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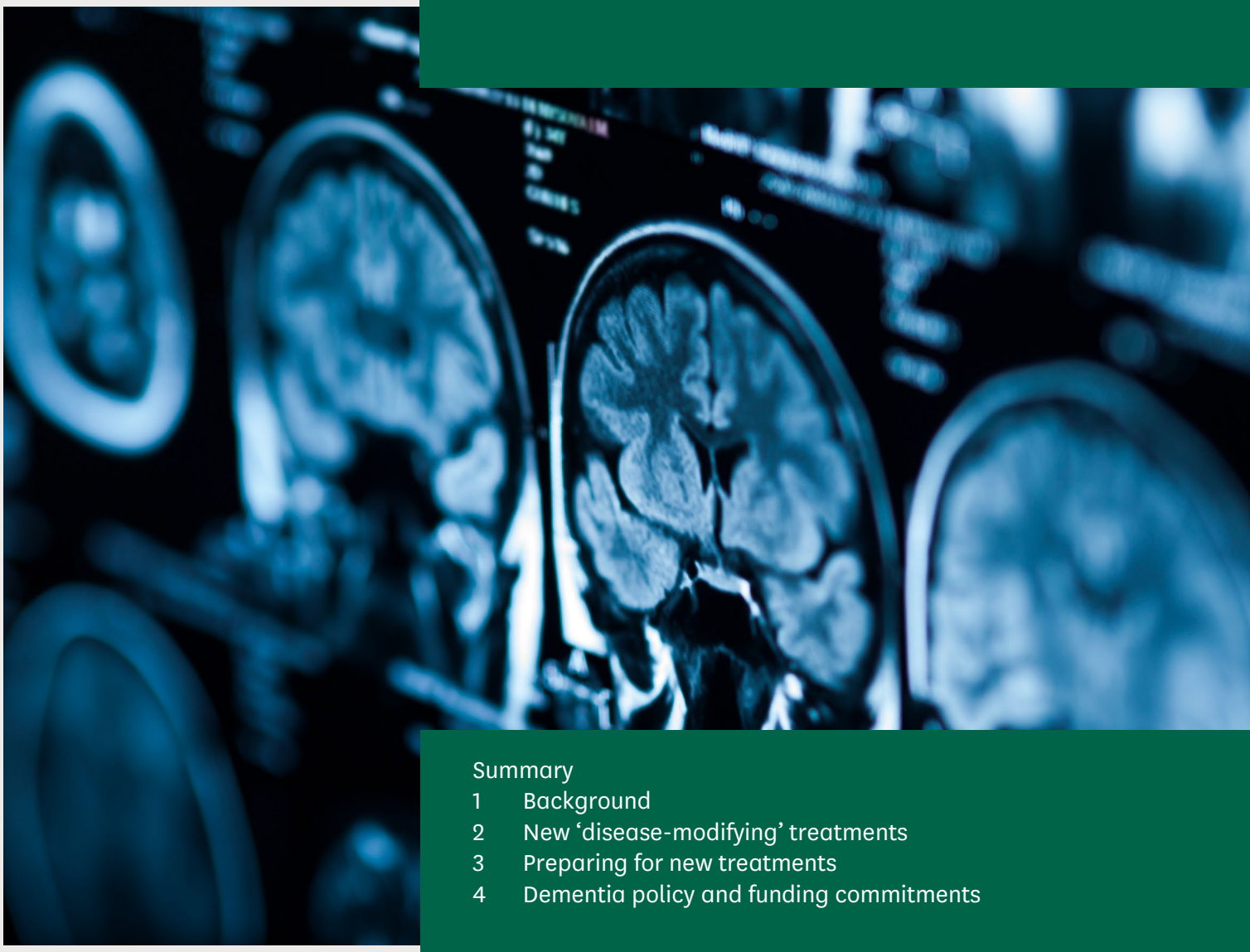
Developments in dementia treatments



Summary

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Summary

Dementia is not a single disease; it is a general term used to describe the progressive deterioration of cognitive functioning ("thinking, remembering and reasoning"). Alzheimer's disease is the most common type of dementia, accounting for between 60% and 70% of all dementia cases. It is thought to be caused by the build-up of two types of proteins, tau and amyloid, in and around brain cells.

There is currently no cure for dementia. There are medicines and treatments that can help manage, or temporarily reduce, some of the symptoms. However, these do not treat the cause of the underlying disease and therefore do not stop its progression.

Disease-modifying treatments

There are some new 'disease-modifying' treatments in development that are aimed at people in the early stages of dementia, who have a mild cognitive impairment / mild dementia, due to Alzheimer's disease. These are drugs that slow (but do not stop) the progression of dementia.

This briefing focuses on two disease-modifying dementia drugs that are currently being appraised by the National Institute for Health and Care Excellence (NICE): lecanemab and donanemab.

The drugs, known as immunotherapies, aim to slow the progression of the disease by helping the immune system to recognise, target and break down the amyloid plaques (clusters of proteins) in the brain. Lecanemab does this by "targeting amyloid as it begins to form fibres", whereas donanemab "binds to amyloid once these fibres have clumped together to become a larger build-up or plaque in the brain".

Neither drug is a cure for Alzheimer's disease. However, a clinical trial of lecanemab reported that it slowed the rate of cognitive decline by 27% in those with early Alzheimer's disease, compared to the placebo group. A clinical trial of donanemab reported that it slowed the progression of Alzheimer's disease by 36% when compared to the placebo group, again in those with early Alzheimer's disease.

As with all drug treatments, both lecanemab and donanemab have side effects; in most instances the clinical trials found that these were 'mild to moderate' (such as fever or headaches). However, there is a potentially more serious adverse event, associated with both lecanemab and donanemab, known as 'amyloid-related imaging abnormalities' (ARIA). These present as

either fluid or bleeding on the brain. While ARIA was typically asymptomatic, and resolved on its own within a few months, there were three fatal cases of ARIA in the donanemab trial. The researchers reported that their deaths were "considered treatment related". Both studies emphasised that further, longer-term trials are needed to understand, and evaluate, the risks of ARIA, as well as how best to manage them.

Preparing for new treatments

In the UK, lecanemab has been approved (licenced) by the Medicines and Healthcare products Regulatory Agency (MHRA – the UK's medicines regulator) to treat adults in the early stages of Alzheimer's disease. Draft guidance on lecanemab, issued by NICE in August 2024, did not, however, recommend lecanemab for use on the NHS. This was on the grounds that its benefits were "too small to justify the costs". Final guidance on lecanemab is expected to be published by NICE in 2025.

Donanemab was approved for use in the UK by the MHRA in October 2024. As with lecanemab, draft guidance issued by NICE has not recommended donanemab for use on the NHS in England: NICE said that its cost-effectiveness estimate "is 5 to 6 times above what [it] normally considers an acceptable use of NHS resources". Final NICE guidance on donanemab is expected in March 2025.

NHS England has described implementing these new treatments, should they be approved by the MHRA and recommended by NICE, as "one of the biggest challenges the NHS has faced in its 75-year history". This is partly because the effectiveness of the treatments depends on both an early diagnosis of dementia, and a further diagnosis of the sub-type, to confirm the treatment is suitable. Diagnosing subtypes of dementia requires more advanced and invasive procedures which, stakeholders say, are not widely available in the NHS. Alongside diagnostic capacity issues in the NHS, psychiatrists have expressed concern about having sufficient staffing, skills and resources to deliver and monitor new treatments.

Dementia policy

A 10-year plan to tackle dementia had been expected in 2022. In January 2023, the Conservative government announced it would instead publish a Major Conditions Strategy (MCS) covering six conditions, including dementia. The Labour government has since paused work on the MCS, later adding that it would consider how best to meet the needs of people with dementia as part of its work to develop a 10-year plan to reform the NHS. The 10-year plan will be informed by the conclusions of Lord Darzi's Independent investigation of the NHS in England.

1 Background

1.1 What is dementia?

Dementia is not a single disease; it is a general term used to describe the progressive deterioration of cognitive functioning.[1] Symptoms of dementias can vary in severity and progress through multiple stages. They include difficulties with thinking, problem-solving, remembering and making decisions, to the extent that daily activities can become challenging. Some people with dementia may also find it hard to control their emotions and aspects of their personality may change.

NHS England estimates that around 676,000 people have dementia in England and 850,000 have dementia across the whole of the UK.[2]

1.2 Types of dementia

There are multiple types of dementia and symptoms may differ depending on the type. It is also possible to have more than one type of dementia at the same time.

Alzheimer's disease

Alzheimer's disease is the most common type of dementia, accounting for between 60% and 70% of all dementia cases.[3] It is thought to be caused by the build-up of two types of proteins, tau and amyloid, in and around brain cells. Amyloid builds up into plaques (clusters/clumps of proteins) while tau forms "neurofibrillary tangles" in the brain.[4] Both damage neurons and disrupt their function. Neurons are specialised cells that transmit messages between different parts of the brain. The NHS notes that researchers "do not fully understand how amyloid and tau are involved in the loss of brain cells", but that research in this area "is continuing".[5]

1 US NIH National Institute on Aging, What Is Dementia? Symptoms, Types, and Diagnosis, National Institute on Aging, December 2022
2 NHS England, Dementia, accessed 1 October 2024
3 Alzheimer's Research UK, Subtypes of dementia - Dementia Statistics Hub, accessed 20 December 2023
4 US NIH National Institute on Aging, What Happens to the Brain in Alzheimer's Disease? | National Institute on Aging, May 2017
5 Causes of dementia – NHS, January 2024

Vascular dementia

Vascular dementia is the second most common type of dementia after Alzheimer's disease. The NHS estimates that it affects 180,000 people in the UK.[6] It is caused by poor blood flow to the brain. This can be the result of a sudden, or gradual, narrowing of blood vessels inside the brain. It can also be prompted by a single stroke (in which blood supply to part of the brain is blocked or reduced), or by multiple 'mini strokes', that cause damage to the brain.[7] Not everyone who has a stroke will go on to develop vascular dementia; Alzheimer's Research UK estimates that "roughly one in three people who have a stroke go on to develop dementia".[8]

Decreased blood flow to the brain due to damaged blood vessels means that brain cells do not receive enough oxygen and nutrients, causing a decline in the brain's normal functions. This can result in symptoms including memory loss and confusion, changes in mood, problems with planning and organising, as well as unsteady movements and urinary problems (such as incontinence).[9]

Other types of dementia include dementia with Lewy bodies and frontotemporal dementia, which are caused by clumps of abnormal proteins developing inside brain cells. An overview of different types of dementia is provided by Alzheimer's Research UK.

1.3 Current treatments for dementia

There is currently no cure for dementia. There are medicines and treatments that can help manage, or temporarily reduce, some of the symptoms. However, these do not treat the cause of the underlying disease. This means that they do not stop or slow its progression.

Medications that aim to temporarily improve the symptoms Alzheimer's disease include 'donepezil', a cholinesterase inhibitor, which works by "boosting levels of a chemical messenger involved in memory and judgment" and 'memantine', which regulates the activity of another chemical messenger in the brain known as glutamate.[10] There are also treatments that do not involve taking medicines, such as occupational therapy (making adaptations to the home to prevent accidents and falls), talking therapies, and alternative

6 Vascular dementia – NHS, June 2023
7 Vascular dementia – NHS, June 2023
8 What is vascular dementia? | Alzheimer's Research UK, December 2023
9 Vascular Dementia | Johns Hopkins Medicine, accessed 30 September 2024; Vascular dementia - Dementia UK, September 2024
10 Dementia - Diagnosis and treatment - Mayo Clinic, September 2024; What are the treatments for dementia? – NHS, July 2023; Dementia treatments - Alzheimer's Research UK, accessed 30 September 2024

therapies that aim to address conditions related to dementia, like sleep problems.[11]

More information on current treatments can be found on the NHS webpage: What are the treatments for dementia? - NHS (July 2023).

[11] What are the treatments for dementia? – NHS, July 2023; Alternative therapies for dementia | Alzheimer's Society, accessed 30 September 2024

2 New ‘disease-modifying’ treatments

Drugs that slow the progression of dementia are sometimes referred to as ‘disease-modifying’ treatments. There are some new disease-modifying treatments in development that are aimed at people with a mild cognitive impairment, or mild dementia, due to Alzheimer’s disease.

The drugs, known as immunotherapies, aim to slow the progression of the disease by helping the immune system to recognise, target and break down the amyloid plaques in the brain.[12] They are not a cure for Alzheimer’s disease.

Immunotherapies are already used in other branches of medicine, such as cancer treatment, but are at various stages of development and regulatory approval for Alzheimer’s disease. Further detail is provided below of two drugs, lecanemab and donanemab, that are being appraised by the National Institute for Health and Care Excellence (NICE) in 2024.[13]

2.1 Lecanemab

Lecanemab, made by the pharmaceutical company Eisai and the biotechnology company Biogen, is a monoclonal antibody designed to reduce amyloid plaques in the brain among those with mild cognitive impairment due to Alzheimer’s disease. It is aimed at those at the very early stages of Alzheimer’s disease, rather than those with moderate to late-stage dementia. It is given to patients via an intravenous drip every two weeks.

Monoclonal antibodies are proteins manufactured in a laboratory. Monoclonal means that they are copies of one antibody. They are designed to act like human antibodies and therefore can enhance, modify, or copy a patient’s own immune system response to disease.

An 18-month Phase III clinical trial, involving 1795 participants, compared lecanemab to a placebo (an inactive substance).[14] The results of the trial were published in the New England Journal of Medicine in January 2023. The researchers reported that lecanemab reduced levels of amyloid in the brain in early Alzheimer’s disease and “resulted in moderately less decline on

12 Three promising drugs for treating Alzheimer's disease bring fresh hope, Alzheimer's Society (alzheimers.org.uk), 19 July 2023

13 NICE gets ready to assess new dementia treatments. | News, NICE, 20 November 2023

14 Clinical trials in humans are typically divided into three stages, known as ‘phases’. Phase III trials are later stage trials that focus comparing new treatments with the currently best available treatment. They generally involve a larger number of participants than Phase I and Phase II trials

measures of cognition and function than [the] placebo at 18 months".[15] More specifically, lecanemab slowed the rate of cognitive decline by 27%.[16] The incidence of adverse events was 44.7% for those who received lecanemab and 22% for those who received a placebo.[17] Infusion-related reactions were the most common adverse event (26.4% in those receiving lecanemab, 7.4% in the placebo group): they tended to occur after the first dose and were "mild to moderate" in nature, such as chills, fever, rash, and body aches.[18]

Lecanemab initially received an "accelerated approval" from the US Food and Drug Administration (FDA) as a treatment for early Alzheimer's disease in patients in the US. This was converted by the FDA to a 'full' approval in July 2023.[19] Further information about licensing and approval in the UK is set out in section 2.3 below.

2.2 Donanemab

Donanemab is manufactured by the pharmaceutical company Eli Lilly and also works by helping the immune system to recognise, target, and break down amyloid plaques in the brain. Alzheimer's Research UK explains some of the differences between lecanemab and donanemab:

> Although both drugs target amyloid protein, they target it at different stages in how it builds up in the brain.
>
> Lecanemab targets amyloid as it begins to form fibres, whereas donanemab binds to amyloid once these fibres have clumped together to become a larger build-up or plaque in the brain.[20]

An 18-month Phase III clinical trial, involving 1736 participants with early symptomatic Alzheimer's Disease and evidence of amyloid and tau pathology, compared donanemab to a placebo. Participants were located in eight countries and received either donanemab or the placebo intravenously, every

15 Christopher H. van Dyck and others, Lecanemab in Early Alzheimer's Disease, N Engl J Med 2023; 388:9-21

16 US National Institute of Aging statement on report of lecanemab reducing cognitive decline in Alzheimer's clinical trial | National Institute on Aging (nih.gov), July 2023

17 Christopher H. van Dyck and others, Lecanemab in Early Alzheimer's Disease, N Engl J Med 2023; 388:9-21, Table 3

18 Christopher H. van Dyck and others, Lecanemab in Early Alzheimer's Disease, N Engl J Med 2023; 388:9-21; Lecanemab, the New Alzheimer's Treatment: 3 Things To Know > News > Yale Medicine, July 2023

19 FDA Converts Novel Alzheimer's Disease Treatment to Traditional Approval | FDA, July 2023. After the accelerated approval was granted by the FDA, the drug manufacturer was required (as part of the approvals process) to conduct a further clinical trial to verify the anticipated clinical benefit of lecanemab. Had these 'post approval' conditions not been met, the FDA could have withdrawn its approval.

20 What is donanemab? | Alzheimer's Society (alzheimers.org.uk), July 2023

four weeks, for 72 weeks.[21] The results were published in JAMA (the Journal of the American Medical Association) in July 2023.

The researchers found that, in those with early-stage Alzheimer's Disease, donanemab was able to slow the progression of the disease (calculated by measuring the memory and thinking skills of participants) by 35% when compared to the placebo group. At 76 weeks, donanemab had cleared amyloid plaques in 76% of participants receiving the treatment.[22]

The drug also caused side effects; 24% of participants reported experiencing side effects, such as headaches, falls, and infusion-related reactions. The incidence of serious adverse events was 17.4% in the donanemab group and 15.8% in the placebo group. Four participants died during the trial; three who received donanemab and one in the placebo group (see further discussion below). The researchers reported that their deaths were "considered treatment related".[23] The US Food and Drug Administration approved donanemab for the treatment of Alzheimer's disease in adults in July 2024.[24]

What are amyloid-related imaging abnormalities (ARIA)?

A side effect of both lecanemab and donanemab is 'amyloid-related imaging abnormalities' (ARIA). ARIA refers to two types of abnormalities that are detected by MRI scans of the brain; fluid formation on the brain (known as ARIA-E) and bleeding / microhaemorrhages (known as ARIA-H).[25] Alzheimer's Research UK describes ARIA as both a "concerning and poorly understood" side effect of the drugs.[26] Tables 1 and 2 below show the occurrence of ARIA in both the lecanemab and donanemab trials.

Table 1: Occurrence of ARIA in the lecanemab Phase III clinical trial

	lecanemab group	Placebo group
ARIA-E	113 participants (12.6%)	15 participants (1.7%)
ARIA-H	126 participants (14%)	69 participants (7.7%)

Source: Christopher H. van Dyck and others, Lecanemab in Early Alzheimer's Disease, N Engl J Med 2023; 388:9-21, Table 3

21 The countries were the United States, Australia, Canada, Czech Republic, Great Britain, Japan, the Netherlands, and Poland.

22 John R. Sims and others, Donanemab in Early Symptomatic Alzheimer Disease. The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA 2023;330(6):512-527

23 John R. Sims and others, Donanemab in Early Symptomatic Alzheimer Disease. The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA 2023;330(6):512-527; NIHR, Drug donanemab hailed as breakthrough in treat Alzheimer's disease following trial, accessed 8 January 2024

24 US Food and Drug Administration, FDA approves treatment for adults with Alzheimer's disease, 2 July 2024

25 Harald Hampel and others, Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics, Brain, 2023 Nov; 146(11): 4414–4424

26 New Alzheimer's drug, donanemab – what is it and how does it work? - Alzheimer's Research UK, July 2024

Table 2: Occurrence of ARIA in the donanemab Phase III clinical trial		
	donanemab group	Placebo group
ARIA-E	205 participants (24.0%)	18 participants (2.1%)
ARIA-H	268 participants (31.4%)	119 participants (13.6%)

Source: John R. Sims and others, Donanemab in Early Symptomatic Alzheimer Disease. The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA 2023;330(6):512-527

In both trials, ARIA was typically asymptomatic and resolved within 10-16 weeks. In the case of ARIA-H, Dr van Dyck, the lead researcher on the lecanemab Phase III trial, said that the haemorrhages detected by the MRI scans were very small:

> Most of the time we're really talking about microhemorrhages that are in the order of millimeters [...] People with Alzheimer's disease are more prone to these events because of the amyloid deposits in their blood vessels, but a catastrophic bleed is quite rare.[27]

There were, however, fatal cases of ARIA: the three deaths in the donanemab group occurred after serious amyloid-related imaging abnormalities.[28] The lecanemab researchers reported that "no deaths were considered to be related to lecanemab or occurred with ARIA".[29] Both studies emphasised that further, longer-term trials are needed to understand, and evaluate, the risks of ARIA, as well as how best to manage them.

2.3 When might new treatments be available on the NHS in England?

Licencing new treatments

Before a medicine can be sold in a country, and administered in people, it must receive a 'marketing authorisation' (sometimes referred to as a 'licence'). In the UK, marketing authorisations are issued by the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA's role is to

27 Lecanemab, the New Alzheimer's Treatment: 3 Things To Know > News > Yale Medicine, July 2023

28 John R. Sims and others, Donanemab in Early Symptomatic Alzheimer Disease. The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA 2023;330(6):512-527; Lilly's Donanemab Significantly Slowed Cognitive and Functional Decline in Phase 3 Study of Early Alzheimer's Disease | Eli Lilly and Company, 3 May 2023

29 Christopher H. van Dyck and others, Lecanemab in Early Alzheimer's Disease, N Engl J Med 2023; 388:9-21;

ensure a medicine is safe, that it works as it is intended and that it can be manufactured to a consistently high-quality standard.

The developers of the drug need to gather sufficient safety and drug effectiveness data during clinical trials to demonstrate that the benefits of the new drug outweigh the risks. This data is then used in their application for a marketing authorisation from the MHRA.

Lecanemab

The manufacturers of lecanemab announced in May 2023 that they had submitted a marketing authorisation to the MHRA for their drug as treatment for early Alzheimer's disease.[30] Lecanemab was designated by the MHRA as suitable for the Innovative Licensing and Access Pathway (ILAP). Established in 2021, ILAP aims to speed up and streamline the regulatory approval process for drugs that target "life-threatening or seriously debilitating" conditions and where there is a "significant patient or public health need".

The MHRA reported in August 2024 that it had approved a product licence for the lecanemab for use in the early stages of Alzheimer's disease. More specifically, it is approved for use in adults who carry one copy of a gene called apolipoprotein E4, also known as ApoE4, or in adults who do not carry this gene.[31]

The MHRA notes that "approximately 15% of those diagnosed with Alzheimer's have two copies of this gene, known as homozygous patients".[32] Lecanemab has not been authorised for use in ApoE4 homozygous patients because of ARIA-associated risks. The MHRA explained that, in the main clinical trial of lecanemab (see section 2.1):

> ApoE4 homozygous patients who received lecanemab were at higher risk of developing Amyloid Related Imaging Abnormalities (ARIAs), which are most commonly seen as temporary swelling in one or more areas of the brain (ARIA-E) or small spots of bleeding in or on the surface of the brain (ARIA-H). Whilst most ARIA events were only seen on a brain scan and did not cause any symptoms, in a small number of patients serious symptoms occurred.[33]

Donanemab

The Guardian newspaper reported in July 2023 that Eli Lilly had applied for regulatory "approval for donanemab in the US and will do so in the UK in the coming weeks".[34] Donanemab was authorised in July 2024 by the US Food and

30 EISAI Submits Marketing Authorization Application for Lecanemab as Treatment for Early Alzheimer's Disease In Great Britain | Biogen, 21 May 2023

31 MHRA, Lecanemab licensed for adult patients in the early stages of Alzheimer's disease - GOV.UK, 22 August 2024

32 MHRA, Lecanemab licensed for adult patients in the early stages of Alzheimer's disease - GOV.UK, 22 August 2024

33 MHRA,Lecanemab licensed for adult patients in the early stages of Alzheimer's disease - GOV.UK, 22 August 2024

34 Andrew Gregory, Experts urge health regulators to approve 'turning point' dementia drugs | Alzheimer's, The Guardian, 17 July 2023

Drug Administration for adults living with early symptomatic Alzheimer's disease with confirmed amyloid plaques.[35]

The National Institute for Health and Care Excellence (NICE) reported in June 2024 that the MHRA's decision on donanemab had been due in July 2024 but had been delayed.[36] The MHRA subsequently approved a product licence for donanemab in October 2024. As with lecanemab, it is approved for use in adults in the early stages of Alzheimer's disease who carry one, or no, copy of the apolipoprotein E4 gene.[37] Donanemab has not been authorised for use in ApoE4 homozygous patients (those with two copies of the ApoE4 gene) because of ARIA-associated risks.

NICE technology appraisal

If a drug receives a marketing authorisation from the MHRA it would also need to be appraised and recommended for use by the National Institute for Health and Care Excellence (NICE) before it could become available to patients via the NHS in England.[38]

In Scotland, the Scottish Medicines Consortium is responsible for reviewing licenced medicines and deciding if they should be made available on the NHS in Scotland.

In England, NICE is responsible for making recommendations on the use of new and existing medicines and treatments within the NHS in England. NICE's recommendations are based on its technology appraisal process. Its technology appraisals are a type of cost/benefit analysis that is based on a review of clinical and economic evidence:

- Clinical evidence shows how well the medicine or treatment works.
- Economic evidence shows how well the medicine or treatment works in relation to how much it costs the NHS: does it represent 'value for money'?

Typically, NICE determines the cost effectiveness of a treatment through looking at 'quality-adjusted life years' (QALYs); how many QALYs may a patient, on average, gain from taking the drug being appraised compared with existing therapies? This is then considered in the context of the price of the new drug and how much each QALY costs, again in comparison to existing treatments (if there are existing treatments).

The different stages in the technology appraisal process are set out by NICE on its website: Single technology appraisal (STA) timeline.

35 FDA approves treatment for adults with Alzheimer's disease | FDA, 2 July 2024

36 Project information | Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222] | Guidance | NICE, accessed 1 October 2024

37 MHRA, Donanemab licensed for early stages of Alzheimer's disease in adult patients who have one or no copies of apolipoprotein E4 gene, 23 October 2024

38 Wales and Northern Ireland both consider NICE recommendations. In Wales, there is a statutory obligation for local health boards to make medicines available when they have been recommended by NICE. The Department of Health in Northern Ireland reviews the results of all NICE technology appraisals, for their applicability to Northern Ireland, before deciding on whether to implement them.

NICE has stated that it has "already begun work in readiness for [...] companies submitting their evidence" for what it terms "disease-modifying dementia treatments (DMDTs)". This work includes:

> [...] work done by NICE's Health Technology Assessment Innovation Laboratory (HTA Lab) to identify the key issues that might arise during planned and future evaluations, based on current knowledge, publicly available evidence and in-depth discussions with researchers, patient groups and NHS colleagues.[39]

Lecanemab

As noted above, NICE has stated that it is scheduled to appraise both lecanemab and donanemab in 2024.[40]

Draft guidance on "Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease" was published by NICE in August 2024.[41] It did not recommend lecanemab for use on the NHS, stating that its benefits were "too small to justify the costs":

> Lecanemab provides on average 4 to 6 months slowing in the rate of progression from mild to moderate Alzheimer's disease, but this is just not enough benefit to justify the additional cost to the NHS.
>
> [...]
>
> And because the clinical trial only reported outcomes when people had been taking lecanemab for 18 months there is a lack of evidence on its long-term effects.[42]

The draft guidance was open for public consultation until 20 September 2024. NICE will consider the responses at a meeting later in 2024 before issuing its final guidance in 2025.

Donanemab

NICE's appraisal of Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease is currently in progress. The appraisal committee met in July 2024 but, as a licence (marketing authorisation) for donanemab had not been issued by the MHRA at that time, it was conducted in private, as NICE explained:

> The reason the meeting needs to be in private is that we have received an update that the licence from the MHRA may not be granted by 3 July. NICE's technology appraisal committees can only make recommendations on medicines licensed by the MHRA. So, it would not be appropriate for NICE to

39 NICE gets ready to assess new dementia treatments. | News | News | NICE, November 2023

40 NICE gets ready to assess new dementia treatments. | News, NICE, 20 November 2023

41 Project documents | Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID4043] | Guidance | NICE

42 Benefits of new Alzheimer's treatment lecanemab are too small to justify the cost to the NHS | NICE, 22 August 2024; The precise cost-effectiveness results of the drug were not reported in NICE's draft guidance on the grounds that they included "confidential prices for lecanemab" (see page 30 of the draft guidance).

> discuss the donanemab data in public or release any recommendations that pre-empt the MHRA decision.[43]

Following the MHRA's licensing of donanemab in October 2024, NICE published its draft guidance on the drug. At this stage NICE has not recommended donanemab for use on the NHS in England, stating:

> Our independent committee looked at all the available evidence, including the benefits for carers. This shows donanemab could slow down cognitive decline by 4-7 months, but this is just not enough benefit to justify the additional cost to the NHS. The cost-effectiveness estimate for donanemab is 5 to 6 times above what NICE normally considers an acceptable use of NHS resources.[44]

NICE estimated that around 70,000 adults in England would have been eligible for treatment with donanemab had it been recommended. To address some of the cost uncertainties associated with the drug, NICE has asked both NHS England and Eli Lilly to provide "additional information to address areas of uncertainty in the evidence".[45] A consultation on the draft guidance closes on 20 November 2024 and the responses will be considered at a committee meeting before the final guidance is published in 2025.[46]

43 Project information | Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222] | Guidance | NICE, accessed 1 October 2024

44 New Alzheimer's treatment donanemab does not currently demonstrate value for the NHS says NICE | NICE, 23 October 2024

45 New Alzheimer's treatment donanemab does not currently demonstrate value for the NHS says NICE | NICE, 23 October 2024

46 Project information | Donanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease [ID6222] | Guidance | NICE, accessed 6 November 2024

3 Preparing for new treatments

NHS England described the potential roll out of new treatments for early Alzheimer's disease as "one of the biggest challenges the NHS has faced in its 75-year history".[47] This section sets out some of those challenges in more detail.

3.1 Diagnosing dementia

Both lecanemab and donanemab are specifically for people with a diagnosis of mild cognitive impairment / mild dementia caused by Alzheimer's disease. In addition, a person must also have high levels of amyloid in their brain, confirmed by a scan, to be eligible for the drugs.

Getting a timely diagnosis of dementia, however, is complicated by challenges in accessing the recommended NICE diagnostics and specialist services for dementia in some areas and among some groups.

Diagnosis rates

NHS England publishes monthly data on dementia diagnosis rates in England. The rate is calculated by comparing the number of people aged 65 and over who are diagnosed with dementia to the estimated number of people aged 65 or over thought to have dementia. The 'national ambition' for the dementia diagnosis rate is for at least two-thirds of people with dementia to have a formal diagnosis (see section 4 below for more information).[48] In August 2024, the diagnosis rate was 65.4%.[49] This means around one in three people with dementia do not have a diagnosis.

There are currently no national standards for waiting times for dementia assessments. In response to a parliamentary question about introducing national standards the government referred to guidance on the dementia care pathway commissioned by NHS England. This sets an aspiration to

47 NHS England, Preparing for a new chapter: disease modifying treatments for early Alzheimer's disease, December 2023

48 Department of Health and Social Care press release, Dementia diagnosis to be overhauled, 15 May 2013

49 NHS Digital, Primary Care Dementia Data, August 2024 - NHS England Digital, 19 September 2024

increase the number of people receiving a diagnosis and starting treatment within six weeks of referral.[50]

The government said it allocated £17 million to NHS England in 2021/22 to address waiting lists and increase dementia diagnosis rates. NHS England reported in July 2024 that dementia diagnosis rates are now at the highest since the start of the Covid-19 pandemic, but that more needs to be done to reach its ambition of "diagnosing 66.7% of the total number of people that estimates suggest are living with a form of the disease".[51]

Inequalities in dementia diagnosis

Inequalities in dementia diagnosis rates between different parts of the country, and different groups of people, was debated in the House of Commons on 16 May 2024.

The debate highlighted regional variations in dementia diagnosis rates and the work of the All-Party Parliamentary Group (APPG) on Dementia. In its October 2023 report on the topic, the APPG cited figures showing that diagnosis rates vary across integrated care systems (ICS) from 73.5% in South Yorkshire, to 53.4% in Herefordshire and Worcestershire.[52] The highest diagnosis rate was in Stoke-on-Trent, where 90% of patients have a diagnosis, while the lowest was in South Hams, Devon, with a diagnosis rate of 44%.[53]

A rural/urban divide in diagnosis was similarly apparent. A report commissioned by the Alzheimer's Society found that diagnosis rates were between approximately five and eight percentage points lower in rural (compared to urban) areas between 2018 and 2023.[54]

Earlier work by the APPG estimated that in 2013, there were 25,000 people living with dementia in the UK from minority ethnic groups; a figure the APPG expected to double to 50,000 by 2026 and rise to over 172,000 by 2051.[55]

The Alzheimer's Society has highlighted research showing that minority ethnic groups are at greater risk of developing vascular and early onset dementia, adding that this was:

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50 PQ 4160 [on Memory clinics: Standards], 28 November 2023; National Collaborating Centre for Mental Health, The Dementia Care Pathway: Full implementation guidance, 2018

51 NHS England » Dementia diagnoses in England at record high, 22 July 2024

52 All-Party Parliamentary Group (APPG) on Dementia, Raising the Barriers: An Action Plan to Tackle Regional Variation in Dementia Diagnosis in England, October 2023, p12, PDF

53 Inequality leaving 115,000 dementia cases 'undiagnosed' in England | Dementia | The Guardian, 23 October 2023

54 Sian Hodgson and others, Evidence Review in England, Wales, and Northern Ireland. Inequalities in Dementia: Unveiling the Evidence and Forging a Path Towards Greater Understanding. OHE Contract Research Report, London: Office of Health Economics, June 2024, PDF

55 All-Party Parliamentary Group on Dementia, Dementia does not Discriminate: The experiences of Black, Asian and ethnic minority communities, July 2013, PDF

> [...] particularly the case for those in Asian and African-Caribbean communities where increased vascular risk factors for dementia – such as cardiovascular disease, hypertension and diabetes– may be more common.[56]

In addition, the Alzheimer's Society reported that people from Black, Asian and minority ethnic communities often face delays in diagnosis and barriers accessing services.[57] Its report on Ethnic minority communities Increasing access to a dementia diagnosis (PDF, 2021) provides further details on some of the barriers to accessing a diagnosis.

Alzheimer's disease: diagnosing the subtype of dementia

There are many diseases that can cause dementia and often individuals receive a general diagnosis of dementia. The new immunotherapy treatments are designed to treat Alzheimer's disease specifically. This means that patients with dementia would need further testing to find out if Alzheimer's is their 'subtype' of dementia in order to be suitable for the new treatments.

Diagnosing subtypes of dementia requires more advanced and invasive procedures, which stakeholders say are not widely available in the NHS. They say diagnostic capacity in the NHS will need to increase significantly to support the use of new treatments.[58]

Diagnostic testing for Alzheimer's disease can require procedures such as lumbar punctures or PET (positron emission tomography) scans.[59] Alzheimer's Research UK estimates that 2% of people can currently access these tests. [60] The charity says there would need to be an increase in lumbar punctures from 2,000 to 20,000 per year to support new treatments. [61] It also says the government needs to invest in new diagnosis methods, such as blood tests that pick up biomarkers for dementia.[62]

In 2023, the Conservative government stated that NHS England has established a national programme team that is working with stakeholders to prepare for the potential roll out of new treatments for Alzheimer's disease. The plans assumed the need for "significant diagnostic capacity, including amyloid PET-CT, lumbar puncture and MRI" to identify patients who could benefit from the treatments and provide safety monitoring.[63] It also said

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56 Alzheimer's Society, Ethnic minority communities Increasing access to a dementia diagnosis, September 2021, p7-8, PDF

57 Black, Asian and minority ethnic communities and dementia research | Alzheimer's Society, June 2022

58 Alzheimer's Society, Alzheimer's Society briefing – Westminster Hall Debate on New Treatments for Dementia (PDF), January 2024; Alzheimer's Research UK, Tipping Point: The Future of Dementia, September 2023

59 National Institute of Health and Care Excellence, Dementia: assessment, management and support for people living with dementia and their carers, section 1.2, 20 June 2018

60 Alzheimer's Research UK, Tipping Point: The Future of Dementia, September 2023, p27

61 As above, p28

62 As above, p28

63 PQ HL320 [on Dementia: Diagnosis], 14 November 2023

research into other modes of diagnosis, including blood-based biomarker and digital tests, is ongoing.[64]

In its 2024 election manifesto, the Labour Party committed to introduce a new "'Fit For the Future' fund to double the number of CT and MRI scanners".[65]

A £5 million project led by Alzheimer's Research UK, the Alzheimer's Society and the National Institute of Health and Care Research hopes to make blood tests for Alzheimer's disease available on the NHS in the next five years.[66]

Early diagnosis

In its appraisal of lecanemab, NICE noted that 'mild cognitive impairment' (MCI) caused by Alzheimer's disease (which refers to the set of symptoms that occur before the dementia stage of the condition) is not included in its diagnostic guideline. It added that most people do not have a confirmed diagnosis of MCI and that there are "no standardised measures to clearly separate the disease stages". Consequently, people may be "discharged from memory clinics back to primary care, with the advice to be rereferred once their symptoms progress".[67] Without an early diagnosis, and scans to confirm amyloid pathology, a person would not be eligible for drugs like lecanemab and donanemab.

3.2 Delivering new treatments

Lecanemab and donanemab are delivered by intravenous drip. This means a liquid medicine is delivered via a cannula into the blood. [68] In delivering new treatments, services would need to consider where, and by which team, treatment is administered and how patients would be monitored for side effects.

A joint project by the Royal College of Psychiatrists and Alzheimer's Research UK, 'Are we ready to deliver disease modifying treatments?', found that around one third of psychiatrists thought their services could deliver new, disease modifying treatments within a year of their approval. Alongside diagnostic capacity, psychiatrists were concerned about having sufficient staffing, skills and resources to deliver and monitor new treatments.[69]

64 PQ HL320 [on Dementia: Diagnosis], 14 November 2023

65 Change. Labour Party Manifesto 2024, June 2024, p97-98, PDF

66 Alzheimer's Research UK, A five-year project to bring Alzheimer's blood tests to the NHS (Accessed 27 December 2023)

67 NICE, Draft guidance consultation: Lecanemab for treating mild cognitive impairment or mild dementia caused by Alzheimer's disease, August 2024, p7, PDF

68 Alzheimer's Society, Three promising drugs for treating Alzheimer's disease bring fresh hope (Accessed 3 January 2024)

69 Royal College of Psychiatrists and Alzheimer's Research UK, Are we ready to deliver disease modifying treatments?, May 2021

Alzheimer's Research UK has called for the rollout of a UK-wide network of 'brain health clinics'. The clinics would work alongside existing dementia services to deliver early intervention to help lower people's risk of dementia, early diagnosis and new treatments, and opportunities to participate in clinical trials. The charity has also called for a 'cross-speciality Alzheimer's Disease Clinical Pathway Council' to develop a new pathway for diagnosing and treating dementia.[70]

The Conservative government said NHS England is aware of the brain health clinic model and it could be considered by NHS England and Integrated Care Boards if disease modifying treatments for Alzheimer's disease are recommended for use in the NHS.[71]

NHS England has said it recognises additional staffing capacity and further training will be needed to deliver new treatments. It said Integrated Care Boards will be the primary commissioners for most of the new referral and treatment pathway, supported by NHS England.[72]

In June 2023, NHS England published the NHS Long Term Workforce Plan. The plan uses modelling to assess demand on the NHS workforce and how it can be met. From 2025/26 onwards, the modelling takes into account the increased complexity of some treatments, such as for dementia, when determining workforce projections.[73]

3.3 Approval and funding

As noted in section 2.3, new treatments need to be approved by NICE (the National Institute for Health and Care Excellence) based on clinical and cost-effectiveness before they can be used in the NHS. Alzheimer's Research UK says it is concerned the treatments might not be determined to be affordable for the NHS compared to the current spend on dementia. It wants NICE to consider the wider context of the cost of informal care for dementia when they review the economic evidence for its approval:

> As the bulk of the cost of dementia falls on social and informal care (£22.7bn per year) rather than the NHS (£1.7bn per year), any new dementia treatment is unlikely to pass the NHS value threshold and will not be approved. A dementia treatment would have far-ranging benefits for society and the economy, beyond the clear benefits for the patient, and it is essential NICE and equivalent bodies in other parts of the UK consider these throughout their assessments.[74]

70 Alzheimer's Research UK, Tipping Point: The Future of Dementia, September 2023, p29
71 PQ 202685 [on Dementia: Clinics], 23 October 2023
72 NHS England blog, Preparing for a new chapter: disease modifying treatments for early Alzheimer's disease, 27 December 2023
73 NHS England, NHS Long Term Workforce Plan, Annex B: Modelling approach and assessment, June 2023, p119
74 Alzheimer's Research UK, Tipping Point: The Future of Dementia, September 2023, p33

The charity is also concerned that it will take time to build up evidence of the long-term clinical benefits of the treatments.[75] During the Commons debate on New Dementia Treatments in January 2024, the Minister for Social Care stated that NICE does consider the "publicly funded cost of social care" in its appraisal process.[76]

New treatments can also require the NHS to invest in diagnostic and treatment capacity. For example, Alzheimer's Research UK estimates that increasing the number of lumbar punctures to 20,000 per year would require a £16 million investment in infrastructure, equipment and staffing.[77]

The charity also wants the NHS and drug companies to consider conditional access arrangements, whereby there is managed access to a treatment whilst further data is collected.[78] This evidence is then used to assess whether the treatment should be made routinely available on the NHS. These arrangements aim to give patients quicker access to promising new treatments whilst addressing any concerns about clinical or cost effectiveness. There are two dedicated NHS England funding sources for treatments in managed access, each with an annual budget of £340 million: the Cancer Drugs Fund and the Innovative Medicines Fund.[79]

75 Alzheimer's Research UK, Tipping Point: The Future of Dementia, September 2023, p33

76 HC Deb, 11 January 2024, c196WH

77 As above, p29

78 As above, p29

79 NICE, Managed access (Accessed 3 January 2024)

4 Dementia policy and funding commitments

A 10-year plan to tackle dementia, and increase research funding for neurogenerative diseases, was announced by the Conservative government in May 2022. [80] The dementia plan was expected to be published by the government at the end of 2022.[81] Instead, the government announced a 'major conditions strategy' (MCS) in January 2023, incorporating six conditions, including dementia.

This section covers the progress made on developing the MCS, research funding commitments, as well as the new Labour government's plans for dementia care and treatment.

4.1 Forthcoming 10-year health plan

In July 2024, Wes Streeting, Secretary of State for Health and Social Care, commissioned Lord Darzi to carry out an independent investigation into the NHS in England.[82] The final report of the investigation ('the Darzi report') was published on 12th September 2024.[83]

The Darzi report noted that the prevalence of dementia in the UK is 19% below the OECD20 but that the UK has a higher rate of dementia deaths (though this may reflect a difference in recording).[84] In addition, it said that dementia diagnosis rates have not improved in recent years and the proportion of patients who received a care plan or care plan review within the last year dropped to below 40% during the Covid-19 pandemic.[85]

Lord Darzi also noted the Alzheimer's Society's submission to the investigation which highlighted "high levels of unwarranted variation in access to diagnosis and treatment [and] insufficient adherence to clinical guidelines". Lord Darzi

80 Health Secretary announces 10-year plan for dementia - GOV.UK, May 2022
81 Health Secretary announces 10-year plan for dementia - GOV.UK, May 2022
82 Department of Health and Social Care press release, Independent investigation ordered into state of NHS, 11 July 2024
83 Lord Darzi, Independent investigation of the NHS in England, 12 September 2024
84 See DHSC, Independent Investigation of the National Health Service in England: Technical Annex, Figure III.9.1: Estimated prevalence of dementia per 1000 population, 2021, p161
85 As above, p48

said, "as society continues to age, there is an important challenge to improve both the quality and quantity of care for people with dementia."[86]

Lord Darzi's conclusions will inform a new, 10-year health plan for England. The government has said work on the 10-year plan "will consider how best to meet the needs of people with dementia."[87]

The 2024 Labour Party manifesto said a Labour government would put Britain "at the forefront of transforming treatment for dementia" by making clinical trials more efficient, speeding up recruitment and improving access to trials through the NHS app.[88]

4.2 Planned Major Conditions Strategy

In January 2023, the Conservative government announced it would publish a Major Conditions Strategy (MCS) covering six conditions, including dementia.[89] The strategy was due to be published instead of a separate strategy for dementia, which had been expected in 2022.[90] The government has said all previous research for the dementia strategy would be used to inform the MCS and that it remained committed to accelerating diagnosis and developing the latest treatments.[91]

In August 2023, the Department of Health and Social Care published the Major conditions strategy: case for change and our strategic framework. The framework committed to recovering the 'national ambition' for dementia. The ambition, first announced in 2013, is for at least two-thirds of people with dementia to have a formal diagnosis. [92]

The framework says the national ambition was not achieved for the first time in four years in March 2020 and there is significant variation in rates of diagnosis across England. The commitment to recovering the diagnosis rate is also included in the NHS 2024/25 priorities and operational planning guidance. The framework notes that the Office for Health Improvement and Disparities will support the investigation of the variation in rates across the country.

86 See DHSC, Independent Investigation of the National Health Service in England: Technical Annex, Figure III.9.1: Estimated prevalence of dementia per 1000 population, 2021, p49

87 PQ 5535 [on Dementia: Health services], 12 September 2024

88 Labour Party Manifesto 2024, 'Build an NHS fit for the future'

89 HCWS514 [on Government Action on Major Conditions and Diseases], 24 January 2023

90 Department of Health and Social Care, press release, Health Secretary announces 10-year plan for dementia, 17 May 2022

91 Department of Health and Social Care blog post, Major Conditions Strategy: What you need to know, 17 May 2023

92 Department of Health and Social Care press release, Dementia diagnosis to be overhauled, 15 May 2013

The Major Conditions Strategy strategic framework also said that NHS England will map medicines for Alzheimer's disease and explore the establishment of a steering group to ensure the system is ready for new treatments. [93] A national programme team for early Alzheimer's treatments was established in summer 2023. [94]

Pausing the Major Conditions Strategy

The Major Conditions Strategy had not been published when the general election was called in May 2024. The new Labour government has said that work on the MCS "has been paused" while it considers how to incorporate the findings from the MCS into its "plans to rebuild the National Health Service"; specifically its 10-year plan to reform the NHS. [95] The government has also said that, as part of this work, it "will consider how best to meet the needs of people with dementia, including whether it is appropriate to develop a dementia strategy". [96]

4.3 Funding for dementia research

Life Sciences Vision 2021

In July 2021, the government and the life sciences sector published Life Sciences Vision, setting out a ten-year strategy to stimulate the sector and address significant healthcare challenges. This included a 'mission' to improve translational capabilities in neurodegeneration and dementia. This means working to translate new research findings into novel treatments for dementia. Alongside the Life Sciences Vision, the government announced a £200 million Life Sciences Investment programme. [97]

Dame Barbara Windsor Dementia Mission 2022

In August 2022, then Prime Minister Boris Johnson launched a national mission to tackle dementia, named in memory of Dame Barbara Windsor who died with dementia. This included £95 million of ringfenced funding and a new taskforce for speeding up dementia research. [98] As part of the Mission,

93 Department of Health and Social Care, Major conditions strategy: case for change and our strategic framework, 21 August 2023

94 NHS England blog, Preparing for a new chapter: disease modifying treatments for early Alzheimer's disease, 27 December 2023

95 PQ 1952 [on Health Services], 1 August 2024

96 PQ 4033 [on Dementia], 9 September 2024

97 Gov.uk press release, Bold new life sciences vision sets path for UK to build on pandemic response and deliver life-changing innovations to patients, 6 July 2021

98 Gov.uk press release, Prime Minister launches 'Dame Barbara Windsor Dementia Mission', 14 August 2022

Innovate UK awarded four UK companies a share of £4.8 million funding for research into dementia diagnosis in July 2024.[99]

Autumn Statement 2023

The Chancellor announced in the 2023 Autumn Statement that up to £20 million of £121 million in funding for improving clinical research in the UK (first announced in May 2023) would be used to launch the first Clinical Trial Delivery Accelerator focused on Dementia.[100] The Accelerator was launched in October 2024.[101]

In addition, the MCS strategic framework recommitted to doubling funding for dementia research by 2024/25, as initially pledged in the 2019 Conservative Manifesto.[102] In December 2023, the government said it remained committed to increasing funding for dementia research to £160 million per year by 2024/25 and had spent over £413 million on dementia research from 2017/18 to 2021/22.[103]

99 Dame Barbara Windsor Dementia Mission - GOV.UK, updated 16 October 2024
100 HM Treasury, Autumn Statement 2023, 22 November 2023, para 4.83
101 New £20m Dementia Trials Accelerator | UK DRI: UK Dementia Research Institute, 24 October 2024
102 Conservative Party, Conservative Party Manifesto 2019, November 2019
103 PQ 4416 [on Dementia: Research], 21 December 2023

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