

Treatments of tomorrow

Preparing for breakthroughs
in dementia



**Alzheimer's
Research
UK**

The Power to Defeat Dementia

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Foreword

Dementia is one of the biggest challenges of our time affecting about 850,000 people in the UK. Without an intervention, this is expected to increase to over two million by 2050.

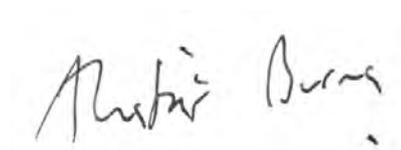
Dementia is a condition for which there is currently no effective curative treatment. Drugs are available for Alzheimer's disease, the most common cause of dementia, are effective and target the symptoms, without any substantial impact on the underlying course of the disease.

Although we are still some time away from effective disease-modifying treatments being available to people living with dementia – the tide is turning and dementia research is in the most promising position for years. For example, there are now double the number of clinical trials for dementia than there were just three years ago.

Considering the lack of efficacy of existing treatments for Alzheimer's disease, the first disease-modifying treatments could fundamentally change the way everyone thinks about dementia and its causes. To put this in context, how did it feel when the first treatments for cancer were introduced?

Our task now is to ensure that when the extensive efforts of dementia researchers result in effective new treatments, they can be accessed by people living with dementia as quickly as possible. There is a pressing need for everyone involved in the assessment, diagnosis and treatment of people with Alzheimer's disease is to plan ahead.

We must take a mature evidence based approach to prospective disease-modifying treatments for Alzheimer's disease but everyone involved in dementia care should work together to prepare for change.



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He graduated in medicine from Glasgow University in 1980 and trained in psychiatry at the Maudsley Hospital and Institute of Psychiatry in London. He became the Foundation Chair of Old Age Psychiatry in The University of Manchester in 1992, where he has been Head of the Division of Psychiatry and a Vice Dean in the Faculty of Medical and Human Sciences, with responsibility for liaison within the NHS. He set up the Memory Clinic in MMHSCT and helped establish the old age liaison psychiatry service in UHSMT. He is a Past President of the International Psychogeriatric Association.

He is Editor of the International Journal of Geriatric Psychiatry and is on the Editorial Boards of the British Journal of Psychiatry and International Psychogeriatrics. His research and clinical interests are in mental health problems of older people, particularly dementia and Alzheimer's disease. He has published over 300 papers and 25 books.

Executive Summary

Dementia is the only leading cause of death, for which there is nothing to prevent, cure or modify the most common causes.¹ There are currently 850,000 people living with dementia in the UK and this is expected to increase to over two million by 2050 unless we find ways to prevent or treat the diseases that cause dementia.²

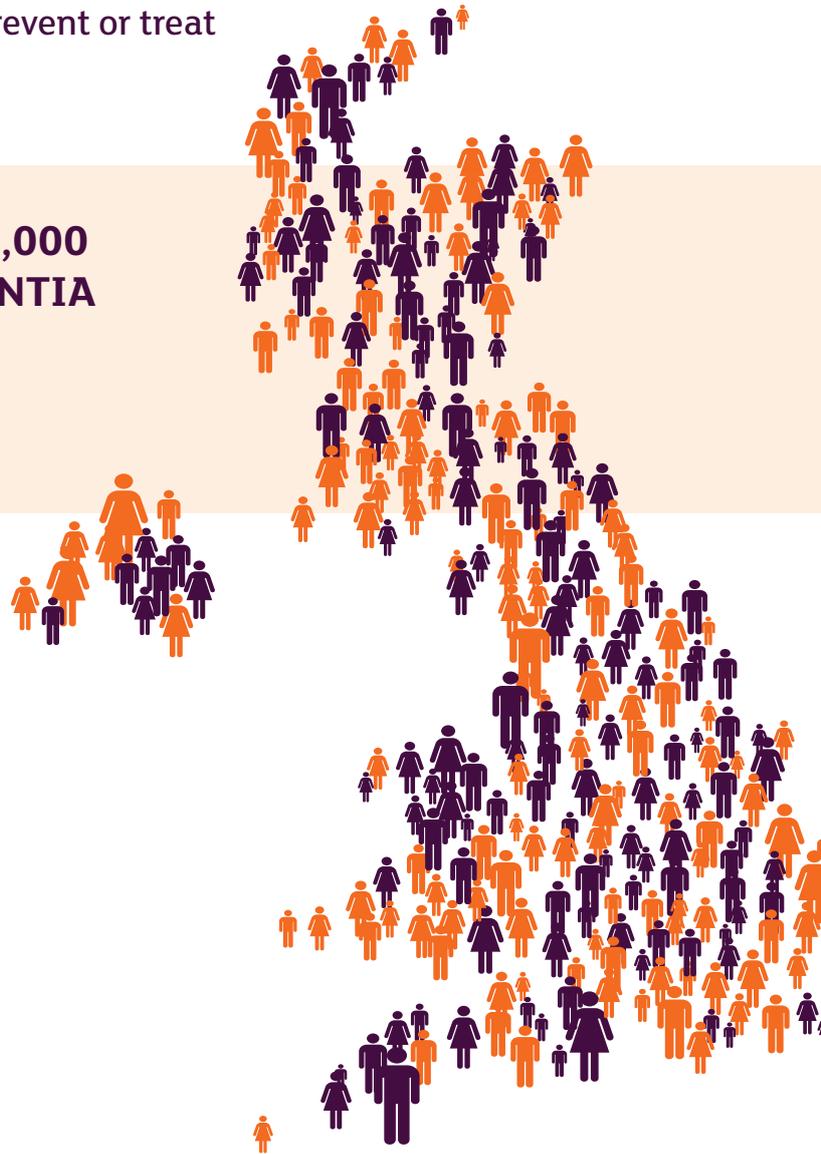
THERE ARE CURRENTLY 850,000 PEOPLE LIVING WITH DEMENTIA IN THE UK

this is expected to increase to over two million by 2050

As well as the devastating human cost, dementia currently costs the UK economy over £24 billion a year. This is more than the cost of cancer and heart disease combined.³ This figure is set to rise to £32.5 billion by 2050 without disease-modifying treatments that can slow the progression or delay the onset of the diseases that cause dementia⁴.

While clinical trials over the last decade have failed to meet their primary endpoints, with political attention and a significant increase in investment in translational research and drug development, dementia therapeutics research is in its most promising position for years. There are now approximately 50 drugs targeting Alzheimer's, the most common form of dementia, in phase II trials and 12 drugs in phase II/III⁵. While the number of later phase trials is still limited when compared to over 1,400 phase II/III trials in cancer⁶, given the escalating economic and human cost of dementia, we must seize the opportunity that this pipeline presents.

Our priority is to make sure that when the extensive efforts of dementia researchers result in a new treatment proven to have disease-modifying properties, there is an environment where innovative treatments can be assessed, valued, adopted and accessed as quickly as possible.



This report identifies the broad challenges disease-modifying treatments are likely to face and suggests a number of actions that could be taken now to better prepare for them. It is the beginning of a programme of work that will see Alzheimer's Research UK continue to work with a wide range of stakeholders to understand the challenges and work to overcome them. For example, as a next step to this report, we have commissioned a significant piece of research to understand the potential impact a disease-modifying treatment for Alzheimer's disease could have on the NHS.

Ensuring potential treatments reach patients

We believe there are a number of challenges – not least the affordability of new treatments and an unprepared NHS – that will be faced in ensuring that disease-modifying treatments proven to be effective reach patients who might be eligible to receive them. We need to address the challenges now to better prepare for the future.

The challenges future disease-modifying treatments could face:

- **Development challenges** – While there are potential new drugs for Alzheimer’s disease in the pipeline and progress is being made, there is still much to learn about the biology of the diseases that cause dementia. Given the slow progression of Alzheimer’s disease, there are challenges to measuring gradual change over the relatively short duration of a clinical trial, especially in the early stages of the disease. This means that either clinical trials need to be long enough to enable endpoints to be measured and efficacy to be demonstrated for regulators, or new biomarkers will need to be validated. Supporting early access to safe and innovative treatments, while collecting ongoing evidence of effectiveness in a real world context, will be important.
- **System challenges** – The health system is not prepared for disease-modifying treatments for Alzheimer’s disease and the first treatments could present challenges for both the National Institute for Health and Care Excellence (NICE) and NHS commissioners. There will be limited data on the impact on health outcomes and cost (as it will be difficult to evidence clinical improvement over a short period of time in the early stages of the disease), and a significant amount of the current costs will be in social care and informal care. Early engagement to prepare for the assessment of disease-modifying treatments is essential, to ensure that the benefit and value to patients can be fully understood. Opportunities for managed access schemes and innovative funding models, based on continued collection of real world evidence over time, should be considered.
- **Affordability challenges** – The cost of a disease-modifying treatment is likely to be high. This is in part due to the higher clinical trial failure rate for dementia than for other disease, as well as the potentially large numbers of people who might be eligible for treatment. A disease-modifying treatment will also potentially transform dementia treatment pathways, requiring additional infrastructure, equipment, staff training and skills. A balance will need to be struck between setting a price that rewards and incentivises innovative research, but is also affordable to the NHS.
- **Cultural challenges** – Addressing the challenges of an ageing population is a priority for the Government and the NHS, and there will be a political desire to find ways to fund new and effective treatments. However, the NHS does not have a culture of adopting innovation quickly and this will be made increasingly difficult during a time of unprecedented financial pressures. In addition, while recognising considerable efforts to date, there still needs to be further education and understanding of dementia across the public and the NHS, and greater communication and collaboration across clinical disciplines.

The Government focus on improving the access pathway to new treatments in England through the forthcoming Accelerated Access Review provides an opportunity to influence the way new treatments might be valued and accessed in England. As this review is focused on England, we have outlined in this report the challenges and opportunities within the NHS in England, but many of the wider considerations will also have implications across the UK.

We have focused on Alzheimer’s disease for this report, as our understanding of the pathobiology, and current therapeutic strategies and trials are more advanced for this disease than for the other diseases that cause dementia. A disease-modifying treatment for Alzheimer’s disease will not be available for at least two to three years, but the challenge is to think ahead, to plan now so that people with the disease get access to effective new treatments as quickly and efficiently as possible. It is important to make sure any system changes, particularly as a result of the Accelerated Access Review, will work for the dementia treatments of tomorrow, and there will be no delay for the people who so desperately need them.

Achieving this goal will involve preparation, cooperation and compromise across a number of key stakeholders including the Government, the Department of Health, NICE, NHS providers and commissioners, and the pharmaceutical industry. This report explores these areas and highlights actions that should be taken in order to ensure the best possible outcomes for people with, or at risk of developing dementia.

The current context

There is no cure or disease-modifying treatment for dementia

There are 850,000 people living with dementia in the UK, a number expected to exceed one million by 2025. There are treatments currently available that may help to alleviate some of the symptoms associated with dementia for some people, there is also some post-diagnostic care and support available and a range of non-pharmacological interventions.⁷ However there are no treatments that can change the course of the most common diseases that cause dementia, we cannot yet slow the progression or delay the onset. There have been no new drug treatments approved for dementia in over ten years.

There is a promising pipeline

While 99.6 per cent of clinical trials in Alzheimer's disease over the last decade have failed,⁸ with political attention and a significant increase in investment in translational research and drug development, dementia research is in the most promising position for years.

There are now double the number of clinical trials for dementia than three years ago⁹, with over 150 interventional phase I-III clinical trials.¹⁰ Although this is still few compared to clinical trials for cancer, where there are over 17,000, we are entering a hopeful new era for dementia treatment.

There is political will to defeat Dementia

There has been a welcome focus on dementia both within the UK and globally. **The UK Government has committed to finding a disease-modifying treatment for dementia by 2025 and the Prime Minister's Challenge has made dementia research a priority in the UK.** This has led the way for the UK to take a global leadership role in dementia research and policy.

We need to harness this momentum and make sure these aspirations are achieved as quickly as possible, translating ambition into a reality for people living with dementia. This will involve commitment from a wide range of organisations and people across the innovation pathway, from research and development through to adoption and uptake within the NHS.

There is political will to accelerate access to transformative treatments

In November 2014, the UK Government launched an independent review into how access to all new innovations, including drugs, diagnostics and medical technologies, could be accelerated. The final report of the Accelerated Access Review, chaired by Sir Hugh Taylor, Chairman of Guy's and St Thomas' NHS Foundation Trust, will present an opportunity to address some of the challenges new diagnostics and treatments are likely to face. **The recommendations of this review will set the scene for access to new treatments for at least the next decade, and we must make sure this works for dementia.**

Adam's story: the impact a disease-modifying treatment could have

“If any treatments were able to prevent or delay the onset of Alzheimer’s I believe it would be the single greatest thing to improve the outlook of my life. I would give anything to see significant advances in treatment and prevention of Alzheimer’s to extend life.”

Alzheimer’s Research UK supporter Adam Graham’s dad Frank died with early-onset Alzheimer’s in 2012, aged just 66.

“One of my greatest fears is having Alzheimer’s. It may be unusual for someone of my age, 32, to be thinking like that but my dad was only in his 50s when symptoms of this cruel disease started creeping on.

Dad was one of the nicest people you could meet. He always worked hard as a civil servant, he saved for his retirement and looked forward to spending time with Mum. But Alzheimer’s robbed him of all that – it was tragic. Looking back, the symptoms had been creeping on for several years but the diagnosis came only two years before he passed away. He was eventually signed off sick from work, but the truth is that he was finding it increasingly hard to cope with the onset of Alzheimer’s.

The development of, and access to, a disease-modifying treatment would be life-changing for people like me who have a history of Alzheimer’s in the family. Alzheimer’s cruelly took away my Dad’s life far too young and it makes me live in fear of the same happening to me and the effect that would have on loved ones around me. Sometimes it can feel inevitable that the disease will strike at some point and it affects the way I live and plan things because I know everything can be cruelly snatched away at no notice.”

Overview of the innovation pathway for new drug treatments

It takes approximately £1.15 billion and 12.5 years to develop a new medicine*



Figure 1 – Summary of the current pathway for new drug treatments, from research through to access. This is a significantly simplified description of the pathway to demonstrate the overall process, it does not reflect the complexity of decision-making or all routes to access. For the purposes of this report we have described the pathway which includes a NICE health technology appraisal but not all treatments will go through this process, some are instead made available for local purchase after launch.

* These figures are adapted from the average timescales estimated by The Association of the British Pharmaceutical Industry (ABPI), these are approximate costs and timescales and these will vary across disease areas

The potential impact of a disease-modifying treatment

The impact of a disease-modifying treatment could be huge, both in terms of the numbers of people who could be treated and the impact on the quality of life for people living with dementia. It could also have a significant impact on the quality of life for family members and those who care for people living with dementia.

When assessing new medicines, a key aspect of the decision making is focused on the health economics of the treatment. Therefore, to understand scale of the impact, Alzheimer's Research UK worked with the Office of Health Economics to develop an economic model that examines the impact of hypothetical disease-modifying treatments that would be effective across all the diseases that cause dementia.¹¹ The model looked at two scenarios, the impact of slowing the progression of dementia, and the impact of delaying the onset of the diseases that cause dementia.¹²

Slowing progression - If from 2020 a new treatment could slow the progression of dementia by 25 per cent or by 50 per cent, each person treated would on average spend 25 or 50 per cent longer with mild dementia before progressing to moderate, and 25 or 50 per cent longer with moderate dementia before progressing to severe dementia. While people would be living for longer with dementia, they would be in the early stages for a longer period of time. Figure 2 shows that by 2050, while there would be more people living with dementia, the proportions of people in the severe stage would significantly reduce as people spend longer in the mild stages.

In terms of the impact on costs, if we had a treatment that could slow the progression of dementia by 25 per cent from 2020, the cost of dementia would steadily reduce each year, resulting in a potential saving of £1.8 billion in 2050 (from £59.4 billion without a treatment compared with £57.6 billion with one). If progression could be slowed by 50 per cent, the total costs would be reduced to £55.2 billion in 2050, £4.2 billion less.

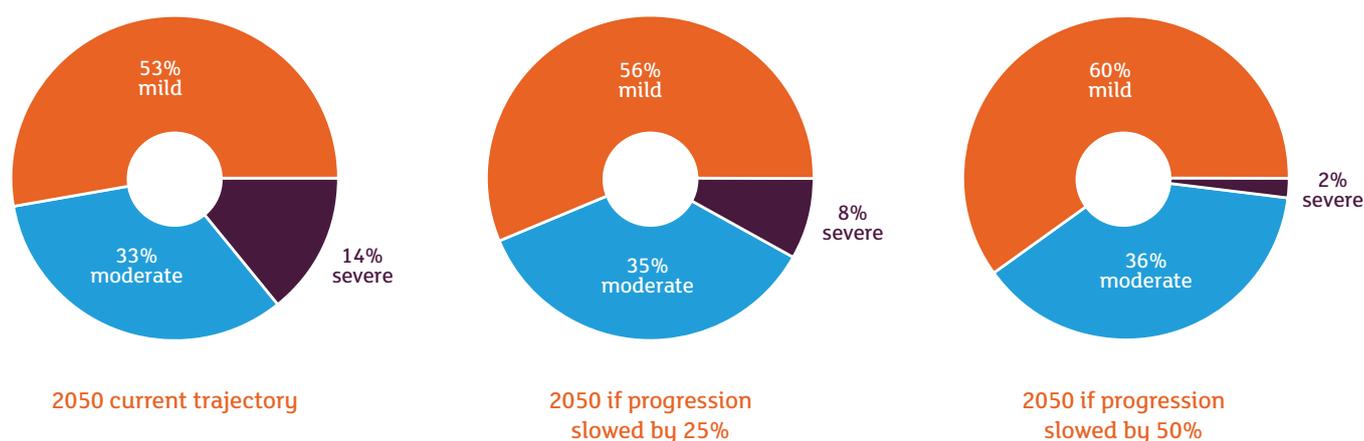


Figure 2: Severity of the dementia population in 2050, with slowed progression.

The potential impact of a disease-modifying treatment

Delaying the onset - If by 2020 a treatment was developed that could delay the onset of dementia by five years, compared to current projections without an intervention, there would be:¹³

- 36 per cent fewer people with dementia by 2030 (850,000 people with dementia instead of 1.3 million if there is no treatment) and almost 400,000 fewer informal carers needed. The reduction in numbers of people with the condition would mean dementia would cost £14.1 billion less in 2030 than without a treatment. This equates to a saving of at least £10,500 per patient.
- 33 per cent fewer people with dementia by 2050 (1.45 million with dementia instead of two million if there is no treatment) and 566,000 fewer informal carers needed. The reduction in numbers of people with the condition would mean dementia would cost £21.2 billion less in 2050 than without a treatment. Thus an intervention that delays the onset of dementia by five years could reduce costs by 36 per cent in 2050.

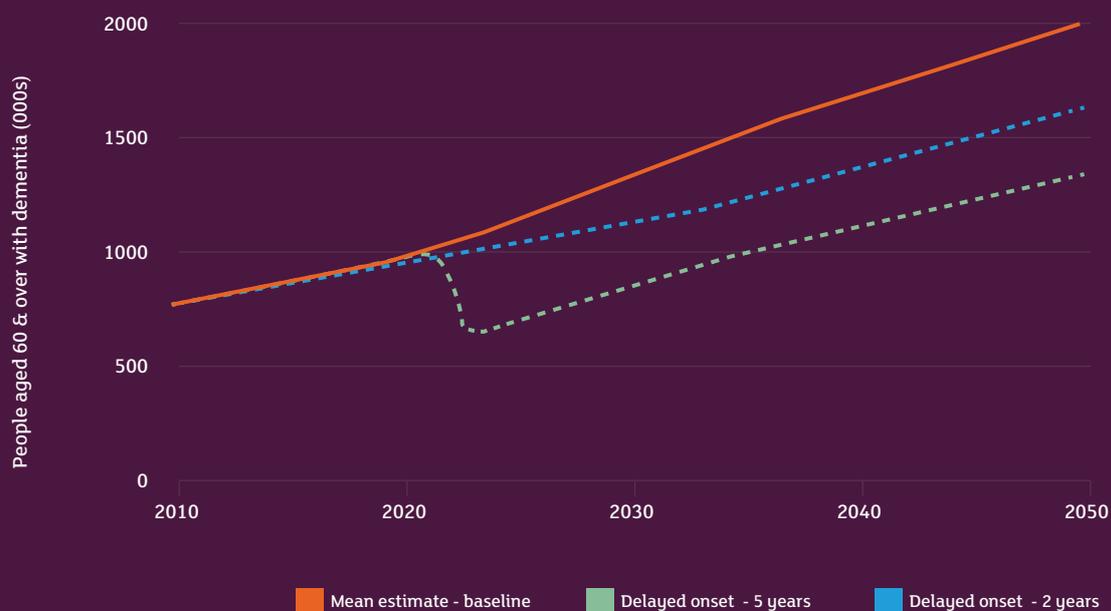


Figure 3: Projections of numbers of people with dementia after an intervention that delays onset (thousands)

These numbers show that there are potential savings over the long term, but that this is likely to require up-front investment.

Building the foundations: right care, right person, right time

To support the introduction of new treatments into the NHS, the foundations need to be set for getting the right people the right care at the right time. This includes increasing understanding and awareness of the diseases that cause dementia and reducing variation in diagnosis rates. Progress has been made across a number of important areas, but more still needs to be done.



GOOD PROGRESS HAS BEEN MADE

There is an increasing focus on patient outcomes that matter

People living with dementia and their carers have a unique perspective through their experience of the condition, including its onset, progression and the daily impacts on their lives. These outcomes, whether they be physical, emotional or social, should act as a continual 'checklist' for innovators, appraisers, commissioners and providers across the research and care continuum.

There are an increasing number of examples of patient outcome measures driving research and health and care decision-making, including tools designed (or in development) to help researchers, commissioners, healthcare providers and policy-makers to understand which outcomes matter most to people living with dementia. For example:

- With the aim of shaping the design and methods of future NIHR disease-modifying trials in mild and moderate dementia, a team of 36 prominent experts in dementia are agreeing a core set of clinical and patient relevant health outcome measures.¹⁴
- In the NHS there is the NHS Outcomes Framework and the CCG Improvement and Assessment Framework, which both include indicators for dementia.
- The International Consortium on Health Outcomes Measures (ICHOM) has developed, in consultation with experts across the world and people living with dementia and their carers, a standard set of outcomes measures that providers and commissioners can use.¹⁵
- The London School of Hygiene and Tropical Medicine, funded by the Department of Health, has conducted research using Patient Reported Outcome Measures (PROM), to understand the effectiveness and impact on quality of life of two different methods of treatment and care for people with dementia.¹⁶

Awareness and understanding of dementia has increased

Charities and the Government are both committed to increasing awareness and understanding of dementia. For example, Alzheimer's Research UK's 'Share the Orange' campaign is urging people to think differently about dementia.¹⁷ It is helping people understand that dementia is caused by brain diseases to help fight the enduring misconception that the condition is just a by-product of age.

The Government has an ambition for all NHS staff to have 'received training on dementia appropriate to their role' by 2020.¹⁸ There has been progress made through the efforts of Health Education England, the national body responsible for providing Tier 1, 2 and 3 dementia training.¹⁹

Diagnosis rates have increased

Progress has been made to increase the dementia diagnosis rate in England, with NHS England achieving the Government's target to have two-thirds of people living with dementia receiving a formal diagnosis. The percentage of people being diagnosed in the early stages of dementia has also increased, albeit modestly, from 49 per cent in 2013 to 52 per cent in 2014.²⁰

Getting a timely diagnosis is essential if people are to access the information, care and support available to them, such as the support services offered by charities including Age UK, Alzheimer's Society and Dementia UK, and opportunities to get involved in research through Join Dementia Research.²¹ It will also enable people to access current symptomatic treatments and help ensure that, when new treatments become available, people living with dementia will be able to benefit from them.

BUT MORE STILL NEEDS TO BE DONE

Patient outcomes that matter most should always be at the forefront of decision-making

Achieving outcomes that matter most to people living with dementia should consistently drive decision-making across the innovation pathway, from research through to access. Researchers, policy-makers, commissioners and providers should use existing tools to help them understand outcomes that matter most and also have clear mechanisms for engaging people living with dementia and their carers, through co-production mechanisms and other engagement activities, to ensure they are responding to their needs.

People living with dementia should also be enabled to hold organisations to account for delivering on outcomes that matter most, including outcomes recognised at a national level such as those included in the NHS Outcomes Framework. Currently, information on outcomes is frequently spread across different organisations and can be difficult to navigate.²² For example, whom should they contact if outcomes are not being achieved, and through which mechanisms can they do this?

Further increases in the understanding of dementia and the diseases that cause it is needed

There is still a lack of public understanding that diseases cause dementia, with many considering dementia to be an inevitable part of ageing. A YouGov survey commissioned by Alzheimer's Research UK in 2015 revealed that, when asked what they think dementia is and who it affects, less than a quarter (23 per cent) of British adults specifically mentioned brain disease or degeneration.²³ It is essential people are aware that dementia is not a natural part of ageing and seek to get a diagnosis and access the care and support available to them. Activities such as Alzheimer's Research UK's 'Share the Orange' campaign can help achieve this.

Meeting the Government's ambition of all NHS staff having training on dementia appropriate to their role by 2020 must also remain a priority. The Royal College of Nursing has previously highlighted that one of the barriers to providing good care can be a lack of staff understanding about dementia and how it affects the person.²⁴ In addition, according to the most recent audit of memory services, the majority of people presenting in some clinics continue to be at the moderate to severe stages of dementia and timely diagnosis could be improved by education of those who make referrals, as well as the public.²⁵

Variation in diagnosis rates and post-diagnostic support needs to be reduced

There is still local variation in diagnosis rates, the length of time it takes to have a diagnosis confirmed²⁶, and access to post-diagnostic care and support. There is considerable emphasis from the Department of Health and NHS England on improving diagnosis rates for people living with dementia²⁷ and the Government's mandate to NHS England reflects the ambition to 'increase the numbers of people receiving a dementia diagnosis within six weeks of a GP referral' by 2020.²⁸ The Government, NHS England and local commissioners, must continue to measure progress against these through Public Health England's Fingertips platform²⁹ and where progress is not being made, ensure reasons are understood and there are plans in place to drive improvement.

Reducing the current variation in access to post-diagnostic support must remain a priority, both for people living with dementia and their carers. The Joint Declaration on Post-Diagnosis support³⁰, a shared declaration across government, health, social care and the third sector to improve access to support, is a very welcome development but must now continue to drive improvement and realise its ambition. Access to post-diagnosis support plays a critical role in helping people to access the medical and non-medical support they need.

The foundations for early detection of the diseases that cause dementia need to be set

As concluded by the National Screening Committee in 2015,³¹ it is not appropriate to introduce screening for dementia at this point, given the paucity of robust biological markers to identify those with or at risk of dementia, along with the lack of an effective early treatment that could improve outcomes. However, it is important that the health system is prepared for early detection when improvements in diagnostic technology make this a possibility. This is because the pathology of most of the diseases that cause dementia appear to develop years before symptoms occur and early treatments are likely to work best if they are given at the earliest possible stage. It is important to consider this now, because it is likely that capacity for infrastructure (e.g. brain imaging or cerebrospinal fluid testing) could be necessary, which will require additional resources, cultural changes and closer working between clinical disciplines.

Early detection of the hallmarks of Alzheimer's disease is already required for several of the current large clinical trials of new treatments, learning from NHS sites where this is done well would help consider what changes could be needed. Although it would not be sensible to commit already scarce resources to an infrastructure that is not currently required, it is important to set the foundations with closer working and shared learning across clinical disciplines, including those working in social care. More joined-up working will also have a positive impact on the care of people with dementia.

Galvanising momentum: the challenges we must address

Addressing the clinical trial failure rate

Historically there have been many failures in dementia clinical trials, largely due to a combination of factors, including regulatory challenges stemming from a complex and incomplete scientific understanding of the diseases that cause dementia.



CHALLENGES

There is still much to learn about the biology of the diseases that cause dementia

A key challenge hindering drug development efforts are the gaps in our basic scientific understanding of dementia. Despite considerable efforts, the causes and pathological mechanisms of these diseases are yet to be fully elucidated and the progress made to date has yet to pull through to clinical development efforts. To gain a better understanding of these mechanisms and identify new targets for treatment, we need further investment in basic research into the diseases underpinning dementia.

Alzheimer's Research UK has funded £33.2 million of research into the underpinning biology of the diseases that cause dementia



The current clinical endpoints for dementia clinical trials are insufficient

Current clinical endpoints of cognition and function required for dementia trials were originally developed for treatments focused on much later and more severe stages of the disease, when the impacts of cognition and function are more explicit.³² As pathological changes occur in the brain before the onset of symptoms, these measures are less sensitive to earlier stages of the disease. This makes it challenging to demonstrate efficacy and evidence of clinical benefit for disease-modifying treatments that may be most effective in the earlier stages. Consequently, clinical trials for these treatments will either need to be longer than average, in order to detect measurable clinical changes and efficacy to be demonstrated for regulators, or new biomarkers responsive to this stage of the disease will need to be validated.

It's difficult to get the right people, at the right time involved in clinical trials

A recent analysis of dementia clinical trials showed that recruitment issues are a key reason why clinical trials are terminated³³. Given the challenges around getting an accurate diagnosis and detecting early pathological changes in the brain, it can be difficult to ensure that people with the right disease pathology are taking part in clinical trials. It has been reported that in previous Alzheimer's disease trials, up to 20 per cent of people who participated did not have the amyloid pathology, which the drug being trialled was targeting.³⁴

According to a YouGov poll commissioned by Alzheimer's Research UK in 2015, whilst almost two thirds of the general public (62 per cent) would be willing to take part in dementia research, more than four out of five people (81 per cent) would not know how to volunteer.³⁵ Pioneering initiatives such as Join Dementia Research (JDR) have since been launched and are making it significantly easier to get involved in studies, with 23,000 currently registered, but awareness of how to get involved in dementia research is still a barrier.

Making it easier to participate in dementia research

"Since Join Dementia Research was launched in February 2015, over 20,000 people have signed up to take part in dementia research. Dementia is a complex condition, impacting more people year on year, and we urgently need more research in order to unravel the biology of the diseases which cause dementia.

Traditionally it has been difficult to identify the right people for the right study at the right time, but Join Dementia Research is streamlining this process and we are already seeing the benefits of this boost in volunteers for research. Join Dementia Research makes it much easier for people, wherever they live, to get involved in studies, and the willingness of the public to help research is vital for us to make the progress that we all hope for. We now need to embed Join Dementia Research in core NHS diagnostic pathways to ensure all people with a dementia diagnosis are offered the opportunity to take part in research."

Professor Martin Rossor, National Director for Dementia Research at the NIHR

ACTIONS

Address the gaps in basic science and stimulate investment in dementia research and development

The gaps in our understanding of the biology of the diseases that cause dementia are hampering current clinical development efforts as trials are testing both the disease hypothesis as well as the treatment's target. Given the recent trial failures in this area, we need to gain a better understanding of the causes and pathological mechanisms as well as identify new, valid treatment targets.

There is a lot of activity in this area and global funders are working to address many of these gaps. The US National Plan for dementia provides significant amounts of new funding. The new £250 million UK Dementia Research Institute, of which Alzheimer's Research UK is a founding partner³⁶, will provide world-leading infrastructure in the UK. In this context, Alzheimer's Research UK will bring together a group of experts to determine what further research needs to be prioritised and how it might be funded.

In addition to improving our understanding of the basic science, there is also a need to stimulate further investment in research to develop the next generation of treatments. There are a number of innovative dementia research collaborations that have launched to speed up the discovery of new treatments and Alzheimer's Research UK has:

- Worked with MRC Technology and industry partners³⁷ to launch the Dementia Consortium.
- Launched a £30 million Drug Discovery Alliance to build up drug discovery capacity in the UK.³⁸
- Worked with the UK Government and pharmaceutical industry, to develop the Dementia Discovery Fund³⁹, a £70 million investment fund for translational dementia research.
- Committed £50 million of new partnership funding for the UK Dementia Research Institute.

This focus on translational research and fast-tracking promising science into benefits for people with dementia as quickly as possible is vital. There is now a need to maintain focus on all of these initiatives and make sure there is an environment where these can flourish and achieve their aims of fast-tracking the search for effective new dementia treatments.

There are now almost 23,000 people now taking part in dementia research studies

Galvanising momentum: the challenges we must address

Promote Join Dementia Research

Join Dementia Research (JDR) (www.joindementiaresearch.nihr.ac.uk) is funded by the Department of Health and delivered by the National Institute of Health Research in partnership with Alzheimer's Research UK, Alzheimer's Society and Alzheimer Scotland. The initiative, the first of its kind in the UK, provides the opportunity for those with or without dementia to get involved in pioneering research, as well as streamlining the recruitment process for researchers.

There are now 23,000 people registered on JDR and there has been a dramatic increase of 60 per cent in the number of people participating in dementia research. This will give scientists a significant advantage in finding new treatments for people living with dementia.

The dementia community and the NHS need to continue to increase promotion of JDR and it will be important to embed recruitment in Memory Clinics.

Brenda's story: getting involved in dementia research

Brenda Whittle, 74, was diagnosed with early-stage Alzheimer's in 2014. Stephen, 76, is Brenda's husband and carer.

Brenda's late diagnosis made things more difficult than they should have been. A very big problem for me, and our family, was having to cope with Brenda's obsessions, anger, irritability and unreasonableness, and knowing that no amount of rational discussion could lead to a change in her view. This can still be a problem but we now fully understand that this is a symptom of her illness and try our best to diffuse potentially angry situations. Although it does nothing to slow down or stop Alzheimer's, Aricept has also really helped with Brenda's symptoms.

When Brenda was diagnosed she decided to take part in a research study which we found out about through Join Dementia Research. It was to test a new drug that might stop or slow the progress of Alzheimer's disease. We don't know whether Brenda is on a high dose of the drug, a low dose, or the placebo, and of course the trial will determine whether it does halt the progress of the disease. But we know that we are making a contribution to the progress of medical science and giving hope to future generations.

Brenda added: "Although I don't know if getting a treatment would help me now, I think it's a great thing to be involved in research for future generations. Being a part of a drug trial can be difficult sometimes but I know that my taking part means if they find a treatment, I could be helping thousands of people worldwide."

Increase knowledge sharing across regulatory agencies

Regulators across the world should share learning and expertise to better support the alignment of pathways and requirements for new dementia treatments, so there can be more consistency in methods used and accepted endpoints for disease-modifying treatments.

Eleven of the drug regulators from 10 agencies in Europe, the United States, Canada and Japan have already come together to discuss how they can better address the challenges posed by new treatments for Alzheimer's disease.⁴⁰ This was the first time the regulators had come together to try and collaboratively tackle the challenge of dementia – a momentous achievement. The European Medicines Agency and the Food and Drug Administration in the United States have also developed draft guidance on assessing disease-modifying dementia treatments. The regulators have now agreed to meet regularly to discuss the challenges and share learnings.

A number of new initiatives have recently been developed to speed up access to new treatments, for example the PRIME scheme at an EU level and the UK Early Access to Medicines Scheme (EAMS). In the UK the Accelerated Access Review will hopefully offer further incentives and risk sharing between government and industry to allow earliest possible access to suitable new treatments, alongside funding for data collection on long-term outcomes.



Gearing up for change in the NHS

Annually, dementia costs the healthcare system approximately £4.3 billion, but the majority of costs are in social care at £10.3 billion and in unpaid care at £11.6 billion.⁴¹

The current pressures facing the NHS are well documented. Balancing increasing financial pressures alongside much needed service redesign and rising demand from patients, sees the NHS trying to meet an unprecedented financial challenge. Adopting new innovation and ‘investing now to save later’ will be critical in helping the NHS meet these challenges and deliver the outcomes that matter most to patients – but the time for investment has never been more challenging.

If the NHS is going to be ready for new dementia treatments, especially the first disease-modifying treatments, it needs to address the challenges now and start gearing up for change.⁴²

CHALLENGES

The first disease-modifying treatments could present challenges for NICE

There are no direct prior examples of how NICE would assess disease-modifying treatments for dementia and it is unclear to what extent NICE Health Technology Appraisal (HTA) assessors will consider wider evidence when appraising new dementia treatments. While the direct cost of dementia to the NHS is substantial, the most significant impact by far is on wider societal and social care costs. This could pose fundamental challenges for NICE HTA assessors, whose focus will be on the cost effectiveness of new innovations in relation to direct healthcare costs. Without considerable weight given to this wider evidence, there is a risk the value of the first disease-modifying treatments may not be fully determined by the NICE assessment framework. This will, however, need to be considered in a way that does not risk putting older people at a disadvantage in the assessment of new health technologies, as highlighted by the abandoned proposals for Value-Based Assessment.

In addition, it is well recognised there are limitations to the outcome measures for Alzheimer’s disease, particularly in the early stages of the disease. This makes it challenging to demonstrate the value of disease-modifying treatments that target the early stages of Alzheimer’s disease, as these patients are yet to experience significant functional decline.⁴³ When considering the cost-effectiveness of a new treatment, the standard measure of the EQ-5D used by NICE is not sensitive to the impact of the condition. It is also difficult to make a comparison with someone not receiving a disease-modifying treatment because the progression of the disease is so difficult to accurately track over a short space of time.



There will be limited evidence on the long term impact on health outcomes

It is likely the cost-effectiveness of the first disease-modifying treatments for Alzheimer's disease will be uncertain, as there will be limited data on their long term impact on health outcomes due to the nature of the disease.⁴⁴ Our modelling suggests that savings could be made (see page 8), but it may take time to realise savings from a treatment that slows the progression or delays the onset of long term conditions such as Alzheimer's disease.

This could pose challenges for NHS commissioners who might be expected to take on additional risk with limited long term data. Especially at a time when Clinical Commissioning Groups are required to balance short term priorities and financial constraints alongside investing in long term health challenges.

New treatments could require significant upfront costs to the NHS

Disease-modifying treatments for dementia are likely to be expensive and could potentially transform dementia treatment pathways. For example, they could require additional equipment to deliver the treatment, including new diagnostic tools, changes to infrastructure and clinical pathways to deliver the drugs and monitor for potentially serious side-effects and additional training and skills to deliver them. If this is the case, this could result in a significant upfront cost to the NHS to deliver them. Alongside this there will also be the ongoing health and social care costs for the many people who are already living in the later stages of dementia.

Accessing disease-modifying therapies: multiple sclerosis (MS)

Understanding of how well disease-modifying treatments work in multiple sclerosis is mainly based on clinical trials of people receiving treatment for 2-4 years only. A number of studies have looked at long term effectiveness but there have been conflicting results as to whether disease-modifying treatments slow down disability. As a result, there is still a lot of debate amongst neurologists and researchers about their long term effects.

In order to examine the unanswered questions, while giving patients access, the UK Department of Health negotiated a Risk Sharing Scheme. The 'risk' element of the Scheme involves a sharing of the financial risk between the NHS and the participating pharmaceutical companies. This agreement also facilitated an ongoing study to observe more than 5,000 people taking one of four disease-modifying drugs and following them over 10 years. People with MS included in the study are being monitored for changes in their disability.

A recently published paper⁴⁵ shows that after six years, the group on treatment have developed lower levels of disability compared to the untreated group. The researchers conclude that all four drugs are effective in slowing the progress of the disease over the six-year time period.

The current dementia treatment pathway is fragmented

Through contact with clinicians it is apparent that there is significant variation in the current dementia pathway, including the existing treatment pathway. For example, current symptomatic treatments are too often discontinued or altered because of a lack of understanding about effect, impact and side-effects. The management of anti-dementia treatments could be vastly improved through better communication of expert clinical practice. In parallel, there are marked differences in the use of bio markers to define the molecular cause of an individual's dementia, which will be vital when it comes to administering disease-modifying therapies targeting specific pathologies.

ACTIONS

Engage now to overcome the challenges disease-modifying treatments for dementia are likely to face

Regulators, NICE, NHS England, Clinical Commissioning Groups, industry and charities should engage with each other now to look at the access pathway collectively and prepare for the challenges new dementia treatments are likely to face, including decisions about their cost-effectiveness and potential changes to pathways of care and infrastructure. There is momentum to do this and in July 2015 Alzheimer's Research UK hosted a roundtable with representatives from all of these stakeholders to discuss the challenges for dementia.

There are existing initiatives that could be used to support this co-production. For example, NICE's Office for Market Access (OMA) is starting to offer Safe Harbour meetings and tailored advice and support for companies, enabling them to engage with NICE and potentially other relevant stakeholders on the most appropriate pathways for future products. This support could help facilitate interactions with Government departments, NHS organisations, research organisations, regulators, clinicians and charities, and could support early conversations on how to overcome the challenges disease-modifying treatments are likely to face. This could also be an opportunity to strengthen the patient voice and increasingly involve charities in NICE decision-making.

In addition, to support earlier engagement, Alzheimer's Research UK is establishing an advisory group of clinicians to help consider the potential impact of new treatments. As part of this, we have commissioned an economic analysis on the potential impact of new dementia treatments on the NHS.

Establish an effective horizon scanning mechanism to oversee new innovation coming through the pipeline

There is currently no horizon scanning mechanism that oversees and communicates to clinicians and commissioners, new innovations coming through the pipeline across a disease area, including new diagnostics and treatments. PharmaScan⁴⁶ offers some of this function, but is limited to new drugs in development. It would be helpful to have a more holistic view of new innovations coming through the pipeline for Alzheimer's disease and other dementias, taking into account pharmacological treatments, non-pharmacological interventions and diagnostics.

A proposed National Innovation Partnership, suggested as part of the interim report for the Accelerated Access Review⁴⁷, would help to address this gap and engage the right stakeholders at the right time, and we look forward to seeing more details when the final report is published. The membership of this type of body will be critical and will need to bring together stakeholders from research through to access. Clear and timely communication will also be a critical characteristic.

Consider flexible reimbursement models to support earlier access and the ongoing collection of evidence

Industry, NICE, NHS England and Clinical Commissioning Groups must work together to establish flexible reimbursement and funding models to support earlier access to treatments and ongoing evidence generation. This is especially important for diseases such as Alzheimer's where data on the long term impact of new treatments on health outcomes and cost is likely to be limited. There must be agreement between the NHS and the pharmaceutical industry about how the cost of access and data collection for treatments with limited real world outcomes data can be met, allowing patients to have appropriate access to innovative products as early as possible.

It is necessary to improve the infrastructure that supports the longer term collection of data in a 'real world' context, including finding innovative ways to link patient records and data sets, with all the necessary consents. This will enable researchers and the NHS to conduct research at a larger scale, investigate other health factors associated with disease risk and outcome, and follow the effectiveness of treatments in a real-world context. There are efforts to do this in the dementia space that could be built on, for example the Dementia Clinical Record Interactive Search (D-CRIS).⁴⁸

Statins: the journey to mass uptake

The use of statins has been shown to improve longer term cardiovascular outcomes for people, without patients necessarily noticing immediate improvements to their health. This could be a similar experience for the first disease-modifying treatments for dementia. Critically, faster regulatory approval of statins was supported through use of a surrogate endpoint (lower cholesterol) and the collection of long term outcome data drove widespread adoption.

Using surrogate endpoints to speed up approval

Lovastatin was shown to lower cholesterol, with limited side-effects in a relatively small number of cases, and was approved by the FDA in only 9 months, one of its shortest approval times in history. The decision to approve cholesterol lowering agents for marketing was based on the surrogate of lowering LDL cholesterol, not on cardiovascular endpoints. Use of a surrogate endpoint was key to the shortened review time. It did, however, take a long time for cholesterol to be widely accepted as an endpoint, with much more qualification and validation needed over a long time period, with associated costs.

Using outcome data to drive uptake

Following market approval, a number of largescale survival studies were carried out on statins that demonstrate that they lower cardiovascular events and mortality. This largescale data on cardiovascular outcomes triggered a global surge in uptake and now tens of millions of people take statins worldwide.

Over the past two decades more evidence on cardiovascular outcomes have been collected. Since its inception in 1994 the Cholesterol Treatment Collaboration (CTC) has reviewed data on over 170,000 participants. The meta-analysis demonstrated, for example, the following reductions in risk of:

- All major cardiovascular events by 21 per cent and major coronary events by 24 per cent
- Stroke by 15 per cent
- Death from any cardiovascular disease by 12 per cent and death from coronary heart disease by 19 per cent

Although evidence is still emerging on potential long-term side effects, as the data on reduction in morbidity and mortality increased, so did the global use of statins.

Support commissioners to make long term population based decisions

Commissioners should be better supported to balance short term financial pressures with longer term investment in population health. To better support long term planning, a longer funding settlement for the NHS and councils could be introduced. This would support commissioners to plan for long-term conditions such as dementia and give local leaders more freedom to better align health and care budgets around the needs of their population.

There is commitment to better integrate health and social care and significant effort and resources is being put in to achieve this. The closer integration of health and social care, including the alignment or merging of budgets, could have a significant impact on how treatments for long term conditions like dementia are valued. The benefits of the integration agenda, including the model of devolution, should be reviewed in the context of adopting new treatments and diagnostics for long term conditions such as dementia, including how this might impact local decision-making.

This approach could build on the work of the NHS vanguard sites and the Sustainability and Transformation Plans to drive new models of care and better integration⁴⁹. It should also be underpinned by a set of incentives that successfully drive the adoption and uptake of new treatments.

Conclusion



Alzheimer's Research UK is committed to ensuring people living with dementia get access to cost-effective new treatments as soon as they are available, providing the leading voice on drug discovery and treatment access within the charity sector. We have outlined the challenges in this report to begin the debate, so that we can work with other stakeholders and develop a coordinated approach to addressing key barriers. Whilst we do not underestimate the task at hand, we are encouraged by the willingness of stakeholders to come together, and the progress that has been made in some areas. We are dedicated to getting the right people around the table to ensure a coordinated approach to address these challenges and ensure people will have access to viable new treatments as quickly as possible.

Glossary

- **Basic science** – any one of the sciences (such as anatomy, physiology, bacteriology, pathology, or biochemistry) fundamental to the study of medicine
- **Biological marker (biomarker)** – A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition
- **Clinical Commissioning Group** – Responsible for planning and commissioning health care services for their local population
- **Early Access to Medicines Scheme** - Scheme to improve access to innovative medicines for patients with life threatening or seriously debilitating conditions without adequate treatment option
- **Endpoints** – In clinical trials, an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial
- **Health Technology Appraisal (HTA)** – Technology appraisals are carried out by NICE and give recommendations on the use of new and existing medicines and treatments within the NHS
- **National Institute of Health and Care Excellence (NICE)** – Provides national guidance and advice to improve health and social care
- **NHS England** – Leads the National Health Service (NHS) in England. Sets the priorities and direction of the NHS and encourages and informs the national debate to improve health and care
- **NHS Vanguard**s – Individual organisations and partnerships chosen by NHS to take the lead on development of new care models which will act as the blueprints for the NHS moving forward
- **UK PharmaScan** - Horizon scanning database populated with information on new medicines in development from up to three years before their launch in the UK

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37. The Dementia Consortium members are Alzheimer's Research UK, technology transfer and drug discovery experts MRC Technology and the pharmaceutical companies, Abbvie, Astex, Eisai, Lilly and MSD.
38. The Alzheimer's Research UK Drug Discovery Alliance is a network of Drug Discovery Institutes embedded within academic institutions across the UK. The first of its kind, the Alliance launched in February 2015 with three flagship Drug Discovery Institutes at the University of Cambridge, University of Oxford and University College London. Their aim is to unite the academic research community with industry-standard drug discovery expertise to fast-track promising science into benefits for people with dementia as quickly as possible.
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