Health Technology Assessment (HTA)

HTA Protocol

Title	Medicines for Dementia due to Alzheimer's Disease and Parkinson's Disease
Author/Affiliation	Mattli R.[1], Tzogiou C.[1], Tomonaga Y.[2], Sharakin M.[1], Vinci L.[1], Carlander M.[1], Wirth B.[1], Grobet C.[1], Egli Ph.[3], Nordström K.[4], Gerber-Grote A.[5], Puhan M.[2], Wieser S.[1] [1]ZHAW Zurich University of Applied Sciences, School of Management and Law, Winterthur Institute of Health Economics [2]University of Zurich, Epidemiology, Biostatistics and Prevention Institute [3]ZHAW Zurich University of Applied Sciences, School of Management and Law, Center for Social Law [4]ZHAW Zurich University of Applied Sciences, School of Health Professions, IGW Institute of Health Sciences [5]ZHAW Zurich University of Applied Sciences, School of Health Professions
Technology	donepezil, galantamine, rivastigmine, memantine
Date	25 October 2021

Executive Summary

Background: In Switzerland, acetylcholinesterase inhibitors donepezil, rivastigmine and galantamine are reimbursed for the treatment of mild to moderate dementia due to Alzheimer's Disease (AD) and rivastigmine is also reimbursed for the treatment of mild to moderate dementia due to Parkinson's Disease (PD). For the treatment of moderate to severe dementia due to AD the N-methyl-D-aspartate (NMDA) receptor antagonist memantine is reimbursed. Due to unclear clinical benefit there is an interest in a health technology assessment (HTA) of donepezil, galantamine, rivastigmine and memantine compared to treatment without these drugs in patients with dementia due to AD or PD in Switzerland.

Objective: This HTA protocol defines the population, intervention, comparator and outcomes (PICO), as well as the HTA key questions and describes the methodology to conduct a systematic literature search, to extract, analyse and synthesise the data in the HTA report. Furthermore, a general description of the economic evaluation and the approach to address ethical, legal, social, and organizational issues related to the topic is provided.

Research questions: 1) What are the benefits and harms of the treatment with donepezil, galantamine, rivastigmine or memantine compared to treatment without these drugs in patients with dementia due to AD or PD? 2) What is the annual budget impact of the treatment with donepezil, galantamine, rivastigmine and memantine compared to treatment without these drugs in Switzerland? 3) How cost-effective is the treatment with donepezil, galantamine, rivastigmine or memantine compared to treatment without these drugs in Switzerland?

Methods: A systematic literature search for evidence on efficacy, effectiveness, safety and health economic outcomes of donepezil, galantamine, rivastigmine, memantine compared to treatment without these drugs in patients with dementia due to AD and PD will be conducted. Meta-analysis will be performed for outcomes with available evidence. The certainty of evidence for relevant outcomes will be assessed by applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Depending on the amount, quality and results of existing health economic evidence, cost-effectiveness will be either assessed by transferring results to the Swiss healthcare setting, by adjusting an existing health economic model or by building a de novo model. The potential budget impact for Switzerland will be estimated over the next five years. The health economic analysis will be conducted from a health care payer perspective. Furthermore, a targeted search for evidence on ethical, legal, social and organisational aspects of antidementia

drugs will be conducted and findings will be summarized and discussed. In addition, we will use the "Hofmann catalogue" to address specific ethical questions and a checklist designed for the Swiss legal system to address legal questions.

Zusammenfassung

Ausgangslage: In der Schweiz werden die Acetylcholinesterase-Hemmer Donepezil, Rivastigmin und Galantamin bei der Behandlung einer leichten bis mittelschweren Demenz infolge einer Alzheimer-Erkrankung (AD) vergütet, ebenso erfolgt eine Vergütung von Rivastigmin bei der Behandlung von leichter bis mittelschwerer Demenz infolge einer Parkinson-Erkrankung (PD). Des Weiteren wird bei einer Behandlung einer mittelschweren bis schweren Alzheimer-Demenz der N-Methyl-D-Aspartat-Rezeptor-Antagonist (NMDA-Rezeptor-Antagonist) Memantin vergütet. Da der klinische Nutzen unklar ist, besteht Interesse an einem Health Technology Assessment (HTA) von Donepezil, Galantamin, Revastigmin und Memantin im Vergleich zu einer Behandlung ohne diese Medikamente bei Patientinnen und Patienten mit einer Demenz infolge einer AD oder PD.

Ziel: Dieses HTA-Protokoll legt Population, Intervention, Comparator und Outcomes (PICO) sowie die wichtigsten HTA-Fragestellungen fest und beschreibt die Methodik, um eine systematische Literaturrecherche durchzuführen sowie die Daten zu extrahieren, zu analysieren und im HTA-Bericht zusammenzufassen. Ausserdem wird eine allgemeine Beschreibung der Bewertung der Wirtschaftlichkeit sowie des Ansatzes zur Behandlung ethischer, rechtlicher, sozialer und organisatorischer Fragen zum Thema bereitgestellt.

Forschungsfragen: 1) Welchen Nutzen bzw. welche Risiken birgt die Behandlung mit Donepezil, Galantamin, Rivastigmin oder Memantin im Vergleich zu einer Behandlung ohne diese Medikamente bei Patientinnen und Patienten mit einer Demenz infolge einer AD oder PD? 2) Wie wirkt sich die Behandlung mit Donepezil, Galantamin, Rivastigmin oder Memantin im Vergleich zu einer Behandlung ohne diese Medikamente in der Schweiz auf das Jahresbudget aus? 3) Welche Kosteneffektivität weist die Behandlung mit Donepezil, Galantamin, Rivastigmin oder Memantin im Vergleich zu einer Behandlung ohne diese Medikamente in der Schweiz auf?

Methoden: In einer systematischen Literaturrecherche wird nach Evidenz betreffend Wirksamkeit, Effektivität, Sicherheit und gesundheitsökonomische Auswirkungen von Donepezil, Galantamin, Revastigmin und Memantin im Vergleich zu einer Behandlung ohne diese Medikamente bei Patientinnen und Patienten mit einer Demenz infolge einer AD oder PD gesucht. Für Ergebnisse mit vorhandener Evidenz wird eine Meta-Analyse durchgeführt. Die Verlässlichkeit der Evidenz für relevante Ergebnisse wird anhand des GRADE-Ansatzes (Grading of Recommendations

Assessment, Development and Evaluation) bewertet. Je nach Umfang, Qualität und Ergebnissen der bestehenden gesundheitsökonomischen Evidenz wird die Kosteneffektivität entweder durch die Ummünzung der Ergebnisse auf das schweizerische Gesundheitswesen, durch die Anpassung eines bestehenden gesundheitsökonomischen Modells oder über den Aufbau eines De-novo-Modells beurteilt. Die potenziellen Budgetauswirkungen für die Schweiz werden für die nächsten fünf Jahre geschätzt. Die gesundheitsökonomische Analyse erfolgt aus Sicht eines Kostenträgers im Gesundheitssystem. Ausserdem wird eine gezielte Suche nach Evidenz zu ethischen, rechtlichen, sozialen und organisatorischen Aspekten von Antidementiva durchgeführt, und die Erkenntnisse werden zusammengefasst und erörtert. Des Weiteren werden wir anhand des «Hofmann-Katalogs» spezifische ethische Fragen behandeln und eine für das schweizerische Rechtssystem entworfene Checkliste einsetzen, um auf rechtliche Fragen einzugehen.

Résumé

Situation initiale : En Suisse, le donépézil, la rivastigmine et la galantamine, tous trois inhibiteurs de l'acétylcholinestérase, sont remboursés pour le traitement d'une démence légère à modérée due à la maladie d'Alzheimer (MA). La rivastigmine l'est également pour le traitement d'une démence légère à modérée due à la maladie de Parkinson (MP). La mémantine, antagoniste des récepteurs N-méthyl-D-asparte (NMDA), est, quant à elle, remboursée pour le traitement d'une démence modérée à sévère due à la maladie d'Alzheimer. Au vu des bénéfices cliniques incertains, il existe un intérêt à réaliser une évaluation des technologies de la santé (ETS) comparant le recours au donépézil, à la rivastigmine, à la galantamine et à la mémantine avec un traitement sans ces substances chez des personnes atteintes d'une démence due à la MA ou à la MP en Suisse.

Objectif : Le présent protocole d'ETS définit la population, l'intervention, le comparateur et les résultats (méthode PICO) ainsi que les questions-clés d'ETS. Il décrit la méthodologie utilisée pour effectuer une recherche documentaire systématique et pour extraire, analyser et synthétiser les données dans le rapport d'ETS. Il fournit également une description générale de l'évaluation économique et de l'approche pour aborder les questions éthiques, juridiques, sociales et organisationnelles liées à la thématique.

Questions de recherche : 1) Quels sont les avantages et les inconvénients d'un traitement au donépézil, à la galantamine, à la rivastigmine ou à la mémantine par rapport à un traitement sans ces médicaments chez les patients atteints d'une démence due à la MA ou à la MP ? 2) Quel est l'impact budgétaire annuel d'un traitement au donépézil, à la galantamine, à la rivastigmine ou à la mémantine par rapport à un traitement sans ces médicaments en Suisse ? 3) Quel est le rapport coût-efficacité d'un traitement au donépézil, à la galantamine, à la rivastigmine ou à la mémantine par rapport à un

traitement sans ces médicaments en Suisse ?

Méthodes : Une recherche systématique dans la littérature spécialisée sera menée pour identifier des preuves de l'efficacité (théorique et pratique), de la sécurité et des résultats en termes économiques et sanitaires du donépézil, de la galantamine, de la rivastigmine et de la mémantine par rapport à un traitement sans ces médicaments chez les personnes atteintes d'une démence due à la MA et à la MP. Une méta-analyse sera effectuée concernant les résultats pour lesquels des données probantes sont disponibles. Le degré de certitude des preuves concernant les résultats pertinents sera évalué au moyen de l'approche GRADE (Grading of Recommendations Assessment, Development and Evaluation, ou classement des recommandations, de l'évaluation, du développement et de l'évaluation). En fonction de la quantité et de la qualité des données existantes en matière d'économie de la santé, et des résultats qu'elles contiennent, le rapport coût-efficacité sera évalué en adaptant les résultats au contexte des soins de santé en Suisse, en ajustant un modèle d'économie de la santé existant ou en construisant un modèle de novo. L'impact budgétaire potentiel pour la Suisse sera estimé sur les cinq prochaines années. L'analyse économico-sanitaire sera menée du point de vue des payeurs de soins. En outre, une recherche ciblée de données sur les aspects éthiques, juridiques, sociaux et organisationnels des médicaments anti-démence sera menée. Les résultats feront l'objet d'un résumé et d'une discussion. Enfin, nous utiliserons le « catalogue Hofmann » pour aborder des questions éthiques spécifiques, ainsi qu'une liste de contrôle conçue pour le système juridique suisse afin de traiter les questions de droit.

Sintesi

Premessa: in Svizzera gli inibitori dell'acetilcolinesterasi donepezil, rivastigmina e galantamina sono rimborsati per la terapia della demenza da lieve a moderata dovuta alla malattia di Alzheimer (AD); la rivastigmina è inoltre rimborsata per il trattamento della demenza da lieve a moderata causata dalla malattia di Parkinson (PD). Per la terapia della demenza da moderata a grave dovuta ad AD è rimborsata la memantina, un antagonista del recettore dell'N-metil-D-aspartato (NMDA). Alla luce della mancanza di chiarezza circa i benefici clinici sussiste interesse verso un Health Technology Assessment (HTA) sull'impiego in Svizzera di donepezil, galantamina, rivastigmina e memantina rispetto a una terapia senza questi farmaci nei pazienti con demenza dovuta ad AD o a PD.

Obiettivo: il presente protocollo di HTA definisce i parametri PICO (popolazione, intervento, comparatore e outcome [= risultato]) nonché i principali quesiti dell'HTA e descrive la metodologia per condurre una ricerca bibliografica sistematica al fine di estrarre, analizzare e sintetizzare i dati nel rapporto di HTA. Viene inoltre fornita una descrizione generale della valutazione economica e dell'approccio utilizzato allo scopo di affrontare le questioni etiche, legali, sociali e organizzative

correlate all'argomento.

Quesiti della ricerca: 1) Quali sono i benefici e gli svantaggi del trattamento con donepezil, galantamina, rivastigmina o memantina rispetto alla terapia senza tali farmaci nei pazienti con demenza dovuta ad AD o a PD? 2) Qual è l'impatto annuale sul budget del trattamento con donepezil, galantamina, rivastigmina e memantina rispetto alla terapia senza tali farmaci in Svizzera? 3) Qual è la convenienza in termini di costi del trattamento con donepezil, galantamina, rivastigmina o memantina rispetto alla terapia senza tali farmaci in Svizzera?

Metodologia: sarà condotta una ricerca bibliografica sistematica al fine di identificare evidenze a livello di efficacia teorica e nella pratica clinica, sicurezza e risultati economico-sanitari per donepezil, galantamina, rivastigmina e memantina rispetto alla terapia senza questi farmaci nei pazienti con demenza dovuta ad AD e a PD. Saranno inoltre svolte meta-analisi per determinare i risultati sulla scorta delle evidenze disponibili. La certezza dell'evidenza per i risultati rilevanti sarà valutata mediante l'applicazione del metodo GRADE (Grading of Recommendations Assessment, Development and Evaluation). In funzione della quantità, della qualità e dei risultati delle evidenze economico-sanitarie, l'efficacia in termini di costi sarà valutata trasferendo i risultati al contesto sanitario svizzero, adattando un modello economico-sanitario già esistente oppure creando un modello *de novo*. L'impatto potenziale sul budget per la Svizzera sarà stimato nell'arco dei prossimi cinque anni. L'analisi economico-sanitaria verrà condotta dalla prospettiva dei soggetti che sostengono i costi sanitari. Sarà inoltre effettuata una ricerca mirata di evidenze sugli aspetti etici, legali, sociali e organizzativi dei farmaci antidemenza e gli elementi raccolti saranno oggetto di sintesi e di discussione. Utilizzeremo altresì il «catalogo Hofmann» per affrontare questioni etiche specifiche, nonché una lista di controllo appositamente redatta per il sistema giuridico svizzero al fine di esaminare le questioni legali.

Table of contents

Abbreviations and acronyms

ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADL	Activities of daily living
AHEAD	Assessment of Health Economics in Alzheimer's Disease
CEA	Cost-effectiveness analysis
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CUA	Cost-utility analyses
ELSO	Ethical, legal, social and organizational
EXPRESS	EXelon in PaRkinson's disEaSe dementia Study
FDA	Food and Drug Administration
FOPH	Federal Office of Public Health
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAS	National Authority for Health (Haute Autorité de Santé)
HTA	Health Technology Assessment
INAHTA	International HTA database
IQWiG	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MMSE	Mini mental state examination
NHSEED	NHS Economic Evaluation Database
NMDA	N-methyl-D-aspartate
PenTAG	Peninsula Technology Assessment Group
PICO	Population, intervention, comparator, outcome
PD	Parkinson's disease
QALY	Quality adjusted life years
RCT	Randomized Controlled Trial
SAMW	Swiss Academy of Medical Sciences
SHTAC	Southampton Health Technology Assessment Centre
SL	List of pharmaceutical specialties (Spezialitätenliste)
SMDM	Society for Medical Decision Making
WHO	World Health Organization

Objective of the HTA Protocol

Based on a preliminary screening of the literature the objective of the HTA protocol is to formulate the research question, to define the population, intervention, comparator, outcomes (PICO) and describe the methodology to conduct a systematic literature search, extract, analyse and synthesise the data in the health technology assessment (HTA) report on the topic. Key questions are defined, addressing the main HTA domains, i.e., efficacy/effectiveness/safety, costs/budget impact/cost-effectiveness, ethical/legal/social and organisational issues.

1 Policy question

1.1 Dementia as a public health challenge

The World Health Organization (WHO) considers dementia as a public health priority.[1] Currently around 144'000 people suffer from dementia in Switzerland.[2] As the prevalence of dementia rises sharply with age and due to the aging of the population, the number of patients with dementia is expected to increase significantly. This is especially relevant for public policy considering that dementia leads also to a remarkable economic burden. The total annual cost of dementia (direct and indirect costs) in Switzerland was estimated at CHF 11.8 billion for the year 2017.[3]

1.2 The disease

The two main causes for dementia are either disturbed central blood flow (central ischemia or bleeding) or a progressive neurodegeneration such as in Alzheimer's Disease (AD). Both lead to a disturbance of cognitive function which is often accompanied by further dementia symptoms such as changes in emotional control, motivation, social behaviour, or sleep-wake rhythm. In case of an underlying neurodegenerative process, a chronic progressive decline/worsening of cognition and behaviour is observed. Furthermore, dementia can occur as a consequence of many different diseases and injures that primarily or secondarily affect the brain.[1,4]

In dementia due to AD and Parkinson's Disease (PD), loss of cholinergic neurons lead to reduced production of the neurotransmitter acetylcholine (ACh).[5] ACh gets metabolized by the enzyme acetylcholinesterase (AChE). The inhibition of AChE by AChE-inhibitors leads to more available ACh in the synaptic cleft, which is associated with an improvement of cognition. Neuritic plaques and neurofibrillary tangles are pathological indicators of AD.[6] They are mainly caused by amyloid-ß accumulation in the brain and the hyperphosphorylation of Tau protein in affected neurons which activate neurotoxic cascades and cause cytoskeletal changes leading to degeneration of the neurons.[6] Excessive flow of calcium into neurons due to dysfunction of the N-methyl-D-aspartate (NMDA) glutamate receptors caused by neuroinflammation contribute also to the AD pathology.[7] Blocking NMDA receptors reduces this continuous stimulation, which prevents apoptosis and enables the neurons to better communicate.

1.3 Pharmaceutical treatment options and current reimbursement status in Switzerland

Several disease modifying drugs are currently investigated in clinical trials. The United States Food and Drug Administration (FDA) recently approved under an accelerated approval pathway Biogen's amyloid beta-directed antibody aducanumab for the treatment of AD. It is the first novel approval for AD since

2003 and it is the first treatment that targets the pathophysiology of the condition.[8] The conventional treatments (AChE inhibitors and memantine) target to alleviate cognitive and neuropsychiatric symptoms.[9]

In Switzerland, AChE inhibitors donepezil, rivastigmine and galantamine are reimbursed for the treatment of mild to moderate dementia due to AD (mini mental state examination (MMSE) ≥ 10; MMSE is a common tool for measuring cognitive function and the score ranges from 0 (most severe) to 30 (normal)). Rivastigmine is also reimbursed for the treatment of mild to moderate dementia due to PD. For the symptomatic treatment of moderate to severe dementia (MMSE 3-19) due to AD, the NMDA receptor antagonist memantine is reimbursed.[10] Based on the list of pharmaceutical specialties ("Spezialitätenliste" or SL) these medications are only reimbursed as monotherapies and under the condition that the cognitive functions are assessed with the MMSE at the beginning of treatment, after three months and subsequently every six months.[11] According to the MediX (a Swiss physician network) guideline, the mean beneficial effects of antidementia drugs are small, but some patients can benefit from them more.[12] The MediX guideline does not recommend a general use of antidementia drugs. Instead, they recommend prescribing them upon the request of the patient or their relatives.[12] The “Therapy Guidelines for the Behavioural and Psychological Symptoms of Dementia” issued by several professional societies from Switzerland also recommends starting with non-pharmacological therapies and only add antidementia drugs where needed.[13]

1.4 Reimbursement in other countries

The NICE guidance as well as the “S3-Leitlinie” recommend the use of AChE inhibitors in mild to moderate AD and memantine in moderate to severe AD.[9,14] Furthermore, AChE inhibitors and memantine are reimbursed in most European countries.[15] However, AChE inhibitors and memantine were removed from the list of reimbursable products in France in 2018. This decision was based on the 2016 report by the French National Authority for Health (HAS).[16] This report concluded that, based on the available clinical data, the drugs have a positive effect on short-term cognitive symptoms compared to placebo. However, the clinical benefit in the real-world setting remains unclear. In addition, side effects were observed in both AChE inhibitors and memantine.

In 2009, the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany assessed the evidence on the benefits and harms of various drug and non-drug therapies for AD.[17] According to their study, AChE inhibitors have positive effects on cognition in patients with mild to moderate AD that use the drug for at least four months. For other outcomes, such as associated symptoms (e.g. agitation and depression), quality of life or need for care, there was not enough evidence, or the evidence could not be interpreted with sufficient certainty. This study also found that there was no evidence to support the benefit of treating moderate to severe dementia due to AD with memantine in cognitive performance

and in activities of daily living (ADL). However, in 2010 IQWiG conducted a further analysis with additional data they received from Merz Pharma, the manufacturer of memantine. The updated results indicated a positive effect of memantine on cognition and ADL.[18] Nevertheless, IQWiG noted that especially the results related to ADL should not be regarded as evidence, due to the uncertainty of the responses and the small effect size. It also noted that the observation period in all studies was up to six months and long-term studies would be required.

1.5 Policy question

Considering this uncertainty regarding the clinical benefit of AChE inhibitors and memantine, and the fact that this HTA topic was submitted twice to the Federal Office of Public Health (FOPH), the treatment of dementia due to AD and PD using these medications was selected in 2019 in Switzerland to be re-evaluated based on an HTA. Consequently, this HTA summarizes the evidence base on AChE inhibitors and memantine for use in patients with dementia due to AD or PD, to inform policy makers in their decision if AChE inhibitors or memantine should continue to be reimbursed by the Swiss social health insurance.

2 Research question

1. What are the benefits and harms of the treatment with donepezil, galantamine, rivastigmine or memantine compared to treatment without these drugs in patients with dementia due to AD or PD?
2. How cost-effective is the treatment with donepezil, galantamine, rivastigmine or memantine compared to treatment without these drugs in Switzerland?
3. What is the annual budget impact of the treatment with donepezil, galantamine, rivastigmine and memantine compared to treatment without these drugs in Switzerland?

3 PICO

Population, intervention, comparator and outcomes (PICO) are defined as:

PICO 1 (mild to moderate dementia due to AD treated with cholinesterase inhibitors**)**

P:	Patients with mild to moderate dementia due to AD, diagnosed according to established criteria (e.g. DSM-III, DSM-IIIR, DSM-IV, DSM-5, ICD-10, NIA-AA, NINCDS-ARDA)
I:	Cholinesterase inhibitors donepezil, rivastigmine and galantamine according to the approved dosage
C:	Treatment without donepezil, rivastigmine or galantamine / placebo
O:	• Effectiveness: Delayed nursing home placement, cognitive function (ADAS-Cog, MMSE, MoCA, executive functioning, episodic memory etc.), functional capacity (ADCS-ADL-sev, etc.), neuropsychiatric symptoms (NPI, BEHAVE-AD etc.), BPSD, QoL, etc. • Safety: serious adverse events, mortality • Costs, cost-effectiveness, cost-utility and budget impact

Abbreviations: AD, Alzheimer's Disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL-sev, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory for Severe Alzheimer's Disease; BEHAVE-AD, Behavioural Pathology in Alzheimer's Disease; BPSD, behavioural and psychological symptoms of dementia; DSM-III, Diagnostic and statistical manual of mental disorder, 3rd edition; DSM-IIIR, Diagnostic and statistical manual of mental disorder, 3rd edition revision; DSM-IV, Diagnostic and statistical manual of mental disorder, 4th edition; DSM-5, Diagnostic and statistical manual of mental disorder, 5th edition; ICD-10, International Classification of Diseases 10th revision; MoCA, Montreal Cognitive Assessment; NIA-AA, National Institute on Aging and Alzheimer's Association; NINCDS-ARDA, National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association; NPI, Neuropsychiatric inventory; QoL, Quality of Life

PICO 2 (moderate to severe dementia due to AD treated with memantine**)**

P:	Patients with moderate to severe dementia due to AD, diagnosed according to established criteria (e.g. DSM-III, DSM-IIIR, DSM-IV, DSM-5, ICD-10, NIA-AA, NINCDS-ARDA)
I:	NMDA antagonist memantine according to the approved dosage
C:	Treatment without memantine / placebo
O:	• Effectiveness: Delayed nursing home placement, cognitive function (ADAS-Cog, MMSE, MoCA, executive functioning, episodic memory etc.), functional capacity (ADCS-ADL-sev, etc.), neuropsychiatric symptoms (NPI, BEHAVE-AD etc.), BPSD, QoL, etc. • Safety: serious adverse events, mortality • Costs, cost-effectiveness, cost-utility and budget impact

Abbreviations: AD, Alzheimer's Disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL-sev, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory for Severe Alzheimer's Disease; BEHAVE-AD, Behavioural Pathology in Alzheimer's Disease; BPSD, behavioural and psychological symptoms of dementia; DSM-III, Diagnostic and statistical manual of mental disorder, 3rd edition; DSM-IIIR, Diagnostic and statistical manual of mental disorder, 3rd edition revision; DSM-IV, Diagnostic and statistical manual of mental disorder, 4th edition; DSM-5, Diagnostic and statistical manual of mental disorder, 5th edition; ICD-10, International Classification of Diseases 10th revision; MoCA, Montreal Cognitive Assessment; NIA-AA, National Institute on Aging and Alzheimer's Association; NINCDS-ARDA, National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association; NPI, Neuropsychiatric inventory; QoL, Quality of Life

PICO 3 (mild to moderate dementia due to PD treated with rivastigmine**)**

P:	Patients with mild to moderate dementia due to PD, diagnosed according to established criteria (e.g. DSM-III, DSM-IIIR, DSM-IV, DSM-5, ICD-10, NIA-AA, NINCDS-ARDA)
I:	Rivastigmine according to the approved dosage
C:	Treatment without rivastigmine / placebo
O:	• Effectiveness: Delayed nursing home placement, cognitive function (ADAS-Cog, MMSE, MoCA, executive functioning, episodic memory etc.), functional capacity (ADCS-ADL-sev, etc.), neuropsychiatric symptoms (NPI, BEHAVE-AD etc.), BPSD, QoL, etc. • Safety: serious adverse events, mortality • Costs, cost-effectiveness, cost-utility and budget impact

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL-sev, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory for Severe Alzheimer's Disease; BEHAVE-AD, Behavioural Pathology in Alzheimer's Disease; BPSD, behavioural and psychological symptoms of dementia; DSM-III, Diagnostic and statistical manual of mental disorder, 3rd edition; DSM-IIIR, Diagnostic and statistical manual of mental disorder, 3rd edition revision; DSM-IV, Diagnostic and statistical manual of mental disorder, 4th edition; DSM-5, Diagnostic and statistical manual of mental disorder, 5th edition; ICD-10, International Classification of Diseases 10th revision; MoCA, Montreal Cognitive Assessment; NIA-AA, National Institute on Aging and Alzheimer's Association; NINCDS-ARDA, National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association; NPI, Neuropsychiatric inventory; PD, Parkinson's disease; QoL, Quality of Life

4 HTA key questions

For the evaluation of the technology the following key questions covering the central HTA domains are addressed:

1. Is donepezil, rivastigmine, galantamine or memantine efficacious/effective compared to treatment without these drugs in the specified populations?
2. Is donepezil, rivastigmine, galantamine or memantine safe compared to treatment without these drugs in the specified populations?
3. What are the annual costs of donepezil, rivastigmine, galantamine and memantine in the specified populations?
4. Is donepezil, rivastigmine, galantamine or memantine cost-effective compared to treatment without these drugs in the specified populations?
5. What is the budget impact of donepezil, rivastigmine, galantamine and memantine compared to treatment without these drugs in the specified populations?
6. Are there ethical, legal, social, or organisational issues related to antidementia drugs?

5 Methodology

5.1 Efficacy, effectiveness and safety

In this section we describe the literature search and meta-analysis on efficacy, safety, and effectiveness.

5.1.1 Databases and search strategy

5.1.1.1 Search strategy

We developed search strategies based on the PICO criteria in collaboration with a medical librarian and according to current best practice guideline.[19] The systematic literature search will be conducted in the following databases: Cochrane Library, Embase and Medline (see 7 Appendix for the detailed search strategy per database). We will also screen the references of included studies after full-text screening to identify additionally relevant evidence.

Our focus was on the population and intervention components of the PICO, and we did not specify comparators or outcomes to avoid undue narrowing of search results. Several Cochrane reviews already address the effectiveness, efficacy and safety aspects of the treatments under investigation.[7,20–26] Several additional systematic reviews including meta-analysis are also available.[27–36] These studies were considered when building our search strategy and we will use these studies to check if we identified all relevant randomised controlled trials (RCTs). This will allow us to obtain a synthesis using inclusion/exclusion criteria approved by the FOPH and include the most recent evidence, e.g. recent studies that were not available to existing systematic reviews. In addition, we will search for ongoing Randomized Controlled Trials (RCTs) on clinicaltrials.gov, the EU Clinical Trials Register (www.clinicaltrialsregister.eu) and the WHO International Clinical Trials Registry Platform (www.who.int/clinical-trials-registry-platform).

5.1.1.2 Study inclusion and exclusion criteria

Inclusion and exclusion criteria were defined according to the PICO criteria (Section 3) and were kept broad, without restricting the publication period or study quality. We will focus on RCTs. Furthermore, we will include studies with adult populations, in line with the age of dementia onset. Studies with a published full text in English, French, German, or Italian will be eligible. We will not specify concrete outcomes as inclusion or exclusion criteria as long as outcomes are within the domains outlined in Section 4.

Inclusion/exclusion criteria for studies on efficacy, effectiveness and safety are listed in Table 1.

Table 1 Inclusion criteria for studies on efficacy, effectiveness and safety

Criterion	Inclusion	Exclusion
Publication period	No restrictions	—
Publication status	Published full text available	Published full text not available (including conference abstracts)
Language	English, French, German or Italian	Not English, French, German or Italian
Setting	No restrictions	—
Study design/type	RCT	Not RCT
Study follow-up	Follow-up ≥24 weeks	Follow-up <24 weeks
Study quality	No restrictions	—
Study population	• PICO 1: Adults (≥ 18 years) with mild to moderate dementia due to AD, diagnosed according to established criteria • PICO 2: Adults (≥ 18 years) with moderate to severe dementia due to AD, diagnosed according to established criteria • PICO 3: Adults (≥ 18 years) with mild to moderate dementia due to PD, diagnosed according to established criteria	• Animal studies • PICO 1: Adults (≥ 18 years) without mild to moderate dementia due to AD • PICO 2: Adults (≥ 18 years) without moderate to severe dementia due to AD • PICO 3: Adults (≥ 18 years) without mild to moderate dementia due to PD
Study intervention	• PICO 1: Donepezil, rivastigmine, galantamine as monotherapies according to the approved dosage • PICO 2: Memantine as monotherapy according to the approved dosage • PICO 3: Rivastigmine as monotherapy according to the approved dosage	• PICO 1: Other drugs than donepezil, rivastigmine, galantamine or combinations of these drugs with memantine • PICO 2: Other drugs than memantine or combinations of memantine with AChE inhibitors • PICO 3: Other drugs than rivastigmine or rivastigmine in combination with memantine
Study comparator	Treatment without drugs under investigation / placebo	Any other comparator
Study outcomes	No restrictions	—

Abbreviations: AChE, Acetylcholinesterase; AD, Alzheimer's disease; PD, Parkinson's disease; PICO, Population, intervention, comparator and outcomes; RCT, Randomized Controlled Trial

5.1.1.3 Study selection

In a first step, the studies will be title-and-abstract-screened in duplicate according to the inclusion/exclusion criteria. In a second step, full texts of studies retained from the first step will be reviewed in duplicate. Any disagreement will be solved by consensus. Where consensus cannot be found, a third reviewer will be consulted. To increase consistency between reviewers, prior training sessions will be held.

5.1.2 Data extraction, analysis and synthesis

5.1.2.1 Data extraction

One reviewer will extract data into a predefined work sheet, which we will pilot-test with selected studies retained after full-text screening. Extracted data will be checked by a second reviewer. Any disagreement will be solved by consensus. Where consensus cannot be found, a third reviewer will be consulted.

We intend to extract the following data:

- Population data, e.g. age and gender structure, MMSE, information on imaging etc.
- Intervention data, e.g. dose, frequency and treatment duration
- Comparator data, e.g. dose, frequency and treatment duration
- Actual results on safety and clinical efficacy outcomes
- Information to assess the quality of studies, i.e. risk of bias

5.1.2.2 Assessment of quality of evidence

5.1.2.2.1 Risk of bias

We will assess the risk of bias according to the Cochrane handbook.[37] If a study adequately addresses the specific risk of bias domain (e.g. adequate generation of random sequence for randomisation), it will be judged as “low risk of bias” in this domain. Description of an inadequate method will be judged as “high risk of bias” and, if incomplete information is given, as “unclear risk of bias”. The assessment will be performed in duplicate and inconsistencies will be solved by consensus. Where consensus cannot be found, a third reviewer will be consulted.

5.1.2.2.2 Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment

To obtain an overall rating of confidence in the estimates of effects, the GRADE approach will be applied and the certainty of evidence of effect for relevant outcomes will be rated in duplicate.[38] Inconsistencies will again be solved by consensus. Where consensus cannot be found, a third reviewer will be consulted.

For the specific question under study, we will specify the decision rule for judging the GRADE item "inconsistency" as serious, if heterogeneity in statistical meta-analysis is at least substantial (i.e. I^2 at least 50 to 90%). The GRADE evidence table will be derived using the online tool.[39]

5.1.2.3 Data synthesis

For each PICO a separate meta-analysis will be performed for outcomes with the highest relevance for the patients, which are most frequently reported by RCTs and are judged as critical outcomes. As we assume effect sizes to vary from study to study, the meta-analysis will be conducted using the random-effects model.[40] The analysis will be performed in Stata or RStudio. Study heterogeneity will be characterized using I^2 and standard assessments for publication bias and effects of small studies will be performed.[41–43] Binary data will be pooled using effect measures such as relative risk and odds ratios.[19] Continuous data will be pooled using weighted mean differences. Uncertainty will be expressed using 95% confidence intervals. For statistical hypothesis testing, a significance level of 0.05 will be used. Sensitivity analyses (e.g. high-quality vs. low-quality studies), subgroup analyses and meta-regression analyses will be performed if needed. Relevant outcome parameters that cannot be included in the meta-analysis and are reported in at least two RCTs will be summarized in a descriptive manner.

5.2 Health economic analysis

In this section, we describe the approach to address the health economic research questions. In brief, we will first conduct a systematic literature review of existing health economic evidence. Depending on the amount, quality and results of existing health economic evidence, cost-effectiveness will be either assessed by transferring results to the Swiss setting, by adapting an existing model, or by building a de novo model. The budget impact will be estimated with a de novo model for the Swiss setting.

In order to get a first impression of the existing health economic models in the field, we conducted a targeted search for this protocol. We also analysed the identified literature to provide an outline of the potential approach to assess the cost-effectiveness and cost-utility of the drugs under investigation.

5.2.1 Systematic literature review

5.2.1.1 Search strategy

To identify health economic evidence, we developed search strategies based on the PICO criteria in collaboration with a medical librarian and according to current best practice guidelines (see 7 Appendix for the detailed search strategy per database).[44–46] In addition to the search in Cochrane Library, Embase and Medline, we will perform a search in EconLit, the international HTA database (INAHTA), the EUnetHTA Planned and Ongoing Projects (POP) database, the NHS Economic Evaluation Database (NHSEED) and the cost-effectiveness analysis (CEA) Registry hosted at Tufts Medical

Center[47].. We will also screen the references of included studies after full-text screening to identify additionally relevant evidence.

5.2.1.2 Study inclusion and exclusion criteria

Inclusion and exclusion criteria were defined according to the PICO criteria (Section 3) and were kept broad, without restricting the publication period or study quality. We will include studies with adult populations, in line with the age of dementia onset. Studies with a published full text in English, French, German, or Italian will be eligible. We will not specify concrete outcomes as inclusion or exclusion criteria as long as outcomes are within the domains outlined in Section 4. Inclusion/exclusion criteria for studies on health economic outcomes are listed in Table 2.

Table 2 Inclusion criteria for studies on health economic outcomes

Criterion	Inclusion	Exclusion
Publication period	No restrictions	—
Publication status	Published full text available	Published full text not available (including conference abstracts)
Language	English, French, German or Italian	Not English, French, German or Italian
Setting	No restrictions	—
Study design/type	Health economic analysis, including within-trial or model-based cost minimization, -effectiveness, -utility, -benefit and budget impact analyses	Not health economic analysis
Study quality	No restrictions	—
Study population	• PICO 1: Adults (≥ 18 years) with mild to moderate dementia due to AD, diagnosed according to established criteria • PICO 2: Adults (≥ 18 years) with moderate to severe dementia due to AD, diagnosed according to established criteria • PICO 3: Adults (≥ 18 years) with mild to moderate dementia due to PD, diagnosed according to established criteria	• Animal studies • PICO 1: Adults (≥ 18 years) without mild to moderate dementia due to AD • PICO 2: Adults (≥ 18 years) without moderate to severe dementia due to AD • PICO 3: Adults (≥ 18 years) without mild to moderate dementia due to PD
Study intervention	• PICO 1: Donepezil, rivastigmine, galantamine as monotherapies according to the approved dosage • PICO 2: Memantine as monotherapy according to the approved dosage • PICO 3: Rivastigmine as monotherapy according to the approved dosage	• PICO 1: Other drugs than donepezil, rivastigmine, galantamine or combinations of these drugs with memantine • PICO 2: Other drugs than memantine or combinations of memantine with AChE inhibitors • PICO 3: Other drugs than rivastigmine or rivastigmine in combination with memantine
Study comparator	Treatment without drugs under investigation / placebo	Any other comparator
Study outcomes	No restrictions	—

Abbreviation: AChE, Acetylcholinesterase; AD, Alzheimer's disease; PD, Parkinson's disease; PICO, Population, intervention, comparator, outcome

5.2.1.3 Study selection

In a first step, the studies will be title-and-abstract-screened in duplicate according to the inclusion/exclusion criteria. In a second step, full texts of studies retained from the first step will be reviewed in duplicate. Any disagreement will be solved by consensus. Where consensus cannot be found, a third reviewer will be consulted. To increase consistency between reviewers, prior training sessions will be held.

5.2.1.4 Data extraction

One reviewer will extract data into a predefined work sheet, which we will pilot-test with selected studies retained after full-text screening. Extracted data will be checked by a second reviewer. Any disagreement will be solved by consensus. Where consensus cannot be found, a third reviewer will be consulted.

We intend to extract the following data:

- Type of economic evaluation
- Conflict of interest
- Model used (where applicable)
- Time horizon
- Discount rate
- Intervention, comparator
- Country
- Population data used
- Perspective of cost assessment (e.g. societal, healthcare)
- Clinical data used
- Quality of life-related data used
- Cost data used (currency, and cost year)
- Key assumptions made for modelling, e.g. regarding adverse events and costs
- Actual results for health economic outcomes
- Information to assess the quality of studies and reporting including information on how uncertainty was handled (type of sensitivity analysis, scenario analysis etc.)

5.2.1.5 Assessment of quality of evidence

The quality of reporting the included health economic evidence will be assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[48] Moreover, we will critically assess the main input variables and sources, and compare them with the results of the clinical part of this HTA, whenever possible.

5.2.1.6 Data synthesis

Relevant study characteristics including outcomes (Section 5.2.1.4) will be summarized in a table grouped by study type and relevant patient sub-populations. Depending on the amount, quality and results of existing health economic evidence, cost-effectiveness will be either assessed by transferring results to the Swiss setting, by adapting an existing model, or by building a de novo model. In order to get a first impression of the amount of existing health economic evidence in the field and published modelling approaches, we conducted a targeted search for this protocol. This search is described in the next section.

5.2.2 Targeted search conducted for this protocol

We conducted a targeted literature search in Medline based on the PICO criteria to obtain a first overview of the amount of published health economic studies. Furthermore, we used this targeted search to investigate modelling approaches used in the field.

A preliminary overview on the retrieved studies can be found in Table 3. In brief, we identified more than 20 health economic studies related to the topic of this HTA including several cost-effectiveness and cost-utility analyses.[49–71] One study was a systematic review of health economic evaluations, two studies were trial-based economic evaluations and all other were model-based. Of the model-based economic evaluations, most were Markov models, but we also identified some discrete event simulations. Only one study examined PICO 3. In addition, we identified one study investigating the budget impact and cost-utility of a combination treatment of AChE inhibitors and memantine in Switzerland.[55] Although the combination therapy is out of the scope of this HTA, this study used a Markov model that might be adaptable to the research questions at hand. Consequently, there seems to be a substantial body of evidence on the health economic aspects of this HTA that needs to be first analysed in detail in order to be able to decide if cost-effectiveness can be assessed by transferring existing results to the Swiss setting, by adapting an existing model, or by building a de novo model.

Table 3 Overview of health economic studies identified as part of the targeted search conducted for this protocol

First Author and year	Country	Sudy type	Model type	PICO	Treatments	Time horizon	Perspective
Knapp et al. 2017[51]	United Kingdom	CEA	Trial-based	II	Memantine	1 year	Healthcare payer & societal
Peters et al. 2013[50]	United Kingdom	CUA	Markov	I	Donepezil	5-20 years	Healthcare payer
Pfeil et al. 2012[55]	Switzerland	CUA	Markov	-	Combination therapy of AChE inhibitors with memantine	5 years	Healthcare payer & societal
Hartz et al. 2012[54]	Germany	CUA	DES	I	Donepezil	10 years	Healthcare payer & societal
Bond et al. 2012[56]	United Kingdom	CUA	Markov	I & II	Donepezil, rivastigmine, galantamine and memantine	20 years	Healthcare payer
Rive et al. 2012[53]	Norway	CUA	Markov	-	Memantine vs. no pharmacological treatment or AChE inh.	5 years	Societal
Hoogveldt et al. 2011[57]	Netherlands	CUA	Markov	II	Memantine	5 years	Societal
Getsios et al. 2010[58]	United Kingdom	CUA	DES	I	Donepezil	10 years	Healthcare payer & societal
Rive et al. 2010[52]	United Kingdom	CUA	Markov	-	Memantine vs. no pharmacological treatment or AChE inh.	5 years	Healthcare payer
Wong et al. 2009[59]	Canada	CEA	Decision tree	I	Donepezil, rivastigmine and galantamine	0.5 years	Societal
López-Bastida et al. 2009[60]	Spain	CUA	Markov	I	Donepezil	2 years	Healthcare payer & societal
Teipel et al. 2007[61]	Germany	CUA	Markov	I	Donepezil	5 years	Healthcare payer
Gagnon et al. 2007[62]	Canada	CUA	Markov	II	Memantine	2 years	Societal
Antonanzas et al. 2006[63]	Spain	CEA	Markov	II	Memantine	2 years	Societal
Loveman et al. 2006[64]	United Kingdom	CUA	Markov	I & II	Donepezil, rivastigmine, galantamine and memantine	5 years	Healthcare payer
Willan et al. 2006[70]	Canada & UK	CUA	Trial-based	III	Rivastigmine	2 years	Societal
Jönsson et al. 2005[69]	Sweden	CUA	Markov	II	Memantine	5 years	Healthcare payer
Happich et al. 2005[65]	Germany	CUA	Markov	I	Galantamine	5 years	Healthcare payer & societal
Green et al. 2005[66]	United Kingdom	CUA	Markov	I	Donepezil, rivastigmine and galantamine	5 years	Healthcare payer
Jones et al. 2004[67]	United Kingdom	CUA	Markov	II	Memantine	2 years	Healthcare payer
François et al. 2004[68]	Finland	CEA	Markov	II	Memantine	5 years	Societal
Wimo et al. 2004[49]	Mix	Review	Review	I	Donepezil, rivastigmine and galantamine	Review	Review
Jönsson et al. 1999[71]	Sweden	CEA	Markov	I	Donepezil	5 years	Healthcare payer

Abbreviations: AChE, Acetylcholinesterase; CEA, Cost-effectiveness analysis; CUA, Cost-utility analysis; DES, discrete event simulation

5.2.3 Cost-effectiveness and cost-utility analysis

Cost-effectiveness and cost-utility will be assessed by transferring existing results to the Swiss setting, by adapting an existing model, or by building a de novo model. These three different approaches are outlined in the following sections.

5.2.3.1 Perspective

The analysis will be performed from a healthcare payer perspective. Costs of health care services covered by the Swiss mandatory health insurance will be analysed, irrespective of the actual payer (mandatory health insurance, other social insurance, government, out-of-pocket). The analysis will not include indirect costs due to informal care or productivity losses and additional non-medical costs for patients, such as travel costs.

5.2.3.2 Transferring existing results to the Swiss setting

Several studies have proposed procedures and unique criteria to assess geographic transferability. The methods vary substantially across these studies and there is no clear agreement on the procedure that should be followed.[72] We will assess the potential of transferring the existing evidence to the Swiss setting by first evaluating the eligibility of the studies. According to the ISPOR Task Force on Good Research Practices[73] that are based on Welte et al. 2004[74], the eligibility will be satisfied if the population, intervention and comparator are the same as in our HTA and the study's quality is acceptable. Based on the inclusion and exclusion criteria defined in Table 2 eligibility of the included studies is by definition satisfied. The quality of reporting will be assessed based on the CHEERS statement. We will also assess if the recovered studies are full-scale health economic evaluations measuring the incremental cost-effectiveness ratios, and the extent to which the country is comparable to Switzerland with respect to the socio-economic characteristics and cost parameters (e.g. costs of intervention and comparator). In addition, we will compare the input variables with the results of the clinical part of this HTA. In a second step, we will evaluate the transferability in the eligible studies based on 14 critical factors (related to the methodology, the health care system and the population characteristics) proposed by Welte et al. 2004[74]. Both assessments will be conducted qualitatively.

If transferability is possible, costs will be converted to Swiss francs by adjusting for differences in purchasing power and per capita health care expenditures in the reference year of the study. Costs will then be extrapolated to the year 2019 using Swiss per capita health care expenditures.

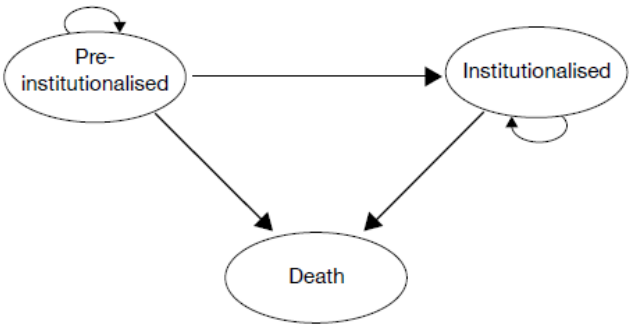
5.2.3.3 Adaptation of an existing health economic model

In case the results from the systematic literature review do not allow the transfer of the published evidence to the Swiss healthcare setting, we will explore the option of adapting one of the existing model structures. In that case we will also assess the model's assumptions. From the studies found in the

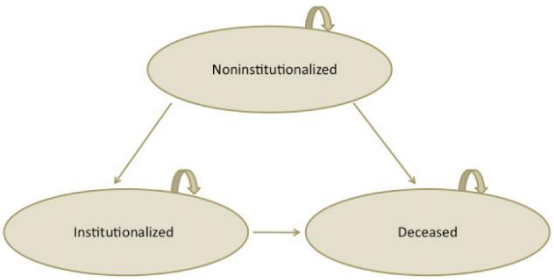
targeted search, we identified two main model structures that could potentially be adapted. One model was developed for the UK and one for Canada.[56,75] Both are three-state Markov models, including pre-institutionalization state, in which patients live in their homes, institutionalization state, in which patients live in a residential or nursing home, and death (Figure 1).

The main difference in the structure between these two models regard the assumptions made for the pre-institutionalization state. In contrast to Lachaine et al. 2011[75], Bond et al. 2012[56] capture the disease progression within the pre-institutionalization state by adding a time dimension in that state. In addition, while Lachaine et al. 2011[75] assume that all patients start in the pre-institutionalization state, Bond et al. 2012[56] assume that 90% of the patients with mild-to-moderate AD start in the pre-institutionalization state and 10% in the institutionalization state. After each successive cycle, patients can move to the institutionalized or deceased state, or remain in the non-institutionalized state. Transition to death from either of the alive states can occur at any cycle. The models, however, do not allow for any backward transitions, hence it is assumed that a patient cannot return to the pre-institutionalized state once institutionalized. In both models the effect of treatment was assumed to delay institutionalization but not affect survival. Both models were developed in Microsoft Excel while Bond et al. 2012[56] conducted some additional analyses using the statistical software R.

Figure 1 Two examples of three-state Markov models in the field



Bond et al. 2012



Lachaine et al. 2011

The model by Bond et al. 2012[56], named after the Peninsula Technology Assessment Group (PenTAG), is a Markov model adjusted for UK based on the Assessment of Health Economics in Alzheimer's Disease decision model developed by the Southampton Health Technology Assessment Centre (SHTAC-AHEAD) .[76] The SHTAC-AHEAD model was developed for the comparison between existing and emerging therapies for AD based on US data. PenTAG is an improved version of the SHTAC-AHEAD model that adapts it to UK and addresses some critiques the model has received. The cohort characteristics, disease progression and costs estimates used in the PenTAG decision model are based

on individual patient data from the study by Wolstenholme et al. 2002[77], which is a UK-based epidemiological cohort study. The study participants were recruited through general practitioners, community psychiatric nurses and consultant geriatricians in the Oxfordshire area during 1988-1989 and were followed for up to 11 years. The cohort includes 92 patients that have an AD diagnosis at study entry at the median for 4.0 years and at the mean for 4.9 years.

Using this UK individual patient data with AD-diagnosed patients,[77] their treatment paths and outcomes, the authors were able to develop a multivariate regression model to predict time to institutionalization. As a result, they adjusted the SHTAC-AHEAD model such that it would allow for disease severity (based on MMSE) to increase as patients approach the time when they become institutionalized. This allows for the gradual increase of costs and reduction in health-related quality of life during the pre-institutionalization state. The main assumption behind this adjustment was that the pre-institutionalization state is too heterogenous to be described by only one single cost and utility value. For people in the non-treatment cohort, mean time to institutionalization and mean time to death were predicted using the mean baseline age, MMSE and Barthel ADL index of the cohort. The model implicitly assumes that patients will then progress to severe AD and be institutionalized. This assumption is not required to model memantine, as this drug is licensed for moderate-to-severe AD. Therefore, memantine will be continued to be used until death, unless it is stopped due to clinical reasons (e.g. patient no longer responding). Furthermore, the model allows for treatment discontinuations and assumes that treatment with AChE inhibitors stops once the patient's disease severity progresses to severe AD (MMSE < 10). Due to lack of data it is, however, assumed that 4% of the total cohort discontinue treatment each month, for all drugs and doses, hence almost no patients are receiving treatment after 2 years. Note that due to treatment discontinuations, not all patients in the pre-institutionalized are on treatment.

The model by Lachaine et al. 2011[75] is a Markov model that was developed for Canada based on US data and has been applied before in a Swiss study by Pfeil et al. 2012[55]. Lopez et al. 2009[78] followed 943 AD patients from the Alzheimer's Research Program (1983–1988) or the Alzheimer disease Research Center at the University of Pittsburgh (1985 to 2009), that were treated with either both AChE inhibitors and memantine, only AChE inhibitors or neither, for 7 years and examined the time to nursing home admission and death. The transition probability to the institutionalized state in the intervention and control group in the model by Lachaine et al. 2011[75] was thus estimated for each one-year cycle for a time horizon of 7 years based on the finding of Lopez et al. 2009[78]. The probability of dying was estimated from Canadian survival tables adjusted for AD, age and sex. The probability of dying was, however, assumed to be independent of the health state. Note that the PICO investigated in this study

is different compared to the PICOs investigated in the current study, in that it compares AChE inhibitors with memantine to AChE inhibitors alone.

Table 4 provides an overview of the two potential models including their pros and cons. In both models an issue for the adaptation to the Swiss healthcare setting concerns the comparability of the patient's management. This includes, for example, the diagnostic (there may be differences between early and late diagnosis) or institutionalization practices (all patients with severe AD are assumed in the models to be institutionalized). It should also be mentioned that if we opt for the model by Bond et al. 2012[56] we will have to request the license to use this model from the authors, as replicating the model and adapting it for Switzerland would require a significant amount of information from the authors and a considerable amount of time.

Table 4 Overview of two Markov models that could potentially be adapted to the Swiss setting

Author; year; country	Population	Intervention	Control	Evaluation	Study type	Time horizon	Discount rate cost	Discount rate benefits	Pros	Cons
Bond et al. 2012[56] UK	Mild-to-moderate AD	AChE inhibitors: donepezil, rivastigmine, galantamine (everyone separately)	placebo or BSC	CUA	Markov (cycle length: 1-month)	20 years[1]	3.5%[2]	3.5%[2]	• Captures heterogeneity of the pre-institutionalization state • Accounts for treatment discontinuation • Captures the treatment paths in the UK in detail	• Is based on a very old observational study with only 92 patients • Cannot be replicated; requires access to data by Wolstenholme et al. 2002, needs to be licensed → costs • Is the assumption that severe AD = institutionalization realistic for Switzerland? • Linear and constant discontinuation • Structural uncertainty
	Moderate-to-severe AD	memantine	placebo or BSC	CUA						
Lachaine et al. 2011[75] Canada	wide range of AD severities	AChE inhibitors (donepezil, rivastigmine, galantamine) in combination with memantine	AChE inhibitors alone	CUA	Markov (cycle length: 1-year)	7 years	5%[3]	5%[3]	Might be replicated	• 1-year cycles • Many simplification assumptions • Structural uncertainty

Abbreviations: AChE, Acetylcholinesterase; AD, Alzheimer's disease; BSC, best supportive care; CUA, cost-utility analysis

Notes: [1] where it is estimated that < 5% of the cohort are still alive, [2] as stated in NICE methods guide, [3] as recommended by the Canadian Agency for Drugs and Technologies in Health

For PICO 3 only one health economic evaluation was identified in the targeted search.[70] This study was based on the EXPRESS (EXelon in PaRkinson's disEaSe dementia Study) Trial, which is a randomised, double-blind, multinational, 24-week trial. It included 541 patients from 12 countries that were older than 50 years. In this study the effect of treating mild-to-moderate dementia due to PD with rivastigmine was assumed to increase the quality-adjusted survival time through the improvement of the MMSE scores. The cost-effectiveness analysis was conducted from a societal perspective with a time horizon of 24 weeks and was performed by applying Canadian and UK cost weights to the healthcare utilisation data collected from the EXPRESS Trial. This study could be potentially adjusted for Switzerland as the health care utilization parameters are documented in the study, thus making it possible to distinguish between the direct medical costs (which are relevant for the health care payer perspective) and the other costs.

We also investigated potential data sources that could be used to populate an adapted model or a de novo model. These are presented in Table 5.

Table 5 Potential model input parameters and data sources for a health economic model

Model input parameters	**Source**
Clinal efficacy/effectiveness	Meta-Analysis of included studies from the systematic literature review regarding efficacy/effectiveness
Population	• Global Burden of Disease • Alzheimer Europe
Mortality	• Swiss life tables
Treatment discontinuation	• Health care claims data from a large health insurance company in Switzerland (e.g. Helsana)
Resource use (drugs)	• Health care claims data from a large health insurance company in Switzerland (e.g. Helsana) • IQVIA
Cost per unit (drugs)	• List of pharmaceutical specialties (in German: "Spezialitätenliste SL") by FOPH
Treatment costs in each health state with and without intervention (resource use and unit costs) Pre-institutionalization: • Home care (Spitex) • Physician costs • Costs for memory clinics Institutionalization: • Nursing home	Combination of sources: • Standard of care guidelines in Switzerland for patients with dementia due to AD or PD with/without drug treatment. If no guidelines available, we will ask clinical experts. • SASIS for cost per consultation (depending on specialist) • Swiss official medical tariff (TARMED) for calculating treatment costs using the latest mean tax point value • Kraft et al. 2010[79] • Statistics of socio-medical institutions (Somed) provided by the Federal Statistical Office • Ecoplan (2019): Alzheimer Schweiz Demenz-kostenstudie 2019
Utility weights	Most probably no studies regarding Switzerland. Therefore, we might draw the utility weights from international studies such as Getsios et al. 2001[80], Ward et al. 2003[81] and Neumann et al. 1999[82]

Abbreviations: AD, Alzheimer's Disease; FOPH: Federal Office of Public Health; PD, Parkinson's disease; SL: Spezialitätenliste; Somed, Statistics of socio-medical institutions; TARMED, Swiss official medical tariff

5.2.3.4 Building a de novo health economic model

In case the results from the systematic literature review do not allow the transfer of the published evidence to the Swiss healthcare setting and we cannot adapt an existing model, we must build a de novo health economic model. According to the International Society for Pharmacoeconomics and Outcomes Research and the Society for Medical Decision Making (ISPOR-SMDM) good modelling research practice, a prerequisite of developing a de novo model is a thorough review of existing health economic models.[83] A starting point for such a review has been provided in the previous sections. In the following paragraphs, we outline the most important aspects of a potential de novo model.

Structure of the model: We would expect a de novo model to be most likely a Markov model. Markov models were most often used in the health economic evidence identified in the targeted search (Table 3, page 26). Although a discrete event simulation model would better reflect patient history, we would expect serious challenges in getting data that could be used to populate a discrete event simulation model. The structure of the model will also be discussed with a clinical expert to ensure it reflects daily clinical practices in Switzerland.

Time horizon: We expect using a lifetime time horizon in order to capture all potential costs and outcomes. Alternative time horizons (e.g. 5 or 10 years) will be investigated as part of the scenario analysis.

Discounting: Both, costs and outcomes will be discounted at 3% in the base-case scenario. Additionally, discount rates of 0% and 5% will be explored in the univariate analysis.

Health outcomes: Quality-adjusted life-years (QALYs) and other outcomes such as for example prevented number of nursing home placements.

Model input parameters and data sources: Potential input parameters and data sources are presented in Table 5 (page 32).

Sensitivity analysis: The effect of parameter uncertainty on the results will be evaluated in deterministic univariate and probabilistic multivariate sensitivity analyses. Structural uncertainty will be evaluated in scenario analyses.

5.2.4 Budget impact analysis

We will build a budget impact model for the Swiss setting based on the following characteristics.

Perspective: The budget impact analysis will be performed from a healthcare payer perspective.

Time horizon: The budget impact will be estimated over a time horizon of five years.

Target population: The target population will be estimated based on the data sources presented in Table 5 (page 32).

Treatment mix: The treatment mix will be estimated based on the data sources presented in Table 5 (page 32).

Cost per patient: Cost per patient will be based on the results of the cost-effectiveness and cost-utility analysis.

Scenario analysis: Scenario analysis will consider uncertainty regarding target population, treatment mix and cost per patient.

5.3 Ethical, legal, social and organizational issues

To address the ethical, legal, social and organizational (ELSO) issues, we will conduct a targeted literature search in Medline (see 7 Appendix for the detailed search strategy). Inclusion and exclusion criteria are presented in Table 6 and were developed in accordance with those of the efficacy, safety, effectiveness, and health economic search (see Table 1 and Table 2). However, we will impose no study design restrictions as we expect discussions of ELSO outcomes to be presented in a variety of study designs. A single researcher will screen and review the literature and identify studies relevant to the ELSO domains. In addition, the quality of evidence for ELSO outcomes will not be formally assessed. The main ELSO aspects identified through this targeted search will be reported in a descriptive manner. Note that this review will not be systematic. We consider this to be an appropriate approach as the primary purpose is to identify key aspects relevant to ELSO outcomes but not to provide an exhaustive or systematic review of the literature on these domains.

Furthermore, we will discuss a range of questions further investigating ethical and legal issues based on the HTA Core Model®.[84] For ethical issues, we will also use the “Hofmann catalogue”.[85,86] In addition, a guideline published by the Swiss Academy of Medical Sciences (SAMW) regarding “Betreuung und Behandlung von Menschen mit Demenz” will be further investigated.[87] For legal issues, we will also take into consideration a checklist designed for the Swiss legal system.[88]

Table 6 Inclusion criteria for studies on ethical, legal, social and organizational outcomes

Criterion	Inclusion	Exclusion
Publication period	As for Table 1 and Table 2	
Publication status		
Language		
Setting	As for Table 1 and Table 2	
Study design/type	No restrictions	—
Study quality	As for Table 1 and Table 2	
Study population	No restrictions	—
Study intervention and comparator	Discussion of antidementia drugs (any symptomatic antidementia drug)	No discussion of antidementia drugs
Study outcomes	Discussion of ethical, legal, social, or organizational aspects	No discussion of ethical, legal, social, or organizational aspects

6 References

1 World Health Organization. Dementia. 2020.https://www.who.int/en/news-room/fact-sheets/detail/dementia (accessed 1 Apr 2021).

2 Alzheimer Schweiz. Demenz in der Schweiz. https://www.alzheimer-schweiz.ch/de/ueber-demenz/beitrag/demenz-in-der-schweiz (accessed 13 Apr 2021).

3 Ecoplan. Alzheimer Schweiz Demenzkostenstudie 2019: Gesellschaftliche Perspektive. Bern: : Alzheimer Schweiz 2019.

4 Alzheimer's Association. What is Dementia? 2021.https://www.alz.org/alzheimers-dementia/what-is-dementia (accessed 1 Apr 2021).

5 Ferreira-Vieira TH, Guimaraes IM, Silva FR, *et al.* Alzheimer's Disease: Targeting the Cholinergic System. *Curr Neuropharmacol* 2016;**14**:101–15. doi:10.2174/1570159X13666150716165726

6 Forlenza OV, Diniz BS, Gattaz WF. Diagnosis and biomarkers of predementia in Alzheimer's disease. *BMC Medicine* 2010;**8**:89. doi:10.1186/1741-7015-8-89

7 McShane R, Westby MJ, Roberts E, *et al.* Memantine for dementia. *Cochrane Database of Systematic Reviews* Published Online First: 2019.https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003154.pub6/full (accessed 6 Apr 2021).

8 United States Food and Drug Administration FDA. Aducanumab (marketed as Aduhelm) Information. FDA. 2021.https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/aducanumab-marketed-aduhelm-information (accessed 16 Jun 2021).

9 S3-Leitlinie: Demenzen. Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde (DGPPN), Deutsche Gesellschaft für Neurologie (DGN) 2016.

10 Monsch, Büla, Hermelink, *et al.* Consensus 2012 – Diagnosis and Treatment of Patients with Dementia in Switzerland. *Praxis* 2012;**101**:1239–49. doi:10.1024/1661-8157/a001085

11 Federal Office of Public Health. Spezialitätenliste. http://www.spezialitaetenliste.ch/ (accessed 13 Apr 2021).

12 Huber F, Beise U. mediX Guideline Demenz. ;:13.

13 Savaskan E, Bopp-Kistler I, Buerge M, *et al.* Empfehlungen zur Diagnostik und Therapie der behavioralen und psychologischen Symptome der Demenz (BPSD). *Praxis* 2014;**103**:135–48. doi:10.1024/1661-8157/a001547

14 NICE. Dementia: assessment, management and support for people living with dementia and their carers. https://www.nice.org.uk/guidance/ng97 (accessed 7 Oct 2021).

15 Alzheimer Europe - Policy - Country comparisons - 2020: European Dementia Monitor, Comparing and benchmarking national dementia strategies and policies. https://www.alzheimer-europe.org/Policy/Country-comparisons/2020-European-Dementia-Monitor-Comparing-and-benchmarking-national-dementia-strategies-and-policies (accessed 7 Oct 2021).

16 Haute Autorité de Santé. Rapport d'évaluation des médicaments indiqués dans le traitement symptomatique de la maladie d'alzheimer. 2016.

17 IQWIG. Alzheimer Demenz: Nur von wenigen Therapien können Patienten nachweislich profitieren. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). 2009.https://www.iqwig.de/presse/pressemitteilungen/pressemitteilungen-detailseite_10950.html (accessed 23 Jun 2021).

18 IQWIG. Langes Ringen um angemessen aufbereitete Hersteller-Daten führt zu Neu-Bewertung von Memantin. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). 2011.https://www.iqwig.de/presse/pressemitteilungen/pressemitteilungen-detailseite_10858.html (accessed 23 Jun 2021).

19 Higgins J, Thomas J, Chandler J, *et al.*, editors. *Cochrane Handbook for Systematic Reviews of Interventions: version 6 (updated July 2019)*. Cochrane 2019.

20 Parsons C, Lim WY, Loy C, *et al.* Withdrawal or continuation of cholinesterase inhibitors or memantine or both, in people with dementia. *Cochrane Database of Systematic Reviews* Published Online First: 2021.https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009081.pub2/full (accessed 6 Apr 2021).

21 Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database of Systematic Reviews* Published Online First: 2018.https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001190.pub3/full (accessed 6 Apr 2021).

22 Birks JS, Chong L-Y, Evans JG. Rivastigmine for Alzheimer's disease. *Cochrane Database of Systematic Reviews* Published Online First: 2015. doi:10.1002/14651858.CD001191.pub4

23 Birks JS. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database of Systematic Reviews* Published Online First: 2006.https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005593/full (accessed 6 Apr 2021).

24 Rolinski M, Fox C, Maidment I, *et al.* Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. *Cochrane Database of Systematic Reviews* Published Online First: 2012. doi:10.1002/14651858.CD006504.pub2

25 Maidment I, Fox C, Boustani M. Cholinesterase inhibitors for Parkinson's disease dementia. *Cochrane Database of Systematic Reviews* Published Online First: 2006. doi:10.1002/14651858.CD004747.pub2

26 Loy C, Schneider L. Galantamine for Alzheimer's disease and mild cognitive impairment. *Cochrane Database of Systematic Reviews* Published Online First: 2006.https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001747.pub3/full (accessed 6 Apr 2021).

27 Tan C-C, Yu J-T, Wang H-F, *et al.* Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis* 2014;**41**:615–31. doi:10.3233/JAD-132690

28 Matsunaga S, Kishi T, Iwata N. Memantine monotherapy for Alzheimer's disease: a systematic review and meta-analysis. *PLoS One* 2015;**10**:e0123289. doi:10.1371/journal.pone.0123289

29 Kishi T, Matsunaga S, Oya K, *et al.* Memantine for Alzheimer's Disease: An Updated Systematic Review and Meta-analysis. *J Alzheimers Dis* 2017;**60**:401–25. doi:10.3233/JAD-170424

30 Kobayashi H, Ohnishi T, Nakagawa R, *et al.* The comparative efficacy and safety of cholinesterase inhibitors in patients with mild-to-moderate Alzheimer's disease: a Bayesian network meta-analysis. *Int J Geriatr Psychiatry* 2016;**31**:892–904. doi:10.1002/gps.4405

31 Blanco-Silvente L, Castells X, Saez M, *et al.* Discontinuation, Efficacy, and Safety of Cholinesterase Inhibitors for Alzheimer's Disease: a Meta-Analysis and Meta-Regression of 43 Randomized Clinical Trials Enrolling 16 106 Patients. *Int J Neuropsychopharmacol* 2017;**20**:519–28. doi:10.1093/ijnp/pyx012

32 Dou K-X, Tan M-S, Tan C-C, *et al.* Comparative safety and effectiveness of cholinesterase inhibitors and memantine for Alzheimer's disease: a network meta-analysis of 41 randomized controlled trials. *Alzheimers Res Ther* 2018;**10**:126. doi:10.1186/s13195-018-0457-9

33 Knight R, Khondoker M, Magill N, *et al.* A Systematic Review and Meta-Analysis of the Effectiveness of Acetylcholinesterase Inhibitors and Memantine in Treating the Cognitive Symptoms of Dementia. *DEM* 2018;**45**:131–51. doi:10.1159/000486546

34 Meng Y-H, Wang P-P, Song Y-X, *et al.* Cholinesterase inhibitors and memantine for Parkinson's disease dementia and Lewy body dementia: A meta-analysis. *Exp Ther Med* 2019;**17**:1611–24. doi:10.3892/etm.2018.7129

35 Thancharoen O, Limwattananon C, Waleekhachonloet O, *et al.* Ginkgo biloba Extract (EGb761), Cholinesterase Inhibitors, and Memantine for the Treatment of Mild-to-Moderate Alzheimer's Disease: A Network Meta-Analysis. *Drugs Aging* 2019;**36**:435–52. doi:10.1007/s40266-019-00648-x

36 Tricco AC, Ashoor HM, Soobiah C, *et al.* Comparative Effectiveness and Safety of Cognitive Enhancers for Treating Alzheimer's Disease: Systematic Review and Network Metaanalysis. *Journal of the American Geriatrics Society* 2018;**66**:170–8. doi:10.1111/jgs.15069

37 Higgins, Julian PT, Savović, Jelena, Page, Matthew J, *et al.* Chapter 8: Assessing risk of bias in a randomized trial. In: *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane 2021. https://training.cochrane.org/handbook/current/chapter-08 (accessed 24 Aug 2021).

38 Schünemann HJ, Higgins JP, Vist G, *et al.* Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane 2020.

39 GRADE. Guideline Development Tool. https://gdt.gradepro.org (accessed 23 Jun 2021).

40 Borenstein M, Hedges LV, Higgins JPT, *et al.* A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010;**1**:97–111. doi:10.1002/jrsm.12

41 Borenstein M, Hedges LV, Higgins JPT, *et al.* A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods* 2010;**1**:97–111. doi:10.1002/jrsm.12

42 Higgins JPT, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557–60.

43 Egger M, Davey Smith G, Schneider M, *et al.* Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34.

44 Thielen FW, Mastrigt GV, Burgers LT, *et al.* How to prepare a systematic review of economic evaluations for clinical practice guidelines: database selection and search strategy development (part 2/3). *Expert Rev Pharmacoecon Outcomes Res* 2016;**16**:705–21. doi:10.1080/14737167.2016.1246962

45 van Mastrigt GAPG, Hiligsmann M, Arts JJC, *et al.* How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: a five-step approach (part 1/3). *Expert Rev Pharmacoecon Outcomes Res* 2016;**16**:689–704. doi:10.1080/14737167.2016.1246960

46 Wijnen B, Van Mastrigt G, Redekop WK, *et al.* How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: data extraction, risk of bias, and transferability (part 3/3). *Expert Rev Pharmacoecon Outcomes Res* 2016;**16**:723–32. doi:10.1080/14737167.2016.1246961

47 CEA Registry - Center for the Evaluation of Value and Risk in Health. https://cevr.tuftsmedicalcenter.org/databases/cea-registry (accessed 23 Jun 2021).

48 Evers S, Goossens M, de Vet H, *et al.* Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *Int J Technol Assess Health Care* 2005;**21**:240–5.

49 Wimo A. Cost effectiveness of cholinesterase inhibitors in the treatment of Alzheimer's disease: a review with methodological considerations. *Drugs Aging* 2004;**21**:279–95. doi:10.2165/00002512-200421050-00001

50 Peters JL, Anderson R, Hoyle M, *et al.* Evolution of a cost-utility model of donepezil for Alzheimer's disease. *Int J Technol Assess Health Care* 2013;**29**:147–54. doi:10.1017/S026646231300007X

51 Knapp M, King D, Romeo R, *et al.* Cost-effectiveness of donepezil and memantine in moderate to severe Alzheimer's disease (the DOMINO-AD trial). *Int J Geriatr Psychiatry* 2017;**32**:1205–16. doi:10.1002/gps.4583

52 Rive B, Grishchenko M, Guilhaume-Goulant C, *et al.* Cost effectiveness of memantine in Alzheimer's disease in the UK. *J Med Econ* 2010;**13**:371–80. doi:10.3111/13696998.2010.491347

53 Rive B, Aarsland D, Grishchenko M, *et al.* Cost-effectiveness of memantine in moderate and severe Alzheimer's disease in Norway. *Int J Geriatr Psychiatry* 2012;**27**:573–82. doi:10.1002/gps.2755

54 Hartz S, Getsios D, Tao S, *et al.* Evaluating the cost effectiveness of donepezil in the treatment of Alzheimer's disease in Germany using discrete event simulation. *BMC Neurol* 2012;**12**:2. doi:10.1186/1471-2377-12-2

55 Pfeil AM, Kressig RW, Szucs TD. Alzheimer's dementia: budget impact and cost-utility analysis of a combination treatment of a cholinesterase inhibitor and memantine in Switzerland. *Swiss Med Wkly* 2012;**142**:w13676. doi:10.4414/smw.2012.13676

56 Bond M, Rogers G, Peters J, *et al.* The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): a systematic review and economic model. *Health Technol Assess* 2012;**16**:1–470. doi:10.3310/hta16210

57 Hoogveldt B, Rive B, Severens J, *et al.* Cost-effectiveness analysis of memantine for moderate-to-severe Alzheimer's disease in the Netherlands. *Neuropsychiatr Dis Treat* 2011;**7**:313–7. doi:10.2147/NDT.S19239

58 Getsios D, Blume S, Ishak KJ, *et al.* Cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease: a UK evaluation using discrete-event simulation. *Pharmacoeconomics* 2010;**28**:411–27. doi:10.2165/11531870-000000000-00000

59 Wong CL, Bansback N, Lee PE, *et al.* Cost-effectiveness: cholinesterase inhibitors and memantine in vascular dementia. *Can J Neurol Sci* 2009;**36**:735–9. doi:10.1017/s0317167100008350

60 López-Bastida J, Hart W, García-Pérez L, *et al.* Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. *J Alzheimers Dis* 2009;**16**:399–407. doi:10.3233/JAD-2009-0965

61 Teipel SJ, Ewers M, Reisig V, *et al.* Long-term cost-effectiveness of donepezil for the treatment of Alzheimer's disease. *Eur Arch Psychiatry Clin Neurosci* 2007;**257**:330–6. doi:10.1007/s00406-007-0727-1

62 Gagnon M, Rive B, Hux M, *et al.* Cost-effectiveness of memantine compared with standard care in moderate-to-severe Alzheimer disease in Canada. *Can J Psychiatry* 2007;**52**:519–26. doi:10.1177/070674370705200810

63 Antonanzas F, Rive B, Badenas JM, *et al.* Cost-effectiveness of memantine in community-based Alzheimer's disease patients: An adaptation in Spain. *Eur J Health Econ* 2006;**7**:137–44. doi:10.1007/s10198-006-0355-0

64 Loveman E, Green C, Kirby J, *et al.* The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease. *Health Technol Assess* 2006;**10**:iii–iv, ix–xi, 1–160. doi:10.3310/hta10010

65 Happich M, Schweikert B, Mühlbacher A. [Cost-effectiveness of galantamine in a german context]. *Psychiatr Prax* 2005;**32**:142–50. doi:10.1055/s-2004-834709

66 Green C, Picot J, Loveman E, *et al.* Modelling the cost effectiveness of cholinesterase inhibitors in the management of mild to moderately severe Alzheimer's disease. *Pharmacoeconomics* 2005;**23**:1271–82. doi:10.2165/00019053-200523120-00010

67 Jones RW, McCrone P, Guilhaume C. Cost effectiveness of memantine in Alzheimer's disease: an analysis based on a probabilistic Markov model from a UK perspective. *Drugs Aging* 2004;**21**:607–20. doi:10.2165/00002512-200421090-00005

68 François C, Sintonen H, Sulkava R, *et al.* Cost effectiveness of memantine in moderately severe to severe Alzheimer's disease : a markov model in Finland. *Clin Drug Investig* 2004;**24**:373–84. doi:10.2165/00044011-200424070-00001

69 Jönsson L. Cost-effectiveness of memantine for moderate to severe Alzheimer's disease in Sweden. *Am J Geriatr Pharmacother* 2005;**3**:77–86. doi:10.1016/j.amjopharm.2005.05.002

70 Willan AR, Goeree R, Pullenayegum EM, *et al.* Economic evaluation of rivastigmine in patients with Parkinson's disease dementia. *Pharmacoeconomics* 2006;**24**:93–106. doi:10.2165/00019053-200624010-00008

71 Jönsson L, Lindgren P, Wimo A, *et al.* The cost-effectiveness of donepezil therapy in Swedish patients with Alzheimer's disease: a Markov model. *Clin Ther* 1999;**21**:1230–40. doi:10.1016/S0149-2918(00)80025-9

72 Goeree R, He J, O'Reilly D, *et al.* Transferability of health technology assessments and economic evaluations: a systematic review of approaches for assessment and application. *CEOR* 2011;**3**:89–104. doi:10.2147/CEOR.S14404

73 Drummond M, Barbieri M, Cook J, *et al.* Transferability of Economic Evaluations Across Jurisdictions: ISPOR Good Research Practices Task Force Report. *Value in Health* 2009;**12**:409–18. doi:10.1111/j.1524-4733.2008.00489.x

74 Welte,Robert, Feenstra, Talitha, Jager, Hans, *et al.* A Decision Chart for Assessing and Improving the Transferability of Economic Evaluation Results Between Countries | SpringerLink. *PharmacoEconomics* 2004;**22**:857–76.

75 Lachaine J, Beauchemin C, Legault M, *et al.* Economic evaluation of the impact of memantine on time to nursing home admission in the treatment of Alzheimer disease. *Can J Psychiatry* 2011;**56**:596–604. doi:10.1177/070674371105601005

76 Caro JJ, Getsios D, Migliaccio-Walle K, *et al.* Assessment of health economics in Alzheimer's disease (AHEAD) based on need for full-time care. *Neurology* 2001;**57**:964–71. doi:10.1212/wnl.57.6.964

77 Wolstenholme J, Fenn P, Gray A, *et al.* Estimating the relationship between disease progression and cost of care in dementia. *Br J Psychiatry* 2002;**181**:36–42. doi:10.1192/bjp.181.1.36

78 Lopez OL, Becker JT, Wahed AS, *et al.* Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease. *J Neurol Neurosurg Psychiatry* 2009;**80**:600–7. doi:10.1136/jnnp.2008.158964

79 Kraft E, Marti M, Werner S, *et al.* Cost of dementia in Switzerland. *Swiss Med Wkly* 2010;**140**:w13093. doi:10.4414/smw.2010.13093

80 Getsios D, Caro JJ, Caro G, *et al.* Assessment of health economics in Alzheimer's disease (AHEAD): galantamine treatment in Canada. *Neurology* 2001;**57**:972–8. doi:10.1212/wnl.57.6.972

81 Ward A, Caro JJ, Getsios D, *et al.* Assessment of health economics in Alzheimer's disease (AHEAD): treatment with galantamine in the UK. *Int J Geriatr Psychiatry* 2003;**18**:740–7. doi:10.1002/gps.919

82 Neumann PJ, Kuntz KM, Leon J, *et al.* Health utilities in Alzheimer's disease: a cross-sectional study of patients and caregivers. *Med Care* 1999;**37**:27–32. doi:10.1097/00005650-199901000-00005

83 Roberts M, Russell LB, Paltiel AD, *et al.* Conceptualizing a model: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-2. *Med Decis Making* 2012;**32**:678–89. doi:10.1177/0272989X12454941

84 EUnetHTA Joint Action 2, Work Package 8. HTA Core Model version 3.0 for the full assessment of diagnostic technologies, medical and surgical interventions, pharmaceuticals and screening technologies. 2016. https://eunethta.eu/wp-content/uploads/2018/03/HTACoreModel3.0-1.pdf (accessed 15 Nov 2019).

85 Hofmann BM. Why ethics should be part of health technology assessment. *Int J Technol Assess Health Care* 2008;**24**:423–9. doi:10.1017/S0266462308080550

86 Hofmann B. Toward a procedure for integrating moral issues in health technology assessment. *Int J Technol Assess Health Care* 2005;**21**:312–8. doi:10.1017/S0266462305050415

87 Betreuung und Behandlung von Menschen mit Demenz. Betreuung und Behandlung von Menschen mit Demenz. https://www.samw.ch/de/Ethik/Themen-A-bis-Z/Behandlung-und-Betreuung-von-Menschen-mit-Demenz.html (accessed 14 Apr 2021).

88 Widrig D. *Health Technology Assessment*. Springer-Verlag 2015.

7 Appendix

7.1 Search strategy Medline (via EBSCOhost)

Concept 1	**PICO 1 and PICO 2:** exp Alzheimer Disease/ OR (alzheimer* OR (diffuse ADJ2 "cortical sclero*")).ti,ab. **PICO 3:** exp Parkinson Disease/ OR (parkinson* OR "paralysis agitans").ti,ab.
	AND
Concept 2	**PICO 1 and PICO 2:** exp Donepezil/ OR exp Rivastigmine/ OR exp Galantamine/ OR exp Memantine/ OR (donepezil OR aricept OR asenta OR "doneliquid geriasan" OR "e 2020" OR e2020 OR eranz OR memac OR memorit).ti,ab. OR (rivastigmine OR alzest OR "ena 713" OR ena713 OR exelon OR nimvastid OR prometax OR rivastigmin OR "sdz 212 713" OR "sdz 212-713" OR "sdz 212713" OR "sdz212 713" OR "sdz212-713" OR sdz212713).ti,ab. OR (galantamine OR acumor OR alenzo OR aneprosil OR bergal OR consion OR elmino OR galantex OR galanthamine OR galanthen OR galanyl OR galatamin OR galatamina OR galema OR galnora OR galsya OR gatalin OR gazylan OR girlamen OR jilkon OR lotprosin OR loxifren OR luventa OR lycoremin OR lycoremine OR margal OR masparen OR "memoton life" OR "memoton-life" OR micol OR natagal OR nivalin OR razadyne OR reminyl OR spegal OR vertusal OR zentan OR zoroflog).ti,ab. OR (memantine OR akatinol OR alzantin OR axura OR "d 145" OR d145 OR ebix OR ebixa OR ebixza OR marixino OR maruxa OR memary OR "mn 08" OR mn08 OR namenda OR nemdatine OR "nsc 102290" OR nsc102290 OR "sun y7017" OR suny7017).ti,ab. **PICO 3:** exp Rivastigmine/ OR (Rivastigmine OR alzest OR 'ena 713' OR ena713 OR exelon OR nimvastid OR prometax OR rivastigmin OR "sdz 212 713" OR "sdz 212-713" OR "sdz 212713" OR "sdz212 713" OR "sdz212-713" OR sdz212713).ti,ab.
	AND
Concept 3a	(randomized controlled trial.pt. OR controlled clinical trial.pt. OR randomized.ab.OR randomised.ab. OR placebo.ab. OR drug therapy.fs. OR randomly.ab. OR trial.ab. OR groups.ab.) NOT (exp animals/ not humans.sh.)
	AND
Concept 3b	exp Cost-Benefit Analysis/ OR "Costs and Cost Analysis"/ OR Health Care Costs/ OR exp Economics, Pharmaceutical/ OR (cost* OR "cost benefit analys*" OR economic* OR price OR prices OR pricing OR expenditure* OR pharmacoeconomic* OR "benefit-cost*").ti,ab.
	AND
Concept 4	limit X to (english or german or french or italian)

7.2 Search strategy Embase (via embase.com)

Concept 1	**PICO 1 and PICO 2:** 'Alzheimer disease'/exp OR (alzheimer* OR (diffuse NEAR/2 'cortical sclero*')):ti,ab **PICO 3:** 'Parkinson disease'/exp OR (parkinson* OR 'paralysis agitans'):ti,ab

	AND
Concept 2	**PICO 1 and PICO 2:** 'donepezil'/exp OR 'rivastigmine'/exp OR 'galantamine'/exp OR 'memantine'/exp OR (donepezil OR aricept OR asenta OR 'doneliquid geriasan' OR 'e 2020' OR e2020 OR eranz OR memac OR memorit):ti,ab OR (rivastigmine OR alzest OR 'ena 713' OR ena713 OR exelon OR nimvastid OR prometax OR rivastigmin OR 'sdz 212 713' OR 'sdz 212-713' OR 'sdz 212713' OR 'sdz212 713' OR 'sdz212-713' OR sdz212713):ti,ab OR (galantamine OR acumor OR alenzo OR aneprosil OR bergal OR consion OR elmino OR galantex OR galanthamine OR galanthen OR galanyl OR galatamin OR galatamina OR galema OR galnora OR galsya OR gatalin OR gazylan OR girlamen OR jilkon OR lotprosin OR loxifren OR luventa OR lycoremin OR lycoremine OR margal OR masparen OR 'memoton life' OR 'memoton-life' OR micol OR natagal OR nivalin OR razadyne OR reminyl OR spegal OR vertusal OR zentan OR zoroflog):ti,ab OR (memantine OR akatinol OR alzantin OR axura OR 'd 145' OR d145 OR ebix OR ebixa OR ebixza OR marixino OR maruxa OR memary OR 'mn 08' OR mn08 OR namenda OR nemdatine OR 'nsc 102290' OR nsc102290 OR 'sun y7017' OR suny7017):ti,ab **PICO 3:** 'rivastigmine'/exp OR (Rivastigmine OR alzest OR 'ena 713' OR ena713 OR exelon OR nimvastid OR prometax OR rivastigmin OR 'sdz 212 713' OR 'sdz 212-713' OR 'sdz 212713' OR 'sdz212 713' OR 'sdz212-713' OR sdz212713):ti,ab
	AND
Concept 3a	'randomized controlled trial'/de OR 'controlled clinical trial'/de OR random*:ti,ab or 'randomization'/de or 'intermethod comparison'/de OR placebo:ti,ab OR (compare or compared or comparison):ti OR ((evaluated or evaluate or evaluating or assessed or assess) AND (compare or compared or comparing or comparison)):ab OR (open NEAR/1 label):ti,ab OR ((double or single or doubly or singly) NEAR/1 (blind or blinded or blindly)):ti,ab OR 'double blind procedure'/de OR "parallel group*":ti,ab OR (crossover or "cross over"):ti,ab OR ((assign* or match or matched or allocation) NEAR/5 (alternate or group* or intervention* or patient* or subject* or participant$)):ti,ab OR (assigned or allocated):ti,ab OR (controlled NEAR/7 (study or design or trial)):ti,ab OR (volunteer or volunteers):ti,ab OR 'human experiment'/de OR trial:ti NOT ((((random* NEAR/1 sampl* NEAR/7 ('cross section*' OR questionnaire$ OR survey* OR database$)):ti,ab) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomized controlled':ti,ab OR 'randomised controlled':ti,ab OR 'randomly assigned':ti,ab) OR ('cross-sectional study'/de NOT ('randomized controlled trial'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'randomized controlled':ti,ab OR 'randomised controlled':ti,ab OR "control group$":ti,ab)) OR ((case NEAR/1 control*) AND random*)) NOT ('randomized controlled':ti,ab OR 'randomised controlled':ti,ab) OR ('systematic review':ti NOT (trial:ti OR study:ti)) OR (nonrandom*:ti,ab NOT random*:ti,ab) OR 'random field*':ti,ab OR (('random cluster' NEAR/3 sampl*):ti,ab) OR (review:ab AND 'review':it NOT trial:ti) OR ('we searched':ab AND (review:ti OR 'review':it)) OR 'update review':ab OR ((databases NEAR/4 searched):ab) OR ((rat:ti OR rats:ti OR mouse:ti OR mice:ti OR swine:ti OR porcine:ti OR murine:ti OR sheep:ti OR lambs:ti OR pigs:ti OR piglets:ti OR rabbit:ti OR rabbits:ti OR cat:ti OR cats:ti OR dog:ti OR dogs:ti OR cattle:ti OR bovine:ti OR monkey:ti OR monkeys:ti OR trout:ti OR marmoset$:ti) AND 'animal experiment'/de) OR ('animal experiment'/de NOT ('human experiment'/de OR 'human'/de)))
	AND
Concept 3b	'cost benefit analysis'/exp OR 'cost effectiveness analysis'/exp OR 'cost utility analysis'/exp OR 'cost'/de OR 'health care cost'/de OR 'pharmacoeconomics'/exp OR (cost* OR 'cost benefit analys*' OR economic* OR price OR prices OR pricing OR expenditure* OR pharmacoeconomic* OR 'benefit-cost*'):ti,ab

	AND
Concept 4	NOT [conference abstract]/lim AND ([english]/lim OR [german]/lim OR [french]/lim OR [italian]/lim)

7.3 Search strategy Cochrane (via EBSCOhost)

Concept 1	**PICO 1 and PICO 2:** (alzheimer* OR (diffuse NEAR/2 "cortical sclero*")):ti,ab,kw **PICO 3:** (parkinson* OR "paralysis agitans"):ti,ab,kw
	AND
Concept 2	**PICO 1 and PICO 2:** (donepezil OR aricept OR asenta OR "doneliquid geriasan" OR "e 2020" OR e2020 OR eranz OR memac OR memorit):ti,ab,kw OR (rivastigmine OR alzest OR "ena 713" OR ena713 OR exelon OR nimvastid OR prometax OR rivastigmin OR "sdz 212 713" OR "sdz 212-713" OR "sdz 212713" OR "sdz212 713" OR "sdz212-713" OR sdz212713):ti,ab,kw OR (galantamine OR acumor OR alenzo OR aneprosil OR bergal OR consion OR elmino OR galantex OR galanthamine OR galanthen OR galanyl OR galatamin OR galatamina OR galema OR galnora OR galsya OR gatalin OR gazylan OR girlamen OR jilkon OR lotprosin OR loxifren OR luventa OR lycoremin OR lycoremine OR margal OR masparen OR "memoton life" OR "memoton-life" OR micol OR natagal OR nivalin OR razadyne OR reminyl OR spegal OR vertusal OR zentan OR zoroflog):ti,ab,kw OR (memantine OR akatinol OR alzantin OR axura OR "d 145" OR d145 OR ebix OR ebixa OR ebixza OR marixino OR maruxa OR memary OR "mn 08" OR mn08 OR namenda OR nemdatine OR "nsc 102290" OR nsc102290 OR "sun y7017" OR suny7017):ti,ab,kw **PICO 3:** (Rivastigmine OR alzest OR 'ena 713' OR ena713 OR exelon OR nimvastid OR prometax OR rivastigmin OR "sdz 212 713" OR "sdz 212-713" OR "sdz 212713" OR "sdz212 713" OR "sdz212-713" OR sdz212713):ti,ab,kw
	AND
Concept 3b	(cost* OR "cost benefit analys*" OR economic* OR price OR prices OR pricing OR expenditure* OR pharmacoeconomic* OR "benefit-cost*"):ti,ab,kw

7.4 Search strategy EconLit

Concept 1	**PICO 1 and PICO 2:** (alzheimer* OR (diffuse N2 cortical sclero*)) **PICO 3:** (parkinson* OR paralysis agitans)
	AND
Concept 2	**PICO 1 and PICO 2:** (donepezil OR aricept OR asenta OR doneliquid geriasan OR e 2020 OR e2020 OR eranz OR memac OR memorit) OR (rivastigmine OR alzest OR ena 713 OR ena713 OR exelon OR nimvastid OR prometax OR rivastigmin OR sdz 212 713 OR sdz 212-713 OR sdz 212713 OR sdz212 713 OR sdz212-713 OR sdz212713) OR (galantamine OR acumor OR alenzo OR aneprosil OR bergal OR consion OR elmino OR galantex OR galanthamine OR galanthen OR galanyl OR galatamin OR galatamina OR galema OR galnora OR galsya OR gatalin OR gazylan OR girlamen OR jilkon OR lotprosin OR loxifren OR luventa OR lycoremin OR lycoremine OR margal OR masparen OR memoton life OR memoton-life OR

	micol OR natagal OR nivalin OR razadyne OR reminyl OR spegal OR vertusal OR zentan OR zoroflog) OR (memantine OR akatinol OR alzantin OR axura OR d 145 OR d145 OR ebix OR ebixa OR ebixza OR marixino OR maruxa OR memary OR mn 08 OR mn08 OR namenda OR nemdatine OR nsc 102290 OR nsc102290 OR sun y7017 OR suny7017) **PICO 3:** (Rivastigmine OR alzest OR ena 713 OR ena713 OR exelon OR nimvastid OR prometax OR rivastigmin OR sdz 212 713 OR sdz 212-713 OR sdz 212713 OR sdz212 713 OR sdz212-713 OR sdz212713)

7.5 Strategy targeted search ELSO

Concept 1 - Antidementia drug	(("Dementia"[Mesh] AND “drug therapy”[Title/Abstract]) OR (“antidementia drug”[Title/Abstract] OR antidementia*[Title/Abstract] OR “dementia drug”[Title/Abstract]))
Concept 2 - Ethical, social, legal items	("Ethical Analysis"[Mesh] OR "Legislation, Drug"[Mesh] OR "Social Change"[Mesh] OR (ethics[Title/Abstract] OR legal[Title/Abstract] OR law[Title/Abstract] OR social[Title/Abstract]))
Concept 3 - Organizational items	("Organization and Administration"[Mesh] OR "Policy"[Mesh] OR "Insurance, Health"[Mesh] OR "Insurance Coverage"[Mesh] OR "Drug Approval"[Mesh] OR "Health Services Accessibility"[Mesh] OR (organization[Title/Abstract] OR policy[Title/Abstract] OR approval[Title/Abstract] OR coverage[Title/Abstract] OR regulation[Title/Abstract] OR regulatory[Title/Abstract] OR reimburse*[Title/Abstract] OR access[Title/Abstract] OR disinvestment[Title/Abstract] OR “drug dispensing”[Title/Abstract]))