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Protocol for a systematic literature review of methodologies and data sources of existing economic models across the full spectrum of Alzheimer's disease and dementia from apparently healthy through disease progression to end of life care

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Protocol for a systematic literature review of methodologies and data sources of existing economic models across the full spectrum of Alzheimer's disease and dementia from apparently healthy through disease progression to end of life care

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Abstract

Introduction: Dementia is one of the greatest health challenges the world will face in the coming decades, as it is one of the principal causes of disability and dependency among older people. Economic modelling is used widely across many health conditions to inform decisions on health and social care policy and practice. The aim of this literature review is to systematically identify, review and critically evaluate existing health economics models in dementia. We included the full spectrum of dementia, including Alzheimer's Disease (AD), from preclinical stages through to severe dementia and end of life. This review forms part of the Real World Outcomes across the AD spectrum for better care: multi-modal data access platform (ROADMAP) project.

Methods and analysis: Electronic searches were conducted in MEDLINE, Embase, CDSR, CENTRAL, DARE, NHS EED, and TRIP for studies published between January 2000 and the end of June 2017. Two reviewers will independently assess each study against predefined eligibility criteria. A third reviewer will resolve any disagreement. Data will be extracted using a pre-defined data extraction form following best practice. Study quality will be assessed using the Phillips checklist, for decision analytic modelling. A narrative synthesis will be used.

Ethics and Dissemination: The results will be made available in a scientific peer-reviewed journal paper, will be presented at relevant conferences, and will also be made available through the ROADMAP project.

Prospero registration number: CRD42017073874

Keywords: dementia, Alzheimer's disease, economic model, disease progression, systematic review

Strengths of study

- This systematic literature review of published economic models of dementia and AD is broad in terms of disease stages since the searches are being conducted across the full spectrum of dementia, including Alzheimer's Disease (AD), from preclinical stages through to severe dementia and end of life.
- The searches cover a wide range of databases using detailed search strategies and include studies from any OECD country published in English language between January 2000 to June 2017.
- The review will be reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis statement and will use the Phillips checklist for decision analytic modelling to assess the quality of the models reported in the studies.

Limitations of study

- We are excluding conference abstracts, commentaries and studies in languages other than English.

Introduction

Dementia is a progressive neurodegenerative disease that encompasses cognitive and functional impairment and behavioural symptoms[1]. People living with dementia may have difficulty with language, memory, perception, behaviour and activities of daily living. Impairments increase as the disease progresses[1], and there is no curative treatment. Caring for a person with dementia may also considerably affect the quality of life and health of caregivers, who experience increased rates of depression and financial difficulties[2].

An estimated 47 million people are believed to be living with dementia worldwide, and – as a result of demographic shifts towards an ageing society and increased survival of people with dementia – that number is expected to rise to around 131 million by 2050[3]. Dementia not only exerts a considerable toll on people living with dementia and their caregivers, its impact reaches health and social care systems and the wider society[1]; the global cost of dementia was estimated to be US$818 billion in 2015 and is projected to rise to US$2 trillion by 2030[4].

Alzheimer's disease (AD) is the most common cause of dementia. AD is a spectrum, the earliest stage of the disease is mild cognitive impairment (MCI) where patients experience a reduction in their cognitive abilities beyond the expected cognitive decline for their age and education[1]. The symptoms may be subtle and MCI may go unrecognized for some time[1]. Whilst MCI may be due to the early stages of AD[5-8], MCI can result from other clinical conditions including depression and medication side-effects, which – unlike AD – may be reversible. The need for early detection and intervention in MCI is therefore crucial[1].

Economic models can examine progression of AD from early stages such as MCI to severe dementia, in order to quantify the impact of AD across the spectrum of clinical severity. Robust economic models guide policy-makers in deciding how best to allocate scarce public

funds. Whilst economic models have been used extensively for other health conditions – such as stroke, diabetes, obesity and cardiovascular diseases[9] – such modelling has been relatively less used for AD[10]. However, as the number of people living with dementia increases, high-quality economic models will be required to provide the tools for governments and other decision-makers to implement cost-effective solutions to make the best use of scarce resources.

Some reviews have discussed the use of economic modelling in AD[10-17], mainly to compare alternative interventions rather than to identify methodological issues and data gaps affecting the economic evaluation[10-14]. Most of the existing systematic literature reviews focused their searches on a limited number of databases (mainly PUBMED, Embase and EconLit). In 2011, Green at al[10] conducted a systematic literature review on methods of modelling disease progression in AD.

This systematic literature review updates and builds upon this existing work. It aims systematically to review existing economic models of dementia – including but not limited to AD – across the full spectrum of disease severity, from preclinical stages through to severe dementia and end of life[18], and including models of the full range of interventions except primary prevention.

This review will inform further stages of the ROADMAP (Real world Outcomes across the Alzheimer's Disease spectrum for better care: Multi-modal data Access Platform) project, in particular the development of a new proof-of-concept model to evaluate the cost-effectiveness of interventions for the full spectrum of dementia, including Alzheimer's Disease (AD), from preclinical stages through to severe dementia and end of life.

In this context, the review aims to meet three specific objectives:

1. To systematically identify previous economic modelling studies across the full spectrum of dementia, including AD, from preclinical stages through to severe dementia and end of life care.
2. To describe the key features of those models in terms of their aim, structure, coverage, data sources and outputs.
3. To assess the quality of existing models and describe their main strengths and weaknesses following best-practice guidelines for the evaluation of model-based economic evaluations.

Methods and analysis

Protocol and registration

This systematic literature review protocol is reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) (Supplementary file 2)[19]. The protocol has been registered with the PROSPERO international prospective register of systematic reviews (CRD42017073874). The results of this review will be reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement[20-22]. Any amendments to this protocol will be reported and published.

Study selection criteria

***Participants*:**

This review focuses on all adults in all care settings in the full spectrum of dementia, including Alzheimer's Disease (AD), from preclinical stages through to severe dementia and

end of life. Although AD is the core of this review, we also include dementia among our search terms.

Study design:

The review includes studies reporting existing economic models across any part of the dementia or AD spectrum (from preclinical stages through to severe dementia and end of life).

The following study designs will be considered for inclusion and further consideration: cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-minimisation analysis, cost analysis, cost-consequences analysis, economic evaluation, health technology appraisal, and treatment pathway study.

We will exclude editorials, case studies, phase I and phase II clinical trials, newspaper articles, book sections, patient and expert opinion or commentary, social media and papers describing adaptations of existing economic models. Papers that fail to meet any one of the above eligibility criteria will be excluded from the review. The number of excluded studies (including reasons for their exclusion) will be recorded.

Outcomes:

The outcome measures of interest include:

- Model type and structure
- Markers/measure used to model disease progression
- Types of clinical/disease pathways
- Data used to structure and parameterise the model

- Summary/synthesis of challenges, limitations and data gaps for developing an economic model for preclinical, MCI and AD/dementia.

Intervention:

All types of AD or dementia interventions (both symptomatic and disease modifying) will be included.

Context:

Models developed in any OECD country will be included as long as the paper is written in English.

Search Strategy

Electronic databases

The following electronic databases were searched for papers published between 1st of January 2000 and 27th of June 2017: Medical Literature Analysis and Retrieval System Online (Ovid MEDLINE); Excerpta Medica dataBASE (Ovid Embase); Economic Literature Database (EconLit); *NHS* Economic Evaluation Database (*EED*); *Cochrane Central Register of Controlled Trials* (Cochrane Library); Cost-Effectiveness Analysis Registry (CEA Registry); Research Papers in Economics (RePEc); Database of Abstracts of Reviews of Effectiveness (DARE); Science Citation Index (SCI); Turning Research Into Practice (TRIP); Open Grey (Supplementary file 2).

The search terms include (but not limited):

-Alzheimer's disease, dementia, mild cognitive impairment

-Cost-effectiveness analysis, cost utility analysis, cost analysis, economic models, Markov chains, pharmaeconomics.

The search strategies are designed such that to be selected for review of title and abstract papers needed to contain a term from each of these two categories. A copy of the search strategies is at the supplementary file 1.

Manual searching

The reference lists of studies included in the review are being hand-searched to identify any additional literature.

Study selection

The electronic reference management tool EndNote X7 by Thomson Reuters will be used in order to export and manage the references. Duplicates will be removed by one reviewer (MKa) and all the remaining titles and abstracts, will be identified through the searches, will be reviewed against the predefined eligibility criteria by two reviewers (MKa and AP) in order to determine if there is a need for a further full text review. The relevance of each study will be assessed according to the inclusion and exclusion criteria. For those studies that appear to meet the inclusion criteria, or in cases where a decision cannot be safely made based on the title/abstract only, a full text will be retrieved for the assessment. Studies that do not fulfil the inclusion criteria will be excluded. Disagreements are will be resolved by a third reviewer (RW).

The full process will be presented in a flow chart and in detail according to PRISMA guidelines[20].

Data extraction

Two reviewers (AP and MKa) will extract the data from the included studies (supplementary file 3). They will each independently check the data extraction forms for accuracy and completeness. Any disagreements will be noted and resolved by a third reviewer (RW).

The following information will be extracted:

- Study details: title, author, publication details, language of the study, aim of the study, countries of the study, funding of the study, study funding source.
- Study design: objective of the study, purpose of the modelling, types of modelling study (i.e. review of models), type of model, model input data, model output, source of data incorporated into the model, model perspective, model time horizon.
- Setting: community setting, institutional setting, primary care, secondary care, tertiary care, mixed setting.
- Participant information: type of participant, number of participants, demographic information.
- Disease-specific information: type of dementia, level of severity, disease progression measurement.
- Outcomes: Outcomes modelled and costs (and cost types).
- Approach to model validation and evidence of validation performance.
- Key findings.
- Author's comments on strengths and weaknesses of the model and potential gaps in available data.

Risk of bias (quality) assessment

The quality of the model is the core of our review. Thus, the quality of identified models will be assessed from the perspective of best current practice. The 'Philips checklist'[23-24],as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*[25], will be used to assess the quality of the models reported in the studies included in the review. Two researchers will independently review and assess the models.

Strategy for data synthesis

A narrative synthesis will be used for the present study.

Ethics and dissemination plans

The included studies will be reviewed to ensure ethical considerations were taken into account. The results will be published in the form of a publication in a peer-reviewed journal. In addition, the results will be presented at conferences and will be published in the ROADMAP project's official website (http://roadmap-alzheimer.org/).

Discussion

Economic models are useful to inform policy decisions by providing evidence on the cost-effectiveness of current and new interventions. The aim of this systematic literature review is to systematically identify and review the existing economic modelling methodologies across the full spectrum of dementia, including Alzheimer's Disease (AD), from preclinical stages through to severe dementia and end of life [18]. The focus will be on the models, their structure and the information and assumptions used to parameterise them, and not on the interventions per se. We will consider modelling of both symptomatic and disease-modifying interventions[18]. The way in which disease progression is represented in

economic models will also be covered[18]. This systematic literature review will inform the design and development of future economic modelling across the full spectrum of dementia, including Alzheimer's Disease (AD), from preclinical stages through to severe dementia and end of and identify research and data gaps.

Funding sources/sponsors

The review is part of the Real World outcomes across the AD spectrum for better care (ROADMAP) project. This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 116020 ("ROADMAP"). This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

Conflicts of interest

MKa, RW, FL, AP, AF, MKn, AMG, IG and JW declare that they have no conflicts of interest.

Antje Tockhorn-Heidenreich is an employee of Eli Lilly and Company Limited and owns stock in Eli Lilly and Company Limited.

Yovanna Castro is an employee of F. Hoffmann-La Roche Ltd.

Ron Handels reports grants from ROADMAP (IMI2; public-private collaboration; 2016-2019) to conduct this study; grants from BIOMARKAPD (EU JPND project; 2012-2016), grants from Actifcare (EU JPND project; 2014-2017), grants from European Brain Council (VoT project; public-private collaboration; 2017), grants from Dutch Flutemetamol Study (public-private collaboration; 2012-2017), personal fees from Piramal (advisory; 2016), personal fees from Roche (advisory; 2017), outside the submitted work.

Pascal Lecomte is employed by, owns stock in, and has stock options in Novartis Pharma AG.

Novartis Pharma AG, GE Healthcare, Biogen, Eli Lilly and Company Limited and Roche are industry partners in the ROADMAP Project.

Contributors

All authors participated in designing this review. MKa and RW wrote this protocol. MKa, RW, AF and AP devised the search strategy. PL, RW, AMG, MKn, FL, IG, JW, ATH, RH, YC critically appraised the protocol and contributed to its development. All authors read and approved the final version of the manuscript.

Acknowledgments

We would like to acknowledge the contributions of the remaining members of Work Package 5 as well as of those of the wider ROADMAP group.

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Supplementary material

Supplementary file 1: PRISMA-P checklist

Section and topic	Item No.	Checklist Item	Reported on page #
A) Administrative Information			
Identification	1a	Identify the report as a protocol of a systematic review	3
Update	1b	Identify protocol as an update of a previous systematic review if applicable	n/a
Registration	2	Name of registry and registration number	PROSPERO CRD42017073874
B) Authors			
Contact		Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions		Describe contributions of protocol authors and identify the guarantor of the review	14-15
Amendments		If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
- Sources	5a	Indicate Sources of financial or other support for the review	13-14
- Sponsor	5b	Provide name for the review funder and/or sponsor	13-14
- Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s) and/or institution(s), if any, in developing the protocol	n/a
C) Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	6-7-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6-7-8
D) Methods			
Eligibility Criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9-10
Information Sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10

Search Strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary file 2
E) Study Records			
Data Management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10
Selection Process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10-11
Data Collection Process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10-11 Supplementary file 3
Data Items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	n/a
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
Section and topic	**Item No.**	**Checklist Item**	**Reported on page #**
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12-13
Data Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	13
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency	13
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	n/a
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n.a.
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed	12

Supplementary file 2: search terms

Medline (1,004)	**Results**
1 *Alzheimer Disease/	64223
2 Alzheimer$.ti.	59334
3 AD.ti.	5366
4 *Dementia/	34251
5 Dementia$.ti.	40800
6 *cognitive impairment/	4771
7 MCI.ti.	900
8 ((mild$ or early$ or preclinical$ or pre-clinical$ or presymptomatic$ or pre-symptomatic$) adj2 "cognit$ impair$").ti.	5620
9 (nMCI or aMCI or mMCI).ti.	28
10 ("N-MCI" or "A-MCI" or "M-MCI").ti.	1
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	122899
12 exp models, economic/	12958
13 exp Decision theory/	11242
14 markov chains/	12259
15 monte carlo method/	26064
16 *Models, Organizational/	5948
17 *Models, Theoretical/	53981
18 econom$ model$.ti,ab.	3043
19 markov$.ti,ab.	19550
20 monte carlo.ti,ab.	42311
21 (decision$ adj2 (tree$ or analy$ or model$)).ti,ab.	18228
22 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	160846
23 11 and 22	487
24 "costs and cost analysis"/ or cost-benefit analysis/	115993
25 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ti,ab.	129287
26 ((economic$ or pharmacoeconomic$ or pharmaco-economic$) adj2 (analy$ or assessment$ or evaluat$)).ti,ab.	17890
27 24 or 25 or 26	209070
28 11 and 27	1037
29 23 or 28	1484
30 limit 29 to (english language and yr="2000 - Current")	
31 (case reports or clinical trial phase i or comment or editorial or letter).pt. or (case report or case study or letter? or editorial).ti.	3422279
32 30 not 31	1009
33 exp animals/ not humans/	4421684
34 32 not 33	1004

Embase (1,625)	**Results**
1 *Alzheimer Disease/	94066
2 Alzheimer$.ti.	77377
3 AD.ti.	7477
4 *Dementia/	47685
5 Dementia$.ti.	52957
6 *cognitive impairment/	42050
7 MCI.ti.	1922
8 ((mild$ or early$ or preclinical$ or pre-clinical$ or presymptomatic$ or pre-symptomatic$) adj2 "cognit$ impair$").ti.	8238
9 (nMCI or aMCI or mMCI).ti.	81
10 ("N-MCI" or "A-MCI" or "M-MCI").ti.	8
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	196654
12 statistical model/ and exp economic aspect/	19488
13 decision theory/	1649
14 "decision tree"/	8693
15 markov chain/	1495
16 monte carlo method/	30330
17 *nonbiological model/	4382
18 *theoretical model/	28156
19 econom$ model$.ti,ab.	4345
20 markov$.ti,ab.	22744
21 monte carlo.ti,ab.	36266
22 (decision$ adj2 (tree$ or analy$ or model$)).ti,ab.	24115
23 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	140325
24 11 and 23	660
25 economic evaluation/ or "cost benefit analysis"/ or "cost effectiveness analysis"/ or "cost minimization analysis"/ or "cost utility analysis"/	202575
26 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ti,ab.	168377
27 ((economic$ or pharmacoeconomic$ or pharmaco-economic$) adj2 (analy$ or assessment$ or evaluat$)).ti,ab.	24734
28 25 or 26 or 27	286727
29 11 and 28	1689
30 24 or 29	1659
31 limit 30 to (english language and yr="2000 -Current")	1652
32 (editorial or letter or note or press).pt. or (case report or case study or letter? or editorial).ti. or case report/ or phase i clinical trial/	4510251
33 31 not 32	1639
34 exp animal/ or exp animal experiment/ or nonhuman/	24796958
35 exp human/ or human experiment/	18601088
36 34 not (34 and 35)	6196899
37 33 not 36	1625

SCI Expanded

20	19 Refined by: [excluding] DOCUMENT TYPES: (PROCEEDINGS PAPER OR NEWS ITEM OR EDITORIAL MATERIAL OR MEETING ABSTRACT OR LETTER)	880
19	14 or 18 AND LANGUAGE: (English)	1,039
18	8 and 17	699
17	15 or 16	188,615
16	TS=((economic* or pharmacoeconomic* or pharmaco-economic*) near/2 (analy* or assessment* or evaluat*))	32,775
15	TS=((cost* near/2 (effective* or utilit* or benefit* or minimi*)))	166,898
14	8 and 13	420
13	9 or 10 or 11 or 12	239,113
12	TS=(decision* near/2 (tree* or analy* or model*))	34,261
11	TS=("monte carlo")	145,136
10	TS=("Markov*")	68,597
9	TS=("econom* model*")	6,638
8	1 or 2 or 3 or 4 or 5 or 6 or 7	92,853
7	TI=("N-MCI" or "A-MCI" or "M-MCI")	5
6	TI=(nMCI or aMCI or mMCI)	52
5	TI=((mild* or early* or preclinical* or pre-clinical* or presymptomatic* or pre-symptomatic*) near/2 "cognit* impair*")	6,590
4	TI=(MCI)	1,272
3	TI=(dementia*)	31,513
2	TI=(AD)	12,378
1	TI=(alzheimer*)	49,389

EconLit

S5	S1 OR S2 OR S3	**Limiters** - Published Date: 2001-01-01-20161231 **Narrow by Language:** - english **Search modes** - Find all my search terms	94
S4	S1 OR S2 OR S3	**Search modes** - Find all my search terms	109
S3	TI "cognit* impair*"	**Search modes** - Find all my search terms	7
S2	TI dementia*	**Search modes** - Find all my search terms	46
S1	TI alzheimer*	**Search modes** - Find all my search terms	58

Cochrane Library (CDSR, DARE, Central, HTA, CMR)

#1 MeSH descriptor: [Alzheimer Disease] this term only 2523
#2 MeSH descriptor: [Dementia] this term only 1737
#3 MeSH descriptor: [Cognitive Dysfunction] this term only 165
#4 alzheimer* or dementia*:ti,ab,kw (Word variations have been searched) 11782
#5 MCI:ti,ab,kw (Word variations have been searched) 1158
#6 (mild* or early* or preclinical* or pre-clinical* or presymptomatic* or pre-symptomatic*) near/2 "cognit* impair*":ti,ab,kw (Word variations have been searched) 1392
#7 #1 or #2 or #3 or #4 or #5 or #6 12720
#8 MeSH descriptor: [Models, Economic] explode all trees 2017
#9 MeSH descriptor: [Decision Theory] explode all trees 929
#10 MeSH descriptor: [Markov Chains] this term only 2165
#11 MeSH descriptor: [Monte Carlo Method] this term only 549
#12 MeSH descriptor: [Models, Organizational] this term only 232
#13 MeSH descriptor: [Models, Theoretical] this term only 959
#14 "econom* model*" or markov* or "monte carlo":ti,ab,kw (Word variations have been searched) 3789
#15 decision* near/2 (tree* or analy* or model*):ti,ab,kw (Word variations have been searched) 3200
#16 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 8524
#17 #7 and #16 78
#18 MeSH descriptor: [Costs and Cost Analysis] this term only 3895
#19 MeSH descriptor: [Cost-Benefit Analysis] this term only 18292
#20 cost* near/2 (effective* or utilit* or benefit* or minimi*):ti,ab,kw (Word variations have been searched) 32418
#21 (economic* or pharmacoeconomic* or pharmaco-economic*) near/2 (analy* or assessment* or evaluat*):ti,ab,kw (Word variations have been searched) 6451
#22 #18 or #19 or #20 or #21 36676
#23 #7 and #22 400
#24 #17 or #23 428 (+the NHS-EED)

NHS EED (on Cochrane Library also)

#1 MeSH descriptor: [Alzheimer Disease] this term only 2523
#2 MeSH descriptor: [Dementia] this term only 1737
#3 MeSH descriptor: [Cognitive Dysfunction] this term only 165
#4 alzheimer* or dementia*:ti,ab,kw (Word variations have been searched) 11782
#5 MCI:ti,ab,kw (Word variations have been searched) 1158
#6 (mild* or early* or preclinical* or pre-clinical* or presymptomatic* or pre-symptomatic*) near/2 "cognit* impair*":ti,ab,kw (Word variations have been searched) 1392
#7 #1 or #2 or #3 or #4 or #5 or #6 88

CEA Registry

dementia, alzheimer, alzheimer's, alzheimers 61

OpenGrey

(dementia* OR alzheimer*) AND (cost* OR economic* OR pharmacoeconomic* OR pharmaco-economic* OR decision*)	**23**

TRIP

(title:(dementia OR alzheimer))(title:(cost OR economic OR pharmacoeconomic OR pharmaco-economic OR decision))	273

RePEc

(dementia* OR alzheimer*) AND (cost* OR economic* OR pharmacoeconomic* OR pharmaco-economic* OR decision*)	**133**

Supplementary file 3: Data extraction from

Data extraction form *on methodologies and data sources of existing health economic models across the AD spectrum from apparently healthy through disease progression to end of life care*

Title of the study	
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*	
Notes	

General Information

Date when form was completed *(dd/mm/yyyy)*	
Name of person extracting data	
Author (s)	
Corresponding author contact details	
Language of the study	
Year published	
Country	
Aim of the study	
Study funding resource	
Possible conflict of interest	
Publication type *(e.g. full report, abstract, letter)*	
Notes:	

Methods

	Descriptions as stated in the study
Type of study	Review of models ☐ (if "*Yes*", please go to Section **A**) Description of a models ☐ (if "*Yes*", please go to Section **B**) Report of an economic evaluation with description of a model ☐ (if "*Yes*", please respond to questions about type of evaluation & then go to Section B) • Economic evaluation study with a model ☐

	Disease progression modelling ☐ Care pathway modelling ☐ Costs modelling ☐ *Cost effectiveness analysis* ☐ *Cost benefit analysis* ☐ *Cost utility analysis* ☐ *Cost minimisation analysis* ☐ Cost-consequences analysis Other (please, specify): …….
Section A *Review model studies*	
Types of modelling study	• Models covered: …… …… …… …… • Key papers referred for each model: …… …… …… …… …… …… • Are those papers included in our review? If **Yes** (*please, specify which of them*): …… …… …… …… …… If **No** (*please, specify which of them*): …… …… …… …… …… • Databases searched: ……

	…… …… • Search terms: …… …… …… • Time period covered: …… …… …… • Author's conclusions: …… …… ……
Important note:	**The rest of the template does not apply to reviews of models.**
	Section B *Purpose of the model*
Type of model	Markov model ☐ Microsimulation model ☐ Discrete events model ☐ Decision tree ☐ Other (*please, specify*): …… ……
Model input data **(*note:* *If there is more than one set of input data, this part needs to be repeated*)**	Country: …… Year: …… Source (e.g. survey of clinics): …… Disease covered (e.g. just AD or all dementias): …… Disease progression measurement: …… Population covered (e.g. just older people): …… Stages covered (e.g. mild, moderate, severe): …… Services covered (e.g. health care, social care): …… Costs covered (e.g. secondary health care): …… Outcomes covered (e.g. DemQol): …… Other (*please, specify*): ……

Model outputs	Disease progression: …… Care pathway: …… Lifetime costs: …… Outcomes for users: …… Outcomes for carers: …… Other (please, specify): ……
Source of data incorporated into the model:	-***Please, tick all that apply***: Data collected alongside a clinical trial ☐ Population survey ☐ *Cohort study* ☐ *Before and after study* ☐ *Expert opinion* ☐ *Other (please, specify)*: …… …… Assumptions made: Yes ☐ No ☐ If the answer is "Yes", please specify: …… ……
Setting *(please describe)*	Community setting: ☐ Institutional setting: ☐ Primary care: ☐ Secondary care: ☐ Tertiary care: ☐ Mixed setting: ☐ Unclear: ☐ Other (*specify*):……
Patient population characteristics *(please describe – if we have more than one data set then we have to fill that part for every data set)*	• Study from which participants are drawn: …… • Definition of dementia: …… …… …… • Type of dementia: …… • Disease severity: Pre-symptomatic AD/dementia: ☐ Mild cognitive impairment (MCI) due to AD: ☐

	Mild AD/dementia: ☐ Moderate AD/dementia: ☐ Severe AD/dementia: ☐ EoL: ☐ • Method used to define disease severity: …… …… …… • Mean age: …… • Number of participants: …… • Sex of participants: …… • Other (*please, specify*): …… …… ……
Perspective of analysis	Societal ☐ Health and care system ☐ Health care provider ☐ Patient and family ☐ Third party payer ☐ Other (please, specify): ……
Time frame of the modeling *(please, specify the time horizon of the study and in the case of a Markov model, please specify the cycle length)*	
Cost data	Primary ☐ Secondary ☐ If secondary, please specify: …… ……
Cost included	**Direct medical** ☐ • *Direct treatment* ☐ • *Inpatient* ☐ • *Outpatient* ☐ • *Day care* ☐ • *Community health care* ☐ • *Medication* ☐ **Other, please specify:** ……

	Direct non-medical ☐ • *Social care* ☐ • *Social benefits* ☐ • *Travel costs* ☐ • *Caregiver out-of-pocket* ☐ • *Training of staff* ☐ **Other, please specify:** ..... **Lost productivity** ☐ • *Income forgone due to illness* ☐ • *Income forgone due to death* ☐ • *Income forgone by caregiver* ☐ **Other, please specify:** .....
Currency	
Year of costing	
Type of discount used	No discount used ☐ For benefits and costs ☐ Only for costs ☐ In the case that a discount rate used, please give details of the discount rate: .....
Notes:	

Other information

	Description as stated in report/paper	
Key findings (if any)		
Quality checklist score		
Author's comments on strengths and weaknesses of model(s)		
Reviewer's comments on strengths and weaknesses of the model(s)		
Further information required from author		
References to other relevant studies		
Correspondence required for further study information *(from whom, what and when)*		
Notes:		

BMJ Open

Protocol for a systematic literature review of methodologies and data sources of existing economic models across the full spectrum of Alzheimer's disease and dementia from apparently healthy through disease progression to end of life care

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020638.R1
Article Type:	Protocol
Date Submitted by the Author:	04-Mar-2018
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Primary Subject Heading:	Health economics
Secondary Subject Heading:	Neurology
Keywords:	Dementia < NEUROLOGY, economic model, disease progression, alzheimer's disease, systematic review

Protocol for a systematic literature review of methodologies and data sources of existing economic models across the full spectrum of Alzheimer's disease and dementia from apparently healthy through disease progression to end of life care

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Abstract

Introduction: Dementia is one of the greatest health challenges the world will face in the coming decades, as it is one of the principal causes of disability and dependency among older people. Economic modelling is used widely across many health conditions to inform decisions on health and social care policy and practice. The aim of this literature review is to systematically identify, review and critically evaluate existing health economics models in dementia. We included the full spectrum of dementia, including Alzheimer's Disease (AD), from preclinical stages through to severe dementia and end of life. This review forms part of the Real World Outcomes across the AD spectrum for better care: multi-modal data access platform (ROADMAP) project.

Methods and analysis: Electronic searches were conducted in MEDLINE, Embase, EconLit, NHS EED, Cochrane Library, CEA Registry, RePec, DARE, CSI, TRIP and Open Grey for studies published between January 2000 and the end of June 2017. Two reviewers will independently assess each study against predefined eligibility criteria. A third reviewer will resolve any disagreement. Data will be extracted using a pre-defined data extraction form following best practice. Study quality will be assessed using the Phillips checklist, for decision analytic modelling. A narrative synthesis will be used.

Ethics and Dissemination: The results will be made available in a scientific peer-reviewed journal paper, will be presented at relevant conferences, and will also be made available through the ROADMAP project.

Prospero registration number: CRD42017073874

Keywords: dementia, Alzheimer's disease, economic model, disease progression, systematic review

Strengths of study

- This systematic literature review of published economic models of dementia and AD is broad in terms of disease stages since the searches are being conducted across the full spectrum of dementia, including Alzheimer's Disease (AD), from preclinical stages through to severe dementia and end of life.
- The searches cover a wide range of databases using detailed search strategies and include studies from any OECD country published in English language between January 2000 to June 2017.
- The review will be reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis statement and will use the Phillips checklist for decision analytic modelling to assess the quality of the models reported in the studies.

Limitations of study

- We are excluding conference abstracts, commentaries and studies in languages other than English.

Introduction

Dementia is a progressive neurodegenerative disease that encompasses cognitive and functional impairment and behavioural symptoms[1]. People living with dementia may have difficulty with language, memory, perception, behaviour and activities of daily living. Impairments increase as the disease progresses[1], and there is no curative treatment. Caring for a person with dementia may also considerably affect the quality of life and health of caregivers, who experience increased rates of depression and financial difficulties[2].

An estimated 47 million people are believed to be living with dementia worldwide, and – as a result of demographic shifts towards an ageing society and increased survival of people with dementia – that number is expected to rise to around 131 million by 2050[3]. Dementia not only exerts a considerable toll on people living with dementia and their caregivers, its impact reaches health and social care systems and the wider society[1]; the global cost of dementia was estimated to be US$818 billion in 2015 and is projected to rise to US$2 trillion by 2030[4].

Alzheimer's disease (AD) is the most common cause of dementia. AD is a spectrum, the earliest stage of the disease is mild cognitive impairment (MCI) where patients experience a reduction in their cognitive abilities beyond the expected cognitive decline for their age and education[1]. The symptoms may be subtle and MCI may go unrecognized for some time[1]. Whilst MCI may be due to the early stages of AD[5-8], MCI can result from other clinical conditions including depression and medication side-effects, which – unlike AD – may be reversible. The need for early detection and intervention in MCI is therefore crucial[1].

Economic models can examine progression of AD from early stages such as MCI to severe dementia, in order to quantify the impact of AD across the spectrum of clinical severity. Robust economic models guide policy-makers in deciding how best to allocate scarce public

funds. Whilst economic models have been used extensively for other health conditions – such as stroke, diabetes, obesity and cardiovascular diseases[9] – such modelling has been relatively less used for AD[10]. However, as the number of people living with dementia increases, high-quality economic models will be required to provide the tools for governments and other decision-makers to implement cost-effective solutions to make the best use of scarce resources.

Some reviews have discussed the use of economic modelling in AD[10-17], mainly to compare alternative interventions rather than to identify methodological issues and data gaps affecting the economic evaluation[10-14]. Most of the existing systematic literature reviews focused their searches on a limited number of databases (mainly PUBMED, Embase and EconLit). In 2011, Green at al[10] conducted a systematic literature review on methods of modelling disease progression in AD.

This systematic literature review updates and builds upon this existing work. It aims systematically to review existing economic models of dementia – all forms of dementia, including but not limited to AD – across the full spectrum of disease severity, from preclinical stages through to severe dementia and end of life[18], and including models of the full range of interventions except primary prevention.

This review will inform further stages of the ROADMAP (Real world Outcomes across the Alzheimer's Disease spectrum for better care: Multi-modal data Access Platform) project, in particular the development of a new proof-of-concept model to evaluate the cost-effectiveness of interventions for the full spectrum of dementia, including Alzheimer's Disease (AD), from preclinical stages through to severe dementia and end of life.

In this context, the review aims to meet three specific objectives:

1. To systematically identify previous economic modelling studies across the full spectrum of dementia, including AD, from preclinical stages through to severe dementia and end of life care.
2. To describe the key features of those models in terms of their aim, structure, coverage, data sources and outputs.
3. To assess the quality of existing models and describe their main strengths and weaknesses following best-practice guidelines for the evaluation of model-based economic evaluations.

Methods and analysis

Protocol and registration

This systematic literature review protocol is reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) (Supplementary file 1)[19]. The protocol has been registered with the PROSPERO international prospective register of systematic reviews (CRD42017073874). The results of this review will be reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement[20-22]. Any amendments to this protocol will be reported and published.

Study selection criteria

***Participants*:**

This review focuses on all adults in all care settings in the full spectrum of dementia, including Alzheimer's Disease (AD), from preclinical stages through to severe dementia and

end of life. Although AD is the core of this review, we cover all forms of dementia and include dementia among our search terms.

Study design:

The review includes studies reporting existing economic models across any part of the dementia or AD spectrum (from preclinical stages through to severe dementia and end of life).

The following study designs will be considered for inclusion and further consideration: cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-minimisation analysis, cost analysis, cost-consequences analysis, economic evaluation, health technology appraisal, and treatment pathway study.

We will exclude editorials, case studies, phase I and phase II clinical trials, newspaper articles, book sections, patient and expert opinion or commentary, social media and papers describing adaptations of existing economic models. Papers that fail to meet any one of the above eligibility criteria will be excluded from the review. The number of excluded studies (including reasons for their exclusion) will be recorded.

Outcomes:

The outcome measures of interest include:

- Model type and structure
- Markers/measure used to model disease progression
- Types of clinical/disease pathways
- Data used to structure and parameterise the model

- Summary/synthesis of challenges, limitations and data gaps for developing an economic model for preclinical, MCI and AD/dementia.

Intervention:

All types of AD or dementia interventions (both symptomatic and disease modifying) will be included.

Context:

Models developed in any OECD country will be included as long as the paper is written in English.

Search Strategy

Electronic databases

The following electronic databases were searched for papers published between 1st of January 2000 and 27th of June 2017: Medical Literature Analysis and Retrieval System Online (Ovid MEDLINE); Excerpta Medica dataBASE (Ovid Embase); Economic Literature Database (EconLit); *NHS* Economic Evaluation Database (*EED*); *Cochrane Central Register of Controlled Trials* (Cochrane Library); Cost-Effectiveness Analysis Registry (CEA Registry); Research Papers in Economics (RePEc); Database of Abstracts of Reviews of Effectiveness (DARE); Science Citation Index (SCI); Turning Research Into Practice (TRIP); Open Grey (Supplementary file 2).

The search terms include (but not limited):

-Alzheimer's disease, dementia, mild cognitive impairment

-Cost-effectiveness analysis, cost utility analysis, cost analysis, economic models, Markov chains, simulation, pharmaeconomics.

The search strategies are designed such that to be selected for review of title and abstract papers needed to contain a term from each of these two categories. A copy of the search strategies is at the Supplementary File 2.

Manual searching

The reference lists of studies included in the review are being hand-searched to identify any additional literature.

Study selection

The electronic reference management tool EndNote X7 by Thomson Reuters will be used in order to export and manage the references. Duplicates will be removed by one reviewer (MKa) and all the remaining titles and abstracts identified through the searches will be reviewed against the predefined eligibility criteria by two reviewers (MKa and AP) in order to determine if there is a need for a further full text review. The relevance of each study will be assessed according to the inclusion and exclusion criteria. For those studies that appear to meet the inclusion criteria, or in cases where a decision cannot be safely made based on the title/abstract only, a full text will be retrieved for the assessment. Studies that do not fulfil the inclusion criteria will be excluded. Disagreements are will be resolved by a third reviewer (RW).

The full process will be presented in a flow chart and in detail according to PRISMA guidelines[20].

Data extraction

Two reviewers (AP and MKa) will extract the data from the included studies (supplementary file 3). They will each independently check the data extraction forms for accuracy and completeness. Any disagreements will be noted and resolved by a third reviewer (RW).

The following information will be extracted:

- Study details: title, author, publication details, language of the study, aim of the study, countries of the study, funding of the study, study funding source.
- Study design: objective of the study, purpose of the modelling, types of modelling study (i.e. review of models), type of model, model input data, model output, source of data incorporated into the model, model perspective, model time horizon.
- The intervention evaluated.
- Setting: community setting, institutional setting, primary care, secondary care, tertiary care, mixed setting.
- Participant information: type of participant, number of participants, demographic information.
- Disease-specific information: type of dementia, level of severity, disease progression measurement.
- Outcomes: Outcomes modelled and costs (and cost types).
- Approach to model validation and evidence of validation performance.
- Key findings.
- Author's comments on strengths and weaknesses of the model and potential gaps in available data.

Risk of bias (quality) assessment

The quality of the model is the core of our review. Thus, the quality of identified models will be assessed from the perspective of best current practice. The 'Philips checklist'[23-24],as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*[25], will be used to assess the quality of the models reported in the studies included in the review. Two researchers will independently review and assess the models. The Phillips checklist was developed for assessing the quality of decision-analytic models in health technology assessment. It was designed to be used both by analysts developing models and by reviewers assessing such models. It comprises nine points on the structure of the model, five on the data used in the model and two on model validation.

Strategy for data synthesis

A narrative synthesis will be used for the present study.

Ethics and dissemination plans

The included studies will be reviewed to ensure ethical considerations were taken into account. The results will be published in the form of a publication in a peer-reviewed journal. In addition, the results will be presented at conferences and will be published in the ROADMAP project's official website (http://roadmap-alzheimer.org/).

Patient and Public Involvement

Alzheimer Europe, representing patient and carer associations across Europe, is a partner in the RoadMap consortium and has been fully involved from the beginning in the design and progress of the overall project, including this systematic literature review.

Discussion

Economic models are useful to inform policy decisions by providing evidence on the cost-effectiveness of current and new interventions. The aim of this systematic literature review is to systematically identify and review the existing economic modelling methodologies across the full spectrum of dementia, including Alzheimer's Disease (AD), from preclinical stages through to severe dementia and end of life [18]. The focus will be on the models, their structure and the information and assumptions used to parameterise them, and not on the interventions per se. We will consider modelling of both symptomatic and disease-modifying interventions[18]. The way in which disease progression is represented in economic models will also be covered[18]. This systematic literature review will inform the design and development of future economic modelling across the full spectrum of dementia, including Alzheimer's Disease (AD), from preclinical stages through to severe dementia and end of life and will identify gaps in data and research. .

Funding sources/sponsors

The review is part of the Real World outcomes across the AD spectrum for better care (ROADMAP) project. This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 116020 ("ROADMAP"). This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

Conflicts of interest

MKa, RW, FL, AP, AF, MKn, AMG, IG and JW declare that they have no conflicts of interest.

Antje Tockhorn-Heidenreich is an employee of Eli Lilly and Company Limited and owns stock in Eli Lilly and Company Limited.

Yovanna Castro is an employee of F. Hoffmann-La Roche Ltd.

Ron Handels reports grants from ROADMAP (IMI2; public-private collaboration; 2016-2019) to conduct this study; grants from BIOMARKAPD (EU JPND project; 2012-2016), grants from Actifcare (EU JPND project; 2014-2017), grants from European Brain Council (VoT project; public-private collaboration; 2017), grants from Dutch Flutemetamol Study (public-private collaboration; 2012-2017), personal fees from Piramal (advisory; 2016), personal fees from Roche (advisory; 2017), outside the submitted work.

Pascal Lecomte is employed by, owns stock in, and has stock options in Novartis Pharma AG. Novartis Pharma AG, GE Healthcare, Biogen, Eli Lilly and Company Limited and Roche are industry partners in the ROADMAP Project.

Contributors

All authors participated in designing this review. MKa and RW wrote this protocol. MKa, RW, AF and AP devised the search strategy. PL, RW, AMG, MKn, FL, IG, JW, ATH, RH, YC critically appraised the protocol and contributed to its development. All authors read and approved the final version of the manuscript.

Acknowledgments

We would like to acknowledge the contributions of the remaining members of Work Package 5 as well as of those of the wider ROADMAP group.

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Supplementary file 1: PRISMA-P checklist

Section and topic	Item No.	Checklist Item	Reported on page #
A) Administrative Information			
Identification	1a	Identify the report as a protocol of a systematic review	3
Update	1b	Identify protocol as an update of a previous systematic review if applicable	n/a
Registration	2	Name of registry and registration number	PROSPERO CRD42017073874
B) Authors			
Contact		Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions		Describe contributions of protocol authors and identify the guarantor of the review	14-15
Amendments		If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
- Sources	5a	Indicate Sources of financial or other support for the review	13-14
- Sponsor	5b	Provide name for the review funder and/or sponsor	13-14
- Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s) and/or institution(s), if any, in developing the protocol	n/a
C) Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	6-7-8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6-7-8

D) Methods			
Eligibility Criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9-10
Information Sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10
Search Strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary file 2
E) Study Records			
Data Management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10
Selection Process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10-11
Data Collection Process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10-11 Supplementary file 3
Data Items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	n/a
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
Section and topic	**Item No.**	**Checklist Item**	**Reported on page #**
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12-13
Data Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	13

	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency	13
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	n/a
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n.a.
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed	12

Supplementary file 2: search terms

Medline (1,004)	**Results**
1 *Alzheimer Disease/	64223
2 Alzheimer$.ti.	59334
3 AD.ti.	5366
4 *Dementia/	34251
5 Dementia$.ti.	40800
6 *cognitive impairment/	4771
7 MCI.ti.	900
8 ((mild$ or early$ or preclinical$ or pre-clinical$ or presymptomatic$ or pre-symptomatic$) adj2 "cognit$ impair$").ti.	5620
9 (nMCI or aMCI or mMCI).ti.	28
10 ("N-MCI" or "A-MCI" or "M-MCI").ti.	1
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	122899
12 exp models, economic/	12958
13 exp Decision theory/	11242
14 markov chains/	12259
15 monte carlo method/	26064
16 *Models, Organizational/	5948
17 *Models, Theoretical/	53981
18 econom$ model$.ti,ab.	3043
19 markov$.ti,ab.	19550
20 monte carlo.ti,ab.	42311
21 (decision$ adj2 (tree$ or analy$ or model$)).ti,ab.	18228
22 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	160846
23 11 and 22	487
24 "costs and cost analysis"/ or cost-benefit analysis/	115993
25 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ti,ab.	129287
26 ((economic$ or pharmacoeconomic$ or pharmaco-economic$) adj2 (analy$ or assessment$ or evaluat$)).ti,ab.	17890
27 24 or 25 or 26	209070
28 11 and 27	1037
29 23 or 28	1484
30 limit 29 to (english language and yr="2000 - Current")	
31 (case reports or clinical trial phase i or comment or editorial or letter).pt. or (case report or case study or letter? or editorial).ti.	3422279
32 30 not 31	1009
33 exp animals/ not humans/	4421684
34 32 not 33	1004

Embase (1,625)	**Results**
1 *Alzheimer Disease/	94066
2 Alzheimer$.ti.	77377
3 AD.ti.	7477
4 *Dementia/	47685
5 Dementia$.ti.	52957
6 *cognitive impairment/	42050
7 MCI.ti.	1922
8 ((mild$ or early$ or preclinical$ or pre-clinical$ or presymptomatic$ or pre-symptomatic$) adj2 "cognit$ impair$").ti.	8238
9 (nMCI or aMCI or mMCI).ti.	81
10 ("N-MCI" or "A-MCI" or "M-MCI").ti.	8
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	196654
12 statistical model/ and exp economic aspect/	19488
13 decision theory/	1649
14 "decision tree"/	8693
15 markov chain/	1495
16 monte carlo method/	30330
17 *nonbiological model/	4382
18 *theoretical model/	28156
19 econom$ model$.ti,ab.	4345
20 markov$.ti,ab.	22744
21 monte carlo.ti,ab.	36266
22 (decision$ adj2 (tree$ or analy$ or model$)).ti,ab.	24115
23 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	140325
24 11 and 23	660
25 economic evaluation/ or "cost benefit analysis"/ or "cost effectiveness analysis"/ or "cost minimization analysis"/ or "cost utility analysis"/	202575
26 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ti,ab.	168377
27 ((economic$ or pharmacoeconomic$ or pharmaco-economic$) adj2 (analy$ or assessment$ or evaluat$)).ti,ab.	24734
28 25 or 26 or 27	286727
29 11 and 28	1689
30 24 or 29	1659
31 limit 30 to (english language and yr="2000 - Current")	1652
32 (editorial or letter or note or press).pt. or (case report or case study or letter? or editorial).ti. or case report/ or phase i clinical trial/	4510251
33 31 not 32	1639
34 exp animal/ or exp animal experiment/ or nonhuman/	24796958
35 exp human/ or human experiment/	18601088
36 34 not (34 and 35)	6196899
37 33 not 36	1625

SCI Expanded

20	19 Refined by: [excluding] DOCUMENT TYPES: (PROCEEDINGS PAPER OR NEWS ITEM OR EDITORIAL MATERIAL OR MEETING ABSTRACT OR LETTER)	880
19	14 or 18 AND LANGUAGE: (English)	1,039
18	8 and 17	699
17	15 or 16	188,615
16	TS=((economic* or pharmacoeconomic* or pharmaco-economic*) near/2 (analy* or assessment* or evaluat*))	32,775
15	TS=((cost* near/2 (effective* or utilit* or benefit* or minimi*)))	166,898
14	8 and 13	420
13	9 or 10 or 11 or 12	239,113
12	TS=(decision* near/2 (tree* or analy* or model*))	34,261
11	TS=("monte carlo")	145,136
10	TS=("Markov*")	68,597
9	TS=("econom* model*")	6,638
8	1 or 2 or 3 or 4 or 5 or 6 or 7	92,853
7	TI=("N-MCI" or "A-MCI" or "M-MCI")	5
6	TI=(nMCI or aMCI or mMCI)	52
5	TI=((mild* or early* or preclinical* or pre-clinical* or presymptomatic* or pre-symptomatic*) near/2 "cognit* impair*")	6,590
4	TI=(MCI)	1,272
3	TI=(dementia*)	31,513
2	TI=(AD)	12,378
1	TI=(alzheimer*)	49,389

EconLit

S5	S1 OR S2 OR S3	**Limiters** - Published Date: 2001-01-01-20161231 **Narrow by Language:** - english **Search modes** - Find all my search terms	94
S4	S1 OR S2 OR S3	**Search modes** - Find all my search terms	109
S3	TI "cognit* impair*"	**Search modes** - Find all my search terms	7
S2	TI dementia*	**Search modes** - Find all my search terms	46
S1	TI alzheimer*	**Search modes** - Find all my search terms	58

Cochrane Library (CDSR, DARE, Central, HTA, CMR)

#1 MeSH descriptor: [Alzheimer Disease] this term only 2523
#2 MeSH descriptor: [Dementia] this term only 1737
#3 MeSH descriptor: [Cognitive Dysfunction] this term only 165
#4 alzheimer* or dementia*:ti,ab,kw (Word variations have been searched) 11782
#5 MCI:ti,ab,kw (Word variations have been searched) 1158
#6 (mild* or early* or preclinical* or pre-clinical* or presymptomatic* or pre-symptomatic*) near/2 "cognit* impair*":ti,ab,kw (Word variations have been searched) 1392
#7 #1 or #2 or #3 or #4 or #5 or #6 12720
#8 MeSH descriptor: [Models, Economic] explode all trees 2017
#9 MeSH descriptor: [Decision Theory] explode all trees 929
#10 MeSH descriptor: [Markov Chains] this term only 2165
#11 MeSH descriptor: [Monte Carlo Method] this term only 549
#12 MeSH descriptor: [Models, Organizational] this term only 232
#13 MeSH descriptor: [Models, Theoretical] this term only 959
#14 "econom* model*" or markov* or "monte carlo":ti,ab,kw (Word variations have been searched) 3789
#15 decision* near/2 (tree* or analy* or model*):ti,ab,kw (Word variations have been searched) 3200
#16 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 8524
#17 #7 and #16 78
#18 MeSH descriptor: [Costs and Cost Analysis] this term only 3895
#19 MeSH descriptor: [Cost-Benefit Analysis] this term only 18292
#20 cost* near/2 (effective* or utilit* or benefit* or minimi*):ti,ab,kw (Word variations have been searched) 32418
#21 (economic* or pharmacoeconomic* or pharmaco-economic*) near/2 (analy* or assessment* or evaluat*):ti,ab,kw (Word variations have been searched) 6451
#22 #18 or #19 or #20 or #21 36676
#23 #7 and #22 400
#24 #17 or #23 428 (+the NHS-EED)

NHS EED (on Cochrane Library also)

#1 MeSH descriptor: [Alzheimer Disease] this term only 2523
#2 MeSH descriptor: [Dementia] this term only 1737
#3 MeSH descriptor: [Cognitive Dysfunction] this term only 165
#4 alzheimer* or dementia*:ti,ab,kw (Word variations have been searched) 11782
#5 MCI:ti,ab,kw (Word variations have been searched) 1158
#6 (mild* or early* or preclinical* or pre-clinical* or presymptomatic* or pre-symptomatic*) near/2 "cognit* impair*":ti,ab,kw (Word variations have been searched) 1392
#7 #1 or #2 or #3 or #4 or #5 or #6 88

CEA Registry

dementia, alzheimer, alzheimer's, alzheimers 61

OpenGrey

(dementia* OR alzheimer*) AND (cost* OR economic* OR pharmacoeconomic* OR pharmaco-economic* OR decision*)	**23**

TRIP

(title:(dementia OR alzheimer))(title:(cost OR economic OR pharmacoeconomic OR pharmaco-economic OR decision))	273

RePEc

(dementia* OR alzheimer*) AND (cost* OR economic* OR pharmacoeconomic* OR pharmaco-economic* OR decision*)	**133**

Supplementary file 3: Data extraction from

Data extraction form *on methodologies and data sources of existing health economic models across the AD spectrum from apparently healthy through disease progression to end of life care*

Title of the study	
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*	
Notes	

General Information

Date when form was completed *(dd/mm/yyyy)*	
Name of person extracting data	
Author (s)	
Corresponding author contact details	
Language of the study	
Year published	
Country	
Aim of the study	
Study funding resource	
Possible conflict of interest	
Publication type *(e.g. full report, abstract, letter)*	
Notes:	

Methods

	Descriptions as stated in the study
Type of study	Review of models ☐ (if "*Yes*", please go to Section **A**) Description of a models ☐ (if "*Yes*", please go to Section **B**) Report of an economic evaluation with description of a model ☐ (if "*Yes*", please respond to questions about type of evaluation & then go to Section B) • Economic evaluation study with a model ☐ Disease progression modelling ☐ Care pathway modelling ☐ Costs modelling ☐ *Cost effectiveness analysis* ☐ *Cost benefit analysis* ☐ *Cost utility analysis* ☐ *Cost minimisation analysis* ☐ Cost-consequences analysis Other (please, specify): ……
Section A *Review model studies*	
Types of modelling study	• Models covered: …… …… ……

	…… • Key papers referred for each model: …… …… …… …… …… …… • Are those papers included in our review? If **Yes** (*please, specify which of them*): …… …… …… …… …… If **No** (*please, specify which of them*): …… …… …… …… …… • Databases searched: …… …… …… • Search terms: …… …… …… • Time period covered: …… …… ……

	• Author's conclusions: …… …… ……
Important note:	**The rest of the template does not apply to reviews of models.**
Section B *Purpose of the model*	
Type of model	Markov model ☐ Microsimulation model ☐ Discrete events model ☐ Decision tree ☐ Other (*please, specify*): …… ……
Model input data (***note:*** *If there is more than one set of input data, this part needs to be repeated*)	Country: …… Year: …… Source (e.g. survey of clinics): …… Disease covered (e.g. just AD or all dementias): …… Disease progression measurement: …… Population covered (e.g. just older people): …… Stages covered (e.g. mild, moderate, severe): …… Services covered (e.g. health care, social care): …… Costs covered (e.g. secondary health care): …… Outcomes covered (e.g. DemQol): …… Other (*please, specify*): ……

Model outputs	Disease progression: …… Care pathway: …… Lifetime costs: …… Outcomes for users: …… Outcomes for carers: …… Other (please, specify): ……
Source of data incorporated into the model:	-***Please, tick all that apply***: Data collected alongside a clinical trial ☐ Population survey ☐ *Cohort study* ☐ *Before and after study* ☐ *Expert opinion* ☐ *Other (please, specify)*: …… …… Assumptions made: Yes ☐ No ☐ If the answer is "Yes", please specify: …… ……
Setting *(please describe)*	Community setting: ☐ Institutional setting: ☐ Primary care: ☐ Secondary care: ☐ Tertiary care: ☐

	Mixed setting: ☐ Unclear: ☐ Other (*specify*):……
Patient population characteristics *(please describe – if we have more than one data set then we have to fill that part for every data set)*	• Study from which participants are drawn: …… • Definition of dementia: …… …… …… • Type of dementia: …….. • Disease severity: Pre-symptomatic AD/dementia: ☐ Mild cognitive impairment (MCI) due to AD: ☐ Mild AD/dementia: ☐ Moderate AD/dementia: ☐ Severe AD/dementia: ☐ EoL: ☐ • Method used to define disease severity: …… …… …….. • Mean age: …….. • Number of participants: …….. • Sex of participants: …….. • Other (*please, specify*): …….. …… ……
Perspective of analysis	Societal ☐ Health and care system ☐

	Health care provider ☐ Patient and family ☐ Third party payer ☐ Other (please, specify): .....
Intervention evaluated	
Time frame of the modeling *(please, specify the time horizon of the study and in the case of a Markov model, please specify the cycle length)*	
Cost data	Primary ☐ Secondary ☐ If secondary, please specify: ....
Cost included	**Direct medical** ☐ • *Direct treatment* ☐ • *Inpatient* ☐ • *Outpatient* ☐ • *Day care* ☐ • *Community health care* ☐ • *Medication* ☐ **Other, please specify:** ..... **Direct non-medical** ☐ • *Social care* ☐ • *Social benefits* ☐ • *Travel costs* ☐ • *Caregiver out-of-pocket* ☐ • *Training of staff* ☐ **Other, please specify:** .....

	Lost productivity ☐ • *Income forgone due to illness* ☐ • *Income forgone due to death* ☐ • *Income forgone by caregiver* ☐ **Other, please specify:** .....
Currency	
Year of costing	
Type of discount used	No discount used ☐ For benefits and costs ☐ Only for costs ☐ In the case that a discount rate used, please give details of the discount rate: .....
Notes:	

Other information

	Description as stated in report/paper	
Key findings (if any)		
Quality checklist score		
Author's comments on strengths and weaknesses of model(s)		
Reviewer's comments on strengths and weaknesses of the model(s)		
Further information required from author		

References to other relevant studies		
Correspondence required for further study information *(from whom, what and when)*		
Notes:		