NICE National Institute for Health and Care Excellence

Potential issues and challenges in evaluation of disease-modifying dementia treatments

HTA Innovation Laboratory Report

November 2023

Disclaimer

Readers should be aware that issues and considerations outlined in HTA Lab reports cannot be taken as indicative or suggestive of any future position and will not be regarded as relevant to any future decision that may be taken by NICE.

The contents of HTA Lab reports are based on scientific knowledge that is publicly available and engagement with stakeholders at the time of writing the reports and cannot account for future changes and developments in scientific knowledge or any referenced material from external sources.

Contents

1 Executive Summary

Recent estimates indicate there were over 850,000 people living with dementia in the UK in 2019. Disease-modifying dementia treatments (DMDTs) are currently being developed with the aim to alter the course of disease progression and reduce its substantial impact. At the time of writing this report, several DMDTs are at various stages of development but none has been licensed for use in the UK, yet. To support timely decision making about their use in the NHS and facilitate the development of useful and useable NICE guidance, the NICE Health Technology Assessment (HTA) Innovation Laboratory (HTA Lab) set out to identify the key issues that might arise during the evaluation of these treatments, based on current knowledge and publicly available evidence.

To achieve this, the HTA Lab carried out various activities including a review of DMDT assessment reports from HTA agencies and a review of economic models of dementia treatments. A multi-stakeholder workshop was also held with representatives from the NHS, patient organisations, clinicians, health economists, international HTA agencies and other leading experts. Primary data analysis and research were also undertaken. In this report, we describe this work and its findings.

The key issues identified as likely to face the evaluation process based on this work included the uncertain disease prevalence estimates, particularly for mild cognitive impairment and the need for invasive diagnostics for identifying the treatment eligible population. The current lack of robust evidence to support the validity of the surrogate endpoints used in the clinical trials and the limited understanding of the natural history of the disease and its progression are also highlighted as issues for consideration. Additionally, issues related to defining treatment duration and the minimum clinically important difference, assessing subgroup effects and long-term effectiveness, incidence of adverse events and the need for regular monitoring are discussed. Challenges related to the economic modelling for assessing cost effectiveness of DMDTs including capturing treatment impact on the quality of life of those receiving

treatment and their carers and the relevance and appropriateness of taking a wider societal perspective are also anticipated to be key issues for consideration. Considerations related to each of these issues are discussed in the report. Despite these anticipated challenges, it could be concluded that NICE current approach and methods are considered appropriate for evaluating these treatments.

2 Background

Dementia is characterised by a group of symptoms caused by different conditions that damage the brain (NHS 2021). The symptoms progressively worsen over time and include memory loss, confusion and needing help with daily tasks, problems with language and changes in behaviour. Recent estimates from 2019 indicate there were over 850,000 people with dementia in the UK, representing 1 in every 14 people aged 65 years and over. At this rate, there will be over 1.5 million people estimated to live with dementia in the UK by 2040 (Alzheimer's Society 2020). The most common type of dementia is Alzheimer's disease (50% to 75%), followed by vascular dementia (up to 20%), Lewy body dementia (10% to 15%) and frontotemporal dementia (2%; Wittenberg et al. 2019). Alzheimer's disease is a progressive neurological disease suggested to be caused by the abnormal build-up of proteins called amyloid beta in and around brain cells (Karran and De Strooper 2022). The natural history of Alzheimer's disease is associated with cognitive and functional decline and behavioural non-cognitive symptoms. Studies have shown that with advancing cognitive decline, non-cognitive symptoms include apathy, depression, agitation, aggression, and psychosis (Masters et al. 2015).

Mild cognitive impairment (MCI) causes cognitive changes that are noticeable by the individuals experiencing them or by other people, but the changes are not severe enough to interfere with daily life or independent function (Handels et al. 2023). People with MCI, especially MCI involving memory problems, are more likely to develop Alzheimer's disease or other dementias than people without MCI (Alzheimer's Society 2020, Masters et al. 2015). The current management of mild dementia caused by Alzheimer's disease aims to target cognitive, non-cognitive and behavioural symptoms (NICE 2018a).

NICE's technology appraisal guidance on donepezil, galantamine, rivastigmine and memantine for Alzheimer's disease (TA217) and NICE's guideline on dementia (NG97) recommend:

- acetylcholinesterase (AChE) inhibitors (donepezil, galantamine and rivastigmine) as options for managing mild to moderate Alzheimer's disease
- memantine as an option for managing severe Alzheimer's disease or for moderate Alzheimer's disease in people who cannot tolerate or who have a contraindication to AChE inhibitors (NICE 2018a, NICE 2018b).

There is currently no licensed pharmacological treatment for MCI caused by Alzheimer's disease. In general, treatment of Alzheimer's disease is focused on supportive care, including treatment of symptoms with medications that do not alter the underlying course of the disease. Some evidence suggests amyloid beta removal slows progression of Alzheimer's disease (Karran and De Strooper 2022). Many new studies for the pharmacological management of Alzheimer's disease are focusing on disease-modifying dementia treatments (DMDTs). These aim to cause an enduring change in the clinical progression of Alzheimer's disease by interfering with the pathophysiological mechanisms of the disease process (Karran and De Strooper 2022, Cummings et al. 2022). These new treatments work through a variety of primary or intermediate mechanisms such as effects on amyloid beta or tau proteins. The aim of DMDTs is to alter the course of disease progression and reduce the substantial impact of Alzheimer's disease on health and healthcare systems (Handels et al. 2023). A recent literature review identified 143 treatments in 172 clinical trials for Alzheimer's disease (Cummings et al. 2022). According to Cummings et al., the drug development pipeline includes 31 treatments in 47 phase 3 trials, 82 treatments in 94 phase 2 trials, and 30 treatments in 31 phase 1 trials. DMDTs represent 83.2% of the total number of treatments in trials for Alzheimer's disease (Cummings et al. 2022).

3 The rationale for this report

At the time of writing this report, several DMDTs are currently at varying stages of development and regulatory approval. The first in class DMDT, aducanumab (Budd Haeberlein et al. 2022), was granted accelerated approval for treating Alzheimer's disease by the U.S Food and Drug Agency

(FDA) in July 2021. However, it did not receive approval by the European Medicines Agency. The NICE evaluation of aducanumab was subsequently discontinued. Lecanemab (van Dyck et al. 2023) received FDA approval in July 2023 (FDA 2023) and donanemab (Riederer 2021) is in the regulatory pipeline. Additional new treatments for Alzheimer's disease may also become available in the foreseeable future (Cummings et al. 2022).

Given the new mechanism of action and the disease-modifying nature of this class of treatments, the Health Technology Assessment (HTA) Innovation Laboratory (from now, HTA Lab) set out to:

- investigate whether evaluating these treatments could pose any unique challenges that might require changes to the methods or processes used by NICE
- identify and outline the potential key issues that might arise during the evaluation process to support and help timely decision making.

This report outlines the approach and activities undertaken by the HTA Lab and presents the list of challenges and issues identified, and the considerations associated with them.

4 Approach to developing the report

To inform its work on this topic, the HTA Lab carried out:

- a review of published assessment reports of DMDTs from HTA agencies (see appendix A)
- a scoping review of published economic models of pharmacological treatments for dementia to understand the challenges associated with evaluating their cost effectiveness using economic modelling (see appendix B).

The HTA Lab also held an engagement workshop on 19 July 2023 with 27 external stakeholders. Workshop participants included:

- representatives from NHS England, NHS Scotland and NHS Wales

- health economists and modellers
- NICE committee members
- NICE's Decision Support Unit (DSU)
- clinicians with expertise in primary care, psychiatry, and neurology
- patient organisation representatives from:
  - Alzheimer's Research UK
  - Alzheimer's Society
  - Dementia UK
- international HTA agency representatives from the:
  - Institute for Clinical and Economic Review (ICER) in the US
  - National Health Care Institute - Zorginstituut Nederland (ZIN) in the Netherlands
  - Canadian Agency for Drugs and Technologies in Health (CADTH)
  - Norwegian Medicines Agency (NoMA)
  - Dental and Pharmaceutical Benefits Agency in Sweden (TLV).

The workshop was structured to enable open discussions relating to the key issues that the HTA Lab identified as considerations that are likely to emerge during evaluations of DMDTs. The workshop included presentations from NHS England, NICE Scientific Advice and ICER. The HTA Lab presented on published international HTA reports evaluating DMDTs. The key issues for evaluation of DMDTs, identified by the HTA Lab, were also presented and discussed with workshop participants. Workshop attendees agreed with the key sources of uncertainty identified by the HTA Lab. These included the:

- absence of a consensus agreement on what constitutes a minimum clinically important difference for changes in Alzheimer's disease status
- lack of validation of the relationship between amyloid biomarker status and clinical outcomes
- impact and long-term consequences of amyloid related imaging abnormalities (ARIA)
- lack of agreement on stopping rules for DMDTs

- unknown treatment effect of DMDTs on clinical outcomes after the end of the trial period, both when stopping and continuing treatment.

To provide estimates of the likely number of people with MCI and mild dementia caused by Alzheimer's disease, the NICE Data and Analytics team did a feasibility study using Clinical Practice Research Datalink (CPRD) data (see appendix C). In addition, the NICE DSU was commissioned to review the available literature to establish the likely proportion of people who have MCI or mild dementia and are positive for amyloid beta, which represents the DMDT-eligible population (see appendix D).

In section 4, we outline in detail the key issues identified and considerations related to each of these issues.

5 Key issues in the evaluation of disease-modifying dementia treatments

Based on the reviews and engagement activities done by the HTA Lab, it was concluded that the evaluation of these new treatments is unlikely to be unique in nature compared with previous NICE evaluations or pose challenges that cannot be addressed using the flexibilities that are currently built into NICE methods and processes. Nevertheless, it was clear that some key issues are likely to arise during the evaluations because of known uncertainties either in the publicly available evidence base or the current understanding of the disease. So, we focused our efforts on outlining the key issues that were identified, providing context and proposing considerations to be taken into account if and when these issues arise in the course of evaluations.

Issue 1: The size of the target population and the DMDT-eligible population

Treatment eligibility in the DMDT clinical trials was contingent on confirmatory amyloid beta positivity by positron-emission tomography (PET) scanning or cerebrospinal fluid (CSF) biomarkers from lumbar puncture.

The NICE Data and Analytics team used CPRD Aurum data of people presenting in primary care for a GP consultation to ascertain estimates and extrapolate these to an English population (see appendix C). Using diagnostic sets validated by external clinical input, it was estimated that a maximum of 80,000 people per year may have mild Alzheimer's disease and therefore be eligible for testing for the presence of amyloid beta plaques. Using this estimate of 80,000 people per year approximates to a current prevalence of around 240,000 people based on the assumed 3-year duration of mild Alzheimer's disease (Brück et al. 2021).

Diagnosis of dementia is a priority for NHS England with targets for diagnosis included in the Clinical Commissioning Groups Assessment Framework (NHS England). However, there are no similar incentives to routinely capture the diagnosis of MCI, and so we expect this diagnosis to be under-reported in the CPRD. In the CPRD, the number of new Alzheimer's disease diagnoses seen each year was relatively stable from 2013 to 2018, with an expected drop in the years in which COVID-19 substantially affected NHS services. These figures equate to a risk of Alzheimer's disease in non-COVID years of 13.66 to 15.76 diagnoses per 10,000 people, or 77,270 to 89,112 diagnoses per year in England.

The DSU used an approach described in 2 publications to provide estimates (with upper and lower thresholds) of the size of the patient population eligible for amyloid beta testing as well as the proportion of those that may be eligible to have a DMDT (Potashman et al. 2020, Gillis et al. 2023). Using this 'funnel-based approach' (see figure 1), the DSU report (see appendix D) estimated the current prevalence of people with MCI and mild dementia to be approximately 283,399 (see table 1).

Figure 1 Funnel approach to estimating the size of the target population (Potashman et al. 2020, Gillis et al. 2023)

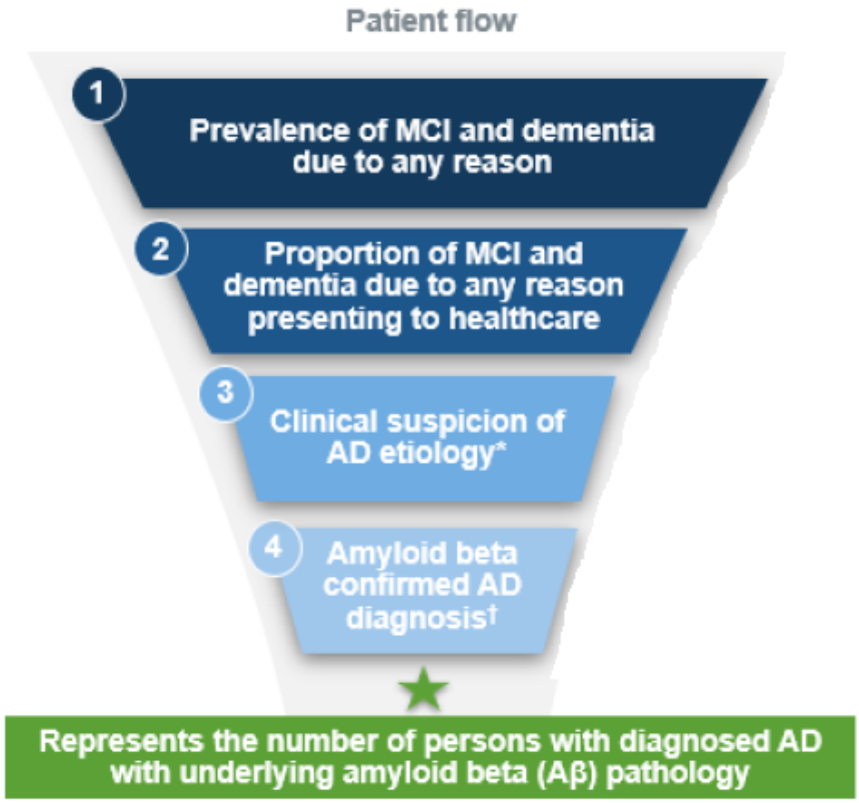

Table 1 Estimates of the size of the testing and treatment populations for England (Wailoo 2023)

Stage	Population	MCI, N (%)	Dementia, N (%)	Total, N (%)
–	Total	20,079,568	20,079,568	20,079,568
1	–	2,108,355 (10.5%)	763,024 (3.8%)	2,871,378 (14.3%)
2	–	280,411 (1.4%)	292,238 (1.5%)	572,649 (2.9%)
3	Testing	210,308 (1.0%)	73,091 (0.4%)	283,399 (1.4%)
4	Treatment	99,476 (0.5%)	61,835 (0.3%)	161,311 (0.8%)

The NICE Data and Analytics team report estimated a rate of 80,000 diagnoses per year and a duration of mild disease of 3 years to give a prevalence of 240,000. Therefore, the estimates from the feasibility study in the CPRD done by the NICE Data and Analytics team agrees with the DSU-estimated prevalence of 283,399 and with independent analysis provided by

Alzheimer's Research UK of 286,000 people with mild Alzheimer's disease (unpublished data).

Considerations for evaluating DMDTs

The NICE guideline on dementia (NG97) recommends considering PET scanning and CSF lumbar puncture:

- in circumstances in which diagnosis is uncertain and
- when using these further tests, alongside validated criteria guiding clinical judgement, would help to diagnose a dementia subtype and this would change disease management.

The literature suggests the average duration of MCI is between 3 and 7 years and mild dementia has an average duration between 2 and 4 years. Even taking into account the high uncertainty in the population estimates, the size of the population with early Alzheimer's disease, and therefore potentially eligible for testing and then going onto treatment, may be substantial (Jönsson et al. 2023, Wailoo 2023).

At present, neither PET scanning nor lumbar puncture are standard tests for confirmation of amyloid positivity in NHS practice. Introducing these tests at the necessary scale represents a major change in the current management pathway. The section on economic evaluation in NICE's methods manual for health technology evaluations states that "If a diagnostic test to identify patients or establish the presence or absence of a particular biomarker is not routinely used in the NHS but is introduced to support the treatment decision for the specific technology, include the associated costs of the diagnostic in the assessments of clinical and cost effectiveness." This is likely to apply to the diagnostic workup for identifying people eligible for DMDTs, in particular models targeting the MCI population for which there is no existing guidance on diagnosis.

Four of the studies identified in the literature review of economic modelling of DMDTs included diagnostic costs in the base case or in scenario analyses. Only 1 study reported in detail how the cost of diagnostic testing was

estimated and applied in the model. This study used a weighted approach based on the number of people tested in the aducanumab phase 3 trial and the donanemab phase 2 trial, and the numbers of negative and positive diagnoses, to calculate the number of PET and MRI scans required per eligible person identified (Ross et al. 2022). This is a useful approach to incorporate the cost of diagnostic testing to identify eligible people for each treatment arm in the model.

During discussions at the HTA Lab workshop, clinicians mentioned important considerations that would impact the number of people who progress on to, and continue with, DMDTs. These include:

- the presence of comorbidities that are contraindications to using these treatments such as unstable medical conditions, stroke or transient ischaemic attacks, bleeding disorders, or seizures in the previous 12 months
- the acceptability of taking DMDTs because of the associated adverse event risk
- patient willingness to undergo continued PET scanning or CSF lumbar puncture tests for monitoring disease progression as well as adverse events.

Participants at the workshop highlighted that these factors could substantially decrease the actual size of the testing and treatment population and are also described in the publications by Jönsson et al. 2023 and Lin 2023.

Our discussions with clinical experts and patient representatives also identified the potential for blood biomarker tests to replace the need for PET scanning or lumbar puncture in the near future. However, reliable blood biomarkers for Alzheimer's disease pathology have not yet been validated or approved and are not currently considered adequate to identify whom treatment is appropriate for (Jönsson et al. 2023).

During the engagement workshop, stakeholders also discussed the extent to which healthcare systems are equipped to identify who is eligible for a DMDT.

Moreover, given the recent publicity and awareness of DMDT trial results and the media focus on the availability of new DMDTs for Alzheimer's disease, participants highlighted that there is likely to be a substantial increase in people presenting to healthcare services for dementia assessment. It was also highlighted that there are large regional differences in access to dementia services across the UK. While beyond the remit of a NICE evaluation, many workshop participants highlighted a pressing need for rapid increases in dementia service infrastructure and workforce training to ensure equity of access to DMDTs, if made available in the NHS.

Issue 2: Definition of standard of care for MCI and mild dementia

Current practice differs in relation to the management of 2 population groups in the published trials (MCI and mild dementia caused by Alzheimer's disease). For MCI caused by Alzheimer's disease, there is no NICE guideline that covers the diagnosis and management of this condition. Moreover, it was highlighted during the HTA Lab engagement workshop that MCI is typically not coded in primary and secondary care memory services. For mild dementia caused by Alzheimer's disease, NG97 recommends an AChE inhibitor plus non-pharmacological management. TA217 also recommends donepezil, galantamine and rivastigmine as monotherapy options for managing mild to moderate Alzheimer's disease.

Considerations for evaluating DMDTs

Given that MCI and mild dementia caused by Alzheimer's disease are 2 distinct populations with different standards of care, the relevant comparators for each population will need to be determined. It is important that these align with currently recommended practice where clinical guidelines exist.

Issue 3: Validity of surrogate end points in Alzheimer's disease

The amyloid beta and tau hypotheses have recently provided valuable insights into Alzheimer's disease pathogenesis. However, they have also

faced criticisms and challenges. Negative trial results for anti-amyloid beta treatments (such as crenezumab and gantenerumab) have heightened the controversies. Overall, the evidence showing meaningful clinical benefits of amyloid beta removal in people with Alzheimer's disease is inconsistent (Karran and De Strooper 2022). Commentators have highlighted that for amyloid beta removal to be an effective substitute for clinical outcomes in Alzheimer's disease, effects of the intervention on this surrogate end point must reliably predict the overall effect on the clinical outcome (Manyara et al. 2022). Using reduction in amyloid beta as an estimate of treatment effectiveness, as was done for some published models identified by the systematic literature review, is not justified until there is enough evidence to demonstrate that amyloid beta levels can predict clinical outcomes (Tahami Monfared et al. 2022, Tahami Monfared et a. 2023, Igarashi et al. 2023).

Considerations for evaluating DMDTs

As outlined in the section on economic evaluation in NICE's methods manual for health technology evaluations, for a surrogate end point to be considered validated, there needs to be good evidence that the relative effect of a technology on the surrogate end point is predictive of its relative effect on the final outcome. This evidence preferably comes from level 1 evidence: a meta-analysis of randomised controlled trials that reported both the surrogate and the final outcomes, using meta-analytic methods recommended in the NICE DSU technical support document 20.

The use of clinical outcomes observed in the clinical trials to inform effectiveness estimates in the models would remove the need for assuming a relationship between the surrogate outcomes and predicted clinical outcomes. This was the approach taken by ICER in their assessment of lecanemab and aducanumab (ICER 2021a, ICER 2021b, Campbell et al. 2022).

Issue 4: Absence of consensus definition for the minimum clinically important difference

At present, there is no consensus on the level of treatment-induced slowing of disease progression that constitutes a clinically important difference for people with symptoms of dementia. In a recent commentary, Andrews et al. described the clinician-anchored minimum clinically important difference (MCID) for the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) as residing between a difference of 0.98 and 1.63 (Andrews et al. 2019). Similarly, a recent study used data from a 3-year phase 3 multicentre study in people with MCI and estimated MCIDs as 1.0 to 2.5 points on the CDR-SB and 2 to 5 points on the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog11) over 1 year (Lansdall et al. 2023).

Considerations for evaluating DMDTs

There may be differences in expert opinion concerning what constitutes a meaningful difference in disease progression during evaluations of DMDTs. The views of people with MCI and mild dementia caused by Alzheimer's disease, as well as their carers, about what constitutes a meaningful clinical benefit will also be important to consider. The relative clinical effectiveness of the treatments compared with standard care will likely be a driver of the incremental cost-effectiveness estimates. Andrews et al. note the study findings represent clinician assessments and may represent conservative MCID estimates (Andrews et al. 2019). Similarly, the Lansdall study reports individual change over time and the methods used in this study are not intended to evaluate the magnitude of change at a group level (Lansdall et al. 2023). Nevertheless, the reported MCIDs for the CDR-SB may help to contextualise the interpretation of results from the clinical trials and aid in decision making.

Issue 5: Potential differences in treatment effect across population subgroups

The recent DMDT trials recruited people with differing levels of disease severity, for example, MCI and mild dementia. This represents 2 separate population groups corresponding to different positions in the Alzheimer's treatment pathway. In the trials, a larger treatment effect was seen in people with mild dementia caused by Alzheimer's disease compared with MCI (van Dyck et al. 2023, Riederer 2021). Other differential treatment effects were also observed in the trials. For example, a larger treatment effect was seen in participants aged 75 years and over compared with those under 65 years. Treatment effect also varied by APOE4 gene carrier status, with a larger effect in APOE4 carriers compared with non-carriers. Treatments were also more clinically effective in people taking concomitant medicines (van Dyck et al. 2023, Lin 2023). Adverse events also differed by APOE4 gene carrier status (Riederer 2021, Lin 2023).

Considerations for evaluating DMDTs

Exploring differential treatment effects in subgroups might be justified, taking into account if subgroup estimates were obtained from post-hoc analysis, because these are likely to be underpowered and may not be corrected for multiple testing (Riederer 2021, Lin 2023).

As stated in the section on analysis of data for patient subgroups in NICE's methods manual for health technology evaluations, the characteristics of the patient subgroup population should be clearly defined and identified based on biological plausibility, social characteristics or other justified factors to avoid data 'dredging'. The committee will only make a recommendation for a subgroup if the decision is clinically justifiable, methodologically robust, ethical, and lawful under equalities legislation.

Differential effects on both positive outcomes and adverse events depending on APOE4 gene carrier status potentially leads to a requirement for genetic testing for the APOE4 genotype. This is not currently routine clinical practice,

so it could be an additional step in the treatment pathway for Alzheimer's disease.

Issue 6: Serious adverse events requiring close monitoring have been reported in the trials

ARIA is a major adverse event seen in the trials of anti-amyloid beta DMDTs. The Clarity AD trial of lecanemab reported 2 types of ARIA: ARIA with oedema or effusions (ARIA-E) and ARIA with cerebral microhaemorrhages, cerebral haemorrhages or superficial siderosis (ARIA-H; van Dyck et al. 2023). The reported incidences of ARIA-E in the lecanemab and placebo groups were 12.6% and 1.7%, respectively, and for ARIA-H were 17.3% and 9.0%, respectively. Infusion-related reactions occurred in 26.4% of the lecanemab group compared with 7.4% of the placebo group. No deaths were attributed to lecanemab during the trial, however, at least 2 deaths have been reported during the open-label extension (van Dyck et al. 2023, Thambisetty and Howard 2023). These are thought to have occurred in people having concomitant anticoagulant or thrombolytic treatment (Thambisetty and Howard 2023).

In the TRAILBLAZER-ALZ 2 trial of donanemab, ARIA-E occurred in 24.0% of participants in the donanemab group. ARIA-H occurred in 31.4% of the donanemab group and 13.6% of the placebo group. The incidence of serious ARIA was 1.6% and included 3 treatment-related deaths after serious ARIA and 1 death in the placebo group (Eli Lilly and Company 2023).

People who carry the APOE4 gene, and especially people with APOE4 homozygosity, appear to have an increased risk for ARIA. In the Clarity AD trial, 69% of participants had at least 1 APOE4 allele; 53% had APOE4 heterozygosity and 16% had APOE4 homozygosity (van Dyck et al. 2023). The rate of ARIA was 5.4% in people who did not carry the APOE4 gene, 10.9% in people with APOE4 heterozygosity, and 32.6% in people with APOE4 homozygosity.

Considerations for evaluating DMDTs

ARIA necessitates additional MRI surveillance and might require suspension of the treatment until the symptoms resolve. The assessment and evaluation of ARIA-related events was resource intensive in the clinical trials of DMDTs. ARIA was assessed at baseline and at 5 timepoints across the study duration in the Clarity AD trial for lecanemab. Commentary from experts during the engagement workshop highlighted that more frequent MRI scans and other clinical assessments would be required in the real-world use of DMDTs compared to those scheduled in the trial protocols to closely monitor ARIA.

As well as being highly resource intensive to monitor, the impact of these adverse events on the health-related quality of life (HRQoL) of people having these treatments and their carers should also be considered. Communication with patients and their families about potential harms of treatment with DMDTs should be balanced by discussions of treatment benefits and the implications of choosing no treatment.

Additional costs related to scheduled MRI monitoring, unplanned MRIs, and other tests, in addition to the immediate and long-term consequences of ARIA adverse events (such as stroke) will all be expected to be incorporated into the economic models.

Issue 7: Health-related quality-of-life and its incorporation in economic models

Lack of quality-of-life estimates in the early stages of dementia

Economic models of Alzheimer's disease usually use health states based on disease severity, or care setting, or both. This modelling approach may not align with how quality of life was measured in the published clinical trials of DMDTs.

The health state utility values most commonly used in the modelling studies identified in our literature review were based on publications from Landeiro et al. (2020) and Neumann et al. (1999). Landeiro et al. (2020) is a systematic review and meta-analysis of studies reporting utility values based on EQ-5D in people with pre-dementia Alzheimer’s disease, MCI or dementia. The

Landeiro review found no data on prodromal disease and limited published data on HRQoL of people with MCI. It also found a significant difference between self-rated HRQoL and carer proxy-rated utility values once people moved on from MCI to more severe stages of dementia, with the self-rated utility values being significantly higher than carer proxy-rated utilities. Neumann et al. (1999) is a cross-sectional study of people with Alzheimer's disease and carers measuring quality of life using HUI-2. The data from Neumann et al. (1999) were used in the ICER assessments of lecanemab and aducanumab. This is because it aligned with the health states in the model developed by ICER and provided values for patients and carers based on care setting. ICER reported that they compared the health state values from Neumann et al. against values reported in Landeiro et al. and found them to be comparable.

Carers' quality of life

Of the published economic evaluations of dementia treatments identified in our literature review, almost half (n=7) incorporated the impact of dementia on carers' quality of life in the base case or in a scenario analysis. ICER's assessments for lecanemab and aducanumab also considered carer quality of life. Not all studies provided sufficient detail on how it was estimated and incorporated in the analysis. However, the studies that did provide this detail reported using an assumption that each patient had 1 primary carer and seemed to follow an additive approach for combining patient and carer utility values. The papers and ICER assessments reported that carer disutility was adjusted for disease severity based on the relationship reported in Mesterton et al. (2010). A justification for the assumption of 1 primary carer was only provided in the ICER reports which stated that evidence on carer impacts was obtained from a single, primary carer. This is consistent with the findings from a systematic literature review by the NICE DSU of cost-utility analyses that included carer quality of life. This found that most cost-utility studies assumed 1 primary carer per patient with no justification provided for this choice (Scope et al. 2022).

Considerations for evaluating DMDTs

It is important to ensure that utility values used for modelling are well aligned to the health states described in the model. Furthermore, it is good practice to carry out sensitivity analyses using alternative utility values when assessing cost effectiveness, when these exist. Doing this for economic models of DMDTs will be especially important given the lack of good quality quality-of-life data in early stages of dementia.

The section on economic evaluation in NICE's methods manual for health technology evaluations recommends taking into consideration all health effects on carers when relevant without a preference for a specific approach. Evidence should be provided to show that the condition is associated with a substantial effect on carers' HRQoL and how the technology affects carers. If an analysis takes into account carer quality-of-life, it is important to be transparent on how it is incorporated and provide a rationale for assumptions and approach taken. It should also be clear how care setting is assumed to impact carer quality-of-life. Scenarios exploring alternative approaches for modelling carers' quality-of-life can also be explored if possible.

Issue 8: Incorporating the full societal impact on patients and their carers

Because MCI and dementia impact on the productivity of patients and carers, companies and other stakeholders may deem that using a societal perspective for the economic evaluation of DMDTs is more appropriate than an NHS and Personal Social Services (PSS) perspective. However, the objective of NICE evaluations is to offer guidance that represents an efficient use of available NHS and PSS resources within a set budget for the NHS. Therefore, the reference-case perspective on costs is that of the NHS and PSS. NICE's guidance-producing programmes, including the Technology Appraisal Programme, already include flexibilities in their approach to consider non-health benefits and other public sector costs when relevant.

The NICE Board has recently considered whether the reference case should adopt a societal perspective. In its considerations, the board took into account that “including economic productivity effects in assessments is ethically problematic because it entails valuing interventions differently based on the working status of the recipient population. Children, long-term sick and unemployed people and retired people are systematically disadvantaged when these effects are ‘counted’. It was also clear that formally broadening the perspective of NICE assessments would require substantial further research being undertaken – notably on valuing non-health benefits and opportunity costs and determining the relative value of health and non-health effects in decision-making. It would also require co-ordination with other public sectors to align methods and maximise outcomes across public expenditure.” (NICE Board Paper, 2022).

Considerations for evaluating DMDTs

As outlined in the section on economic evaluation in NICE's methods manual for health technology evaluations, when care by family members, friends or a partner might have otherwise been provided by the NHS or PSS, it may be appropriate to consider the cost of the time of providing this care, even when adopting an NHS or PSS perspective. This can be presented as a non-reference case analysis.

Issue 9: Type of economic model

Based on findings from previous literature reviews and our review, economic models of pharmacological treatments for dementia are broadly split into Markov cohort models and discrete event simulation models simulating individual patient experience. While both types of models have advantages and limitations, an important factor to consider for models used for decision making is transparency and credibility (Davis et al. 2014). Markov models, for example, are more transparent than patient-level simulation models which have increased data and computational requirements, may require specialised software to run and increase the time required for model validation and critique (Standfield, Comans and Scuffham, 2014).

Considerations for evaluating DMDTs

When choosing which type of model should be used in submissions for DMDTs, it is important to consider transparency and ease of validation of the model. A simple model that is transparent and can be easily interrogated and validated within the evaluation timelines will increase the credibility of its outputs and be more informative for decision making. This needs to be balanced against any additional benefit that may be gained by using a more complex modelling approach, which should be clearly explained and justified.

Issue 10: Modelling the natural history of the disease

As outlined in the section on economic evaluation in NICE's methods manual for health technology evaluations, economic models used for cost-utility analysis should be informed by the natural history of the disease and checked for clinical plausibility. The baseline risk of health outcomes should be quantified in addition to how the disease naturally progresses in the absence of treatment. There is currently limited data on the natural history of MCI, which would make it challenging to reflect in economic models and might require clinical expert input.

Considerations for evaluating DMDTs

The methods for identifying and critically evaluating the sources of data informing the natural history of the disease and baseline risks should be clearly presented and justified. Efforts should be made to ensure that the natural history data informing economic models is applicable to a UK setting and scenarios should be presented exploring alternative data sources if possible.

Issue 11: Incorporating a stopping rule in the economic model

In the published trials of some DMDTs, no stopping rules were applied. For example, the FDA marketing authorisation for lecanemab states lecanemab is indicated for the treatment of Alzheimer's disease. Treatment "should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials" (FDA

2023). The FDA label stipulates treatment discontinuation for patients with mild clinical symptoms and moderate or severe ARIA-E and for mild symptomatic ARIA-H. It is unclear whether patients who do not have adverse events with DMDTs should continue treatment indefinitely or discontinue treatment when a certain degree of amyloid clearance or defined point in the progression of the disease is reached. Continuing treatment unnecessarily would incur costs without associated benefit.

Considerations for evaluating DMDTs

Both the length of time on treatment and what happens to outcomes when people stop treatments are likely to be key drivers of cost effectiveness for DMDTs. In the ICER assessment of lecanemab it was assumed that people stop treatment when their condition progresses to moderate Alzheimer's disease. This was based on the absence of clinical-effectiveness evidence for lecanemab for moderate Alzheimer's disease (van Dyck et al. 2023).

Cost-effectiveness estimates of DMDTs are likely to be highly uncertain, given the paucity of data on key modelling parameters. In these circumstances, exploration of various scenarios together with input from clinicians on how the treatments will be used in routine clinical practice will likely be required. In line with what is outlined in the section on evidence in NICE's methods manual for health technology evaluations, using structured expert elicitation approaches would be highly recommended.

Issue 12: Extrapolating estimates of treatment effectiveness in economic models

The randomised phase of the clinical trials assessing the effectiveness of DMDTs for Alzheimer's disease that have been completed so far lasted 18 months. Therefore, modelling the treatment effectiveness to assess the lifetime benefit in terms of quality and length of life will require long-term extrapolation of the outcomes observed in the trials.

Considerations for evaluating DMDTs

The section on economic evaluation in NICE's methods manual for health technology evaluations highlights that extrapolation assumptions should have both internal and external validity. Demonstrating the validity and plausibility of the extrapolations will be difficult because DMDTs are new treatment modalities and there is no long-term published data on their effectiveness. Therefore, assumptions will need to be made to implement extrapolations, especially around what happens to disease progression beyond the trial duration and after treatment stops.

Whatever model assumptions are considered most appropriate, the paucity of evidence for the effects of DMDTs in the long term will likely generate cost-effectiveness estimates with high uncertainty. In these circumstances, it is useful to explore alternative modelling scenarios, changing key assumptions about the long-term treatment effects that underpin extrapolations and assessing their impact on estimates of cost effectiveness.

Issue 13: Acceptability and associated resources of intravenous administration of DMDTs

Lecanemab is administered every 2 weeks and donanemab every 4 weeks. Both medicines are administered by intravenous infusion and require hospital visits. Additionally, as is the case for all infusions, the likelihood of injection site reactions will need to be considered.

Considerations for evaluating DMDTs

It is anticipated that, at some point, a subcutaneously administered formulation for some DMDTs will become available and this is likely to have favourable administration costs and patient acceptance. However, until a subcutaneous formulation becomes available the costs of intravenous administration and its associated reactions should be included in any economic model assessing these treatments. Patient and carer perspectives about the in-hospital treatment administration are also likely to affect preferences for receiving treatment.

6 Conclusion

The development of disease-modifying treatments for dementia represents a long-awaited change in management of a condition associated with a considerable burden of illness. It is important, however, that the value of these treatments compared to currently available management options is demonstrated. Because of the nature of the disease and the absence of long-term evidence about the effectiveness of these treatments, a number of key issues that are likely to arise during their evaluation have been identified and discussed in this report. Nevertheless, it can be concluded that NICE current evaluation approach and methods would be appropriate for evaluating DMDTs.

7 List of appendices

Appendix A: Review of published appraisals

Appendix B: Systematic review of economic models

Appendix C: Alzheimer's disease and mild cognitive impairment in UK general practice: a feasibility study

Appendix D: Estimates of the size of the English eligible population for amyloid-targeting therapies in Alzheimer's disease (report by the Decision Support Unit)

8 Project team

Roshni Joshi, Scientific Adviser

Fatima Salih, Scientific Adviser

Tuba Saygin Avsar, Scientific Adviser

Magda Bugajska, Project Manager

Carole Longson, Special Adviser

Dalia Dawoud, Associate Director

9 Acknowledgements

HTA Lab Project Working Group

HTA Lab Delivery Group

Workshop participants

NICE Publishing and Editorial Team

9 References

Alzheimer's Society. How many people have dementia in the UK? [online; accessed 9 September 2023]

Andrews JS et al. (2019) Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimer's & Dementia Translational Research & Clinical Interventions 5:354–363

Brück CC et al. (2021) Heterogeneity in Reports of Dementia Disease Duration and Severity: A Review of the Literature. Journal of Alzheimer's. Disease 84:1515–1522

Budd Haeberlein S et al. (2022) Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. The Journal of Prevention of Alzheimer's Disease 9:197–210

Campbell JD, Whittington MD, Pearson SD (2022) Performing Cost-Effectiveness Analyses to Support Policy Making. Neurology 98:360–365

Cummings J et al. (2022) Alzheimer's disease drug development pipeline: 2022. Alzheimer's & Dementia Translational Research & Clinical. Interventions 8(1)

Davis S. et al. (2014) NICE DSU Technical Support Document 15: Cost-effectiveness modelling using patient-level simulation

Dementia: assessment, management and support for people living with dementia and their carers (2018a) NICE guideline NG97

Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (2018b) NICE technology appraisal guidance 217

Eli Lilly and Company (2023) Lilly's Donanemab Significantly Slowed Cognitive and Functional Decline in Phase 3 Study of Early Alzheimer's Disease [online, accessed 9 September 2023]

FDA. Drugs@FDA: FDA-Approved Drugs [online, accessed 9 September 2023]

FDA (2023) FDA Converts Novel Alzheimer's Disease Treatment to Traditional Approval [online, accessed 9 September 2023]

Gillis C et al. (2023) Estimating prevalence of early Alzheimer's disease in the United States, accounting for racial and ethnic diversity. Alzheimer's & Dementia 19(5):1841–1848

Handels R et al. (2023) The value of maintaining cognition in patients with mild cognitive impairment: The innovation headroom and potential cost-effectiveness of roflumilast. Alzheimer's & Dementia 19(8):3458–3471

ICER (2021a) Aducanumab for Alzheimer's Disease: Effectiveness and Value Draft Evidence Report Prepared for the California Technology Assessment Forum

ICER (2021b) Aducanumab for Alzheimer's Disease: Effectiveness and Value Final Evidence Report and Meeting Summary

Igarashi A et al. (2023) Predicting the Societal Value of Lecanemab in Early Alzheimer's Disease in Japan: A Patient-Level Simulation. Neurology and Therapy 12(4):1133–1157

Jönsson L et al. (2023) The affordability of lecanemab, an amyloid-targeting therapy for Alzheimer's disease: an EADC–EC viewpoint. The Lancet Regional Health: Europe 29:100657

Karran E, De Strooper B (2022) The amyloid hypothesis in Alzheimer disease: new insights from new therapeutics. Nature Reviews. Drug Discovery. 21(4):306–318

Landeiro F et al. (2020) Health-related quality of life in people with predementia Alzheimer's disease, mild cognitive impairment or dementia measured with preference-based instruments: a systematic literature review. Alzheimer's Research and Therapy 12(54)

Lansdall CJ et al. (2023) Establishing Clinically Meaningful Change on Outcome Assessments Frequently Used in Trials of Mild Cognitive Impairment Due to Alzheimer's Disease. The Journal of Prevention of Alzheimer's Disease 10(1):9–18

Lin GA et al. (2023). Beta-Amyloid Antibodies for Early Alzheimer's Disease: Effectiveness and Value; Evidence Report.

Manyara AM, Ciani O, Taylor RS (2022) A call for better reporting of trials using surrogate primary endpoints. Alzheimer's & Dementia Translational Research & Clinical Interventions 8(1)

Masters MC, Morris JC, Roe CM (2015) "Noncognitive" symptoms of early Alzheimer disease: A longitudinal analysis. Neurology 84(6):617–622

Mesterton J et al. (2010) Cross sectional observational study on the societal costs of Alzheimer's disease. Current Alzheimer's Research 7(4):358–367

Mintun AM et al. (2021) Donanemab in Early Alzheimer's Disease. New England Journal of Medicine 384(18):142–143

Neumann PJ et al (1999) Health utilities in Alzheimer's disease a cross-sectional study of patients and caregivers. Medical Care 37(1):27–32

NHS (2021) Alzheimer's disease [online, accessed 9 September 2023]

NHS England Dementia [online, accessed 29 September 2023]

NICE Board (2022) Options appraisal for adopting a wider perspective in NICE assessments: NICE Board Paper

Potashman M et al. (2020) PND59 Estimating the Prevalence of Aβ-Confirmed Alzheimer's Disease Using a Funnel-Based Approach Value in Health 23(2):S633–S634

Ross EL, Weinberg MS, Arnold SE (2022) Cost-effectiveness of Aducanumab and Donanemab for Early Alzheimer Disease in the US. JAMA Neurology 79(5):478–487

Scope A, Bhadhuri A, Pennington B (2022) Systematic Review of Cost-Utility Analyses That Have Included Carer and Family Member Health-Related Quality of Life. Value in Health 25(9):1644–1653

Standfield L, Comans T, Scuffham P (2014) Markov modeling and discrete event simulation in health care: a systematic comparison. International journal of technology assessment in health care 30(2):165–172

Tahami Monfared AA et al. (2023) Estimated Societal Value of Lecanemab in Patients with Early Alzheimer's Disease Using Simulation Modeling. Neurology and Therapy 12(3):795–814.

Tahami Monfared AA et al. (2022) The Potential Economic Value of Lecanemab in Patients with Early Alzheimer's Disease Using Simulation Modeling. Neurology and Therapy 11(3): 1285–1307

Thambisetty M, Howard R (2023) Lecanemab trial in AD brings hope but requires greater clarity. Nature Reviews: Neurology 19(3):132–133

Van Dyck CH et al (2023) Lecanemab in Early Alzheimer's Disease. New England Journal of Medicine 388(1):9–21

Wailoo, A (2023) Estimates of the size of the English eligible population in for amyloid targeting therapies in Alzheimer's Disease. NICE DSU Report.

Wittenberg R et al (2019) Care Policy and Evaluation Centre (CPEC) Working Paper 5, Projections of older people living with dementia and costs of dementia care in the United Kingdom, 2019–2040. The London School of Economics and Political Science