Dyck CH, O'Dell RS, Mecca AP. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimers Dement (N Y)* 2023; **9:** e12388.
17 McLeod LD, Coon CD, Martin SA, Fehnel SE, Hays RD. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. *Expert Rev Pharmacoecon Outcomes Res* 2011; **11:** 163–69.
18 Hays RD, Peipert JD. Between-group minimally important change versus individual treatment responders. *Qual Life Res* 2021; **30:** 2765–72.
19 Liu KY, Villain N, Ayton S, et al. Key questions for the evaluation of anti-amyloid immunotherapies for Alzheimer's disease. *Brain Commun* 2023; **5:** fcad175.
20 Ferreira G, Maher CG. Problems with responder analysis in clinical trials: in response to Korownyk et al. Jan 20, 2021. https://www.bmj.com/content/372/bmj.m4825/rr-2 (accessed Oct 13, 2023).
21 Assunção SS, Sperling RA, Ritchie C, et al. Meaningful benefits: a framework to assess disease-modifying therapies in preclinical and early Alzheimer's disease. *Alzheimers Res Ther* 2022; **14:** 54.
22 Petersen RC, Aisen PS, Andrews JS, et al. Expectations and clinical meaningfulness of randomized controlled trials. *Alzheimers Dement* 2023; **19:** 2730–36.
23 US Food and Drug Administration. FDA's decision to approve new treatment for Alzheimer's disease. https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease (accessed Oct 13, 2023).
24 Ackley SF, Zimmerman SC, Brenowitz WD, et al. Effect of reductions in amyloid levels on cognitive change in randomized trials: instrumental variable meta-analysis. *BMJ* 2021; **372:** n156.
25 Ackley SF, Wang J, Chen R, Power MC, Allen IE, Glymour MM. Estimated effects of amyloid reduction on cognitive change: a Bayesian update across a range of priors. *medRxiv* 2023; published online May 3. https://doi.org/10.1101/2023.04.28.23289223 (preprint).
26 Dickson SP, Wessels AM, Dowsett SA, et al. 'Time saved' as a demonstration of clinical meaningfulness and illustrated using the donanemab TRAILBLAZER-ALZ study findings. *J Prev Alzheimers Dis* 2023; **10:** 595–99.
27 Cision, Alzheimer's Association. Alzheimer's Association welcomes US FDA traditional approval of leqembi. July 6, 2023. https://www.prnewswire.com/news-releases/alzheimers-association-welcomes-us-fda-traditional-approval-of-leqembi-301871621.html (accessed Aug 27, 2023).
28 Schober P, Vetter TR. Survival analysis and interpretation of time-to-event data: the tortoise and the hare. *Anesth Analg* 2018; **127:** 792–98.
29 Ayton DR, Gardam ML, Pritchard EK, et al. Patient-reported outcome measures to inform care of people with dementia—a systematic scoping review. *Gerontologist* 2021; **61:** e185–94.
30 US Food and Drug Administration Center for Drug Evaluation and Research. Peripheral and central nervous system drugs advisory committee meeting transcript. Nov 6, 2020. https://www.fda.gov/media/145691/download (accessed Oct 19, 2023).
31 Weinfurt KP. Clarifying the meaning of clinically meaningful benefit in clinical research: noticeable change *vs* valuable change. *JAMA* 2019; **322:** 2381–82.
32 Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst Rev* 2018; **6:** CD001190.
33 Courtney C, Farrell D, Gray R, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet* 2004; **363:** 2105–15.
34 Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med* 2012; **366:** 893–903.
35 Profyri E, Leung P, Huntley J, Orgeta V. Effectiveness of treatments for people living with severe dementia: a systematic review and meta-analysis of randomised controlled clinical trials. *Ageing Res Rev* 2022; **82:** 101758.
36 Howard R, McShane R, Lindesay J, et al. Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial: secondary and post-hoc analyses. *Lancet Neurol* 2015; **14:** 1171–81.
37 Liu KY, Thambisetty M, Howard R. How can secondary dementia prevention trials of Alzheimer's disease be clinically meaningful? *Alzheimers Dement* 2022; **19:** 1073–85.
38 Walsh S, King E, Brayne C. France removes state funding for dementia drugs. *BMJ* 2019; **367:** l6930.
39 Cummings J, Rabinovici GD, Atri A, et al. Aducanumab: appropriate use recommendations update. *J Prev Alzheimers Dis* 2022; **9:** 221–30.

40 Eisai US. Eisai's approach to US pricing for leqembi (lecanemab), a treatment for early Alzheimer's disease, sets forth our concept of "societal value of medicine" in relation to "price of medicine." Jan 6, 2023. https://media-us.eisai.com/2023-01-06-eisais-approach-to-u-s-pricing-for-leqembi-tm-lecanemab-,-a-treatment-for-early-alzheimers-disease,-sets-forth-our-concept-of-societal-value-of-medicine-in-relation-to-price-of-medicine (accessed Aug 30, 2023).

41 Avins AL, Cherkin DC, Sherman KJ, Goldberg H, Pressman A. Should we reconsider the routine use of placebo controls in clinical research? *Trials* 2012; **13:** 44.

42 Wessels AM, Belger M, Johnston JA, et al. Demonstration of clinical meaningfulness of the integrated Alzheimer's Disease Rating Scale (iADRS): association between change in iADRS scores and patient and caregiver health outcomes. *J Alzheimers Dis* 2022; **88:** 577–88.

43 Planche V, Villain N. Advocating for demonstration of disease modification—have we been approaching clinical trials in early Alzheimer disease incorrectly? *JAMA Neurol* 2023; **80:** 659–60.

44 Mouelhi Y, Jouve E, Castelli C, Gentile S. How is the minimal clinically important difference established in health-related quality of life instruments? Review of anchors and methods. *Health Qual Life Outcomes* 2020; **18:** 136.