PSSRU

Personal Social Services Research Unit

Economic Modelling of Disease-Modifying Therapies in Alzheimer's Disease

Robert Anderson[1], Martin Knapp[1], Raphael Wittenberg[1], Ron Handels[2], Jonathan M Schott[3]

1 Personal Social Services Research Unit, London School of Economics and Political Science
2 Department of Psychiatry and Neuropsychology, Alzheimer Centre Limburg, Maastricht University; and Department of Neurobiology, Karolinska Institute, Stockholm
3 Dementia Research Centre, UCL Institute of Neurology, London

Personal Social Services Research Unit
March 2018
www.lse.ac.uk/pssru

London School of Economics and Political Science

Houghton Street
London
WC2A 2AE
Tel: 020 7955 6238
pssru@lse.ac.uk

LSE THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

Summary

There is growing interest in studying the impact of potential disease-modifying treatments (DMTs) for dementia, and in particular for Alzheimer's disease (AD). At present no such treatments exist, but there is a real prospect of their development.

The UK Government, along with other G7 governments, has committed to aiming for such treatments by 2025 and has increased resources for research and development on dementia treatment and care. The life science sector in the UK and other countries is undertaking work to develop and trial disease-modifying treatments.

A relatively recent development is that the potential interventions being explored include not only products to halt or slow disease progression among those who are living with AD dementia but also products to prevent or delay the development of dementia. This means that there is now interest in modelling the impact of products which would, if successfully developed, be prescribed at pre-symptomatic stages of AD, before neurodegeneration takes place.

Alzheimer's Research UK (ARUK) commissioned the Personal Social Services Research Unit (PSSRU) at the London School of Economics and Political Science (LSE) to conduct a study to examine the economics of future treatments for AD. The objective of the study is to model the factors affecting the cost-effectiveness of a hypothetical new drug for AD so as to provide decision-makers with a tool to inform decisions regarding future treatments and to prompt discussions about how to prepare the health sector for them. The modelling aims to estimate the potential savings and quality of life gains that could be realised in the event that a disease-modifying treatment should become available.

ARUK have been keen to explore a number of options so as to get a better understanding of the parameters that could be required to ensure that any new treatment reaches patients. In particular, they want to know what would be the likely maximum price for a hypothetical new disease-modifying treatment (DMT) for AD in order for it to satisfy the cost-effectiveness requirements associated with the National Institute of Health and Care Excellence (NICE).

This report presents the methods and findings of this study. It is intended to constitute an independent resource to encourage debate and negotiation around the issue of drug pricing. The findings also seek to anticipate NICE's information needs when they come to assess disease-modifying treatments.

Background

In 2013, there were estimated to be around 816,000 people with dementia in the UK, of whom 42,000 were aged under 65 years and 774,000 were aged 65 or over (Dementia UK 2014 report). These figures were calculated on the basis of the prevalence rates of dementia for people aged 65 or over from the Delphi consensus conducted as part of the Dementia UK study. The prevalence rates from this consensus are higher – but only slightly higher – than those in the Cognitive Function and Ageing Study (CFAS II). The incidence rates from CFAS II imply that there are 180,000 new cases of dementia among older people each year. The estimated number of people with dementia in the UK today is around 850,000 (ARUK website, November 2017).

The total annual costs of dementia care were estimated to be £26.3 billion in 2013 (at 2012/3 prices), with an average annual cost of £32,250 per person. This comprised £4.3 billion health care costs, £10.3 billion social care costs (public and private combined), £11.6 billion costs of unpaid care and £0.1 billion other costs.

Alzheimer's Disease (AD) accounts for around 70% of dementia cases when mixed dementia is included in the AD figures (advice from ARUK). This suggests that there are now around 570,000 people living with AD in the UK, of whom 540,000 are aged 65 or over, that there are some 140,000 new cases of AD annually among older people and that the annual cost of AD is around £18.4 billion (at 2012/3) prices, of which £17.5 billion relates to older people.

The data and estimates in this report all relate to the United Kingdom (UK) in 2014 with a price base of 2012/3 prices.

Data and methods

Disease progression is the basis of our modelling. For the purpose of this report, we consider five different clinical states on the AD spectrum: (1) cognitive normality (CN) with AD biomarkers (pre-symptomatic AD); (2) mild cognitive impairment with AD biomarkers (MCI-AD; prodromal AD); (3) mild AD dementia; (4) moderate AD dementia; and (5) severe AD dementia. In this report, we describe the final three stages of Alzheimer's disease as Alzheimer's dementia to differentiate it from all-cause dementia. Similarly, we will refer to MCI caused by Alzheimer's disease as MCI-AD or prodromal AD. [Further information can be found in Appendix 2.]

The progressive nature of AD, with an annual risk of moving to the next severity stage, can be considered and modelled as a Markov process. We developed a set of Markov models for this study (Appendix 3), designed to address the five treatments described below. The model used for treatment 1 starts at the onset of AD dementia and tracks an individual from mild through moderate to severe AD dementia and on to end of life. The other three models link to it, starting at earlier points in the natural history of the disease. The models take account of the risk of mortality at each stage of the disease. They have been developed using the TreeAge software, which is designed for this type of modelling and is user-friendly.

The key data required for these models are rates of transitions between the five disease states and mortality rates by disease state. On the basis of a focused review of relevant recent literature and consultation with experts we have used the data sources listed at Appendix 1.

We have conducted our modelling by age band: this is essential since AD incidence rates and mortality rates vary by age. Although they also vary by gender, we have not conducted modelling by gender since there is no precedent for the price of new therapies varying by gender. We have calculated all person rates from gender-specific rates using appropriate gender weights.

For people with all-cause MCI (i.e. treating this as a clinical syndromic diagnosis), the annual transition rate to overt AD is 16%; but for the 40% of people in this group with the prodromal form (i.e. with evidence of AD pathology on the basis of biomarkers), the annual transition rate is 27%. These data are from Vos et al (2015). MCI does not entail excess mortality.

Within AD, the transition and mortality rates we use for the mild, moderate and severe estates, drawn from various sources (Brookmeyer et al 2007, Neale et al 2001, Spackman et al 2012, ONS 2017) are set out in Table 1.

Table 1: Alzheimer's disease: Annual transition rates between severity stages and death[1]

		To			
		Mild	Moderate	Severe	Death
from	Mild	1 - 0.167 - pop rate	0.167	-	pop rate
	Moderate	-	1 - 0.2 - (pop rate +0.11)	0.2	pop rate + 0.11
	Severe	-	-	1 - (pop rate + 0.11)	pop rate + 0.11

Pop rate – general population age-specific death rate

[1] An alternative use of these data would be to assume that the transition rate applies after applying the mortality rate. A sensitivity test is shown for treatment 1 below.

The interpretation of these data is that, for example:

- a person aged 80 with prodromal AD has an annual probability of 27% of developing Alzheimer's dementia and an annual probability of 4.8% of mortality;
- a person who has mild Alzheimer's dementia has an annual probability of 16.7% of developing moderate Alzheimer's dementia and an annual probability of 4.8% (at age 80) of mortality;
- a person of the same age with moderate Alzheimer's dementia has a 20% probability of developing severe Alzheimer's dementia and 15.8% probability of mortality.

The other key data for our modelling are estimates of the average costs of dementia care at each stage of the disease and the average quality of life of people living with each stage of the disease. For quality of life we consider quality-adjusted life years (QALYs), which take account of duration and health-related quality of life. The sources are set out in Appendix 1.

The estimates we have used are set out in Table 2.

Table 2: Alzheimer's disease: annual cost of care per person by sector and stage of disease; QALY status by stage of disease

	Mild	Moderate	Severe
Social care	£5,362	£21,455	£22,176
NHS treatment	£2,932	£7,837	£9,300
Unpaid care	£17,781	£9,865	£9,575
Other	£136	£136	£136
Total	£26,211	£39,293	£41,187
QALY	0.71	0.64	0.38

The NHS costs cover the full costs of health care for people with dementia and not just costs specifically for dementia care. The social care costs include costs of both publicly funded and privately funded care. The unpaid care estimates relate to opportunity costs.

There is no evidence on costs of care for MCI or on the impact of MCI on health-related quality of life. In the absence of suitable evidence we assume that the costs of MCI – which by definition does not impact on activities of daily living – are zero. Whilst MCI may well be associated with anxiety, for the purpose of this analysis we assume that it does not impact on quality of life.

Methods

The aim is to estimate the maximum justifiable price for the different disease-modifying treatments within the £20,000 cost per QALY benchmark associated with NICE recommendations.

The lifetime AD path of a patient is tracked from the point of intervention, in terms of health-related quality of life (QALYs) and costs associated with utilisation of health services, social care services and support from unpaid carers. Two trajectories are compared, one with and the other without the intervention.

The calculation is as follows:

Maximum acceptable cost of the intervention =

QALY gain x NICE threshold in terms of £ per QALY

+ saving in cost of treatment and care

– cost of services to support the intervention, such as tests of eligibility

These variables are lifetime totals expressed in terms of the present value at the point of initiation of therapy.

On this approach, no intervention will recover its cost in terms of expenditure saved on health or social care services, partly because the cost savings include monetised savings to carers but also because of monetised gains to the patient in health-related quality of life.

Assessment criteria

We have adopted NICE recommendations when developing our methodological approach, including discounting both costs and benefits at a rate of 3.5% per annum. For an intervention in the early stages of disease, the benefits of deferring the onset of overt disease may not be apparent for many years. Discounting at 3.5% per annum will have the effect of reducing the present value of the benefits and costs saved quite markedly. For example, a monetary benefit of £1 which arises 20 years from the point of intervention has a discounted present value of 50 pence.

On the costs side we include opportunity costs to carers as well as cost to social services and health services (NICE 2014).

NICE also uses a benchmark of £30,000 per QALY in some circumstances. In our analysis this would affect only the QALY component of benefit. We investigate the sensitivity of results to the choice of benchmark for selected interventions.

Modelling

The pattern of the disease, its progressive nature, with an annual risk of moving to the next stage, can – as explained above – be modelled as a Markov process. The Markov models are a form of life-table and require age-specific death rates as well as transition rates between disease stages.

Our approach is to follow an 'average' patient – average, that is, in relation to the group selected for therapy – for the rest of his or her life, noting the cost and QALY level in each year for the appropriate stage of the disease. The results, and the cost-effectiveness of the intervention, do not depend on the prevalence of the condition. Each intervention is assessed separately as the only one being implemented. For example, assessments of interventions in MCI do not take account of any prior interventions which aimed to prevent the onset of cognitive symptoms.

For each treatment the following results are presented:

- the maximum justifiable price of the therapy per person per year, and
- for the average recipient of the therapy
    - increase in life expectancy
    - increase in QALY expectancy (a combination of the increase in life expectancy and the increase in health-related quality of life per year of survival)
    - the change in lifetime cost of AD treatment and care, usually a reduction from current patterns of care
    - the duration of therapy, taking account of rules for withdrawing therapy.

The impact on annual NHS expenditure is estimated by combining

- the number of patients at initiation of therapy
- the annual cost of therapy
- the average duration of therapy.

This represents the value in steady state, that is, annual expenditure not in the early years after the intervention has been adopted but after it has been in use for long enough for all those who received it in the early years to have died.

For interventions in the pre-Alzheimer's stages (preclinical and prodromal), the models are able to produce estimates of the lifetime risk of AD with and without intervention. These data can be combined with estimates of the numbers of people initiating therapy to

produce estimates of the annual number of cases averted in steady state. To focus attention on the impact of the factors under study, all other influences are kept, or left, unchanged. For example, factors affecting the scale of overall prevalence such as population, age-specific mortality rates and the natural history of AD (as implied by CFAS II age specific incidence rates) are taken at their current values.

Estimates of the impact of the different interventions on the prevalence of AD and its cost are produced using our assumptions relating to reductions in incidence rates. Prevalence is estimated by applying CFAS II age-specific incidence rates to the population at each age and then applying current age-specific mortality rates to estimate the prevalent numbers at older ages. It should be noted that, because of declining mortality rates, this approach when implemented from age 50 produces an estimate of numbers aged 70 some 30% higher than current number of people aged 70.

The methods outlined above could be extended to derive useful results beyond the scope of the present study, for example, trajectories towards steady state.

The nature of the intervention and criteria of eligibility

In our modelling the disease modifying treatments (DMTs) are assumed similar to current therapies in preventive medicine — flu vaccination for treatment 5 and antihypertensive or statin medication for the other treatments. In practice, the DMT interventions might be more complex and require more monitoring in primary care than those interventions. We have not made separate allowance for the costs of monitoring: the estimated maximum prices for the DMTs consistent with cost-effectiveness should be regarded as including the costs of monitoring as well as the cost of the intervention. We assume that the treatments have no significant side effects.

Eligibility criteria are also simple and straightforward, but this reflects the current state of knowledge and in particular the high risk of conversion associated with amyloid positivity.

Current methods for determining amyloid-positivity include the use of amyloid PET imaging or CSF analysis based on lumbar puncture. There are advantages and disadvantages of each technique, which are however reasonably comparable in terms of sensitivity and specificity. In our analyses, we assume that CSF is the leading testing method, covering 90% of those tested, whereas 10% will require a PET scan. A lumbar puncture/CSF test costs £450 and a PET scan £900 so that, with 90% receiving CSF and 10% PET testing, the average unit cost of a test is £500. In due course blood testing for determining AD risk or stratification for more complex tests may be available, which is likely to reduce the costs of testing.

Treatments

ARUK and PSSRU developed, with advice and guidance from the study's Clinical Advisory Group, five treatments for analysis. These differ principally in the target group to receive the new DMT and the assumed impact of the DMT.

The aim is to slow the progression between:

- mild and severe Alzheimer's dementia – **Treatment 1**
- MCI and mild Alzheimer's dementia **–Treatment 2**
- MCI and severe Alzheimer's dementia – **Treatment 3**
- cognitively normal at high risk and mild Alzheimer's dementia – **Treatment 4**
- to delay onset of Alzheimer's disease by initiating therapy in a cognitively normal population – **Treatment 5**

Further details at Appendix 2

Treatment 1 – To slow progression between mild and severe Alzheimer's dementia

The onset of Alzheimer's dementia is a natural starting point for a disease-modifying therapy. We consider a drug given at first diagnosis and reducing transition rates from mild to moderate and moderate to severe stages by 5%, 10%, 25% or 50%. The therapy would be taken continuously at regular intervals, perhaps weekly or monthly, during the mild and moderate stages.

In AD, the value of benefit, and hence the maximum acceptable price, is likely to vary by age of onset. However, there has to be a single price. The method is to estimate the maximum price allowable under the NICE threshold of £20,000 per QALY for each age at five-yearly intervals and combine the results to derive a single price. The values for each age group are weighted by the distribution of incidence of AD from CFAS II, taking account of the different durations of therapy — the duration is longer with onset at younger ages. The results for ages 75 and 85 are shown in Table 3.

Table 3: Therapy to reduce annual rate of onward transition from mild to moderate and moderate to severe stages of AD by 5%, 10%, 25% or 50% by selected age at onset: Discounted lifetime cost saving, gain in life expectancy and discounted QALY per person treated; maximum price of therapy per annum per person treated; annual expenditure in steady state

At age 75				
	5%	10%	25%	50%
Cost saving[2]	- £517	- £1,054	- £2,797	- £6,209
QALY	0.071	0.145	0.389	0.881
Duration therapy (yrs)	6.6	6.8	7.4	8.8
Gain in life expectancy (yrs)	0.089	0.184	0.503	1.189
Annual price of a year's therapy per person	£30	£190	£670	£1470
At age 85				
Cost saving	£112	£231	£630	£1,473
QALY	0.033	0.067	0.175	0.376
Duration therapy (yrs)	4.4	4.5	4.8	5.2
Gain in life expectancy (yrs)	0.033	0.067	0.179	0.401
Annual price of a year's therapy per person	£14	£210	£802	£1,780
Single price	£19	£176	£660	£1,460
Annual expenditure in steady state £m	£8	£78	£318	£812

As a means of distinguishing Alzheimer's dementia from other forms of dementia, it is assumed that all patients diagnosed through testing to identify amyloid positives are deemed to have AD and to receive therapy. A cost of £714 for testing is attributed to each AD patient at onset, as 70% of dementia will prove to be AD. The annual expenditure for testing would then be £100m.

It is worth noting that intervention leads to an increase in the lifetime cost in 75-year olds, but a decrease in 85-year olds. This effect arises from the interplay of the relative cost by stage (£26,000, £39,000 and £41,000 for mild, moderate and severe respectively, which is a ratio of roughly 2:3:3), the effect of therapy on time spent with AD, the stage breakdown and the underlying age-specific mortality rate. The higher background mortality rate by age serves to restrict the time spent in the costlier moderate and severe stages in older groups.

[2] Includes carers' opportunity cost in this table and similar tables for the other treatment options.

The maximum annual price justifiable under the NICE £20,000 threshold ranges from £19 at 5% effectiveness to £1,460 at 50%[3]. The corresponding annual expenditure in steady state ranges from £87 million to £896 million, including the cost of diagnosis.

Treatment 1, which involves a reduction in the annual transition rates from mild to moderate AD and from moderate to severe AD, would have no impact on the numbers of older people experiencing onset of AD. It would, however, lead to an increase in the numbers of people living with AD in view of the increase in life expectancy resulting from the delay in onset of moderate and severe AD. If the therapy reduced the annual transition rates by 30% there would be a gain in life expectancy of 6 months for those starting to receive the therapy at age 75, or 2 months for those starting to receive it at age 85 (Table 3). The increase in life expectancy would be mainly in the mild stage of AD and the duration of the severe stage of AD would fall. Overall, the number of older people living with AD would rise by some 29,400. Within this total, the number living with mild AD would rise by 60,700 and the number living with moderate AD by 900, but the number living with severe AD would fall by 32,100.

The impact of this treatment on costs is complex. For those starting to receive the therapy at age 75 there would be an increase in costs even before taking account of the costs of the therapy: this is due to the increase in life expectancy. For those starting to receive the therapy at age 85, however, there would be savings before taking account of the costs of the therapy: this is because the increase in life expectancy is lower for this group than for those starting to receive therapy at an earlier age.

The increase in the costs of care before taking into account the costs of the new therapy would be an estimated £300 million. The net impact after taking account of the costs of testing and therapy would be £700 million. These estimates again relate to a 'steady state', which would exist now if everyone currently alive who has AD had received the new therapy from onset of mild AD (to onset of severe AD).

Treatment 2 –To slow progression between MCI-AD and mild Alzheimer's dementia

Mild Cognitive Impairment

Mild cognitive impairment reflects a state of objective, progressive cognitive difficulties not sufficient to interfere with daily living. MCI has many potential causes and not all individuals will develop dementia. Those with evidence of AD pathology through biomarkers have

[3] If the transition rate is applied after applying the mortality rate, the effect is to reduce the maximum permissible price by 5% for those diagnosed at 75 and 11%-12% for those diagnosed at 85.

higher conversion rates, and can be classified according to contemporary criteria as having prodromal AD. Extrapolating from US evidence of age-specific prevalence rates, the prevalence of MCI in the UK may be 1.2 million with an annual incidence of 480,000 (Petersen et al. 2010). A recent study by Vos et al. (2015) implies an annual transition rate of 16% from all-cause MCI to AD, with rates higher in those with prodromal AD (27%) than in other forms (7%).

The study by Vos et al reviews the different criteria for prodromal AD and their effectiveness for stratifying the rate of progression in a sample of subjects identified as MCI. We illustrate prodromal AD defined through IWG-2 criteria (Dubois et al. 2014), because of its combination of simplicity, effectiveness, and likely economy[4]. In this scheme prodromal status is defined as any cognitive impairment plus low CSF Aβ1-42 or a positive amyloid PET scan. We assume 90% of patients accept a lumbar puncture and 10% require a PET scan.

The results as to rates of progression to AD relate to a subsample which excludes "diagnosis of dementia at baseline or any other vascular, somatic, psychiatric or neurological disorder that might have caused the cognitive impairment"**Error! Bookmark not defined.**. In the modelling here, eligibility is confined to those free of dementia and major vascular disease sufficient to account for the cognitive symptoms. The age specific prevalence of dementia is taken from CFAS II, the prevalence of vascular disease from the Health Survey for England 2005. It is further assumed that those suffering from dementia have the same prevalence of cardiovascular disease (CVD) as those who are not.

Applying IWG-2 to the sample in the study by Vos et al identifies 40% of MCI as having prodromal AD.

APOE-ε4 is twice as common (66% vs 33%) in the prodromal group but there are no findings as to its predictive value as an alternative, or additional, test. In due course it might be included as part of a screening test either alone or as part of a polygenic risk score, but this is not included in the current modelling.

As the DMT remains hypothetical at this stage, we illustrate an agent which reduces the risk of conversion in amyloid positive individuals. The therapy is assumed to reduce the annual transition rate by 10%, 30% or 50% in prodromal subjects[5], and to be taken continuously at given intervals – daily, weekly or monthly – until the onset of AD. Certain treatments might

[4] IWG-2 identifies 40% of MCI as prodromal of which 60% progress to AD in three years: with IWG-1 the proportions are 53% and 50%. While, therefore, both identify 25-26% of the cohort as progressing, applying the IWG-2 criteria can achieve the same result by treating a smaller proportion of the MCI cohort to do so.

[5] Table 4 shows that the results are broadly in proportion to the reductions, that is, the effect produced by 30% is about three times greater than 10%, so that intermediate reductions such as 15% can be found by interpolation.

be needed to give more infrequently or perhaps only once which would reduce costs further, but these are not included in the current modelling.

We illustrate a programme of screening people age 70-89 diagnosed with MCI, with therapy offered to those screening positive for prodromal AD.

MCI is assumed not to impose cost on health services or to require care from social services or informal carers. There is no QALY penalty (Ekman et al. 2007).

The results are summarised in Table 4.

Table 4: Therapy to reduce annual rate of transition from prodromal AD to Alzheimer's dementia by 10%, 30% or 50% in 70-89 year olds:
Discounted lifetime cost saving, gain in life expectancy and discounted QALY per person treated; maximum price of therapy per annum per person treated

	10%	30%	50%
Cost saving	£5,560	£19,660	£39,660
QALY	0.079	0.276	0.543
Gain in life expectancy (yrs)	0.08	0.3	0.61
Annual price of a year's therapy per person	£1,890	£6,480	£10,980
Total expenditure on therapy in steady state £m pa	£480	£2,050	£4,400

The number of cases averted is estimated by combining the population eligible with the change in lifetime risk of AD as a result of therapy.

Table 5: Therapy to reduce annual rate of transition from MCI to severe AD by 10%, 30% or 50% in 70-89 year olds: cases averted; reduction in prevalence; reduction in care expenditure

	10%	30%	50%
Cases averted	1,570	6,140	13,370
Reduction in AD incidence	2%	8%	18%
Reduction in AD prevalence	3%	11%	23%
Reduction in expenditure on care	3%	11%	23%

A screening programme in those aged 70 and over with a diagnosis of MCI to identify prodromal MCI would cost about £110 million per year. If those screening positive were to be given a therapy reducing annual risk of progression by 30% to be taken until onset of AD, a price of £6,480 per person per year would be justified. The likely duration of therapy would be about 3.6 years. The annual expenditure on therapy would be about £2,050 million.

Treatment 2 with a 30% reduction in the annual transition rate from prodromal MCI would, if it had been implemented many (around 20) years ago, mean today around 6,140 fewer people experiencing onset of AD per year and around 59,600 fewer people living with AD. The lifetime risk of AD among people with prodromal MCI would be 77% under the new therapy compared with 84% without it.

The saving in the costs of care before taking into account the costs of the new therapy would be an estimated £1,960 million. The net impact after taking account of the costs of the therapy and test would be a net cost of £200 million. These estimates again relate to a 'steady state', which would exist now if everyone currently alive who had prodromal MCI at aged 70 or over had received the new therapy until onset of AD.

Treatment 3 – Slow progression between MCI-AD and severe Alzheimer's dementia

We illustrate an agent which reduces the risk of conversion in amyloid positive individuals and, in those who do convert, reduces the progression from mild to moderate and moderate to severe. The therapy is assumed to reduce the annual transition rate by 10%, 30% or 50% in prodromal subjects, and to be taken continuously at given intervals – daily, weekly or monthly – until the onset of severe AD.

We illustrate a programme of screening people age 70-89 diagnosed with MCI, with therapy offered to those screening positive for prodromal AD.

The results are summarised in and table 6.

Table 6: Therapy to reduce annual rate of transition from prodromal Alzheimer's dementia to the mild, to moderate and finally severe forms of established AD by 10%, 30% or 50% in 70-89 year olds:
Discounted lifetime cost saving, gain in life expectancy and discounted QALY per person treated; maximum price of therapy per annum per person treated

	10%	30%	50%
Cost saving	£5,240	£18,480	£37,050
QALY	0.157	0.503	0.889
Gain in life expectancy (yrs)	0.203	0.668	1.209
Annual price of a year's therapy per person	£1,000	£3,620	£6,770
Total expenditure on therapy in steady state £m pa	£700	£2,750	£5,620

The number of cases averted is estimated by combining the population eligible with the change in lifetime risk of AD as a result of therapy.

Table 7: Therapy to reduce annual rate of transition from MCI to severe AD by 10%, 30% or 50% in 70-89 year olds: cases averted; reduction in AD epidemic; reduction in expenditure on care

	10%	30%	50%
Cases averted	1,570	6,140	13,370
Reduction in AD incidence	2%	8%	18%
Reduction in AD prevalence	1%	6%	15%
Reduction in expenditure on care	3%	10%	21%

A screening programme in those aged 70 and over with a diagnosis of MCI to identify prodromal MCI would cost about £110 million per year. If those screening positive were to be given a therapy reducing annual risk of progression by 30% to be taken until onset of severe AD, a price of £3,620 per person per year would be justified. The likely duration of therapy would be about 8.6 years. The annual expenditure on therapy would be about £2,800 million.

The saving in the costs of care before taking into account the costs of the new therapy would be an estimated £1,750 million. The net impact after taking account of the costs of the therapy and test would be a net cost of £1,150 million. These estimates again relate to a 'steady state', which would exist now if everyone currently alive who had prodromal MCI at aged 70 or over had received the new therapy until onset of severe AD.

Treatment 4 – To slow progression between high risk cognitively normal (CN) and mild Alzheimer's dementia

Cerebral amyloid-β aggregation is an early pathological event in AD. It is a necessary condition for the development of AD: the risk of progression to Alzheimer's dementia requires the presence of neurodegeneration in addition. From a study of participants in the Mayo Clinic Study of Aging there are estimates of the prevalence of amyloid status (A) and neurodegeneration (N) in the population from age 50 (Jack et al. 2016). This source also provides estimates of age-specific annual transition rates from amyloid positive (A+) neuro-degenerative negative (N-) (cognitively normal)) to amyloid positive (A+) neuro-degenerative positive (N+) and from A+N+ to dementia, which is assumed to be AD dementia because the target group is selected for A+ status.

The patient group we focus on is A+ (amyloid positive) 70 year olds. The Mayo Clinic study used amyloid PET to measure A+/- status; and FDG PET and MRI to measure N+/- status. Since we are selecting all A+ at age 70 there is no need to test for neurological status.

However, the modelling has to take account of the initial split at age 70 between A+N+ and A+N- subjects. At this age the great majority (69%) are N- (with no sign of neurodegeneration).

Nearly one in three 70 year olds test A+. The cost of identifying one A+ CN 70-year old would be about £1560. The numbers receiving the DMT at any time would be around 2.6 million. The annual cost of testing the whole cohort of 70-year olds would be £307 million. In due course it seems likely that some form of screening (genetic and/or blood testing) would be conducted to identify individuals at risk of being amyloid positive which may then need to be confirmed through CSF/PET testing with the potential to reduce cost, but that is not assumed here.

As the DMT remains hypothetical at this stage, we illustrate an amyloid modifier which reduces the annual transition rate from A+N+ to AD by 5%, 10%, 25% or 50%, to be taken continuously at given intervals, daily, weekly or monthly, until the onset of Alzheimer's dementia.

The results are summarised in Table 8.

Table 8: Therapy to reduce annual rate of transition to Alzheimer's dementia by 5%, 10%, 25% or 50% in CN 70 year olds with amyloid+
Discounted lifetime cost saving; gain in life expectancy and discounted QALY per person treated; maximum price of therapy per annum per person treated; annual expenditure on therapy

	5%	10%	25%	50%
Cost saving	£1167	£2,862	£8,218	£18,173
QALY	0.020	0.040	0.102	0.216
Gain in life expectancy (yrs) (base level 15.2 years)	0.024	0.048	0.124	0.262
Annual price of a year's therapy per person	£30	£157	£540	£1,180
Annual expenditure on therapy in steady state £m	£75	£390	£1,420	£3,230

It is noteworthy that 37% of those people who are amyloid positive at 70 will progress to AD[6]. As a consequence, 63% will be on lifelong therapy without any benefit. The average time on therapy is about 13 years. (Advances in biomarkers that might predict proximity to dementia in A+ individuals, which might allow for further sub-stratification of those who should be treated with consequent reductions in costs, but this is not modelled here).

[6] 44.6% of those who are also N+.

These estimates relate to a population from a mid-west US state and they may not apply exactly in England.

The number of cases averted is estimated by combining the population eligible (32% of 70-year olds in England), the change in lifetime risk of AD as a result of therapy (base of 37%).

Table 9: Therapy to reduce annual rate of transition to Alzheimer's dementia by 5%, 10%, 25% or 50% in CN 70-year olds with amyloid+: lifetime risk of AD; cases averted; reduction in prevalence; reduction in expenditure on care

	5%	10%	25%	50%
Lifetime risk of AD	0.359	0.347	0.307	0.228
Cases averted	2,360	4,700	12,600	28,100
Reduction in AD incidence	3.2%	6.5%	17.3%	38.5%
Reduction in AD prevalence	3.6%	7.3%	19.2%	41.7%
Reduction in expenditure on care	3.9%	7.3%	19.4%	41.4%

A screening programme using to identify amyloid positivity in 70-year olds would cost about £307 million per year. If those screening positive were to be given a therapy reducing annual risk of progression by 25% to be taken until onset of Alzheimer's dementia, a price of £540 per person per year would be justified. The mean duration of therapy would be 13 years. The annual expenditure on testing and therapy would be about £1,400 million. The scale would be reduced by just under 4% compared with what it would otherwise be in this group.

Treatment 4 with a 25% reduction in the annual transition rate to AD among people aged 70 years who are cognitively normal but amyloid positive would, if it had been implemented many years ago, mean today around 12,600 fewer people experiencing onset of AD per year and around 76,600 fewer people living with AD. The saving in the costs of care before taking into account the costs of the new therapy would be an estimated £2,800 million. The net impact after taking account of the costs of the therapy (£1,420 million if the therapy cost £540 per year) would be a net cost saving of £1,400 million, or £1090 million after testing costs. The lifetime risk of AD at age 70 would be 30.7% under the new therapy compared with 37.1% without it.

These estimates relate to a 'steady state'; and the impact is simulated as if the steady state had already been reached. A steady state for this treatment would exist now if everyone currently alive who was cognitively normal but amyloid positive at age 70 had received the new therapy from age 70 (until onset of AD).

Treatment 5 – To delay the onset of Alzheimer's disease by preventive therapy in the cognitively normal population

Drug treatment programme (e.g. β-secretase inhibition) to defer the onset of AD by preventing β-amyloid accumulation

Current research suggests that β-amyloid is the upstream cause of Alzheimer's disease. AD requires the presence of β-amyloid pathology; and a rare mutation in the APP gene that decreases the deposition of β-amyloid prevents AD (Jonsson et al. 2012). Preventing the deposit of β-amyloid plaques is therefore a viable strategy to preventing the development of the disease. Aβ accumulation is not seen in 50 year-olds, increasingly exponentially thereafter. This is mirrored by the prevalence of AD dementia with a delay of a decade or more. This is postulated to reflect a pre-symptomatic period between becoming amyloid positive and developing AD dementia.

We therefore illustrate a treatment to delay the aggregation of β-amyloid, e.g. a β-secretase inhibitor offered at the age of 50 with boosters every two or five years during which time no, or very few, individuals would be expected to have any cognitive deficits.

We assume that the intervention would be offered to *everyone* at age 50 without any screening or risk assessment and illustrate a range of effects including deferral of onset of Alzheimer's dementia by 1, 3 or 5 years. We assume that the treatment works for everyone at risk of subsequently developing AD pathology, and has no significant side-effects.

The average path of a 50-year old without the intervention is assumed to follow the age-specific incidence rates emerging from CFAS II (Matthews et al. 2016). No account is taken of intermediate stages such as MCI on the strength of evidence that the condition does not give rise to a QALY penalty (Ekman et al. 2007) and the absence of evidence of excess costs for clinical treatment or social or informal care.

Annual expenditure with full implementation of the programme, that is once the life-cycle of the first cohort is complete, is calculated by combining the cost per dose, the number of doses received before onset of AD, taking account of survival to different ages, and the current numbers of 50-year olds.

The results are set out in Table 10.

Table 10: Drug treatment programme at age 50 with booster every 2 years until onset of AD or death deferring onset of AD by 1, 3 or 5 years: Discounted lifetime cost saving, gain in life expectancy and discounted QALY gain per person treated; maximum price per dose; annual expenditure in steady state

	1	3	5
Cost saving	£1,727	£4,701	£7,095
QALY	0.026	0.069	0.101
Life expectancy (yrs)	0.060	0.161	0.238
Treatment cost per dose	£230	£620	£920
Total expenditure in steady state £m pa	£3,450	£9,300	£13,900

As shown in table 10, an assumed delay of 3 years in onset of AD would yield a saving of £4,701 (after discounting) in health, social care and unpaid care costs per person over the person's life-time and would provide an increase in life expectancy of 0.161 years and in QALYs (discounted) of 0.069. The maximum price per dose consistent with achieving cost-effectiveness at a threshold of £20,000 per QALY would be £620 per dose if a booster was offered every two years until the onset of AD or death if AD does not develop. There would also be a fee of £10 per dose for GPs under an enhanced services specification (NHS England 2016).

The number of cases averted is estimated by combining the population eligible for vaccination (937,000 50-year olds in the UK), and the change in lifetime risk of AD as a result of therapy (from a base of 21%). For purposes of comparison, the expected number of cases over the lifetime of the current cohort of 50-year olds is around 197,000 based on CFAS II age-specific incidence data[7]. The reduction in the prevalence of AD exceeds the reduction in the incidence because intervention reduces the length of time with Alzheimer's dementia as well as its incidence.

Table 11: Lifetime risk of AD in 50-year olds for a programme deferring the onset of AD by 1, 3 or 5 years: cases averted; percentage reduction in scale of the epidemic; percentage reduction in expenditure on care.

	1	3	5
Lifetime risk of AD	0.192	0.159	0.129
Cases averted	16,900	47,900	76,000
Reduction in incidence	8.6%	24.3%	38.6%
Reduction in prevalence	10.7%	30.0%	45.7%
Reduction in expenditure on care	10.8%	30.1%	46.3%

[7] Combining this figure with an estimate of the average time with AD would yield an estimate of the population prevalence of AD.

The maximum justifiable price per dose depends on the interval between doses and the assumed efficacy. A biennial programme deferring onset by three years would justify a cost per dose of £620. The annual expenditure in steady state would be £9.3 billion. The corresponding impact on the prevalence would be substantial, even for a deferral of one year. This treatment with 3-year deferral of onset of Alzheimer's dementia would, if it had been implemented many years ago, mean today around 47,900 fewer people experiencing onset of Alzheimer's dementia per year and 394,000 fewer people living with Alzheimer's dementia. The saving in the costs of care before taking into account the costs of the programme would be an estimated £12.7 billion. The net impact after taking account of the costs of the programme would be a net saving of £3.4 billion.

The costs would accrue to the NHS and the savings would accrue mainly to social services (publicly and privately funded) and to unpaid carers (reduced opportunity cost reflecting reduced hours of care). The net monetary cost needs to be seen in the context of the gains in quality-adjusted life expectancy experienced by the older population as a result of the programme. The lifetime risk of Alzheimer's dementia at age 50 would be 15.9% under the programme, compared with 21% without it, and each person aged 50 would gain on average around 2 months extra life expectancy.

These estimates relate to a 'steady state'; and the impact is simulated as if the steady state had already been reached. A steady state for this treatment would exist now if everyone aged 50 and over currently had received the drug from age 50 years.

Sensitivity to transition rates, costs, the NICE threshold and alternative estimates of age- and stage-specific mortality in AD

The estimates of the maximum justifiable price of therapy were tested for their sensitivity to (a) doubling the transition rate from mild to moderate AD (b) a 10% increase in all costs (c) a threshold of £30,000 per QALY rather than £20,000 (d) alternative estimates of age- and stage-specific mortality rates in AD.

(a) Doubling the transition rate from mild to moderate AD

For treatments 2-5, there is a modest increase in the maximum price in the range 0.5% to 4.2%. Analysis of the one-year deferral case in treatment 5, for example, shows that the doubling of the transition rate from mild to moderate AD reduces the time spent with AD. Consequently, the potential from deferral is reduced, and indeed the effect of therapy on time spent with Alzheimer's dementia is lower. However, the QALY gain from deferral is slightly higher as the time spent in more severe stages is longer. The difference in cost from stage to stage is not very marked, in the ratio 2:3:3, with the result that the effect of doubling the transition rate is to lower the cost saving delivered by deferral. This explains the modest scale of the increase in the maximum price.

In treatment 1 analysis of a 5% reduction in transition in 85-year olds with AD shows that doubling the transition rate has little effect on the time spent with AD. The effect is to move the distribution by stage towards the more severe stages. Since the stage-specific QALY loss and the stage-specific cost is higher in the more severe stages, intervention both reduces QALY loss and increases cost saving. Since both elements of cost per QALY move in a favourable direction, the maximum price is more strongly affected by intervention, with increases in the region of 20%.

(b) A 10% increase in costs

The benefits from intervention fall into two categories: (a) savings in cost to the NHS, social services and carers; and (b) improvements in health related quality of life measured by QALYs. The impact of a 10% increase in cost depends on the balance between these two categories of benefit. If half the benefit takes the form of cost savings, the impact on the maximum justifiable price will be an increase of 5% and so on. In treatments 2-5, the impact on maximum price lies between 7.4% and 10.4%. For treatment 1, the impact for age 75 is negative because the effect of intervention on cost is to increase it, so that if costs are higher the maximum acceptable price of the treatment will fall.

(c) A threshold of £30,000 per QALY rather than £20,000

The effect of increasing the willingness-to-pay threshold by 50% to £30,000 per QALY depends upon the proportion of benefit accounted for by QALYS rather than cost savings. If the ratio is fifty-fifty the effect would be to increase the maximum justifiable price by 25%. For treatments 2-5 the increase in maximum price lies in the range 9.6%-15.1%. There is, however, a very high impact in treatment 1 for 75-year olds, in the range 79%-118% because intervention raises costs. The proportion of benefit accounted for by QALYs therefore exceeds 100%.

(d) Alternative estimates of age- and stage-specific mortality in AD

The AD results underlying the analysis above are based on age- and stage-specific mortality rates from Brookmeyer et al (2007): population mortality rates from life tables with an addition of 11% in the moderate and severe stages.

There are also estimates from CFAS I by Neale et al (2001). They follow Brookmeyer in not distinguishing moderate and severe stages. Moreover, the age ranges in CFAS I are wide.

Stage-specific transition rates are based on estimates by Spackman et al (2012), both when using CFAS I based mortality estimates as well as when using Brookmeyer based mortality estimates.

The two sets of rates were compared in terms of their impact on the maximum prices for treatment 1 for onset of AD at age 70 or 80. The differences proved small t both ages.

In the CFAS I estimates the open ended upper age range may be too wide to take account of the steep increases in rates by age in the very oldest age groups, which are important in AD.

Discussion

There is growing interest in studying the impact of potential disease-modifying treatments (DMTs) for dementia, and in particular for AD. ARUK commissioned this study from PSSRU to investigate the likely maximum price for a hypothetical new DMT for AD in order for it to satisfy the cost-effectiveness requirements associated with NICE.

The nature of AD suggests major benefits from deferring its onset, reducing the transition rate from prodromal AD to Alzheimer's dementia or reducing the transition rate to more severe stages of the condition. AD lasts for the rest of the patient's life and steadily gets worse. Its impact on health-related quality of life, its increased mortality risk and its cost to health and social care services and to unpaid carers all increase from stage to stage. The annual cost of the mild stage is £26,000 per year and the QALY penalty is about 0.1 per year depending on age. The benefit from deferring onset by one year is therefore about £28,000, other things being equal, if a QALY is valued at £20,000 (as represented by the willingness-to-pay threshold associated with NICE). It is therefore no surprise that the therapies considered in this paper would be cost-effective under the NICE threshold of £20,000 per QALY even at a substantial price and, given the incidence and prevalence of AD, that the impact of providing the therapies on NHS expenditure would be considerable.

The nature of the disease with its precursors and the substantial pre-clinical period has suggested several points for intervention. We have examined five treatment options developed in discussion with clinical experts. Treatment 1 relates to a DMT which reduces the transition rates between the stages of Alzheimer's dementia; treatments 2 and 3 relate to DMTs which reduce the rate of transition from prodromal AD to Alzheimer's dementia and to its severe stage respectively; treatment 4 relates to cognitively normal people at high risk and slows progression to Alzheimer's dementia; treatment 5 relates to a DMT offered to the entire population with the aim of delaying the onset of amyloid positivity, a necessary step in the development of AD.

Testing for eligibility is required for all the treatments except the fifth (treatment of all 50 year olds). For the other treatments, demonstration of amyloid pathology using PET or CSF extracted by lumbar puncture is assumed. Lumbar puncture is invasive, requires trained operators, and standardised methods for quantification, and costs about £450per test, but it is already used The currently available alternative, amyloid PET imaging, is considerably

more expensive; advances in due course may bring costs closer to those of CSF, and in due course blood-based biomarkers of AD pathology may reduce costs yet further.

The therapies are hypothetical at this stage. We have assumed that they are similar to current programmes or therapies in making modest demands on health services. Analogues would be the flu immunisation programme and preventive drug therapy such as anti-hypertensives and statins. In practice, new AD therapies might be much more demanding with side-effects requiring regular monitoring in general practice or secondary care. Our estimates also assume full compliance.

The annual expenditure on therapy is substantial, even on apparently modest assumptions about effectiveness. Moreover, because the benefits of therapy include not only savings on health and social care services but also (a) reduced opportunity costs of unpaid care and (b) monetised health-related quality of life (QALYs) gains, no intervention will-if priced at the maximum price compatible with the cost-effectiveness threshold of £20,000 per QALY-fully recover its cost to NHS budgets.

We have modelled the impacts of the DMTs both at individual and at collective level. At the *individual level*, we have estimated the impact on lifetime risk of onset of Alzheimer's dementia (from assumed age of commencement of therapy), except in the case of treatment 1 which relates to people already living with mild Alzheimer's dementia. We have also estimated at individual level the lifetime duration of therapy, annual cost of therapy, gain in life expectancy, gain in (discounted) quality-adjusted life expectancy and (discounted) lifetime savings on care costs. At the *collective level*, we have estimated the overall reduction in the annual incidence of Alzheimer's dementia, in the prevalence of Alzheimer's dementia and in expenditure on care as well as the overall annual cost of the therapy to NHS budgets.

The estimated impacts of the DMTs inevitably vary with their assumed effectiveness in deferring onset of Alzheimer's dementia (treatment 5), reducing transitions to Alzheimer's dementia (treatments 2-4) or reducing transitions to more severe stages (treatment 1). On our central assumptions, ***treatment 5*** has a much bigger impact on incidence, prevalence and costs than the other treatment options (see the summary of results in Table 12). ***Treatment 4*** has a substantial impact on incidence and prevalence of Alzheimer's dementia at relatively low net cost to health and social services. ***Treatments 2 and 3*** have a lower impact on incidence and prevalence of Alzheimer's dementia but higher net cost than treatment 4. ***Treatment 1*** has no impact on incidence of Alzheimer's dementia (by definition of the treatment option) and increases prevalence of AD due to its positive impact on life expectancy. It is essential to note that these findings are a function of the assumed effects of the hypothetical DMTs and of the assumption that they are priced at the maximum compatible with the NICE cost-effectiveness threshold of £20,000.

Table 12: Change in annual incidence, change in prevalence, reduction in annual cost, annual cost of intervention, annual net cost, UK

Treatment option	Reduction in rate of transition or delay in onset	incidence	prevalence	cost saved £ bn	cost of intervention £ bn	net increase £ bn
1	25%	-	+ 32,000	- 0.3	0.4	0.7
2	30%	6,100	- 59,600	2.0	2.1	0.2
3	30%	6,100	- 32,000	1.8	2.8	1.0
4	25%	12,600	-76,000	2.8	1.6	- 1.1
5	three year delay	47,900	- 394,000	12.7	9.4	- 3.3

There are inevitably uncertainties in the data on transition rates from prodromal AD to Alzheimer's dementia and from stage to stage within Alzheimer's dementia and on excess mortality rates by stage. We explored the sensitivity of results to different assumptions about mortality rates, transition rates and costs of care and to a different cost per QALY cost-effectiveness threshold. The alternative mortality rates for people with AD and higher transition rates between mild and moderate AD, which we examined, had little impact on our findings. A variant with higher costs of care produced findings for treatments 2-5 with higher maximum prices for the DMT, but the estimated maximum price rose in most cases by less than the assumed cost of care. The effect of this variant in treatment 1 is complex because the DMT increases life expectancy. Use of a cost-effectiveness threshold of £30,000 rather than £20,000 per QALY produces higher estimates for the maximum price of the DMT. In treatments 2-5 the estimated maximum price of the DMT is 10% to 15% higher under the £30,000 threshold than under the £20,000 threshold. In treatment 1, however, the maximum price is much higher under the higher threshold: this is because the main effect of the DMT in treatment 1 is to produce QALY gains rather than savings in care costs.

The analyses and findings presented in this report need to be treated with caution because of data uncertainties and because the nature, positive effects and side-effects, delivery and uptake of the hypothetical DMTs are necessarily assumptions. These data are therefore intended to be the first steps in promoting discussion and further modelling rather than as definitive answers.

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Appendix 1

Data Sources

Source of data on the age-specific incidence and prevalence of the different disease states and relevant transition rates.		
Amyloid and neuro-degeneration biomarker states	Prevalence by age, rates of transition by age	Jack CR, Therneau TN, Wiste HJ, Weigand SD, Knopman DS et al. (2016)
MCI	Incidence	Roberts RO, Geda YE, Knopman DS, Cha RH et al. (2012)
	Prevalence	Petersen RC, Roberts RO, Knopman DS, Geda YE et al. (2012)
	Transition	Vos SJB, Verhey F, Frölich L, Kornhuber J et al. (2015)
AD	Incidence	Matthews FE, Stephan BC, Robinson L, Jagger C et al; Cognitive Function and Ageing Studies (CFAS) Collaboration (2016)
	Prevalence	Matthews FE, Arthur A, Barnes LE, Bond J et al; Medical Research Council Cognitive Function and Ageing Collaboration (2013)
Within AD	Transition rates and mortality rates in AD	1. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM (2007) 2. Neale R, Brayne C, Johnson AL, Medical Research Council Cognitive Function Ageing Study Writing Committee (2001) 3. Spackman DE, Kadiyala S, Neumann PJ, Veenstra DL, Sullivan SD (2012) 4. National Life Tables, England Period expectation of life Based on data for the years 2012-2014 (ONS 2017)
	Costs by stage in AD	Dementia UK update Table 5.2 (Prince et al 2014)
	QALYS by stage in AD	Mild and moderate states Wimo A, Reed CC, Dodel R, Belger M, Jones RW, Happich M, et al (2013) Severe state Neumann PJ, Kuntz KM, Leon J, Araki SS, Hermann RC, Hsu MA, et al (1999) Population QALYs (for the comparator group) Health Survey for England (HSCIC 2013)
Cost of tests		Lumbar puncture/CSF[8] PET[9]

[8] PSSRU estimate based on data from Dr Jonathan Schott, National Hospital for Neurology and Neurosurgery

Appendix 2

Alzheimer's disease stages

Alzheimer's disease is characterised by a long pre-symptomatic stage that lasts around 15 years and consists of several, broadly sequential, mechanisms (NICE 2011). The first pathology that is detectable is the build-up and deposition of amyloid in the brain, which be tested for using a PET amyloid scan or a CSF amyloid test. Tau diagnostics are available but these are not well validated compared to amyloid and are not necessary for diagnosis of Alzheimer's disease.

As the disease progresses, neurodegeneration can be detected using FDG PET scanning and volumetric MRI, and clinical symptoms are likely to begin. Once symptoms begin to appear, the disease has progressed to the prodromal Alzheimer's disease stage. As neurodegeneration continues, these symptoms gradually become more severe until they can be classified as dementia, defined by an MMSE score of <27 by NICE though there are factors that can influence which cut-offs are used such as education.

- Pre-symptomatic Alzheimer's disease: Alzheimer's disease without cognitive impairment.
- Prodromal Alzheimer's disease: Alzheimer's disease with clinical diagnosis of mild cognitive impairment.
- Alzheimer's dementia: Alzheimer's disease with clinical diagnosis of dementia.

Cognitive ability

The cognitive stages of dementia can be grouped into the following and match the disease stages detailed above;

- Cognitive normality: no impairment
- Mild cognitive impairment: a broad and imperfectly defined syndrome characterised by a clinical diagnosis of a mild impairment that is not severe enough to be classed as dementia. Commonly defined as a Clinical Dementia Rating (CDR) score of 0.5 though no consensus on Mini Mental State Examination (MMSE) cut-offs.

[9] Planning a Clinical PET Centre. IEAE Huan Health Series. No. 11. Vienna. 2010.

- Dementia: a syndrome, a collection of symptoms diagnosed through a clinical assessment that can be caused by a number of different conditions. Impairment is severe enough to affect ADL and commonly defined by a MMSE score of <27 or CDR of 1.

Dementia is then split into three groups based on increasing severity;

  - Mild dementia: CDR = 1 or MMSE = 26 - 21
  - Moderate dementia: CDR = 2 or MMSE = 20 - 10
  - Severe dementia: CDR = 3 or MMSE = <10 [23]

Diagnostic criteria

In this paper, we have used two sources for diagnostic criteria not including the well-established guidelines for dementia and Alzheimer's dementia.

The first is from the Jack et al. (2016)[Error! Bookmark not defined.] diagnostic criteria, which is used in treatment 4 to define the cognitively normal but amyloid positive patient group. Amyloid positivity (A+) and evidence of neurodegeneration (N+) are the biomarkers used. Amyloid positivity without clinical symptoms is referred to as pre-symptomatic Alzheimer's disease, from above.

For treatment 4, we are interested in people who are clinically normal though with amyloid and so the diagnostic needed is CSF amyloid to confirm A+, while N status is not necessary.

The second is the Vos et al. (2015)[Error! Bookmark not defined.], which is used in treatments 2 and 3 to define the prodromal Alzheimer's disease patient group using the International Working Group 2 criteria (2014). Testing for any cognitive impairment, CSF amyloid and, CSF tau positivity or abnormal amyloid PET are the criteria used. Amyloid positivity and mild cognitive impairment is referred to as prodromal Alzheimer's disease, from above.

For treatment 4, we are interested in people who are mildly impaired with amyloid and therefore the diagnostic needed is CSF amyloid and tau as we assume that MCI has been ascertained.

Treatment Summaries

In this report, we seek to model several treatments, each with a different patient group defined by their cognitive ability and Alzheimer's disease stage, and age. The target groups

for each treatment are set out below, though testing specificity and sensitivity as well as the lack of homogeneity in Alzheimer's disease, there may be some overlap between them in reality.

Treatment 1

- Patient group: All those with a diagnosis of dementia.
- Cognitive stage: Dementia.
- Alzheimer's disease stage: Alzheimer's dementia.
- Biomarker diagnostic used: Amyloid CSF.
- Pathologies present: Amyloid, tau, inflammation and severe neurodegeneration.

Treatments 2 and 3

- Patient group: Aged 70-89
- Cognitive stage: Mild cognitive impairment.
- Alzheimer's disease stage: Prodromal Alzheimer's disease.
- Biomarker diagnostic used: Amyloid and tau CSF.
- Pathologies present: Amyloid, tau, inflammation and neurodegeneration.

Treatment 4

- Patient group: Aged 70.
- Cognitive stage: Cognitively normal.
- Alzheimer's disease stage: Pre-symptomatic Alzheimer's disease.
- Biomarker diagnostic used: Amyloid CSF.
- Pathologies present: Amyloid, possibly tau and inflammation, and possibly very minor neurodegeneration.

Treatment 5

- Patient group: Aged 50+.
- Cognitive stage: Cognitively normal.

- Alzheimer's disease stage: None.
- Biomarker diagnostic used: None.
- Pathologies present: None.

Appendix 3: Cost effectiveness using a Markov process model

A Markov model is used to represent flow of patients from prodromal AD through the three stages of Alzheimer's dementia and on to death. Time progresses in a series of units of fixed length, in this case a year. In each year in the sequence, the patient either dies, moves to the next stage or remains in the stage, according to input transition and mortality rates. The death rates vary by age and AD stage. In the cost effectiveness application the base node is identical to the intervention node except that there is no factor modifying the rate of transition from prodromal AD to Alzheimer's dementia. There are underlying values for

- mean QALY in the different states,
- costs in the different states (to the NHS, to formal and informal care),
- the front end cost of testing for eligibility

The price of the therapy can also be an input and the associated cost per QALY produced by the model, but in this study the price was estimated by threshold analysis, pinpointing the value at which the cost effectiveness (cost per QALY) of the intervention just meets the NICE threshold, here taken to be £20,000 per QALY. All cost and QALY values are discounted at a rate of 3.5% pa.

The model is run from the stage selected for intervention for a long enough period for everyone in the cohort to have completed their life cycle.