MONASH University

Real-World Evidence Generation and Economic Evaluation for Healthcare Decision-Making on Alzheimer's Disease Treatment in Thailand

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Notice 1

Abstract

Background: The global epidemic of Alzheimer's disease (AD), the most prevalent type of cognitive disorders under the umbrella of dementia, is now in process. The early prescription of AD medications is highly recommended in order to allow the patients to achieve the optimal treatment benefits. Thailand, a member of low- and middle-income countries (LMICs) where health needs are large but resources are limited, is also experiencing with the increase of AD population. Not to mention, only is a certain group of the patients (8% of Thai population) covered for AD prescription costs, apparently causing inequity in access to the treatment. The decision of making AD medications publicly financed potentially minimises this issue, but country-specific evidence necessary for facilitating the government's ability to make such decision is scarce and out-of-date. This thesis, therefore, aimed to generate real-world and cost-effectiveness evidence of AD treatment to inform health-policy decision makers in Thailand.

Methods: This thesis consists of three studies. The first study focused on estimating economic and humanistic burdens of AD in terms of societal costs of AD care and health-related quality of life (HR-QoL) of people with AD. Structured interviews and analyses of a hospital's electronic database were conducted. The second study investigated the prescribing patterns and the levels of compliance and persistence of AD medications using electronic databases from five hospitals across Thailand. Finally, the last study combined real-world findings from both previous studies to perform a cost-effectiveness analysis using a discrete-event simulation to identify the most cost-effective treatment for AD in Thailand.

Results: The average annual total societal costs of AD care, which were USD8,014 per patient in 2017, were considered enormous. These high economic burdens largely stemmed from direct

medical costs (constituting 47.9% of the total costs), and AD prescription costs played a big part (39.8%) in this cost category. HR-QoL of the patients were severely deteriorated when the disease progressed from mild (0.87) to severe stage (0.40), reflecting huge humanistic burdens associated with AD. Besides, due to the observed low level of medication persistence (78.9% of the patients discontinued the treatment within one year), AD treatment users in Thailand may have received suboptimal therapeutic benefits. Remarkably, the patients who were not covered for AD prescription costs were not equally accessible to the treatment and more likely to be non-persistence. Finally, donepezil was identified as the most cost-effective AD treatment based on the current real-world evidence in Thailand.

Conclusions: This thesis provides real-world and cost-effectiveness evidence of AD medications, which could serve as key information for the decision-making process. Despite its high priority based on the selection criteria and its favourable value for money, AD medications may not be recommended for adoption due to its high budget impact. Yet, the decision-making process is dynamic, and the speculated recommendation may be positively changed if modifiable factors such as treatment persistence and AD treatment costs have been improved. This thesis also serves as an initiative for other LMICs to prepare for the upcoming breakthrough in the treatment of AD.

Declaration

Thesis is an original work of my research and contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

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Date: 12 June 2019

Publications during enrolment

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5. Ounsirithupsakul T, Dilokthornsakul P, Kongpakwattana K, Ademi Z, Liew D, Chaiyakunapruk N. Estimating the productivity burden of pediatric pneumococcal disease in Thailand. Under review.
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Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes two original papers published in peer reviewed journals and another submitted publication. The core theme of the thesis is real-world evidence generation and economic evaluation for healthcare decision-making on Alzheimer's disease treatment in Thailand. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Jeffrey Cheah School of Medicine and Health Sciences under the supervision of Professor Nathorn Chaiyakunapruk.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapter 2-4 my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution	Co-author(s), Monash student
2	A real-world evidence analysis of associations between costs,	In press	70%. Concept, ethical clearance, data collection, data analysis and	1) Charungthai Dejthevaporn, input into manuscript 5%	No

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution	Co-author(s), Monash student
	quality of life and disease-severity indicators of Alzheimer's disease in Thailand		writing manuscript	2) Orapitchaya Krairit, input into manuscript 5% 3) Piyameth Dilokthornsakul, input into manuscript 5% 4) Devi Mohan, input into manuscript 5% 5) Nathorn Chaiyakunapruk, input into manuscript 10%	No No No No
3	Compliance and persistence with Alzheimer's disease treatment: A retrospective analysis of multiregional hospital databases in Thailand	Published	70%. Concept, ethical clearance, data acquisition, data analysis and writing manuscript	1) Piyameth Dilokthornsakul, input into manuscript 10% 2) Charungthai Dejthevaporn, input into manuscript 5% 3) Oraluck Pattanapreteep, input into manuscript 5% 4) Nathorn Chaiyakunapruk, input into manuscript 10%	No No No No
4	Application of discrete-event simulation in health	Submitted	85%. Concept, data acquisition, model	1) Nathorn Chaiyakunapruk, input into manuscript 15%	No

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution	Co-author(s), Monash student
	technology assessment: A cost-effectiveness analysis of Alzheimer's disease treatment using real-world evidence in Thailand		development, data analysis and writing manuscript		

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student name: Khachen Kongpakwattana

Student signature: **Date:** 12 June 2019

I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author, I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor name: Nathorn Chaiyakunapruk

Main Supervisor signature: **Date:** 12 June 2019

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“This is a final call for Emirates flight EK035 to Newcastle closing now at gate number A12”, heard a Ph.D. candidate, embarking on a journey to the final research mobility in his Ph.D. life. The announcement brought back his memories when he had just removed his wing and reverted to pursue the advancement of his professional origin.

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Now, my Ph.D. journey is about to reach the destination. I will make sure to capture every moment in my heart and carry all positive memories as encouraging fuels to propel my future flights to countless destinations.

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CHAPTER 1

Introduction

Research motivation and background

How could you imagine if one day the person you have spent over half of your lifetime with gradually acted like you were a stranger? Apart from grief, you may leave no stone unturned in the search for trails to bring back his memory. All of your time and effort may also be devoted to taking care of your beloved, who forgets even how to bathe and feed himself. Unavoidably, this unpleasant life experience of dementia keeps happening to the elderly around the world, one every three seconds [1]. More than 50 million older people, excluding family members and carers, are now suffering from dementia [1]. This number almost doubles every 20 years, and much of the increase is occurring in low- and middle-income countries (LMICs) [1] where health needs are large but resources are limited. If the global burden of dementia is monetized, its economic value has already exceeded one trillion United States Dollar (USD), and will continue to spiral [1]. Dementia is not merely a natural degenerative problem of the elderly, but it actually is a key global issue, which causes devastating consequences expanding from a family unit to lager society, a country, a region and the world.

Alzheimer's disease (AD) is the most prevalent type (50-75%) of cognitive disorders under the umbrella of dementia [2]. AD progressively deteriorates a person's memories, behaviours and abilities to perform everyday activities until the person becomes totally dependent. While curative treatment for AD is still under the process of discovery, symptomatic relieving medications (donepezil, galantamine, rivastigmine and memantine) are the best hope for people living with AD. These medications can help alleviating behavioural disturbances such as agitation and depression and delaying the decline of cognitive and functional status [3]. In addition, the early prescription of AD medications is reported to be cost-effective and may lower

the overall costs of AD care [4-6]. Thus, the earlier the patients receive AD medications, the better overall benefits the patients could achieve from the treatment. Yet, how could we make this optimal scenario happened? As lessons learned from HICs, a great deal of country-specific AD research, which on the one hand emphasizes the importance of AD and on the other hand provides necessary decision-making information to their policy makers, is a key enabler for AD medications to be publicly financed and equally accessible to the patients since the early course of AD [7,8].

Turning to consider another part of the world, it is a paradox that in such a greater disease burden region like LMICs where AD population is remarkably on the rise, there can be so little research conducted for AD. Even though the evidence base of AD in LMICs is now increasing since the establishment of 10/66 Dementia Research Group [9,10], it is typically inadequate to facilitate local policy makers' ability to make a decision on their AD issues which are different from country to country [11]. Provided that healthcare resources are generally scarce in LMICs, the decision to allocate existing budgets for making AD medications available to the population is highly problematic without country-specific evidence. Hence, more country-specific research for AD is deemed vital to help raising awareness about AD, shaping AD-related policy and ultimately improving the health and welfare of the patients residing in this region.

As a member of LMICs, the situation of AD in Thailand is not better than other countries in the same region. While there are no less than half a million Thai elders currently affected by AD [12,13], the majority of them are not fina cxvncially supported for AD prescription costs. This is because AD medications are not included in the Thai national list of essential medicines (NLEMs) [14], from which the universal coverage scheme (UCS, covering 75% of population) refers its reimbursable medication items [15]. Only are the patients insured under the civil

servant medical benefit scheme (CSMBS, covering 8% of population) subsidized for their AD medication costs. It should be underlined that AD medications are so expensive that the monthly costs of usage could incur up to 30% of Thai average monthly income [16,17]. As a consequence, it is quite difficult for the patients insured outside the CSMBS to gain access to AD medications. Apparently, the lack of financial support causes inequity in the access to AD medications among AD patients insured under different health coverage schemes in Thailand.

How should the government do to minimize this inequity? One of capable solutions is that cost-effective AD medications are considered to adopt in the NLEMs. Due to the fact that relevant scientific evidence to support health-policy decision making on AD in Thailand is scarce and out-of-date, additional country-specific research, especially full health economic evaluation on AD medications based on real-world evidence, is warranted. Real-world evidence refers to healthcare information derived from sources outside clinical research settings, reflecting what really happens in reality thereby enhancing the generalizability of research findings [18]. Full health economic evaluation refers to the comparison of two or more alternative interventions in terms of costs and health effects, which is often known as a cost-effectiveness analysis (CEA) [19]. Findings from a CEA could answer the question "which of the alternatives provides the best value for money?" and support the government to make a coverage decision [19]. As a result, this thesis aimed to generate real-world and cost-effectiveness evidence of AD treatment to inform health-policy decision makers in Thailand.

Research questions

Against the abovementioned background, the principal research question of this thesis is "concerning limited healthcare resources, should AD medications be publicly financed for AD population in Thailand?"

There are three sub-questions:

1. How large is the issue of AD in Thailand in terms of economic and humanistic burdens?
2. What is the current situation of AD prescriptions and their usage in Thailand?
3. Which of AD medications provides the best value for money when prescribed to AD patients in the real-world practice in Thailand?

Outline of the thesis

This thesis consists of three studies, which individually addresses each of the stated research sub-questions. The following outline (**Figure 1**) illustrates the big picture of this thesis.

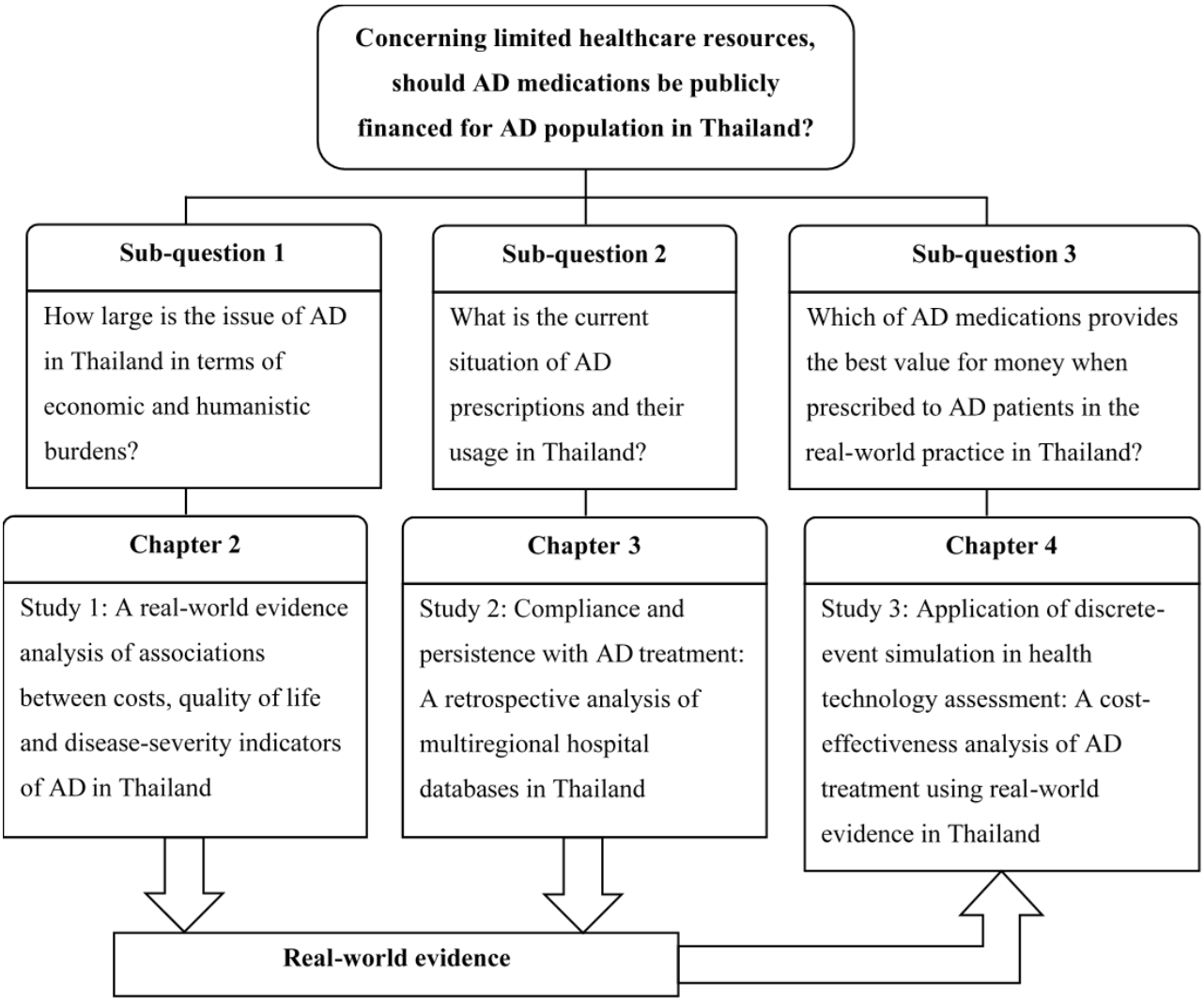

Figure 1 Overview of outline of the thesis by research questions

Chapter 2 replies to the research sub-question 1 and simultaneously attempts to fulfil the scarce body of literature pertaining to economic and humanistic burdens in LMICs [1,20]. A cross-sectional study was conducted to collect real-world primary cost, health-related quality of life (HR-QoL) and disease-related data. Data collection was performed by interviewing patients and their caregivers at a university-affiliated tertiary hospital in Thailand as well as using the hospital's electronic database. Economic burdens were estimated as average annual total societal costs of AD care, while humanistic burdens were described in terms of patient's and caregiver's HR-QoL. Besides, this study also identified the most influential disease-severity indicators (i.e. cognitive, behavioural or functional status) on costs and HR-QoL, which helped suggesting critical areas to lessen the economic and humanistic burdens of AD in Thailand.

In **Chapter 3**, the electronic databases of five multiregional hospitals in Thailand, capturing essential information on AD demographics and prescriptions, were retrospectively analysed. This study discovered not only the current prescribing patterns of, but also the levels of compliance and persistence on AD medications in Thailand, which altogether respond to the research sub-question 2. Compliance assesses how well a patient acts in accordance with the prescribed regimen, whereas persistence measures how long a patient continues the treatment for the prescribed duration [21]. High levels of both compliance and persistence are advisable for all AD treatment users in order to achieve the optimal treatment benefits, but the investigation of both behaviours has been neglected in Thailand, or even in LMICs [22].

The real-world evidence, generated from the previous two chapters, was incorporated into the cost-effectiveness model of **Chapter 4**. The model, which represents natural history of AD, was conceptualised using a discrete-event simulation (DES). By applying the DES, individual patients with unique demographic and disease characteristics could be simulated based on the

real-world dataset, and their disease characteristics could be updated overtime depended on discrete-events that randomly occurred to each patient [23]. The model was also tailored to reflect real-world practice in Thailand by using much of country-specific evidence such as patient characteristics, levels of medication persistence, mortality, healthcare utilization, costs and HR-QoL. Outputs from the model indicated the most cost-effective treatment for AD in Thai context, which directly address the research sub-question 3.

Finally, **Chapter 5** integrates findings from all previous chapters in order to answer the principal research question "concerning limited healthcare resources, should AD medications be publicly financed for AD population in Thailand?". It then provides practical recommendations and future directions for assisting health-policy decision making on a curative or a disease-modifying therapy for AD, which is globally committed to be invented by 2025 [24].

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CHAPTER 2

Study 1 – A Real-World Evidence Analysis of Associations Between Costs, Quality of Life and Disease-Severity Indicators of Alzheimer's Disease in Thailand

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Abstract

Objectives: Although an increase in the burden of Alzheimer's disease (AD) is evident worldwide, knowledge of costs and health-related quality of life (HR-QoL) associated with AD in low- and middle-income countries (LMICs) is still lacking. We, therefore, aimed to collect real-world cost and HR-QoL data, and investigate their associations with multiple disease-severity indicators among AD patients in Thailand.

Methods: We recruited AD patients aged ≥60 years accompanied by their caregivers at a university-affiliated tertiary hospital. One-time structured interview was conducted to collect disease-severity indicators, HR-QoL and caregiving information using standardized tools. The hospital's database was used to retrieve healthcare resource utilization occurred over 6 months preceding the interview date. Costs were annualized and stratified based on cognitive status. Generalized linear models were employed to evaluate determinants of costs and HR-QoL.

Results: Among 148 community-dwelling patients, average annual total societal costs of AD care were USD8,014 (95% CI: USD7,295-USD8,844) per patient. Total costs of patients with severe stage (USD9,860; 95% CI: USD8,785-USD11,328) were almost twice as high as those of mild stage (USD5,524; 95% CI: USD4,649-USD6,593). The major cost driver was direct medical costs, particularly those incurred by AD prescriptions. Functional status was the strongest determinant for both total costs and patient's HR-QoL (p-value <0.001).

Conclusions: Our real-world findings suggest the distinct major cost driver which results from expensive AD treatment, emphasizing the demand of country-specific cost evidence. Increases in cognitive and functional status are significantly associated with decreases in total costs of AD care and improvement on patient's HR-QoL.

Introduction

Alzheimer's disease (AD) is one of the cognitive disorders under the umbrella of dementia, which has been ranked first among other leading chronic diseases such as limb paralysis, stroke and depression as the major contributors to disability and dependence in the elderly worldwide [1]. As the number of older people is growing, the number of people living with dementia is also expanding particularly in low- and middle-income countries (LMICs). In 2015, there were 46.8 million people living with dementia globally, and 58% of those resided in LMICs. Nevertheless, by 2050, it is estimated that the number will soar to 131 million with 68% dwelling in LMICs [1]. The global societal costs of dementia, which are projected to reach a trillion United States dollar (USD) or approximately 1.2% of worldwide gross domestic product (GDP) by 2018, are also tremendous [1]. A series of studies that evaluates resource utilization and costs associated with a certain disease is useful to inform policy decision-makers about the quantity of demand for medical, social and financial support, which may change over time [2]. The Alzheimer's Disease International (ADI) have attempted to estimate the global economic burden of dementia, but a great number of imputations need to be made due to missing cost evidence from many LMICs, especially those in Asia and Africa [1].

Thailand, a member of LMICs situated in Southeast Asia, is also becoming aged society with at least a half million of people living with AD by 2021 [3,4]. Nonetheless, there has been no study investigating complete societal costs of AD in Thailand. Since the differences in cultural characteristics and healthcare settings can cause significant variations in AD cost estimates [5], it is important that each country has their own cost data to precisely discern the extent of impact that AD imposes on their economy. A review of relationships between costs and different measures of disease severity has suggested that costs of AD care are associated with not only

cognitive, but behavioural and functional status [6]. Moreover, current international policy and practice are emphasizing on enabling people living with chronic diseases as well as AD to experience a good quality of life [7], but the evidence on the current status of quality of life among AD patients in Thailand is still missing. We, therefore, aimed to collect real-world cost and health-related quality of life (HR-QoL) data, and investigate their associations with multiple disease-severity indicators among AD patients in Thailand.

Methods

Study design

This was a cross-sectional study conducted in a 1,378-bed university-affiliated tertiary hospital in the capital city of Thailand. Patients aged 60 years or more with a clinical diagnosis of AD (as documented in medical records) for at least six months prior to the interview date were eligible for inclusion. An accompanying caregiver who was at least 18 years old was required for all patients. Study procedures were carried out only after caregivers and, when possible, patients provided their consent to participate in the study. The study was approved by the hospital's Committee on Human Rights (Documentary Proof of Ethical Clearance No. MURA2017/540).

Data collection

One-time structured interview was conducted to collect demographics and caregiving information, disease-severity indicators and HR-QoL using standardized tools. The hospital's database was used to retrieve healthcare resource utilization occurred in the past six months, to assess whether the patients had been prescribed with psychotherapeutic agents (antidepressants and antipsychotics), and to derive the Charlson comorbidity index (CCI) [8] based on the

international classification of diseases-10 (ICD-10) diagnosis codes recorded over the past year, prior to the interview date.

Demographics and caregiving information

Demographics and caregiving information were collected from caregivers using the resource utilization in dementia (RUD) instrument [9]. Data on informal care (unpaid caregiving activities) were collected under three heading based on types of care: basic activities of daily living (BADL), instrumental activities of daily living (IADL) and supervision. We cross-checked the reported informal caregiving time using caregiver's sleeping and working hours. If the total amount of time exceeded 24 hours per day, we would ask caregivers to reconsider their responses.

Disease-severity assessments

Three different domains of disease severity were assessed: cognitive, behavioural and functional status of the patients. Cognitive status was measured using the Thai version of the mini–mental state examination (MMSE) instrument [10,11]. The total score of this instrument ranged from 0 to 30. The higher scores indicated better cognitive status. Different disease-severity states were classified based on MMSE score: mild (MMSE ≥20), moderate (MMSE = 10-19) and severe (MMSE <10) [5]. Behavioural status was assessed using the Thai version of the neuropsychiatric inventory (NPI) [12,13]. Caregivers were inquired to rate both frequency and severity of behavioural disturbance, if existed, of their patients. The total score of this questionnaire ranged from 0 to 144. The higher scores indicated greater behavioural disturbance. Functional status was measured using the Thai version of the disability assessment for dementia (DAD) scale [14,15]. Caregivers were asked to assess their patient's performance in initiating, planning, and executing

ADLs. The total score of this scale ranged from 0 to 100. The higher scores indicated that less support was needed to execute BADL and IADL.

HR-QoL assessments

AD patient's HR-QoL was assessed using the Thai version of the EuroQoL-5 dimension-5 level of severity (EQ-5D-5L) questionnaire [16,17]. All patients with severe disease had their EQ-5D-5L assessed by caregivers, whereas patients with mild to moderate disease were asked to complete EQ-5D-5L themselves. However, if the attempt was failed, their caregivers would assess EQ-5D-5L on behalf of the patients. A scoring calculator was applied to EQ-5D-5L data to derive corresponding health utility scores [17]. Meanwhile, caregiver's HR-QoL was measured using the Thai version of the short form-36 (SF-36) health survey [18,19]. Data from the SF-36 were converted into the short form-6 dimension (SF-6D) health states and corresponding health utility scores [20]. A health utility score of 1 referred to perfect health, whereas 0 was equivalent to death.

Cost estimates

Costs of AD care were estimated in accordance with the recommendation of the ADI to enhance the comparability of our findings [21]. Direct medical costs included costs incurred by outpatient, inpatient and emergency visits, medications and out-of-pocket (OOP) payments. In order to convert the hospital's charges, retrieved from the hospital's databases, to costs, the hospital-specific cost-to-charge ratio of 0.9438 was used to multiply the charges (**Supplementary appendix 2**). Direct non-medical costs included costs associated with transportation (quantified using micro-costing estimations, in which the number of transportation usages (round-trip) was the doubling number of hospital visits, derived from the hospital's

database) and formal caregiving services used (paid domestic helps and nursing-home placement, obtained from the RUD). Indirect costs were valued from unpaid caregiving time spent for assisting the patients with BADL and IADL (obtained from the RUD). In the base-case analysis, the opportunity cost (time cost) approach was selected to estimate indirect costs using average national wage rates in Thailand to reflect the equity of time lost regardless of individual's economic status [22]. Sensitivity analyses were also performed by quantifying indirect costs using the replacement cost approach, resulting in lower-bound estimates, and using the time cost approach with supervision time included, resulting in upper-bound estimates [23]. Costs were annualized and inflated to represent 2017-year value using consumer price index [24]. The average market exchange rate in 2017 was 1 USD = 34.1008 Thai baht (THB) [25]. References of all unit costs used for micro-costing estimations are presented in **eTable 1**.

Statistical analyses

Details of sample size calculation are provided in **Supplementary appendix 3**. Descriptive statistics were used to summarize the data of patient's and caregiver's characteristics, resource utilization and costs of AD care. The multiple imputation with predictive mean matching on log-transformed costs strategy was adopted to deal with missing cost data [26], which were 6.6% of the OOP payment and 3.9% of the paid domestic help data. Comparison of differences in means across AD severity groups was examined using the one-way analysis of variance (one-way ANOVA) tests, and differences in proportions using the chi-square tests. Confidence intervals of cost data were estimated using the bias-corrected and accelerated bootstrapping methods [27,28]. Generalized linear models (GLMs) were employed to identify the determinants and predictive regression functions of costs and HR-QoL [27,29]. The modified Park's test was implemented to identify the most suitable family to a specified link, based on the relationship between raw-scale

mean and variance functions, for each GLM model [27,30]. After the models were developed, the bootstrapping validation technique was used to assess the goodness of fit and to estimate bootstrap-corrected calibration coefficients [31]. For ease of interpretation, the impacts of disease-severity indicators and other significant variables on different cost categories were illustrated as marginal estimates. All statistical computations were executed using Stata version 13 (Stata Corp., College Station, Texas).

Results

Demographics, disease-severity indicators and HR-QoL

Between November 2017 and April 2018, 153 AD patient-caregiver dyads were interviewed. Almost all patients (149/153, 97.4%) were community-dwelling, whereas only four of them (2.6%) were living in nursing homes. There was one community-dwelling patient whose age was under 60 years, thus being necessarily excluded. We decided not to include nursing-home patients in our main analysis due to the small sample size, but still presented their findings separately in the last section of the results. Therefore, a total of 148 community-dwelling patients was included in our main analysis.

Table 1 shows descriptive statistics of demographics, disease-severity indicators and HR-QoL of both patients and their caregivers. The mean (standard deviation (SD)) age of the patients was 80.1 (8.0) years, with a majority being female (105/153 (71.0%)). Based on the MMSE scores, there were 35, 59 and 54 patients classified into mild, moderate and severe stage, respectively. Comorbidities of the patients, summarized using CCI, as well as the use of psychotherapeutic agents were not significantly different across the disease stages (p-value = 0.232 and 0.106,

respectively). All disease-severity indicators (MMSE, NPI and DAD) and patient's HR-QoL were significantly worsened (p-value <0.001), when the disease progressed to more severe stage. Most of the caregivers interviewed were middle-aged with mean (SD) age of 55.1 (13.3) years, and three quarters of them were female (111/148, 75.0%). The caregiver's HR-QoL was not significantly different across the disease stages (p-value = 0.561).

Resource utilization

Our sample of patients attended to outpatient department approximately nine times per year, but they were barely admitted to either inpatient or emergency department. The use of paid domestic help significantly increased with disease severity (p-value = 0.039). Informal caregivers spent more than nine hours per day (278.6 hours per month) on average to take care of their patients for all activities. Among these activities, supervision (143.7 hours per month) was the one that the caregivers spent most of the time for, followed by IADL (76.1 hours per month) and BADL (58.8 hours per month), respectively. The overall caregiving time was significantly higher with increasing disease severity (p-value <0.001). Details of resource utilization stratified by the disease stages are presented in **Table 2**.

Costs of AD care

The annual societal costs of AD care per patient, disaggregated into different cost categories, are illustrated for the different disease-severity stages in **Table 3**. The annual total costs significantly escalated according to the AD severity (p-value < 0.001), with the average (bootstrapped 95% Confidence Interval (95% CI)) of USD8,014 (USD7,295-USD8,844) per patient. The total costs of severe stage (USD9,860; 95% CI: USD8,785-11,328) were almost twice as high as those of mild stage (USD5,524; 95% CI: USD4,649-6,593).

Overall, the major cost driver was direct medical costs, which constituted almost half (47.2%) of the total costs of AD care (**Figure 1**). Within direct medical costs, 63.9% of the costs were incurred by medications. Not to mention, the largest portion (62.3%) of these medication costs were resulted from AD treatment prescriptions (donepezil, galantamine, rivastigmine and memantine).

Following direct medical costs, the opportunity costs of unpaid caregiving time (indirect costs), which represented 39.0% of all cost categories, were found to be the second most expensive cost category. In a similar way to the total costs, there was a significant increase in indirect costs associated with increases in the AD severity (p-value <0.001). The indirect costs were more than double from mild (USD2,043; 95% CI: USD1,492-USD2,881) to severe stage (USD4,294; 95% CI: USD3,673-USD4,996). These results were consistent with those in the sensitivity analyses. However, indirect costs would become the major cost driver instead of direct medical costs if the supervision time was also considered in the opportunity cost valuation (upper-bound estimates).

Associations between costs, HR-QoL and disease-severity indicators

Results of multivariate GLM analyses for costs are presented in **Table 4**, and those for HR-QoL are presented in **eTable 2**. We found that the correlation between MMSE and DAD was very high, resulting in multicollinearity when both indicators were used simultaneously in the model. Therefore, in the case that both MMSE and DAD were significant predictors of a dependent variable, we constructed models separately for each of them.

Among the three disease-severity indicators, functional status (DAD) was significantly associated with all of the cost categories. Cognitive status (MMSE) was also significant predictor for indirect costs and total costs. On the other hand, behavioural status (NPI) was not a

determinant for any type of costs. Overall, a marginal increase in cognitive (MMSE) and functional (DAD) status was significantly associated with decreases in the total costs of AD care (standard error) by USD190 (USD48) and USD76 (USD12), respectively.

Turning to consider determinants of HR-QoL, we found that both functional (DAD) and behavioural (NPI) status exerted significant influences on patient's HR-QoL. Better patient's HR-QoL was also observed with spousal caregivers. Moreover, self-rating on HR-QoL resulted in significant higher estimates, compared to informant rating. On the contrary, a strong predictor for caregiver's HR-QoL was not discovered. Only the higher CCI (more patient's comorbidities) was found to be a possible explanation for the deteriorated caregiver's HR-QoL at 10% significant level.

For each of the models developed, a mean optimism [31] from the whole bootstrap replications was approaching zero, reflecting a less bias and good model.

Costs of AD care for nursing-home patients

Summaries of the annual societal costs of AD care for patients living in nursing homes are provided in **eTable 3**. Of the four patients, two (50%) had moderate AD, while another two (50%) had severe AD. The total costs also tended to increase with the higher AD severity (p-value = 0.370), with the average of USD12,290 (95% CI: USD8,162-USD23,450) per patient. Noticeably, direct non-medical costs (49.4%), especially those incurred by nursing-home placement, were found to play more important role than direct medical costs (41.8%) in being the most expensive cost components.

Discussions

Principal findings

Our real-world findings filled in the gap of sparse cost and HR-QoL evidence from LMICs. We found that the total costs of AD care, which almost doubled from mild to severe stage, were enormous. Direct medical costs, particularly the costs incurred by AD prescriptions, were the most expensive cost category, followed by indirect costs valued from unpaid caregiving time. Among the disease-severity indicators examined, functional status (DAD) was the strongest determinant for both costs and patient's HR-QoL. Improvements on the cognitive (MMSE) and functional status (DAD) were found to be associated with reduction in the total costs of AD care.

Comparison of cost findings to existing evidence

When expanding our perspective to compare costs of AD care internationally, we found that our major cost driver is different from all other countries across the world (**Figure 2**) [32-39]. Direct medical costs, constituting 47.2% of the total costs, were the major cost driver of AD exclusive to Thailand. Notably, the costs incurred by AD prescriptions were the largest part (39.8%) within the direct medical costs. Thus, in order to scrutinize this critical difference, we compared the costs of AD treatment in Thailand [40] with those available from the National Health Service (NHS), the main purchaser of medicines in the United Kingdom (UK) [41]. It is surprising that costs per monthly use of AD treatment in Thailand are approximately 2 (rivastigmine capsules 4.5 mg) to 20 (donepezil tablets 10 mg) times more expensive, which can be an explanation for its distinctively high direct medical costs. Pharmaceutical prices in the UK are among the lowest in the developed world because of not only the NHS's purchasing power itself but the recommendation on cost-effective treatment from the National Institute for Health and Care

Excellence (NICE) [42,43]. As a result, it is crucial that Thai government take action to curtail these expensive AD treatment prices. Apart from their unchanging purchasing power, evidence on cost-effective AD treatment is still needed to facilitate the government's ability to make a strong negotiation with pharmaceutical companies.

Indirect costs, on the other hand, have been reported to be the most expensive category of the costs of AD care in the community setting across the world. Their proportion ranges from 41.9% of the total costs in Taiwan [35] to 93.2% of the total costs in Brazil [33]. In Thailand, indirect costs were the second-place cost driver, accounting for 39.0% of the total costs. However, their monetary values were not minor (USD3,126 per year) and were more than double in amount from mild to severe AD. These findings reflect that AD generally imposes huge economic burden upon informal caregivers in terms of opportunity costs of time lost. In addition to the loss of time, physical health, psychological state, self-efficacy and subjective well-being of these caregivers are also significantly deteriorated, compared to non-caregivers [44]. As a consequence, strategies for supporting those informal caregivers are in great need. It has been suggested that early AD screening and treatment is a potential strategy to lower overall costs of care [45,46] and is associated with decrease in economic burden of informal care by 32% over 10 years [47]. Nevertheless, it should be emphasized that the currently available AD treatment is not a disease-modifying therapy, and what it does offer is symptomatic controlling effects.

Finally, we found that components of the costs of AD care are somewhat different among countries, even with the countries classified in the same region or income-country group (**Figure 2**). This emphasizes that country-specific studies are essential, and global estimates of costs of AD care are still needed to be improved since imputations of missing country data from the available ones are prone to be inaccurate.

Impacts of disease-severity indicators on costs and HR-QoL

In our multivariate cost analyses, we found that two (cognitive and functional status) out of the three disease-severity indicators had significant impacts on the costs of AD care. These two indicators were highly associated with informal and total costs, but it was necessary to consider them in separated models due to multicollinearity. The bootstrap-corrected calibration coefficients of the models with functional status were noticeably higher than those with cognitive status, indicating that functional status has the greater explanatory power for these cost categories. A previous review of 29 articles on this topic has reported inconsistencies in the findings of associations between costs and disease-severity indicators, but functional status is generally regarded as the best predictor of the costs of AD care [6], which is consistent with our findings. Likewise, in the multivariate analysis of patient's HR-QoL, we found that two (behavioural and functional status) out of the three disease-severity indicators were strong determinants of patient's HR-QoL. Better functional status was found to exert a positive influence on patient's HR-QoL, whereas worsening behavioural status had the opposite effect. These findings are totally in agreement with a recent meta-analysis of 199 articles on the same topic [7]. Taken together, it is evident that functional status is the most important disease-severity indicator, which is highly associated with both costs and patient's HR-QoL. Hence, improving functional status of people with AD is deemed vital.

Comparison of cost findings between community and nursing-home settings

Although the majority of our patients were living in community, the information we received from those living in nursing homes is also worth mentioning. We found that the average total costs of AD care in nursing-home patients (USD12,290 per year) were higher than those of community-living patients (USD8,014 per year). A six-time increase in direct non-medical costs

among nursing-home patients could be an explanation for the higher total costs. We found that the average costs of nursing-home placement were approximately USD500 per month. This amount goes beyond the average national wage rates of USD405 per month [48], reflecting that the nursing-home placement is very expensive in Thailand. The impact of this expensive nursing-home placement was remarkably evident on the patients with severe AD, who appeared to spend approximately USD7,074 more total costs each year, compared to those living in community. The high price of nursing-home placement together with the perceived responsibility to take care of one's own parents according to the cultural belief can be the reasons why there were few elders with AD (2.6%) placed in nursing homes in Thailand.

Strengths and limitations

Being the first study examining 'real-world' societal costs of AD care and HR-QoL of both patients and their caregivers among LMICs in Southeast Asia is considered an important strength of this study. Another noteworthy strength is the finding of relatively expensive AD treatment costs, which represents great variations in the costs of AD care, thus encouraging availability of the cost evidence from each country and demanding for relevant cost-effectiveness studies. Nonetheless, there are several limitations worth being addressed. First, since our study participants were recruited from a single university-affiliated tertiary hospital, the findings may not be nationally representative. However, given that in Thailand AD medications can only be prescribed in tertiary hospitals where AD specialists are available [11], and a retrospective analysis of five large-size tertiary hospital's databases in Thailand has shown that a university-affiliated tertiary hospital accounts for 56.6% of all AD diagnosis and treatment between 2013 and 2017 [49], the findings from Ramathibodi Hospital is considered holding qualifications in representing the current AD population who receives diagnosis from specialists in Thailand.

Second, for the process of asking participants to report past events based on their memory, a recall problem is a matter of concern. However, it has been asserted that a recall of three months or less does not deteriorate the accuracy of self-report information [50], and our standardized tools used in the interview process require the maximum recall period of only one month. Third, due to the fact that informant ratings of patient's HR-QoL typically result in more negative findings than self-ratings do [7], our findings of patient's HR-QoL are susceptible to underestimation, especially for those of severe patients whose EQ-5D-5L was totally assessed by caregivers. The predictive equation of patient's HR-QoL, in which the effect of types of raters was adjusted for, should be preferably used in future health economic evaluations. Lastly, since we retrieved healthcare resource utilization information from the hospital's database, we could have missed some of the healthcare resources if patients had visited several hospitals, which potentially resulted in underestimation of direct medical costs.

Conclusions

With the marked differences in cultural characteristics and high pharmaceutical prices, direct medical costs are found to be the major cost driver of AD care in Thailand, which are distinct from other countries across the world. Cost-effectiveness evidence is warranted to help the government curb the costliness of AD medications. Country-specific cost data are essential because available data from other countries in the same region or income-country group may not be good representatives of the missing ones. Improvements on cognitive and functional status are significantly related to not only reduction in the total costs of AD care but promotion of patient's HR-QoL.

Table 1 Characteristics of study patients and their caregivers stratified by different levels of cognitive status

Characteristics	Mild (n = 35)	Moderate (n = 59)	Severe (n = 54)	p-value[a]	All severity levels (n = 148)
Patient's characteristics					
Age (years) [mean (SD)]	77.6 (6.3)	80.5 (7.8)	81.2 (8.9)	0.100	80.1 (8.0)
Gender [n (%)]				0.003	
- Male	17 (48.6)	18 (30.5)	8 (14.8)		43 (29.1)
- Female	18 (51.4)	41 (69.5)	46 (85.2)		105 (71.0)
Time since AD diagnosis (years) [mean (SD)]	3.3 (3.0)	4.4 (3.1)	7.0 (3.8)	<0.001	5.1 (3.7)
Charlson comorbidity index (CCI) [mean (SD)]	2.1 (1.4)	2.2 (2.0)	1.7 (1.3)	0.232	2.0 (1.7)
AD medications[b] [n (%)]				0.056	
- Use	33 (94.3)	51 (86.4)	41 (75.9)		125 (84.5)
- Not use	2 (5.7)	8 (13.6)	13 (24.1)		23 (15.5)
Psychotherapeutic agents[c] [n (%)]				0.106	
- Use	18 (51.4)	34 (57.6)	39 (72.2)		91 (61.5)
- Not use	17 (48.6)	25 (42.4)	15 (27.8)		57 (38.5)
Marital status [n (%)]				0.305	
- Single	2 (5.7)	3 (5.1)	5 (9.3)		10 (6.8)
- Married/ Lived with a partner	24 (68.6)	35 (59.3)	25 (46.3)		84 (56.8)
- Divorced/ Separated/ Widowed	9 (25.7)	21 (35.6)	24 (44.4)		54 (36.5)

Characteristics	Mild (n = 35)	Moderate (n = 59)	Severe (n = 54)	p-value[a]	All severity levels (n = 148)
Educational level [n (%)]				<0.001	
- No education	2 (5.7)	2 (3.4)	8 (14.8)		12 (8.1)
- Primary school graduate	5 (14.3)	29 (49.2)	30 (55.6)		64 (43.2)
- Secondary school/ Vocational school graduate	9 (25.7)	8 (13.6)	6 (11.1)		23 (15.5)
- Bachelor's degree or above	19 (54.3)	20 (33.9)	10 (18.5)		49 (33.1)
Health insurance scheme used for Alzheimer's treatment [n (%)]				0.224	
- CSMBS	26 (74.3)	47 (80.0)	39 (72.2)		112 (75.7)
- UCS	4 (11.4)	7 (11.9)	4 (7.4)		15 (10.1)
- SHI	0 (0)	1 (1.7)	0 (0)		1 (0.7)
- Others	1 (2.9)	0 (0)	6 (11.1)		7 (4.7)
- None	4 (11.4)	4 (6.8)	5 (9.3)		13 (8.8)
Cognitive status (MMSE score) [mean (SD)]	22.6 (2.0)	15.2 (2.7)	3.7 (3.3)	<0.001	12.8 (7.9)
Behavioural status (NPI score) [mean (SD)]	4.7 (5.4)	12.4 (10.6)	21.2 (16.3)	<0.001	13.8 (13.7)
Functional status (DAD score) [mean (SD)]	77.3 (17.6)	54.5 (22.1)	18.2 (19.1)	<0.001	46.6 (30.7)
Health-related quality of life (EQ-5D-5L index score) [mean (SD)]	0.87 (0.12)	0.73 (0.23)	0.40 (0.21)	<0.001	0.64 (0.28)
Caregiver's characteristics					
Age (years) [mean (SD)]	54.5 (15.4)	55.4 (12.4)	55.3 (12.9)	0.951	55.1 (13.3)

Characteristics	Mild (n = 35)	Moderate (n = 59)	Severe (n = 54)	p-value[a]	All severity levels (n = 148)
Gender [n (%)]				0.006	
- Male	6 (17.1)	23 (39.0)	8 (14.8)		37 (25.0)
- Female	29 (82.9)	36 (61.0)	46 (85.2)		111 (75.0)
Relationship with the patient [n (%)]				0.502	
- Spouse	9 (25.7)	14 (23.7)	8 (14.8)		31 (21.0)
- Child	20 (57.1)	35 (59.3)	35 (64.8)		90 (60.8)
- Child-in-law	0 (0)	2 (3.4)	1 (1.9)		3 (2.0)
- Sibling	2 (5.7)	0 (0)	2 (3.7)		4 (2.7)
- Grandchild	1 (2.9)	2 (3.4)	3 (5.6)		6 (4.1)
- Friend/ neighbour/ acquaintance	0 (0)	4 (6.8)	1 (1.9)		5 (3.4)
- Paid domestic helper	3 (8.6)	2 (3.4)	4 (7.4)		9 (6.1)
Marital status [n (%)]				0.159	
- Single	13 (37.1)	24 (40.7)	20 (37.0)		57 (38.5)
- Married/ Lived with a partner	19 (54.3)	34 (57.6)	26 (48.2)		79 (53.4)
- Divorced/ Separated/ Widowed	3 (8.6)	1 (1.7)	8 (14.8)		12 (8.1)
Educational level [n (%)]				0.359	
- No education	0 (0)	1 (1.7)	1 (1.9)		2 (1.4)
- Primary school graduate	3 (8.6)	7 (11.9)	12 (22.2)		22 (14.9)
- Secondary school/ vocational school graduate	10 (28.6)	12 (20.3)	7 (13.0)		29 (19.6)
- Bachelor's degree graduate or above	22 (62.9)	39 (66.1)	34 (63.0)		95 (64.2)

Characteristics	Mild (n = 35)	Moderate (n = 59)	Severe (n = 54)	p-value[a]	All severity levels (n = 148)
Health-related quality of life (SF-36 index score) [mean (SD)]	0.69 (0.09)	0.71 (0.12)	0.70 (0.12)	0.561	0.70 (0.11)

[a] p-value for comparison of differences in means across AD severity groups (one-way analysis of variance (one-way ANOVA) tests) and differences in proportions (chi-square tests)

[b] AD medications included donepezil, galantamine, rivastigmine and memantine

[c] Psychotherapeutic agents included antidepressants and antipsychotics

Abbreviations: n, number of patients; SD, standard deviation; CCI, Charlson comorbidity index; CSMBS, the civil servant medical benefit scheme; UCS, the universal coverage scheme; SHI, the social health insurance; MMSE, mini-mental state examination; NPI, neuropsychiatric inventory; DAD, disability assessment for dementia; EQ-5D-5L, EuroQoL-5 dimension-5 level of severity questionnaire; SF-36, short form-36 health survey

Table 2 Healthcare and non-healthcare resource utilization

Resource utilization	Mild (n = 35)	Moderate (n = 59)	Severe (n = 54)	p-value[a]	All patients (n = 148)
Healthcare resource utilization					
Frequency of outpatient visits [mean (SD)] (times per year)	9.5 (5.0)	10.1 (9.2)	8.5 (6.4)	0.535	9.4 (7.4)
Frequency of inpatient visits [mean (SD)] (times per year)	0 (0)	0.04 (0.29)	0.14 (0.54)	0.185	0.07 (0.38)
Frequency of emergency department visits [mean (SD)] (times per year)	0 (0)	0.17 (0.61)	0.44 (0.88)	0.008	0.23 (0.68)
Non-healthcare resource utilization					
Number of patients using paid domestic helps [n (%)]	4 (11.4)	14 (23.7)	19 (35.2)	0.039	37 (25.0)
Unpaid caregiving time spent on basic activities daily living (BADL) [mean (SD)] (hours per month)	14.7 (37.3)	49.6 (60.2)	97.5 (69.1)	<0.001	58.8 (67.2)
Unpaid caregiving time spent on instrumental activities daily living (IADL) [mean (SD)] (hours per month)	73.5 (77.9)	66.9 (58.1)	87.9 (70.5)	0.254	76.1 (67.9)

Resource utilization	Mild (n = 35)	Moderate (n = 59)	Severe (n = 54)	p-value[a]	All patients (n = 148)
Unpaid caregiving time spent on supervision [mean (SD)] (hours per month)	116.2 (136.0)	136.8 (102.3)	169.0 (112.0)	0.091[b]	143.7 (115.6)
Overall caregiving time spent on a patient [mean (SD)] (hours per month)	204.4 (184.3)	253.3 (162.3)	354.4 (156.2)	<0.001	278.6 (175.3)

[a] p-value for comparison of differences in means across AD severity groups (one-way analysis of variance (one-way ANOVA) tests) and differences in proportions (chi-square tests)

Remarks: Our study reported means to be usable for health economic evaluations. Thus, ANOVA was used to test differences in means. Despite some degree of non-normality in data, in most cases, p-values from parametric (the ANOVA) and non-parametric tests (the Kruskal-Wallis) were consistent, except for 'supervision time' (p-value of the Kruskal-Wallis test = 0.018[b]).

Abbreviations: n, number of patients; SD, standard deviation; BADL, basic activities daily living; IADL, instrumental activities daily living

Table 3 Disaggregated annual costs of AD care per patient by different levels of cognitive status, among patients living in community

Cost categories [mean (95% CI)] (2017 USD)	**Mild (n = 35)**	**Moderate (n = 59)**	**Severe (n = 54)**	**p-value[a]**	**All patients (n = 148)**
Direct medical costs					
- Outpatient visit	264.03	272.07	286.37	0.962	275.39
	(179.64-411.53)	(195.99-438.06)	(210.11-447.74)		(226.39-355.15)
- Inpatient visit	0	368.70	152.95	0.626	202.79
	(-)	(0-2,580.90)	(39.56-604.42)		(33.51-884.24)
- Emergency visit	0	13.79	40.00	0.062	20.09
	(-)	(2.16-58.34)	(17.72-78.23)		(10.24-37.69)
- Medication	2,223.50	2,444.12	2,507.90	0.701	2,415.22
	(1,830.29-2,807.45)	(2,051.83-2,805.33)	(2,087.18-2,949.16)		(2,176.27-2,676.12)
- AD medication	1,280.95	1,576.89	1,571.91	0.470	1,505.09
	(972.38-1,723.31)	(1,279.78-1,885.15)	(1,255.45-1,898.51)		(1,325.47-1,716.62)
- Non-AD medication	942.55	867.24	935.99	0.886	910.13
	(684.84-1,230.78)	(675.48-1,118.12)	(724.96-1,184.16)		(790.40-1,055.66)
- Out-of-pocket	508.86	950.90	1,003.09	0.383	865.41
	(247.45-1,000.51)	(526.89-1,579.98)	(646.77-1,650.42)		(644.48-1,201.85)
- Total	**2,996.39**	**4,049.58**	**3,990.32**	**0.249**	**3,778.89**
	(2,549.84-3,578.81)	**(3,367.26-5,661.43)**	**(3,377.23-4,879.46)**		**(3,376.44-4,486.51)**

Cost categories [mean (95% CI)] (2017 USD)	Mild (n = 35)	Moderate (n = 59)	Severe (n = 54)	p-value[a]	All patients (n = 148)
Direct non-medical costs					
- Transportation	82.14 (68.70-97.00)	89.33 (73.08-116.52)	79.02 (65.38-96.63)	0.708	83.87 (74.81-97.04)
- Paid domestic help	402.28 (120.65-985.54)	963.67 (519.07-1,926.58)	1,497.13 (908.03-2,451.17)	0.100	1,025.55 (718.00-1,489.70)
- Total	**484.42 (200.23-1,098.38)**	**1,053.00 (609.77-2,004.50)**	**1,576.16 (989.47-2,537.73)**	**0.103**	**1,109.42 (802.52-1,569.67)**
Indirect costs (informal care)					
- Opportunity cost without supervision (Base-case)	**2,042.89 (1,492.15-2,881.28)**	**2,699.07 (2,108.62-3,370.22)**	**4,294.00 (3,672.97-4,995.87)**	**<0.001**	**3,125.82 (2,745.39-3,560.02)**
- Replacement cost without supervision (Lower-bound)	1,461.28 (1,068.54-2,062.67)	1,939.23 (1,519.84-2,426.14)	3,090.44 (2,643.53-3,579.99)	<0.001	2,246.24 (1,973.58-2,558.56)
- Opportunity cost with supervision (Upper-bound)	4,734.39 (3,581.50-6,572.42)	5,866.66 (4,892.31-6,818.60)	8,207.57 (7,184.25-9,133.11)	<0.001	6,453.01 (5,845.24-7,191.99)

Cost categories [mean (95% CI)] (2017 USD)	Mild (n = 35)	Moderate (n = 59)	Severe (n = 54)	p-value[a]	All patients (n = 148)
Total costs[b]					
- Base-case	**5,523.70 (4,649.05-6,593.49)**	**7,801.64 (6,695.33-9,518.22)**	**9,860.47 (8,784.51-11,327.64)**	**<0.001**	**8,014.13 (7,294.83-8,843.80)**
- Lower-bound	4,942.08 (4,161.84-5,825.48)	7,041.80 (6,039.02-8,797.00)	8,656.91 (7,693.09-10,055.44)	<0.001	7,134.54 (6,486.14-7,931.16)
- Upper-bound	8,215.20 (6,939.93-10,087.30)	10,969.23 (9,597.22-12,637.83)	13,774.05 (12,522.35-15,278.24)	<0.001	11,341.32 (10,455.60-12,289.73)

[a] p-value for comparison of differences in means across AD severity groups (one-way Analysis of Variance (one-way ANOVA) test)

[b] Total costs for the base-case estimates included indirect costs valued by the opportunity cost approach without supervision time included; total costs for the lower-bound estimates included indirect costs valued by the replacement cost approach without supervision time included; and total costs for the upper-bound estimates included indirect costs valued by the opportunity cost approach with supervision time included.

Remarks: 95% CI based on bias-corrected and accelerated bootstrapping

Abbreviations: n, number of patients; USD, United States dollar; 95% CI, 95% confidence interval; AD, Alzheimer's disease

Table 4 Evaluations of the impact of disease-severity measures (cognitive, behavioral and functional status) and other variables on different cost categories (direct medical, direct non-medical, indirect and total costs of AD care)

Variables (2017 USD)	Direct medical costs AME (SE)[a]	Direct non-medical costs AME (SE)[b]	Indirect costs		Total costs	
			MMSE model AME (SE)[c]	DAD model AME (SE)[c]	MMSE model AME (SE)[b]	DAD model AME (SE)[b]
Cognitive status (MMSE score)	-	-	-103.39 (23.54)***	-	-190.06 (47.71)***	-
Behavioral status (NPI score)	-	-	-	-	-	-
Functional status (DAD score)	-11.82 (6.31)*	-28.62 (13.51)**	-	-39.89 (6.05)***	-	-76.14 (11.85)***
Patient's age	86.93 (26.19)***	53.45 (32.68)*	-12.01 (24.42)	-29.27 (20.92)	142.51 (43.78)***	114.35 (40.34)***
Female patient (vs. male)	734.83 (412.12)*	625.64 (610.89)	537.23 (485.88)	410.65 (437.89)	1,676.17 (825.13)**	1,602.65 (735.58)**
Charlson Comorbidity Index (CCI)	387.53 (175.22)**	90.74 (170.60)	180.89 (119.65)	169.54 (97.39)*	475.33 (230.26)**	432.07 (211.68)**
Use of psychotherapeutic agents[d] (vs. no use)	968.33 (397.79)**	-	-	-	-	-

Variables (2017 USD)	Direct medical costs AME (SE)[a]	Direct non-medical costs AME (SE)[b]	Indirect costs		Total costs	
			MMSE model AME (SE)[c]	DAD model AME (SE)[c]	MMSE model AME (SE)[b]	DAD model AME (SE)[b]
Caregiver's age	-	-50.25 (27.45)*	-	-	-	-
Female caregiver (vs. male)	-	-	907.63 (513.80)*	688.21 (451.07)	-	-
Bootstrap-corrected calibration coefficient	0.412	0.319	0.385	0.517	0.479	0.579

[a] Estimates were derived from the multivariable generalized linear model with inverse Gaussian distribution and log link after the modified Park's test.

[b] Estimates were derived from the multivariable generalized linear model with gamma distribution and log link after the modified Park's test.

[c] Estimates were derived from the multivariable generalized linear model with Gaussian distribution and log link after the modified Park's test.

[d] Psychotherapeutic agents included antidepressants and antipsychotics.

***, **, * denotes significance at 1%, 5% and 10% levels, respectively.

Remarks: The modified Park's test basis: (1) if the variance was constant, the test would suggest the Gaussian family; (2) if the variance is proportional to the mean, the test would suggest the poison family; (3) if the variance is proportional to the square of the mean, the test would suggest the Gamma family; and (4) if the variance is proportional to the cube of the mean, the test would suggest the inverse Gaussian or Wald family.

Abbreviations: AD, Alzheimer's disease; USD, United States dollar; AME, average marginal effect; SE, standard error; MMSE, mini-mental state examination; NPI, neuropsychiatric inventory; DAD, disability assessment for dementia; CCI, Charlson comorbidity index

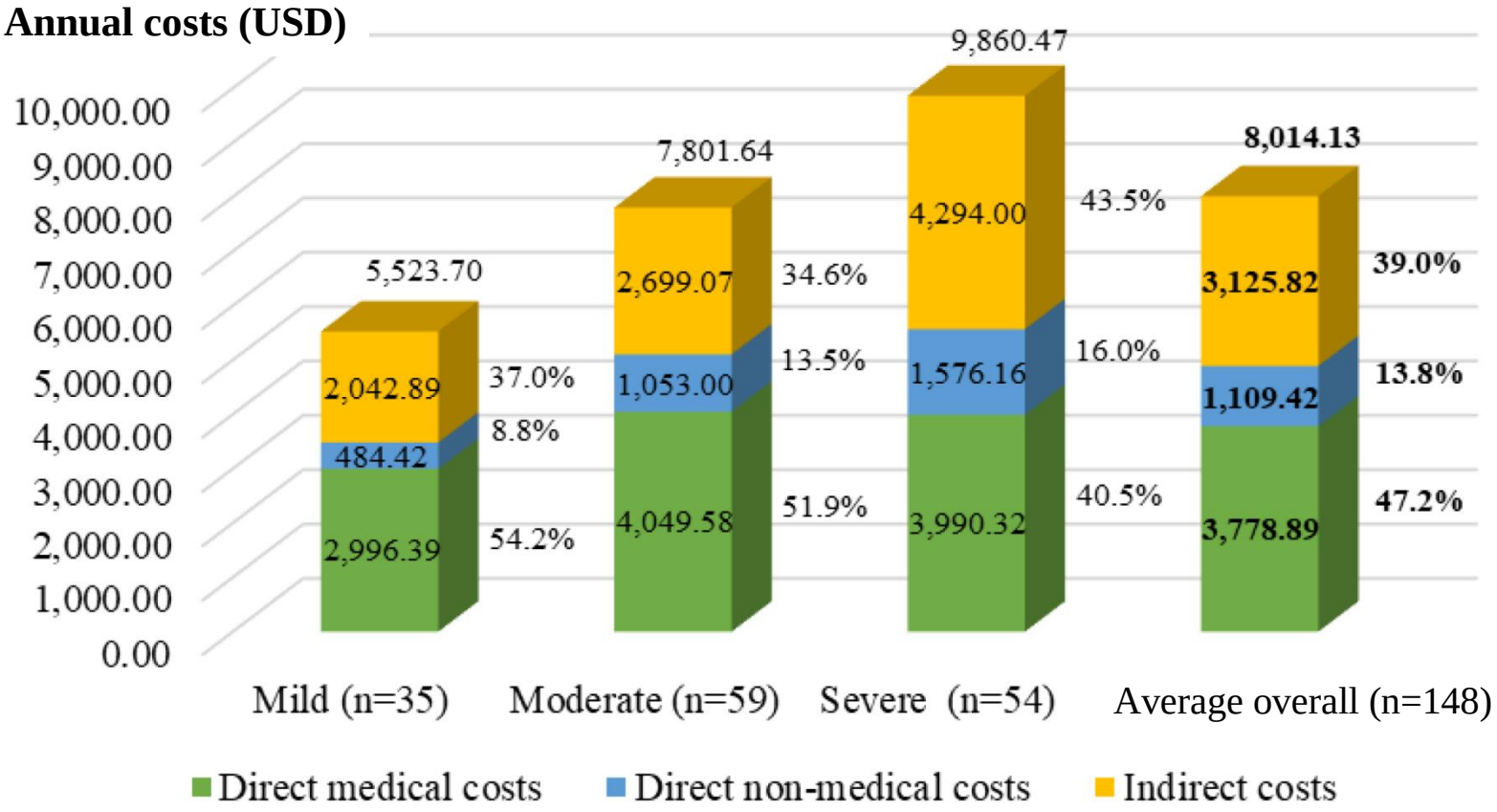

Figure 1 Estimated average annual costs of AD care per patient stratified according to different severity levels of cognitive status

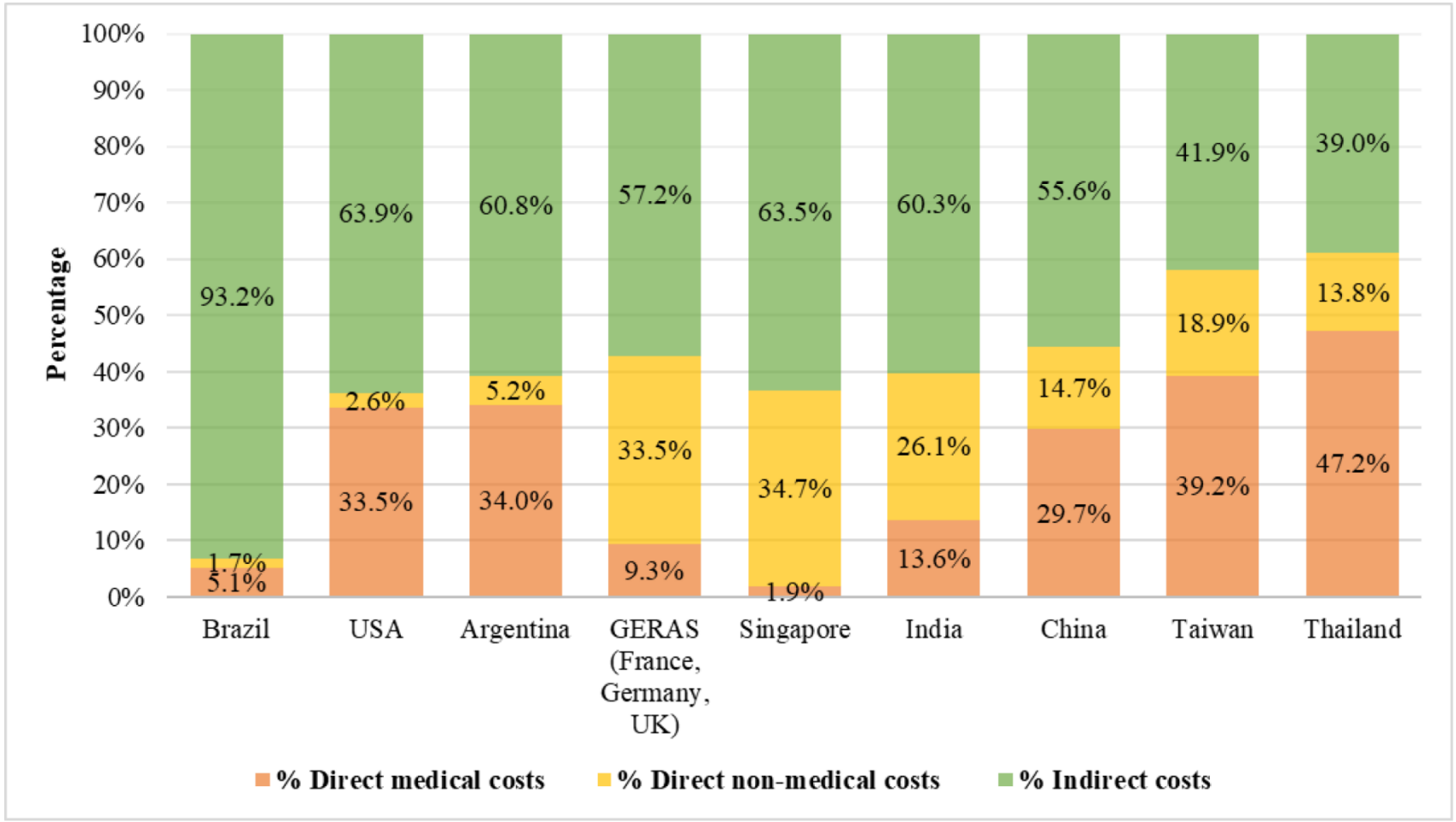

Figure 2 Comparison of disaggregated total costs of AD care among community-living patients between Thailand and other countries across the world

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CHAPTER 3

Study 2 – Compliance and Persistence with Alzheimer's Disease Treatment: A Retrospective Analysis of Multiregional Hospital Databases in Thailand

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Abstract

Aims: Due to lack of study evaluating compliance or persistence with Alzheimer's Disease (AD) treatment outside High-Income Countries (HICs), we aimed to assess compliance, persistence and factors associated with non-compliance and non-persistence by utilizing existing 'real-world' information from multiregional hospital databases in Thailand.

Materials and methods: We retrospectively identified study subjects from databases of five hospitals located in different regions across Thailand. AD patients aged ≥60 years who were newly prescribed with donepezil, galantamine, rivastigmine or memantine between 2013 and 2017 were eligible for analysis. The Medication Possession Ratio (MPR) was used as a proxy for compliance, while the Kaplan–Meier survival analysis was employed to estimate persistence. Logistic and the Cox regressions were used to assess determinants of non-compliance and non-persistence, adjusted for age and gender.

Results: Among 698 eligible patients, mean (SD) MPR was 0.83 (0.25) with 70.3% of the patients compliant to the treatment (having MPR ≥0.80). Half of the patients discontinued their treatment (having a treatment gap >30 days) within 177 days with 1-year persistence probability of 21.1%. The patients treated in the university-affiliated hospital were more likely to be both non-compliance (OR 1.71; 95% CI: 1.21-2.42) and non-persistent (HR 1.33; 95% CI: 1.12-1.58). In addition, non-compliance was higher for those prescribed with single AD treatment (OR 2.52; 95% CI: 1.35-4.69), while non-persistence was higher for those unable to reimburse for AD treatment (HR 1.34; 95% CI: 1.11-1.62).

Limitations: By using retrospective databases, a difficulty in validating whether the medications are actually taken after being refilled may overestimate the levels of compliance and persistence.

Meanwhile, possible random coding errors may underestimate the strength of association findings.

Conclusions: This study reveals the situation of compliance and persistence on AD treatment for the first time outside HICs. The determinants of non-compliance and non-persistence underline key areas for improvement.

Introduction

By 2050, nearly two thirds of countries across the world will have become aged society [1], where at least 20% of the population is aged 60 years or over. As incidence of dementia doubles with every 6.3-year increase in age after 60 years, up to 131.5 million people worldwide will have lived with dementia by the same year [2]. Approximately three quarters of all dementia cases are caused by Alzheimer's disease (AD) [3]. AD is a chronic disorder of the brain, causing a progressive deterioration of cognitive functions. People with AD gradually lose abilities to execute daily activities and become dependent [4]. There are two classes of medications having efficacy of improving cognition, behaviour and global status of people with AD: (1) cholinesterase inhibitors (ChEIs: donepezil, galantamine and rivastigmine); and (2) N-methyl-D-aspartate receptor antagonist (NMDA antagonist: memantine) [5-7].

Compliance and persistence play a crucial role in allowing patients to achieve highest benefits from their prescriptions. The Special Interest Group (SIG) of the International Society for Pharmacoeconomics and Outcome Research (ISPOR) has recommended that compliance and persistence should be defined and considered separately [8]. Compliance assesses how well a patient acts in accordance with the prescribed regimen, while persistence measures how long a patient continues the treatment for the prescribed duration. A review of long-term use of ChEIs has suggested that treatment with ChEIs be continued for at least one year before discontinuation so that treatment effects can remain for up to five years [9]. Furthermore, a cohort study of 8,614 AD patients has found that the sustained use of ChEIs for more than two years decreases annual mortality risk by 24%, compared to the short-term use for less than one year [10].

Despite the paramount importance of compliance and persistence on patient's outcomes, to date, the studies evaluating such behaviour specifically with AD treatment have only been conducted in high-income countries (HICs) [11]. The evaluation of compliance and persistence could be performed using either subjective (i.e. patient's self-report and healthcare professional assessments) or objective (i.e. pill counts, electronic monitoring, secondary database analysis and biochemical measures) methods [12]. With the possibility of resource constraints in non-HICs, analysing compliance and persistence behaviour using secondary database analysis, which requires minimal time and expenditure, is considered appropriate particularly for those non-HICs where pharmacy or claimed databases have been available [13].

Thailand, a member of non-HICs, has also experienced with the growing number of the elderly with no less than a half million of AD cases in 2015 [14,15]. Nonetheless, access to AD treatment for Thai patients has been limited. AD medications can only be prescribed in tertiary hospitals [16], and are only subsidized by the civil servant medical benefit scheme (CSMBS, covering 8% of entire Thai population) [17]. While this is an important issue to be addressed, without the availability of relevant health technology assessments (HTAs), decision-making on health policies for tackling this issue is susceptible to uncertainty [18]. The study of compliance and persistence behaviour of AD treatment would provide crucial insights into the current situation of compliance and persistence levels among AD treatment users in Thailand. Knowledge of compliance and persistence can serve not only as a key input parameter for its own future full HTAs, but also as a reference for other non-HICs to develop their own study. We, therefore, aimed to assess compliance, persistence and factors associated with non-compliance and non-persistence by utilizing existing 'real-world' information from multiregional hospital databases in Thailand.

Methods

This study was reported in accordance with the recommendation of the ISPOR Medication Compliance and Persistence SIG to ensure the consistency and quality of compliance and persistence findings [19].

Data sources

We retrospectively identified study population from five hospital's databases located in different regions of Thailand: (1) Ramathibodi Hospital, Bangkok, central Thailand (a 1,378-bed university-affiliated hospital); (2) Sunpasithiprasong Hospital, Ubon Ratchathani, northeastern Thailand (a 1,188-bed regional hospital); (3) Buddhachinaraj Hospital, Phitsanulok, lower northern Thailand (a 1,063-bed regional hospital); (4) Chiangrai Prachanukroh Hospital, Chiangrai, upper northern Thailand (a 787-bed regional hospital); and (5) Suansaranrom Hospital, Surat Thani, southern Thailand (a 1,300-bed psychiatric hospital). We requested de-identified datasets consisting of outpatient and inpatient information on demographics, diagnosis, hospital visits and prescribed medications from each hospital. The first four hospitals provided datasets from 1 January 2013 to 31 December 2015, while another from 3 October 2014 to 3 August 2017 due to data availability. Ethical approvals on the study protocol were granted from all five hospital's ethics committee.

Study subjects

Study subjects included elderly people aged 60 or above with diagnosis of AD according to the International Classification of Diseases, Tenth Edition (ICD-10) codes as F00 (dementia in Alzheimer's disease) and G30 (Alzheimer's disease) [20], who were newly prescribed with at least two successive prescriptions of donepezil, galantamine, rivastigmine or memantine within

the first six months [21]. New AD treatment users were identified as not receiving any of the four AD medications during the past six months prior to the index prescription date (the date of the first AD treatment prescription for each subject) [13,22]. Datasets of each eligible study subject were analysed in one-year period following their index date.

Measurements of compliance and persistence

We estimated the medication possession ratio (MPR) as a proxy for compliance to AD medications. MPR was calculated by summing the number of days for which the treatment had been supplied during the observational period without the last refill, divided by the number of days between the first and the last refill [19]. Patients with MPR ≥ 0.8 were considered to be compliant AD treatment users [23]. In the case that MPR was greater than 1.0, which reflected patients refilling AD treatment before the depletion of their previous supply, we capped the MPR value at 1.

We employed the estimated level of persistence with therapy (ELPT) approach to measure time to non-persistence and persistence probabilities [13,19]. Time to non-persistence, equivalent to time to treatment discontinuation, was defined as duration that the patient continuously stayed on AD treatment without a permissible gap (a period of time between the expected exhaustion of one prescription and the initiation of subsequent prescription) exceeding 30 consecutive days, counting from the index date [22,24]. Persistence probabilities were identified as proportions of patients persistent with their AD treatment at a given time throughout the observational period of one year [13,19].

Since switching from initial AD treatment to another was neither non-adherent nor non-persistent behaviour, while benefited the patients as it lengthened the overall treatment duration; therefore,

we allowed the switchers to remain in the analyses [25]. Measurements of compliance and persistence are illustrated using a hypothetical example of AD treatment refilling course in **Figure 1**.

Statistical analyses

Descriptive statistics were used to summarize the data of patient characteristics, compliance (MPR, percent of compliant subjects) and persistence (median time to non-persistence, persistence probability). The survival curve of persistency probabilities over the observational period was generated using the Kaplan–Meier estimate [26]. Bivariate analyses, logistic and the Cox proportional hazard models were used to determine factors that potentially had influences on compliance and persistence [27]. These factors included age, gender, types of hospital, types of AD treatment, use of AD combination treatment, use of patch dosage form, polypharmacy (prescription of ≥five medications during six months preceding the index date) and reimbursement status for AD prescription costs [28,29]. Sensitivity analyses were carried out to check robustness of the findings as follows: (1) excluding the datasets from a hospital which captured different period of prescribing information; and (2) varying the permissible gap of persistence analysis to 15, 45, and 60 days [24]. Results from the sensitivity analyses were compared to those from the main analyses using the nonparametric Kruskal-Wallis test [30]. All data processing and statistical analyses were undertaken in STATA (version 13.0, StataCorp, College Station, TX, USA).

Results

Characteristics of study subjects

A total of 698 eligible AD patients were identified from all five hospital databases. Details of study subject selection are outlined as a flow diagram in Figure 2. Of the 698 patients, the mean (standard deviation (SD)) age was 78.1 (7.8) years; and 445 (63.8%) were female. Donepezil (339/698, 48.6%) was most frequently prescribed as the first AD treatment, followed by memantine (169/698, 24.2%), rivastigmine (111/698, 15.9%) and galantamine (79/698, 11.3%). About 1 in 10 patients (88/698, 12.6%) initiated their treatment with AD combination treatment, which was comprised of one type of ChEIs plus memantine. None of the patients starting with multiple AD medications had their AD treatment switched, whereas 11.8% (72/610) of those starting with single AD medication did. The majority of patients (478/698, 68.5%) were found to have polypharmacy in the past six months prior to the index date. Almost three quarters of new AD treatment users (517/698, 74.1%) were the patients insured under the CSMBS (8% of all population whose AD treatment costs were subsidized), leaving a small proportion (25.9%) of accessibility to new AD treatment prescriptions to the rest of Thai population (92%). Characteristics of study subjects are presented in **Table 1**.

Measures of compliance and persistence with AD treatment

Medication compliance among Thai AD treatment users was fairly high with the mean MPR (SD) of 0.83 (0.25). When applying the cut-off value of MPR at 0.80, we found that 7 out of 10 patients (70.3%; 95% confidence interval (95% CI): 66.8% to 73.7%) were compliant to AD treatment. According to the survival curve of persistence probabilities with AD treatment as shown in Figure 3, median time to non-persistence was slightly shorter than 6 months (177 days;

interquartile range (IQR): 72 to 330 days). However, there were only 21.1% (95% CI: 18.1% to 24.2%) of the patients persistent with their treatment for one-year period following the index date.

Determinants of medication non-compliance

Factors potentially associated with non-compliance to AD treatment (**Table 2**) were found to be (1) receiving AD treatment from university-affiliated hospital, (2) using single AD medication and (3) using non-patch dosage form (p-value of the chi-square statistics < 0.2). These factors were further verified using the multivariate logistic regression. According to the forward selection process, the final model (**Table 4**), adjusted for age and gender, revealed that (1) receiving AD treatment from the university-affiliated hospital (odds ratio (OR) 1.71; 95% CI: 1.21 to 2.42; p-value = 0.003) and (2) using single AD medication (OR 2.52; 95% CI: 1.35 to 4.69; p-value = 0.004) were statistically significant determinants of non-compliance to AD treatment.

Determinants of medication non-persistence

Factors potentially related to non-persistence with AD treatment (**Table 3**) included (1) receiving AD treatment from university-affiliated hospital and (2) being ineligible for AD treatment reimbursement (p-value of the chi-square statistics < 0.2). We, therefore, further investigated these factors using the multivariate Cox regression. Based on the forward selection process, the final model (**Table 4**), adjusted for age and gender, disclosed that (1) receiving AD treatment from the university-affiliated hospital (hazard ratio (HR) 1.33; 95% CI: 1.12 to 1.58; p-value = 0.001) and (2) being ineligible for AD treatment reimbursement (HR 1.34; 95% CI: 1.11 to 1.62; p-value = 0.002) were statistically significant determinants of non-persistence with AD

treatment. These determinants did not violate the proportional-hazards assumption of the Cox model.

Sensitivity analyses

In the sensitivity analyses (**Table 5**), exclusion of the datasets, in which different period of prescribing information was captured, did not significantly alter the results from the main analysis (p-values of the Kruskal-Wallis tests on mean MPR and median time to non-persistence > 0.05). However, variations of permissible gap in persistence analysis leaded to significant differences in median time to non-persistence and 1-year persistence probability, compared to the main analysis (p-values of the Kruskal-Wallis tests ≤ 0.05). Not surprisingly, both of the persistence outcomes were increased with more flexible permissible gaps.

Discussion

Principal findings

This study generates the first 'real-world' evidence of compliance and persistence on AD treatment outside HICs. We found that most of the patients (70.3%) were compliant to their treatment, whereas only 21.1% could manage to persist with the treatment throughout the one-year observational period. Co-prescription of AD medications was found to exert a positive influence on the level of compliance. However, the patients who received AD treatment from the university-affiliated hospital were deemed to have significantly higher chances of being both non-compliant and non-persistent. Only a small portion of Thai population, particularly those whose AD treatment expenses were subsidized, had access to AD treatment and remained on the treatment for longer duration. These findings reveal the current status of compliance and

persistence behaviour and highlight specific areas to consider for improving levels of such behaviour among AD treatment users in Thailand.

Levels of compliance and persistence with AD treatment

Compliance and persistence provide different perspectives of medication-taking behaviour. As recommended by the SIG of ISPOR [8], we defined and assessed both of them independently. Overall, Thai AD patients appeared to have high-compliant (70.3% were found to be compliant to AD treatment over one year) but low-persistent (21.1% were found to be persistent with AD treatment over one year) behaviour. They may possess enough medications to consume with respect to the prescribed regimen, but they intermittently take the medications with an early treatment gap that goes beyond the tolerable level. Since it has been reported that interruption of donepezil for more than six weeks can lead the patients to lose all benefits gained from the previous treatment [31], we decided to use the 30-day permissible gap, which is more sensitive to detect discontinuation, in our main analysis. The large difference between compliant and persistent levels could be explained by the differences in methodology between the MPR and the ELPT. The major difference is that the calculation of MPR does not consider the gaps between refills, thus tolerating the gaps of every level [13], resulting in the higher estimates. Hence, the recommendation of the SIG should be encouraged because considering only one measure instead of another could lead to partial understanding or even misapprehensions of medication-taking behaviour.

When compared to existing literature, although our compliance and persistence levels are somewhat similar to those of other countries, the levels are fallen on the lower half percentile of worldwide results. The majority of studies have used the MPR to quantify compliance on AD treatment, though the variations of MPR formulas are found across the studies [10,23,32-36].

The reported MPRs have been ranged from 0.59 [35] to 0.94 [33], placing our MPR of 0.83 on about 45th percentile of all available results from the seven studies. Turning to consider the studies assessing persistence on AD treatment [10,22-24,29,32,35-43], a wide range of permissible gaps have been used from 30 [22,24,32,35,37,38] to 180 days [43]. Most of the studies have defined the gaps of 30 days and reported 1-year persistence probabilities between 18.4% [35] and 57.3% [38]. As a result, our 1-year persistence probability of 21.1% is ranked about 25th percentile in all available results from the six studies. We also conducted sensitivity analyses using a variety of the permissible gaps; however, at the gaps of 45 and 60 days, our levels of persistence were still below those from other countries. These findings indicate that AD treatment users in Thailand may have not received adequate therapeutic benefits from AD medications.

Significant determinants of non-compliance and non-persistence

The combination treatment between one kind of ChEIs and memantine demonstrated a positive impact on compliance behaviour of newly treated AD patients. This finding is consistent with a large population-based study conducted in the Republic of Ireland, in which the co-prescription of AD treatment has been reported to almost double the time to treatment discontinuation [29]. This finding is also in agreement with the most recent network meta-analysis of 142 studies comparing effectiveness of AD treatment, in which donepezil plus memantine has been found to be the most effective therapy [7]. Synergistic effects of the combination treatment, which result in increased therapeutic benefits, could be a possible explanation for the better compliance and persistence behaviour among AD treatment users.

On the other hand, the higher rates of non-compliance and non-persistence were found in the patients who were prescribed with AD treatment from the university-affiliated hospital. This type

of hospital has been renowned for its proficiency of medical specialists, but it is situated in only a few major cities across the country. The major reason behind these higher non-compliance and non-persistence rates is probably due to the farther distance from patients' residences to the university-affiliated hospital. In Thailand, to date, only tertiary hospitals where AD specialists are available are capable of prescribing AD medications. Generally, patients need to visit the outpatient department of their regular tertiary hospital every 2-16 weeks, depended on stage of the disease, in order to refill their AD medications. To allow the patients to refill AD treatment from nearby non-specialized hospital, the World Health Organization's Mental Health Gap Action Program (WHO's mhGAP) [44] should be considered to put into action. This program provides evidence-based guidance enabling non-specialists to deliver psychosocial and pharmacological interventions for mental health conditions under the necessary supervision of specialists. Together with the fact that face-to-face interventions delivered by pharmacists are the most effective strategy in improving medication adherence [45], nationwide hospital pharmacists are encouraged to get involved in the WHO's mhGAP. After the program is successfully implemented, not only the AD patients but patients with other psychological disorders would gain benefits from the ease of access to mental health services, which potentially ameliorates the levels of compliance and persistence.

Another great concern has arisen when we found that the vast majority of Thai people were possibly inaccessible to AD treatment due to the inability to reimburse for the treatment costs. The lack of financial support was also significantly associated with the increased risk of early AD treatment discontinuation. Previous studies from HICs have found the similar possibility of socioeconomic barriers to AD treatment [36,41,46,47]. Maxwell et al. (2014) has suggested that the worsened compliance and persistence may have been contributed from the increased out-of-

pocket expenses with the sustained use of AD treatment along the course of the disease [48]. As a consequence, to tackle with both limited accessibility and early treatment discontinuation issues, the expensive expenditure incurred by AD treatment should be considered to equitably cover for all Thai citizens. Nonetheless, in order to facilitate policy maker's ability to make such decision, future full HTAs, assessing whether or not AD treatment is cost-effective and able to contribute considerable positive effects to the whole society, are warranted.

Strengths and limitations

An important strength of this study is that study subjects were identified from the databases of five hospitals located in different regions across the country, thus enhancing the generalizability of the findings. Moreover, since the diagnosis and prescription data have been documented as a part of routine practice by healthcare professionals, another strength is that recall bias is negligible. Nevertheless, the findings should be interpreted in light of some limitations. First, although the hospital databases in Thailand have been evaluated as having a high level of validity [49], the possibility of random coding errors could not be excluded. This may lead to non-differential misclassification, resulting in underestimation of the strength of the association findings. Second, we are unable to investigate other variables that may be associated with the levels of compliance and persistence such as cognitive status, functional ability, psychiatric symptoms, individual health behaviours and healthcare system factors [10,48], for these variables have not been captured in the hospital databases. Finally, the retrospective analyses using prescription refills may overestimate the levels of compliance and persistence because it is difficult to validate whether or not the medications are actually taken after being refilled. However, it is reasonable to assume that the patients would not return to refill a prescription without the intention to comply or persist with the treatment [13].

Conclusions

Our study applies the joint approach of compliance and persistence analyses to scrutinize the situation of compliance and persistence behaviour among AD treatment users in Thailand. The somewhat inferior levels of compliance and persistence, when compared to other countries, serve a useful purpose in calling the attention of healthcare professionals and policy makers to take action on the modifiable determinants to promote both compliance and persistence levels. Ultimately, these 'real-world' findings not only make valuable contributions to future full HTAs of AD treatment in Thailand but also represent themselves as the commencement of compliance and persistence study on AD treatment outside HICs.

Table 1 Distribution of study subject's characteristics

Characteristics of study subjects	Number of subjects (%)
Gender	
Male	253 (36.3)
Female	445 (63.8)
Age (mean ± SD)	78.1 ± 7.8
60-69	96 (13.8)
70-79	259 (37.1)
80-89	293 (42.0)
90 and above	50 (7.2)
Medical institutions	
Ramathibodi Hospital	395 (56.6)
Sunpasithiprasong Hospital	78 (11.2)
Buddhachinaraj Hospital	71 (10.2)
Chiangrai Prachanukroh Hospital	118 (16.9)
Suansaranrom Hospital	36 (5.2)
AD medications	
Donepezil	339 (48.6)
Galantamine	79 (11.3)
Rivastigmine	111 (15.9)
Memantine	169 (24.2)
Single AD treatment	610 (87.4)
Switchers	72 (11.8)
Non-switchers	538 (88.2)
Combination AD treatment	88 (12.6)
Switchers	0 (0)
Non-switchers	88 (100)
Polypharmacy (prescription of ≥ five medications during six months preceding the index date)	478 (68.5)

Characteristics of study subjects	Number of subjects (%)
Health insurance schemes	
UCS	67 (9.6)
SHI	3 (0.4)
CSMBS	517 (74.1)
Self-payment	111 (15.9)

Abbreviations: SD, standard deviation; AD, Alzheimer's disease; UCS, the universal coverage scheme; SHI, the social health insurance; CSMBS, the civil servant medical benefit scheme

Table 2 Bivariate analyses exploring associations between patient characteristics and compliance with AD treatment

Patient characteristics	Compliance (%)	Odds ratios of compliance (95% CI)	*p*-value of the chi-square statistics
Gender			0.224
Male	73.1	1	
Female	68.8	0.81 (0.57, 1.14)	
Age			0.867
60-69 years	67.7	1	
70-79 years	69.9	1.11 (0.67, 1.83)	
80-89 years	71.0	1.17 (0.71, 1.92)	
90 years and above	74.0	1.36 (0.63, 2.91)	
University-affiliated hospital			<0.001
Yes	65.3	1	
No	76.9	1.77 (1.26, 2.48)	
Types of AD treatment			0.530
Donepezil	69.0	1	
Galantamine	72.2	1.16 (0.68, 2.00)	
Rivastigmine	75.7	1.40 (0.85, 2.28)	
Memantine	68.6	0.98 (0.66, 1.46)	
Multiple AD medications			<0.001
Yes	85.2	1	
No	68.2	0.37 (0.20, 0.69)	
Patch dosage form			0.173
Yes	75.7	1	
No	69.3	0.73 (0.46, 1.16)	

Patient characteristics	Compliance (%)	Odds ratios of compliance (95% CI)	*p*-value of the chi-square statistics
Polypharmacy (prescription of ≥five medications during six months preceding the index date) Yes No	71.6 67.7	1 0.83 (0.59, 1.18)	0.307
Reimbursable for AD treatment Yes No	71.0 68.5	1 0.89 (0.62, 1.28)	0.531

Abbreviations: SD, standard deviation; 95% CI, 95% confidence interval; AD, Alzheimer's disease

Table 3 Bivariate analyses exploring associations between patient characteristics and persistence probabilities with AD treatment

Patient characteristics	Persistence probabilities at 1 year (%)	95% CI of persistence probabilities	*p*-value of the log-rank statistics
Gender			0.676
Male	20.1	15.8, 25.7	
Female	21.4	17.7, 25.3	
Age			0.210
60-69 years	22.9	15.1, 31.7	
70-79 years	22.4	17.5, 27.6	
80-89 years	20.5	16.1, 25.3	
90 years and above	14.0	6.2, 25.0	
University-affiliated hospital			<0.001
Yes	17.5	13.9, 21.4	
No	25.7	21.0, 30.8	
Types of AD treatment			0.903
Donepezil	20.9	16.8, 25.4	
Galantamine	20.3	12.2, 29.7	
Rivastigmine	22.5	15.3, 30.7	
Memantine	20.7	15.0, 27.1	
Multiple AD medications			0.744
Yes	14.8	8.3, 23.0	
No	22.0	18.8, 25.3	
Patch dosage form			0.774
Yes	22.5	15.3, 30.7	
No	20.8	17.6, 24.2	

Patient characteristics	Persistence probabilities at 1 year (%)	95% CI of persistence probabilities	*p*-value of the log-rank statistics
Polypharmacy (prescription of ≥five medications during six months preceding the index date)			0.948
Yes	21.1	17.6, 24.9	
No	20.9	15.8, 26.5	
Reimbursable for AD treatment			0.002
Yes	23.8	20.2, 27.5	
No	13.3	8.8, 18.6	

Abbreviations: SD, standard deviation; 95% CI, 95% confidence interval; AD, Alzheimer's disease

Table 4 Multivariate analyses of the patient characteristics selected from the bivariate analyses to investigate determinants of non-compliance and non-persistence

Patient characteristics	Adjusted odds ratio* of non-compliance (95% CI)	Adjusted hazard ratios* of non-persistence (95% CI)
University-affiliated hospital		
Yes	1.71 (1.21, 2.42)	1.33 (1.12, 1.58)
No	1	1
Multiple AD medications		
Yes	1	-
No	2.52 (1.35, 4.69)	-
Reimbursable for AD treatment		
Yes	-	1
No	-	1.34 (1.11, 1.62)

* adjusted for age and gender

Abbreviations: SD, standard deviation; 95% CI, 95% confidence interval; AD, Alzheimer's disease

Remarks: odds ratios (ORs) and hazard ratios were derived from logistic and the Cox proportional hazard models, respectively.

Table 5 Sensitivity analyses

Sensitivity analyses	Mean MPR (SD)	% Compliance (95% CI)	Median time to non-persistence (days) (IQR)	1-year persistence probability (95% CI)
Excluding the datasets which captured the different period of prescribing information				
Main analysis	0.83 (0.25)	70.3 (66.8, 73.7)	177 (72, 330)	21.1 (18.1, 24.2)
After the exclusion	0.83 (0.25)	69.3 (65.7, 72.8)	174 (70, 324)	20.4 (17.4, 23.5)
Varying the permissible gap of persistence analysis				
Gap < 15 days	-	-	129 (47, 281)**	17.7 (15.0, 20.7)
Gap < 30 days (Main analysis)	-	-	177 (72, 330)	21.1 (18.1, 24.2)
Gap < 45 days	-	-	208 (90, 358)*	24.2 (21.1, 27.4)
Gap < 60 days	-	-	213 (99, NA)**	26.6 (23.4, 29.9)

* p-value of the Kruskal-Wallis test < 0.05

** p-value of the Kruskal-Wallis test < 0.001

Abbreviations: SD, standard deviation; 95% CI, 95% confidence interval; IQR, interquartile range; AD, Alzheimer's disease

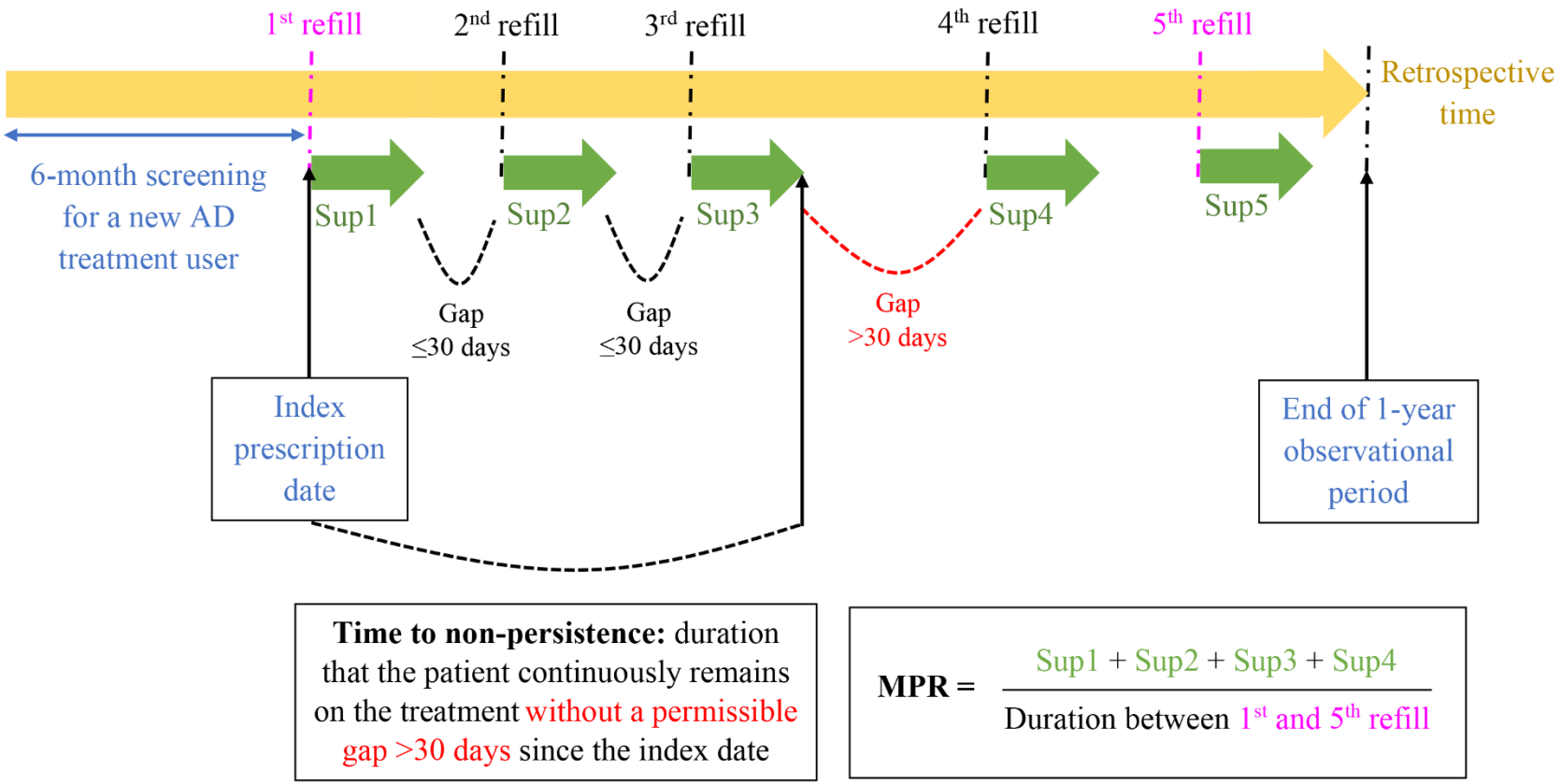

Figure 1 A hypothetical example of AD treatment refilling course illustrating measurements of compliance (MPR: medication possession ratio) and persistence (time to non-persistence)

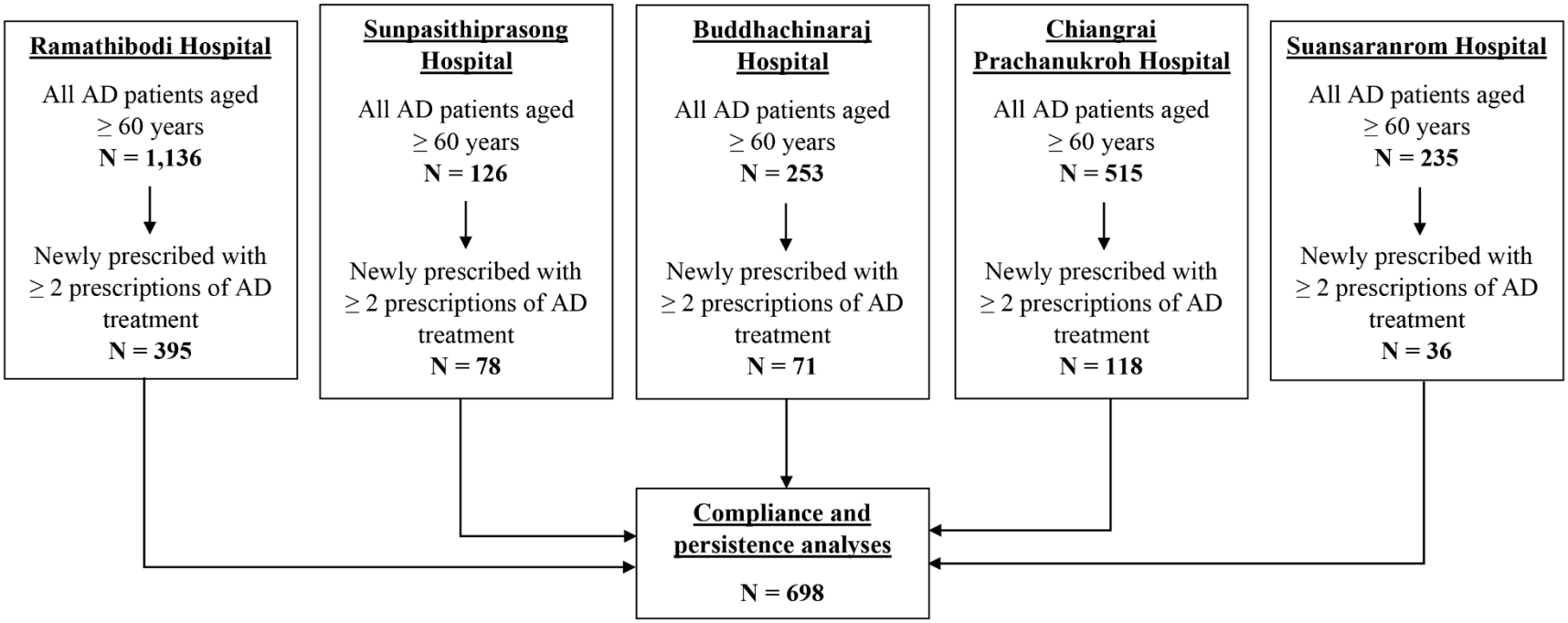

Figure 2 Identification of eligible study subjects from five hospitals' databases in Thailand for compliance and persistence analyses

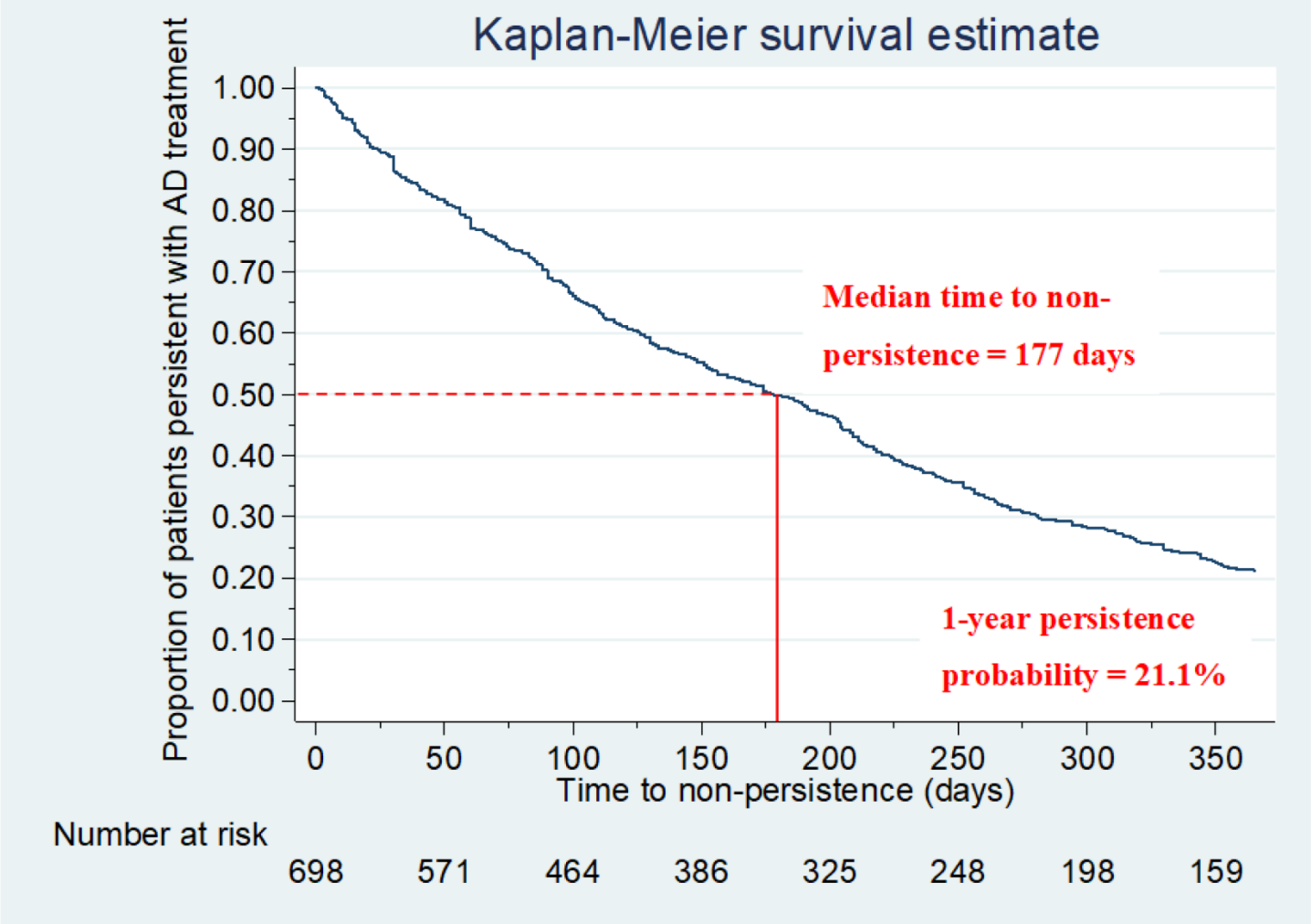

Figure 3 A survival curve illustrating persistence probabilities with AD treatment over 1-year observational period

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CHAPTER 4

Study 3 – Application of Discrete-Event Simulation in Health Technology Assessment: A Cost-Effectiveness Analysis of Alzheimer's Disease Treatment Using Real-World Evidence in Thailand

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Submitted

Abstract

Objectives: Decision-analytic models for Alzheimer's disease (AD) have been advanced to a discrete-event simulation (DES), in which individual-level modelling of disease progression across continuous severity spectra become feasible. This study aimed to apply the DES to perform cost-effectiveness analysis of AD treatment in Thailand.

Methods: A dataset of Thai AD patients, representing unique demographic and clinical characteristics, was bootstrapped to generate a baseline cohort of 50,000 patients. Each patient was cloned and assigned to donepezil, galantamine, rivastigmine, memantine or no treatment. Correlated changes in cognitive and behavioural status over time were developed using patient-level data. Treatment effects were obtained from the most recent network meta-analysis. Treatment persistence, mortality and predictive equations for functional status, costs (Thai baht (THB) in 2017) and quality-adjusted life year (QALY) were derived from country-specific real-world data.

Results: Under a societal perspective, only was the prescription of donepezil to AD patients with all disease-severity levels found to be cost-effective [incremental cost-effectiveness ratio (ICER): 138,524 THB/QALY (4,062 USD/QALY)]. Regardless of whether the treatment stopping rule when the mini-mental state examination score (MMSE) <10 was introduced, providing early treatment with donepezil to mild AD patients further reduced the ICER. Extensive sensitivity analyses indicated robust simulation findings.

Conclusions: The DES greatly enhances real-world representativeness of decision-analytic models for AD. Donepezil is the most cost-effective treatment option for AD in Thailand, which is worth being considered for universal financial coverage. Application of the DES in heath

technology assessment should be encouraged, especially when validity of the model is questionable with classical modelling methods.

Introduction

Decision-analytic models are a mathematical framework that integrates information, numerical variables and assumptions to generate a possible solution for actual interest [1]. In the aspect of heath technology assessment (HTA), decision-analytic models have been used to assess cost effectiveness of healthcare interventions to inform policy decision-makers that which of the interventions provides the best value for money, and thus should be adopted and reimbursed [2,3]. In order to select the most appropriate model for a certain research question, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and Society for Clinical Decision Making (SMDM) Task Force have recommended that the model be simple and transparent, but complex enough to ensure face validity and credibility of the model's results [3,4].

Over two decades, decision-analytic models for Alzheimer's disease (AD) have been developed to overcome methodological challenges, starting from state-transition or Markov models to a discrete-event simulation (DES) [3]. Modelling AD using Markov models necessarily requires simplification of the disease into a small number of health states, mostly based on cognitive severity-levels and the need of full-time care [3]. This may oversimplify the disease, adversely impact face validity of the model and mask potential benefits of the treatment being considered [3,5]. In contrast, the DES allows modelers to simulate heterogeneity in AD progression for individual patients based on correlated changes of multiple dimensions (i.e. cognitive, behavioral and functional status) on continuous scales [5]. In addition, structural flexibility of the DES [6] makes several scenario analyses such as consideration of individuals with different baseline disease severity-levels and incorporation of real-world treatment persistence into the model become more feasible.

The DES technique has been employed to assess economic values of AD treatment in high-income countries (HICs) such as the United Kingdom [5], Germany [7,8] and the United States [9], illustrating more realistic representation of AD progression and thereby creating improvements in cost-effectiveness findings. Despite its manifold advantages towards AD modelling, the DES technique has still been under-adopted, especially in low- and middle-income countries (LMICs). Therefore, this study aimed to apply advancement of the DES technique to perform cost-effectiveness analysis of treatment for AD in Thailand, where application of the DES in HTA is generally under-recognized.

Methods

Overall description

The DES model, which was adapted from Getsios et al. (2010) [5], was generated using TreeAge Pro 2019 software. Simulated individuals with unique demographic and disease characteristics were first generated by bootstrapping from a cohort of 148 Thai AD patients [10]. A total of five identical copies of each patient was then created and allocated to different treatment options: (1) oral donepezil 10 mg once daily, (2) oral galantamine 16 mg twice daily, (3) transdermal rivastigmine twice daily, (4) oral memantine 10 mg twice daily or (5) no AD treatment. Throughout the simulation period, the model randomly assigned each patient to discrete events including hospital visits, treatment discontinuation and death. The patients had their disease characteristics updated each time they experienced the events. Three domains of disease characteristics were measured: (1) cognitive (using the Mini–Mental State Examination (MMSE) score), (2) behavioural (using the Neuropsychiatric Inventory (NPI) score) and (3) functional

status (using the Disability Assessment for Dementia (DAD) score). The patient's change in cognitive status was first estimated, sequentially followed by behavioural and functional status to ensure the interdependencies among these disease characteristics. Model outputs including costs and quality-adjusted life years (QALYs) were imputed and accumulated over time based on patient's demographic and disease characteristics. In order to capture life-time costs and outcomes, a median lifespan of people with AD after diagnosis of 10 years [11] was chosen as the time horizon. Both costs and outcomes were discounted at 3% per annum, and the study was undertaken under both the health system and societal perspectives, in accordance with the HTA guidelines in Thailand [12]. An overview of the model flow is presented in **Figure 1**.

Model parameters and data sources

Patient's demographic and disease characteristics at baseline

A baseline cohort of 50,000 simulated patients was generated by sampling with replacement from a dataset of Thai patients with AD (**eTable 1**) [10]. The dataset captured information on patient age, gender, AD duration, Charlson comorbidity index (CCI), use of psychotherapeutic agents, MMSE and NPI scores, as well as caregiver age, gender and relationship with the patient. These patients had a mean age of 80.1 (range: 60.8-93.5) years and 71.0% were female, representing the current AD population who received diagnosis and treatment, as appropriate, from specialists in Thailand [13].

Disease progression

Disease progression was modelled based on the correlated changes in cognitive, behavioural and functional status over time. Rates of change in MMSE and NPI scores from baseline for patients receiving no AD treatment were obtained from a published study [5]. This study applied a

piecewise linear equation to imitate the natural history of change in MMSE observed in the consortium to establish a registry for Alzheimer's disease (CERAD) registry [14] and constructed the equation for change in NPI based on data from four randomized controlled trials (RCTs) [15-18]. However, our study modelled the predictive equation for DAD scores using patient-level data from a cross-sectional study conducted in Thailand [10]. All equations for disease progression are provided in **Table 1**, showing that the change in NPI scores was influenced by MMSE scores, while DAD scores were dependent on both MMSE and NPI scores.

Treatment effects

Treatment effects on cognitive function were extracted from the most recent systematic review and network meta-analysis (NMA) of 110 RCTs comparing effectiveness and safety of AD treatment [19]. This study reported pooled treatment effects as mean differences (MDs) with corresponding 95% credible intervals (95% CrIs), which were applied to the aforementioned MMSE equation to reflect disease progression of patients receiving AD treatment. Treatment effects of all treatment options are shown in **Table 1**.

Treatment persistence and time to hospital visits

To reflect the real-world medication-taking behaviour of Thai AD patients, information on treatment persistence was derived from a retrospective analysis of multiregional hospital databases in Thailand [13]. This study provided patient-level survival data of treatment persistence, which were used in the DES to predict time to treatment discontinuation for each patient actively receiving AD treatment (**eTable 2-5**). Patients who discontinued their treatment were assumed to lose all treatment benefits gained from the previous treatment over the following six weeks [20]. In addition, the real-world observation of appointment for the next

hospital visit among AD patients in Thailand [10] was used to predict time to hospital visits for all patients in the simulation (**eTable 6**).

Mortality

Since there were no disease-specific survival data of AD patients available in Thailand, we performed a systematic review and meta-analysis to estimate hazard ratios (HRs) for mortality associated with AD using data from 10 observational studies. Details of systematic searches, studies included and the meta-analysis are provided in **Supplementary appendix 3**. The pooled HR of 2.13 (95% confidence interval (95% CI): 1.80-2.47) was then applied to adjust the age- and gender-specific mortality tables of general Thai population [21], yielding a cumulative probability table used for predicting death age of Thai AD patients in the simulation (**eTable 7**).

Cost parameters

All cost parameters were obtained from local sources and are illustrated in **Table 1**. As per Thai HTA guidelines [22], costs due to patient's productivity loss, or indirect costs, were not included in the cost-utility analysis where QALY was already accounted for the morbidity and mortality effects. Therefore, only were direct medical costs considered in analysis under the health system perspective, while both direct medical and direct non-medical costs were included in the analysis under the societal perspectives.

Direct medical costs included costs associated with outpatient, inpatient and emergency visits, medications and out-of-pocket payments. Besides, direct non-medical costs were valued from transportation, formal caregiving services used and unpaid informal caregiving time. In the simulation, these costs were classified into hospital visit costs (costs of outpatient visits, inpatient visits, emergency visits, all medications except those for AD and transportation), fixed costs

(costs of out-of-pocket payments and formal caregiving services), AD treatment costs and informal caregiving costs.

Derived from a cross-sectional study conducted in Thailand [10], hospital visit and fixed costs were stratified based on disease-severity levels according to MMSE scores: mild (MMSE ≥20), moderate (MMSE = 10-19) and severe (MMSE <10) [23]. Unpaid caregiving time costs were estimated based on a published regression equation from the same study [10], while AD treatment costs were obtained from the national report of Drug Medical Supply and Information Center (DMSIC) in Thailand [24]. All cost estimates were presented in 2017-year value, where the average market exchange rate was 1 United State Dollar (USD) = 34.1008 Thai Baht (THB) [25].

Health utility data

Health utility data was obtained from a cross-sectional study conducted in Thailand [10]. This study assessed quality of life (QoL) of Thai AD patients using the EuroQoL-5 dimension-5 level of severity (EQ-5D-5L) questionnaire and QoL of caregivers using the Short Form-36 (SF-36) health survey. As the study reported that there was no difference in QoL of caregivers across the disease-severity levels according to MMSE scores (p-value = 0.561), our study decided not to consider QoL of caregivers in the simulation. Patient's QoL was predicted based on a published regression equation [10], which are presented in **Table 1**.

Analyses

To determine differences in life-time effectiveness when introducing AD treatment to patients with different baseline cognitive status, analyses were run for several scenarios: (1) a universal treatment scenario (AD cohort with all disease-severity levels) without consideration of stopping

the treatment when MMSE <10, (2) a late treatment scenario (moderate and severe AD cohort) without consideration of stopping the treatment when MMSE <10, (3) an early treatment scenario (mild AD cohort) without consideration of stopping the treatment when MMSE <10 and (4) an early treatment scenario (mild AD cohort) with consideration of stopping the treatment when MMSE <10. Cost effectiveness of all treatment options was then evaluated based on the willingness-to-pay (WTP) threshold of 160,000 THB/QALY gained (4,994 USD/QALY gained) in Thailand [26].

Extensive one-way sensitivity analyses were undertaken for all aforementioned scenarios under a societal perspective to ensure the model's proper functioning and identify key determinants of cost-effectiveness findings: (1) varying treatment effects based on their 95% CrI, (2) assuming 100% treatment persistence, (3) varying HR for mortality associated with AD based on its 95% CI, (4) varying hospital visit costs by ±25%, (5) varying fixed costs by ±25%, (6) varying AD treatment costs by ±25%, (7) varying the discount rate to 0 and 6% and (8) decreasing the time horizon to 5 years.

Probabilistic sensitivity analyses (PSAs) were also performed for all aforementioned scenarios under a societal perspective to account for uncertainties from multiple key parameters using the Monte Carlo simulation. Each of key parameters was assigned with a probability distribution to reflect their feasible ranges: (1) treatment effects on cognitive function (normal distribution), (2) hospital visit costs (gamma distribution) and (3) fixed costs (gamma distribution).

Model validation

In order to check face validity [27] of our model, average MMSE annual rates of change from 50,000 simulated patients were compared to those observed in the CERAD registry and RCTs

[5]. Furthermore, average values of NPI and DAD throughout the simulation of 50,000 patients were plotted against their corresponding MMSE to see disease progression trends and check for technical validity [27]. The validation results (**eFigure 1-3**) indicated that our model produced outputs that were consistent with the theoretical basis of the disease and the pharmacological intervention.

Results

Base-case analyses

For ease of interpretation, key base-case simulation results are shown in **Table 2**, while full details of the results are provided in **eTable 8**. When determining to initiate AD treatment among the patients with all disease-severity levels, only was donepezil found to be cost-effective under a societal perspective. Compared to untreated AD patients, although the patients receiving donepezil incurred additional discounted costs of 2,161 THB (63 USD), they experienced a discounted gain in QALY of 0.015, resulting in an incremental cost-effectiveness ratio (ICER) of 138,524 THB/QALY (4,062 USD/QALY). Moreover, the ICER was further decreased to 61,652 THB/QALY (1,808 USD/QALY) when prescribing early treatment with donepezil to mild AD patient cohorts. Nevertheless, the superior of donepezil appeared to wane when delayed treatment was given to a cohort of moderate and severe AD patients [ICER: 284,388 THB/QALY (8,340 USD/QALY)]. Introduction of a treatment stopping rule when MMSE goes below 10 to a mild AD cohort did not change the cost effectiveness of donepezil at the current treatment persistence level [ICER: 116,835 THB/QALY (3,426 USD/QALY)]. On the other

hand, none of AD medications were cost-effective when being considered under a healthcare perspective.

One-way sensitivity analyses

Full details of one-way sensitivity analysis results are presented in **eTable 9**. In most cases, donepezil was the treatment option that remained cost-effective or dominant compared to other AD medications and no AD treatment strategy. These findings were in agreement with the base-case results. Besides, as shown in **Figure 2**, the tornado diagrams suggested that changes in treatment effects, treatment persistence, AD treatment costs, HR for mortality associated with AD and time horizon had the strongest influence on the ICERs. Discussion for one-way sensitivity analysis results is provided in **Supplementary appendix 4**.

Probabilistic sensitivity analyses

The cost-effectiveness scatterplots (**eFigure 4**) and the cost-effectiveness acceptability curve (CEAC) (**Figure 3**), generated from 250 replications of 50,000 patients (**Supplementary appendix 5**), revealed that providing early donepezil to mild AD patients without implementing the treatment stopping rule had the highest chance (71.6%) of being cost-effective at the current WTP threshold. This was followed by providing early donepezil to mild AD patients with enforcing the treatment stopping rule (60%), providing donepezil to patients with all disease-severity levels (45.2%) and providing late donepezil to moderate to severe AD patients (34.8%), respectively. These findings were consistent with the base-case results, ensuring robustness of our simulation model.

Discussions

The results from our developed DES indicate that treatment with donepezil improves patient's quality of life and is considered cost-effective when used to treat AD patients with all disease-severity levels under a societal perspective in Thailand. Besides, the earlier the patients receive donepezil, the better cost-effectiveness benefits the patients could gain from the treatment. Based on the findings from one-way and probabilistic sensitivity analyses, it is almost certain that donepezil remains a superior treatment option compared to other AD medications and no AD treatment strategy. Narrowing the perspective to consider only healthcare resources, where the pivotal opportunity costs of caregivers are omitted, greatly diminishes the value for money of AD treatment.

The cost effectiveness of AD treatment has been assessed by several DES studies conducted in HICs [5,7-9]. Their findings indicate favourable value for money of AD medications. To illustrate, treatment with donepezil, compared to no AD treatment, is reported to be dominant when used to treat mild to moderate AD patients in the United Kingdom [5] and Germany [8], while treatment with galantamine is cost-saving in Germany [7]. Moreover, in moderate to severe AD patients, a combination between memantine and cholinesterase inhibitors is found to be dominant to cholinesterase inhibitor monotherapy in the United States [9]. Although our study has a similar model structure to these studies, several model parameters such as treatment persistence, mortality, costs and QoL have been tailored in our simulation to reflect local context. The greatest difference in the model parameters is found to be treatment persistence. While 1-year treatment discontinuation rates range from 0 [9] to 20% [7] in the models of HICs, the real-world treatment discontinuation rates are extraordinarily higher in Thailand (78.9%) [13]. In our base-case analyses where treatment persistence is taken into consideration, treatment

benefits lost from this remarkably low treatment persistence are substantial, which renders the cost-effectiveness findings of AD treatment (donepezil) in Thailand not as strong as those reported in HICs.

Prescription of AD medications in Thailand could only be done in tertiary hospitals where neurologists, psychiatrists or geriatricians are available. As there is no treatment stopping rule suggested in current clinical practice in Thailand, the specialists could make a decision, as appropriate, to prescribe AD treatment to the patients with any disease-severity levels. Expenses incurring from the prescriptions of AD treatment are not covered by the universal coverage scheme (UCS), the main national health insurance system, covering 75% of Thai population. Health Intervention and Technology Assessment Program (HITAP), a research organization under Thailand's Ministry of Public Health, has performed a cost-effectiveness study to evaluate value for money of AD treatment in 2011 [28]. However, the findings are not so definitive that they could support adoption of AD treatment in the UCS.

Comparing between the study conducted by the HITAP and ours, a great number of differences in methodology, which constitute dissimilarities in findings, could be identified. First, the modelling approach employed by each of the studies is different. The HITAP's study dichotomizes AD into requiring full-time care and not requiring full-time care in order to fit in a Markov model. In contrast, our study conceptualizes AD using the DES, which allows tracking disease progression in multiple dimensions (i.e. cognitive, behavioural and functional status), reflecting more realistic representation in natural history of the disease. With the DES, our study could generate simulated individual patients with unique demographic and disease characteristics by sampling from a real-world dataset, rather than following a cohort with assumed average characteristics. Furthermore, instead of restricting complexity of AD into limited health states,

tracking patients on a continuous basis in the DES also enables outcomes (costs and QoL) to be measured on a finer gradient, capturing higher accuracy of potential treatment benefits. Second, treatment persistence, which exerts considerable influence on treatment outcomes, is totally not considered in the HITAP's study. Our study incorporates real-world treatment persistence into the simulation, which helps adjusting the treatment effects derived from RCTs to be more applicable for the real-life scenario. Third, while the HITAP's study obtains relative risks of death associated with AD from a single study, our study performs a systematic review and meta-analysis to generate the higher generalizable pooled estimate of this key parameter. Fourth, our input parameters for costs and QoL are based on the most recent local evidence, unlike the HITAP's study in which older cost estimates and foreign QoL data are used.

Altogether, it is evident that using the DES to model AD leads to a great improvement in the disease representation and thus strengthens cost-effectiveness findings. Our study illustrates AD as an example of diseases whose natural history is too complicated to be simplified into limited health states, and the DES is proven to be the method capable of conceptualizing such diseases. Performing the DES demands intensive patient-level data, a high-performance computer and simulation software. However, a well-planned data collection and spontaneous advancements in computer technology around the world could be the enablers to overcome these difficulties. Since Thailand, a member of low- and middle-income countries (LMICs), could perform the DES for AD, it would be encouraging for other LMICs to adopt this modelling breakthrough, where appropriate, to improve their HTA on certain disease areas. Insufficient knowledge on the DES should not be a reason to stick on using classical methods, which are simple and transparent, but prone to dismal failures in holding face validity and reliability of the model's results.

Nonetheless, our study also contains limitations. To begin with, treatment effects on behavioural and functional status are not considered in our simulation because their MDs are below the minimum clinically important differences (MCIDs) as specified in Howard et al. (2010) [29]. However, changes in behavioural and functional status are indirectly influenced by treatment effects on cognitive status through the interrelated disease progression equations. In addition, as there has been no longitudinal patient-level data capturing AD progression available in Thailand, it is necessary that our study apply the disease progression equations developed using patient-level data from other countries. An attempt to establish a national registry for tracking AD progression in multiple dimensions overtime should be made in Thailand, as well as other LMICs, to strengthen local disease foundations for future AD research.

Conclusions

This is the first cost-effectiveness study that adopts the DES to investigate the value for money of AD treatment in LMICs. When considering which AD treatment should be publicly funded, donepezil is most encouraged as it is the most cost-effective AD treatment option based on current real-world evidence in Thailand. It is clear that, with the DES, the representativeness of decision-analytic models for AD is greatly improved. Despite its advancements and advantages in disease modelling, the DES is not developed solely for advanced countries, and application of the DES in HTA should be more encouraged in LMICs, especially when representativeness of the disease is compromised with classical modelling methods.

Table 1 Model parameters

Model parameters	Values or equations	Sources
1. Population		
Patient's demographic and disease characteristics	Patient age, gender, AD duration, CCI, use of psychotherapeutic agents, MMSE and NPI scores, as well as caregiver age, gender and relationship with the patient (**eTable 1**)	[10]
2. Transitional equations and related parameters		
Disease progression		
- Annual rate of change in MMSE[a]	5.4663 – 0.4299PM1 – 0.0042PM2 + 0.1415PM3 – 0.0791PrevRate +0.0747Age + δi	[5]
- NPI change from baseline[b]	(5.74 + 0.03Weeks – 0.59NPIbase + 0.012NPIWeeks + 0.24NPIrecent – 1.74White – 3.82Black + 2.34PsyMed + 0.12MMSEbase – 0.22MMSErecent + δi) x 1.44	[5]
- DAD predictive equation[c]	53.1769 + 2.8529MMSEcurrent – 0.2525NPIcurrent – 0.4930Agecurrent	[10]
Treatment effects (compared to placebo)		[19]
- Donepezil	NMA MD: 1.39; 95% CrI: 0.53 to 2.24	
- Galantamine	NMA MD: 0.61; 95% CrI: -1.19 to 2.38	
- Rivastigmine	NMA MD: 2.02; 95% CrI: 0.02 to 4.08	
- Memantine	NMA MD: 0.22; 95% CrI: -1.38 to 1.79	
Treatment persistence	Time to treatment discontinuation (**eTable 2-5**)	[13]
Mortality	Pooled HR for mortality associated with AD of 2.13 (95% CI: 1.80 to 2.47) (**Supplementary appendix 3**) was applied to adjust the age- and gender-specific mortality tables of general Thai population (**eTable 7**)	[21]
3. Resource utilization and economic parameters		

Model parameters	Values or equations	Sources
Hospital visits	Time to hospital visits (**eTable 6**)	[13]
Hospital visit costs per visit (THB) - MMSE ≥20 - MMSE 10-19 - MMSE ≤9	 Healthcare: 4,349.56; SD: 3,315.28 Societal: 4,645.55; SD: 3,360.97 Healthcare: 5,047.94; SD: 10,673.89 Societal: 5,344.28; SD: 10,731.86 Healthcare: 5,303.70; SD: 6,830.39 Societal: 5,599.69; SD: 7,003.28	[10]
Fixed costs per year (THB) - MMSE ≥20 - MMSE 10-19 - MMSE ≤9	 Healthcare: 17,352.53; SD: 34,532.18 Societal: 31,070.52; SD: 52,794.38 Healthcare: 32,426.45; SD: 69,829.91 Societal: 65,288.27; SD: 121,665.18 Healthcare: 34,206.17; SD: 60,193.03 Societal: 85,259.60; SD: 105,882.88	[10]
AD treatment costs per year (THB) - Donepezil 10 mg OD - Galantamine 16 mg BID - Rivastigmine transdermal BID - Memantine 10 mg BID	 11,439.15 84,201.75 89,799.71 11,529.91	[24]
Predictive equation for unpaid caregiving costs per year (THB)[d]	[EXP(8.9430) x EXP(-0.0093Agecurrent) x EXP(0.1311Female) x EXP(0.0541CCI) x EXP(0.2197FemaleCG) x EXP(-0.0127DADcurrent)] x 34.1008	[10]
4. Health utility		
Predictive equation for patient's quality of life[e]	0.4095 + 0.0005Agecurrent + 0.0160Female - 0.0023AgeCGcurrent + 0.0984SpousalCG + 0.1373SelfRating - 0.0023NPIcurrent + 0.0054DADcurrent	[10]

[a] PMs stand for patient's previous MMSE measurements, partitioned over the scale of MMSE; PrevRate represents the patient's last known rate of decline per year; Age denotes patient's age at baseline; δi is a random intercept parameter

[b] Weeks indicates weeks of follow-up in the simulation; NPIbase represents the patient's NPI at baseline; NPIrecent denotes the patient's last NPI; White and Black are dummy variables for race; PsyMed is a dummy variable for patients receiving psychotherapeutic agents at baseline; MMSEbase stands for the patient's MMSE at baseline; MMSErecent represents the patient's most recent MMSE; δi is a random intercept parameter

[c] MMSEcurrent is the patient's current MMSE; NPIcurrent represents the patient's current NPI; Agecurrent stands for the patient's current age

[d] Agecurrent represents the patient's current age; Female is a dummy variable for female patients; CCI stands for the patient's CCI score at baseline; FemaleCG is a dummy variable for female informal caregivers; DADcurrent indicates the patient's current DAD

[e] Agecurrent denotes the patient's current age; Female is a dummy variable for female patients; AgeCGcurrent represents the caregiver's current age; SpousalCG is a dummy variable for spousal caregivers; SelfRating is a dummy variable for quality of life rating done by the patients themselves; NPIcurrent indicates the patient's current NPI; DADcurrent represents the patient's current DAD

Abbreviations: AD, Alzheimer's disease; CCI, Charlson comorbidity index; MMSE, mini-mental state examination; NPI, neuropsychiatric inventory; DAD, disability assessment for dementia; NMA, network meta-analysis; MD: mean difference; 95% CrI, 95% credible interval; HR, hazard ratio; 95% CI, 95% confidence interval; THB, Thai baht; SD, standard deviation; OD, once daily; BID, twice daily; EXP, exponential

Table 2 Key base-case results by four different scenarios

Base-case results per patient	Societal perspective				
	No AD treatment	**Donepezil**	**Galantamine**	**Rivastigmine**	**Memantine**
1. A universal treatment scenario (AD cohort with all disease-severity levels) without consideration of stopping the treatment when MMSE <10					
Total costs (THB) [USD]	952,246 [27,924]	954,406 [27,988]	1,019,533 [29,898]	1,018,175 [29,858]	951,701 [27,908]
Quality of life (QALYs)	2.491	2.506	2.495	2.512	2.485
ICER (THB/QALY) [USD/QALY]	-	Cost-effective (138,524) [4,062]	Extended dominated	Not cost-effective (11,029,657) [323,443]	Less effective
2. A late treatment scenario (moderate and severe AD cohort: MMSE <20) without consideration of stopping the treatment when MMSE <10					
Total costs (THB) [USD]	983,729 [28,848]	988,575 [28,990]	1,050,728 [30,812]	1,050,514 [30,806]	983,566 [28,843]
Quality of life (QALYs)	2.249	2.266	2.252	2.267	2.244
ICER (THB/QALY) [USD/QALY]	-	Not cost-effective (284,388) [8,340]	Extended dominated	Not cost-effective (73,395,541) [2,152,311]	Less effective
3. An early treatment scenario (mild AD cohort: MMSE ≥20) without consideration of stopping the treatment when MMSE <10					
Total costs (THB)	867,590	869,995	934,407	928,734	No indication

Base-case results per patient	Societal perspective				
	No AD treatment	**Donepezil**	**Galantamine**	**Rivastigmine**	**Memantine**
[USD]	[25,442]	[25,512]	[27,401]	[27,235]	
Quality of life (QALYs)	3.297	3.336	3.303	3.327	No indication
ICER (THB/QALY) [USD/QALY]	-	Cost-effective (61,652) [1,808]	Extended dominated	Extended dominated	No indication
4. An early treatment scenario (mild AD cohort: MMSE ≥20) with consideration of stopping the treatment when MMSE <10					
Total costs (THB) [USD]	862,738 [25,300]	867,085 [25,427]	927,145 [27,188]	927,871 [27,210]	No indication
Quality of life (QALYs)	3.282	3.319	3.300	3.327	No indication
ICER (THB/QALY) [USD/QALY]	-	Cost-effective (116,835) [3,426]	Extended dominated	Not cost-effective (7,512,676) [220,308]	No indication

Abbreviations: AD, Alzheimer's disease; MMSE, mini-mental state examination; THB, Thai baht; QALYs, quality-adjusted life years; USD, United States dollar, ICER, incremental cost-effectiveness ratio

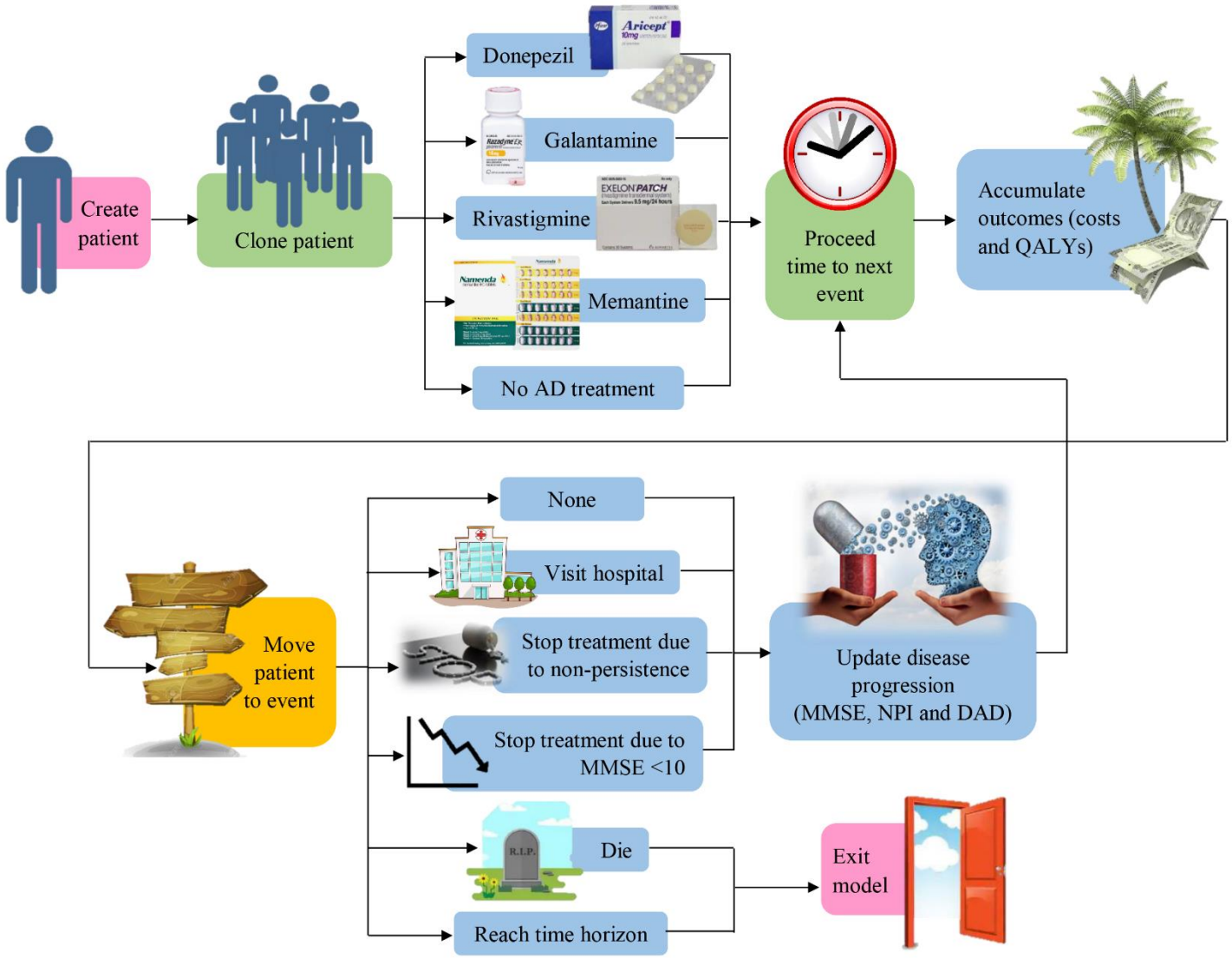
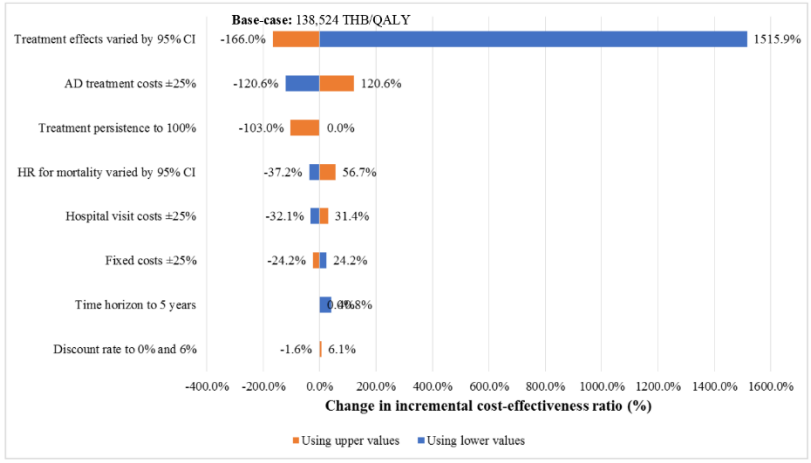
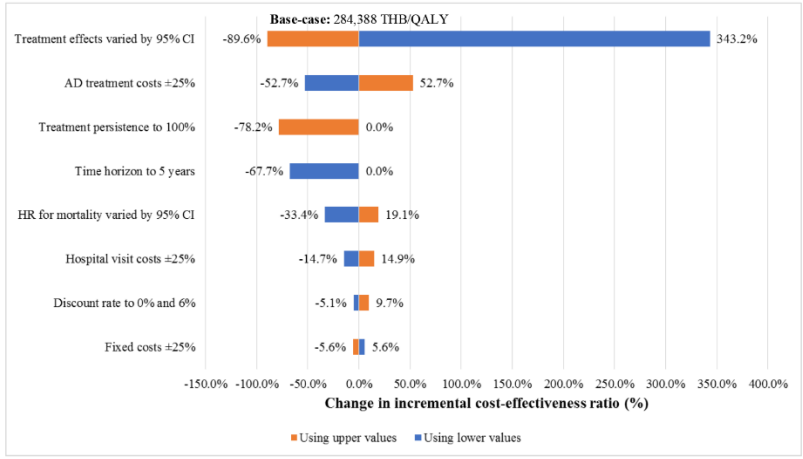


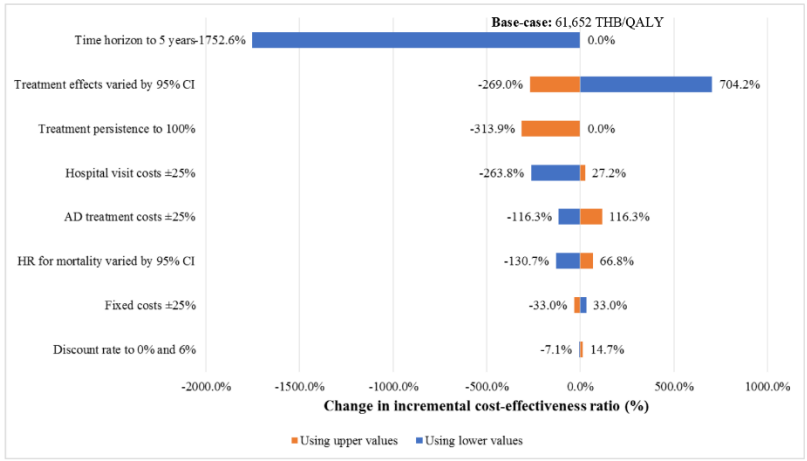
Figure 1 Model diagram



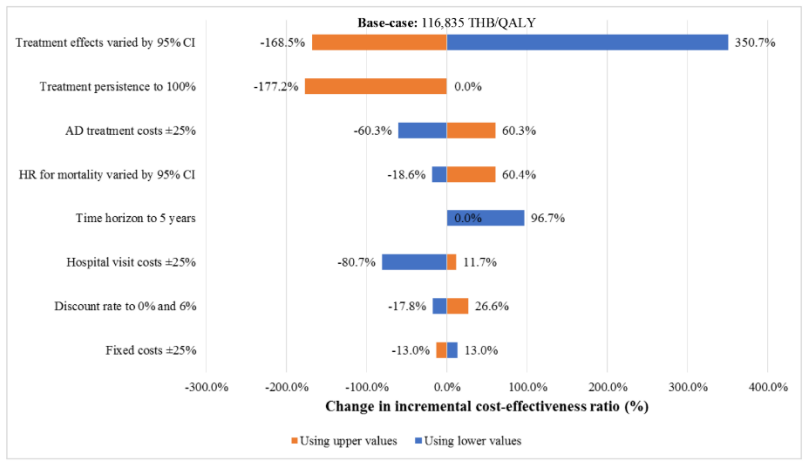
A. A universal treatment scenario without the stopping rule when MMSE <10



B. A late treatment scenario without the stopping rule when MMSE <10



C. An early treatment scenario without the stopping rule when MMSE <10



D. An early treatment scenario with the stopping rule when MMSE <10

Figure 2 Tornado diagrams illustrating sensitivity analyses for donepezil under a societal perspective

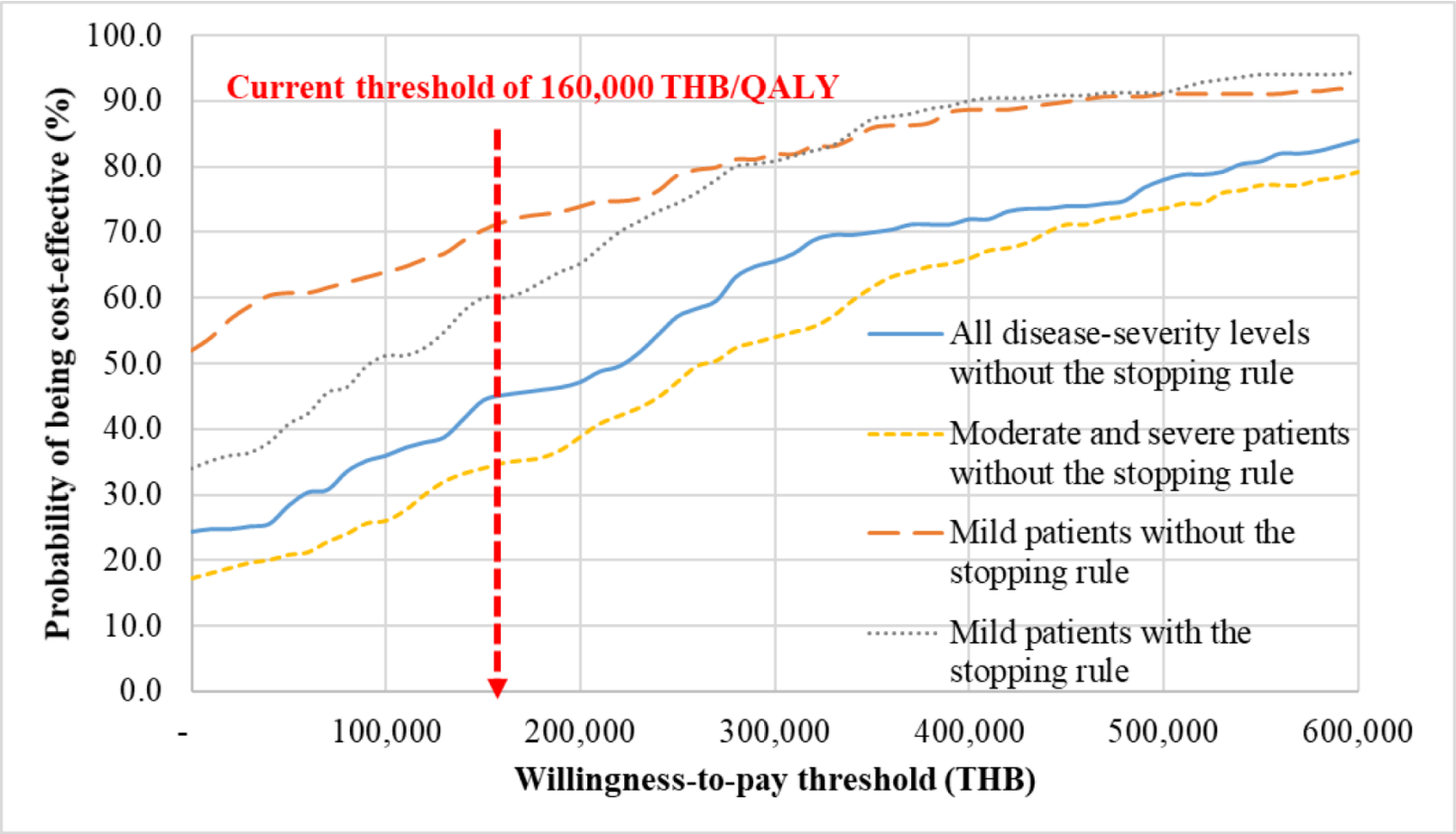


Figure 3 Cost-effectiveness acceptability curve (CEAC) for donepezil under a societal perspective

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CHAPTER 5

General Discussions and Future Directions

General discussions

Overall, this thesis presents three studies, which are inter-related and help supporting each other to address the principal research question "concerning limited healthcare resources, should AD medications be publicly financed for AD population in Thailand?". The following paragraphs are to revisit the key findings from those three studies by replying to each of research sub-questions, before we embark upon the answer to the principal research question.

Research sub-question 1: How large is the issue of AD in Thailand in terms of economic and humanistic burdens?

Based on the estimations from **Chapter 2**, the average annual total societal costs of AD care were USD8,014 (95% CI: USD7,295-USD8,844) per patient in 2017. The total costs of AD care, which were equivalent to 121.5% of the country's gross domestic product (GDP) per capita (USD6,595) in the same fiscal year [1], are considered enormous. Direct medical costs (47.9%), specifically the costs incurred by AD prescriptions, were the distinct major cost driver of AD care in Thailand. Informal care costs (39.0%) were the second most expensive cost category, reflecting that foregone opportunity costs due to time loss among informal caregivers are also importantly high. Besides, humanistic burdens of AD patients were substantially impacted when the disease progressed from mild (HR-QoL = 0.87) to severe (HR-QoL = 0.40) stage. Improvements in cognitive and functional status were associated with decreases in overall economic and humanistic burdens of AD in Thailand.

Research sub-question 2: What is the current situation of AD prescriptions and their usage in Thailand?

As presented in **Chapter 3**, donepezil was most prescribed (48.6%) to newly diagnosed AD patients. Overall, Thai AD patients had high-compliant (70.3% were found to be compliant to AD treatment over one year) but low-persistent (21.1% were found to be persistent with AD treatment over one year) behaviour. They may possess enough medications to consume with respect to the prescribed regimen, but they intermittently take the medications with an early treatment gap that goes beyond the tolerable level. These findings indicate that AD treatment users in Thailand may have not achieved the optimal therapeutic benefits. Remarkably, the patients who refilled AD prescriptions from university-affiliated hospitals, which are situated in a few major cities across the country thereby causing difficulties in transportation, were more likely to be both non-compliance (OR: 1.71; 95% CI: 1.21 to 2.42) and non-persistence (HR: 1.33; 95% CI: 1.12 to 1.58). Not to mention, the majority of patients in Thailand (92%) were lacking of the financial support on AD medications, and thus experienced not only the difficulty in access to the treatment (only 25.9% of all AD prescriptions were prescribed to this large group of patients) but also a higher chance of early treatment discontinuation (HR: 1.34; 95% CI: 1.11 to 1.62).

Research sub-question 3: Which of AD medications provides the best value for money when prescribed to AD patients in the real-world practice in Thailand?

According to the findings from **Chapter 4**, if AD medications were to provide to all prevalent patients with any disease-severity levels, donepezil (discounted gain in QALY: 0.015; ICER:

4,062 USD/QALY; being cost-effective in 45.2% of replications) would be the most cost-effective treatment option based on the real-world practice in Thailand. Furthermore, providing early treatment to a subgroup of mild AD patients further enhanced the value for money of donepezil (discounted gain in QALY: 0.039; ICER: 1,808 USD/QALY; being cost-effective in 71.6% of replications). Conversely, the cost effectiveness of donepezil would be waned (discounted gain in QALY: 0.016; ICER: 8,340 USD/QALY; being cost-effective in 34.8% of replications), if delayed treatment was given to a subgroup of moderate and severe AD patients. The value for money of donepezil was predominantly influenced by treatment effects, treatment persistence, AD treatment costs, HR for mortality associated with AD and time horizon.

The principal research question: Concerning limited healthcare resources, should AD medications be publicly financed for AD population in Thailand?

In Thailand, the principle of multi-criteria decision analysis (MCDA) has been used to guide the coverage decisions on adopting health interventions in the UCS [2]. The MCDA refers to "a collection of approaches that support decision making by taking explicit account of multiple criteria" [3]. In a nutshell, the priority setting for health interventions in Thailand involves with multiple stakeholders and multiple deliberative processes. First, health interventions for assessment are nominated, and then being prioritised based on six criteria: (1) size of population affected by disease, (2) severity of disease, (3) effectiveness of health intervention, (4) variation in practice, (5) economic impact of household expenditure and (6) equity/ethical and social implication (**Figure 1**). Each criterion rewards the maximum score of five, and healthcare interventions are ranked and selected according to their total scores. Next, the selected

interventions are undergone the process of HTA, which generally evaluates value for money and budget impact of the interventions, before being apprised for final decision [2].

In reality, after healthcare interventions are nominated from multiple stakeholders, in most cases, country-specific evidence is not readily available to use for the selection process, and relevant existing information from other countries are necessarily considered instead. In similar fashion, country-specific cost-effectiveness and budget impact findings are also not available unless the interventions are selected for further assessment. However, this thesis, in which research questions are formulated solely from my personal research motivation that strives to make contributions towards the improvements in the quality of life of AD patients and caregivers, makes almost all key information available for the priority-setting processes.

To illustrate, if AD medications are nominated as health interventions for assessment, in the selection process, 'severity of disease' and 'effectiveness of health intervention' criteria could be answered by the information from **Chapter 4**. As providing AD medications to the patients with all disease-severity levels could save 0.01 QALY in average, both of the criteria could be scored 2/5 and 1/5, respectively. For 'variation in practice' criterion, due to the fact that unequal accessibility to AD medications is evidently seen in **Chapter 3**, the full score should be awarded. Turning to consider 'economic impact on household expenditure' criterion, since **Chapter 2** has found that the annual total costs of AD care are as high as USD8,014 (THB273,284) per patient, the full score is also deserved for this criterion. Together with existing evidence from other sources (**Table 1 and Table 2**), the scores of 'size of population affected by disease' (score = 5/5) and 'equity/ethical and social implication' (score = 1/5) criteria could also be marked. Thus, the total score of 19/30 could be obtained, which is most likely that AD medications will be selected for further evaluation based on the history of selection in 2010 (**Figure 2**).

After being selected, value for money and budget impact of AD medications will need to be evaluated prior to the final appraisal. According to **Chapter 4**, donepezil is the most cost-effective option [ICER: 4,062 USD/QALY (138,517 THB/QALY) when prescribed to the patients with all disease-severity levels] compared to other AD medications and no AD treatment provided. Hence, the value for money of donepezil is favourable. After that, in order to generate up-to-date evidence for the budget impact of donepezil, necessary information is drawn from **Chapter 4** and other sources (**Table 1 and Table 2**). To reflect the current practice of AD care in Thailand, all prevalent patients, regardless of their disease-severity levels, are considered in the budget impact analysis (BIA). In addition, incident patients are also incorporated into the BIA for each following year. It is found that healthcare payers will have to spend an incremental budget of approximately 15,000 million THB (440 million USD) if they make a decision to financially support donepezil for all AD patients over 10 years (**Table 3**). Accordingly, with its good value for money but high budget impact, donepezil may not be recommended for inclusion in the national benefit package based on the history of appraisal in 2010 (**Figure 3**).

Nevertheless, as treatment persistence and AD treatment costs are among the most influential factors for the cost-effectiveness results of donepezil (**Chapter 4**), improvements on these modifiable factors potentially enhance the value for money and the budget impact of donepezil. Low treatment persistence may be ameliorated by implementing the WHO's mhGAP (**Chapter 3**), while expensive AD treatment costs may be curtailed by using cost-effectiveness findings to strongly negotiate with pharmaceutical companies (**Chapter 2**). Since the decision making on healthcare interventions is a dynamic process, the speculated final decision towards AD medications may be positively changed provided that the aforementioned factors have been

improved. In turn, there is still the hope for AD patients and their caregivers to equally gain access to necessary but costly AD medications through the national health coverage in the future.

Future directions

According to the 2015 conference on global action against dementia in Switzerland, the global aspiration for inventing a curative or a disease-modifying therapy (DMT) for AD has been committed to be achieved by 2025 [4]. Even if this global aspiration is fulfilled on time, AD patients in Thailand as well as those in LMICs are susceptible to have their access to the DMT delayed. This is because health-policy decision makers in this region are unable to make a prompt decision to adopt and make such new therapy nationally available, again, due to the lack of decision-supporting evidence. Thus, the initiation to prepare the decision-supporting evidence for the DMT is warranted.

The DMT is expected to alter the course of AD through a direct effect on the underlying pathophysiology, thereby it potentially offers long-term effectiveness and prolongs the patient's life expectancy [5]. The decision-analytical framework for evaluating the cost effectiveness of the DMT should be able to handle the long-term effectiveness and the positive impact on survival, which introduce additional uncertainties to the model beyond classical AD medications. Since it has been suggested that the DES modelling approach as applied in **Chapter 5** is sufficiently flexible and adaptable to incorporate new parameters and account for uncertainties relating to the DMT [5], this thesis could serve as both a foundation and an initiative for LMICs to prepare for the upcoming major breakthrough in the treatment of AD.

Table 1 Parameters required for constructing the budget impact analysis and their sources

Parameters	Sources
1. Number of elderly people aged ≥60 in Thailand, stratified by age	[6]
2. Prevalence of dementia in Thai elderly population by age group	[7]
3. Estimated proportion of AD cases among all dementia cases	[8]
4. Meta-analysed estimates of dementia incidence	[9]

Abbreviation: AD, Alzheimer's disease

Table 2 Estimated number of Thai AD patients by age groups for the budget impact analysis

Age group	Elder population in 2018	Estimated prevalent AD patients	Estimated incident AD patients
60-64	3,390,015	101,700	10,382
65-69	2,678,454	80,354	11,718
70-74	1,779,855	85,656	11,458
75-79	1,242,527	59,797	11,959
80+	1,575,952	222,603	31,154
Total	**10,666,803**	**550,110**	**76,671**

Abbreviation: AD, Alzheimer's disease

Table 3 Budget impact analysis for donepezil when provided to AD patients with all disease-severity levels over 10 years

Year	No AD treatment (million THB)			Donepezil (million THB)			Final total budget impact (million THB)
	Prevalent cases	Incident cases	Total	Prevalent cases	Incident cases	Total	
1	26,331	-	26,331	29,686	-	29,686	3,355
2	24,530	30,383	54,913	25,378	31,434	56,812	1,899
3	25,053	26,773	51,825	25,636	27,760	53,396	1,570
4	24,930	23,199	48,129	26,186	24,155	50,341	2,212
5	25,906	19,663	45,569	26,285	20,514	46,799	1,230
6	25,664	16,134	41,798	26,042	16,935	42,976	1,178
7	25,856	12,569	38,426	26,085	13,332	39,417	992
8	25,270	9,092	34,363	26,108	9,815	35,923	1,560
9	25,904	5,784	31,688	25,645	6,453	32,098	410
10	19,031	2,774	21,805	19,177	3,349	22,526	720
Total	**248,475**	**146,371**	**394,846**	**256,226**	**153,747**	**409,973**	**15,127**

Abbreviations: AD, Alzheimer's disease; THB, Thai baht

Criteria	Definition	Parameter	Scoring
1. Size of population affected by disease	Number of people affected by the disease or health problem that is treated or prevented by the proposed intervention among Thai population at a specified time	Prevalence	5 = >500,000 4 = 100,001–500,000 3 = 50,001–100,000 2 = 10,001–50,000 1 = ≤10,000
2. Severity of disease	Severity of disease or health problem that is treated or prevented by the proposed intervention by considering its impact on the patients' QOL	QOL score	5 = >0.60 4 = 0.41–0.60 3 = 0.21–0.40 2 = 0.01–0.20 1 = ≤0
3. Effectiveness of health intervention	The final outcomes of the proposed intervention that benefit the patients with regard to the objective of the intervention		
	3.1 For treatment/rehabilitation: Capacity of the proposed intervention to treat or rehabilitate the patients from the disease and its impact on the patients' QOL	The clinical benefit of the proposed intervention and improvement in QOL	5 = cure 4 = prolong life and major improvement in QOL 3 = prolong life and minor improvement in QOL 2 = major improvement in QOL 1 = minor improvement in QOL
	3.2 For screening/diagnostic: Quality of the proposed intervention to screen or diagnose the disease of the patients and the expected outcome beyond the screening or diagnostic	Accuracy of the intervention and whether the screened disease could be cured	5 = accuracy >80% and screened disease could be cured 4 = accuracy 60%–80% and screened disease could be cured 3 = accuracy >80% but screened disease could *not* be cured 2 = accuracy 60%–80% and screened disease could *not* be cured or accuracy <60% and screened disease could be cured 1 = accuracy <60% and screened disease could be cured
	3.3 For prevention: Risk reduction or preventive capacity provided by the proposed intervention to the population	Effectiveness of the intervention to prevent the disease	5 = >90% 4 = 81%–90% 3 = 71%–80% 2 = 61%–70% 1 = ≤60%
4. Variation in practice	Variation of implementing the intervention in practice that leads to unequal accessibility to the intervention among Thais. Variation in practice could be identified from the different coverage of the three publicly funded health insurance schemes in Thailand and/or could be identified from the different distribution of the intervention throughout the country	The difference of the benefit packages between the three health insurance schemes in Thailand The difference of health interventions distribution	5 = national evidence presenting variation in practice in Thailand 4 = national evidence presenting variation in practice in some areas 3 = international evidence presenting variation in practice in other countries that could assume there is variation in practice in Thailand 2 = no evidence but we could assume there is variation in practice in Thailand 1 = no variation in practice
5. Economic impact on household expenditure	Impact on household expenditure as a consequence of providing health intervention to a family member with consideration of catastrophic illness or health catastrophe	Direct medical and nonmedical household expenditure as a consequence of the disease or health problem per year	5 = >62,500 baht/y 4 = 35,601–62,500 baht/y 3 = 20,801–35,600 baht/y 2 = 12,000–20,800 baht/y 1 = <12,000 baht/y
6. Equity/ethical and social implication	Priorities for specific groups of patients, i.e., the poor with rare disease, reflect the moral values that should be considered by policymakers	Disease of the poor Prevalence <1,000 (rare disease)	5 = targeting the poor and prevalence <1,000 4 = targeting the poor and prevalence 1,000–10,000 3 = targeting the poor and prevalence >10,000 2 = *not* targeting the poor and prevalence <1,000 or *not* targeting the poor and prevalence 1,000–10,000 1 = not targeting the poor and prevalence >10,000

QOL, quality of life.

Figure 1 Selection criteria for heath interventions [2]

Health interventions	Selection criteria						
	Size of population affected by disease	Severity of disease*	Effectiveness of health intervention	Variation in practice	Economic impact on household expenditure	Equity/ethical and social implication	Total
1. Anti-immunoglobulin E for severe asthma	4	—	3	5	5	1	18
2. Treatment for people with chronic hepatitis B	5	—	4	2	3	3	17
3. System for screening, treatment, and rehabilitation of alcoholism	5	—	5	4	1	1	16
4. Implant dentures for people who have problem with conventional complete dentures	5	—	2	2	5	1	15
5. Screening for risk factors for leukemia in people living in the industrial areas	4	—	3	5	1	2	15
6. Treatment for severe lupus nephritis	2	—	4	2	5	1	14
7. Smoking cessation program	5	—	3	2	1	3	14
8. Treatment for people with chronic hepatitis C	3	—	5	2	3	1	14
9. Absorbent products for urinary and fecal incontinence among disabled and elderly people	4	—	2	2	4	1	13
10. Treatment for unfertilized women	5	—	0	2	5	1	13
11. Renal replacement by dialysis for new final stage renal failure patients	2	—	1	5	4	1	13
12. Screening and treatment for liver cancer	2	—	3	2	5	1	13
13. Physical examination package (following the Civil Servant Medical Benefit Scheme)	5	—	0	5	1	1	12
14. *Cissus quadrangularis* L. for hemorrhoid	5	—	1	4	1	1	12
15. Biological agents for psoriasis	1	—	1	2	5	2	11
16. Screening for gall bladder cancer	2	—	2	2	1	3	10
17. Orbital implant and plastic surgery of orbit and facial bones	1	—	2	1	1	2	7

* Severity of disease was omitted from the criteria list in the first year of the project (2010).

Figure 2 Scores of the proposed health interventions against the selection criteria in 2010 [2]

Health interventions	Results		Policy recommendations
	Cost-utility analysis*	Budget impact analysis*	
1. Treatment for people with chronic hepatitis B	Lamivudine (produced by GPO) is the most cost-effective (cost-saving) compared with palliative care and with the other alternatives: - Lamivudine (original), - Adefovir + lamivudine (GPO), - Entecavir, - Telbivudine, and - Pegylated interferon alpha	The budget of providing lamivudine (GPO) is THB 50 million higher than that of providing palliative care in a first year of implementation and will increase to THB 500 million at the fifth year	The most cost-effective intervention for treating chronic hepatitis type B, lamivudine, has already been covered under the benefit package
2. Treatment for people with chronic hepatitis C	Pegylated interferon alpha 2a (Peg2a) + ribavirin for treating hepatitis type C subtype 1, 4, 5, and 6 is the most cost-effective (ICER = THB 86,600 per QALY) compared with palliative care and with other alternatives: - Interferon alpha + ribavirin, Peg2a + ribavirin, pegylated interferon alpha 2b (Peg2b) 1 μg/1 kg of body weight + ribavirin, Peg2b 1.5 μg/1 kg of body weight + ribavirin	Providing Peg2a for treating hepatitis type C subtype 1, 4, 5, and 6 is increasing budget by THB 3,500 million. Providing Peg2b for treating hepatitis type C subtype 3 is increasing budget by THB 8,600 million. Therefore, it would be in total THB 12,000 million in 5 years	Not recommended because of high budget impact
3. Treatment for severe lupus nephritis	Intravenous cyclophosphamide (IVC) + azathioprine (AZA) for 3 y is the most cost-effective (cost-saving) compared with the standard treatment for treating lupus nephritis (IVC with decreasing dose for 3 y) and with the other alternatives (i.e., IVC + mycophenolate mofetil [MMF] for 3 y, MMF + AZA for 3 y, MMF with decreasing dose for 3 y)	Budget of treatment is approximately THB 1.4–1.5 million per patient	The most cost-effective intervention for treating lupus nephritis (i.e., IVC 1,000 mg/mo for 6 mo and then AZA 50 mg/d for further 2.5 y) has already been covered under the benefit package
4. Smoking cessation program	Every intervention for smoking cessation is cost-effective (cost-saving) (i.e., counseling at the hospital, counseling by quit line, counseling + nicotine gum, counseling + nicotine patch, counseling + bupropion, counseling + nortriptyline, and counseling + varenicline) compared with no intervention (suddenly quit smoking by themselves; smokers)	In case of providing nortriptyline (as a first-line drug) 80% + nicotine gum 10% + varenicline (as a second-line drug) 10%, the budget would be THB 273 million in a first year and would increase to THB 566 million at the fifth year	All interventions for smoking cessation are cost-effective. Therefore, the program is recommended for further consideration to be adopted in the benefit package
5. Anti-IgE for severe asthma	Omalizumab (anti-IgE) is not cost-effective (ICER = THB 414,503 per QALY) compared with standard clinical practice guideline (steroid) for severe asthma	Providing omalizumab to treat patients with severe asthma increases the budget by THB 54,000 million per year and will increase the budget by THB 270,000 million in 5 y	Not recommended because it is not a cost-effective intervention and the budget estimation per year is very high
6. Implant dentures for people who have problem with conventional complete dentures	Implant dentures is cost-effective (ICER = THB 5,147 per QALY)	The 5-y budget will be THB 280–781 million on the basis of expected target population and will be THB 83–208 million on the basis of human resource (health professionals) capacity	Not recommended because problems of access to standard treatment of dental care were still unsolved
7. Absorbent products for urinary and fecal incontinence among disabled and elderly people	Absorbent product is cost-effective (ICER = THB 54,000 per QALY)	Budget of providing absorbent products to the disabled and elderly is approximately THB 4,800 million per year	Not recommended because of high budget impact
8. System for screening, treatment, and rehabilitation of alcoholism	N/A	N/A	Not recommended because of inadequate information (in 2010)
9. Screening for risk factors for leukemia in people living in the industrial areas	N/A	N/A (the researchers estimated social costs of illness instead: from the model of 50,000 populations who are living in the industrial areas with migration of 1,000 people per year, social costs of illness would be THB 3,500 million in 30 y)	Recommended for further consideration to be adopted in the benefit package because the problem causes considerable loss in terms of cost of illness at THB 3,500 million in 30 y

GPO, the government pharmaceutical organization; IgE, immunoglobulin E; ICER, incremental cost-effectiveness ratio; N/A, not available; QALY, quality-adjusted life-year; SLE, systemic lupus erythematosus; THB, Thai baht.
* In 2010, US $1 was approximately 30.17 baht [26].

Figure 3 Health intervention assessment results and policy recommendations in 2010 [2]

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SUPPLEMENTARY

APPENDIX

Supplementary appendix for Chapter 2

Appendix 1 Supplementary tables

eTable 1 Unit costs used for micro-costing estimations

Resources	Unit cost (2017 THB)	Reference
Transportation, per ride	148.09[a] (USD4.34)[d]	Riewpaiboon A. Standard cost lists for health technology assessment. Nonthaburi: Health Intervention and Technology Assessment Program (HITAP); 2011.
Average national wage rate, per hour (used to value caregiving time in the base-case analysis, time cost approach)	65.39[b] (USD1.92)[d]	Statistical Forecasting Bureau, National Statistical Office. Employee and average wage by sex, whole kingdom: 2007-2016. The Labor Force Survey, National Statistical Office, Ministry of Information and Communication Technology. [cited 2018 June 21]; Available from: http://service.nso.go.th/nso/web/statseries/statseries05.html
Average wage rate, per hour, for human health and social work activities (used to value caregiving time spent on basic activities daily living (BADL) in the sensitivity analysis, replacement cost approach)	46.35[c] (USD1.36)[d]	Ministry of Labour. The report of survey on labour's essential expenditures for efficiency improvement in the industrial sector. Bangkok: Ministry of Labour; 2014.

Resources	Unit cost (2017 THB)	Reference
Average wage rate, per hour, for activities of households as employers; undifferentiated goods- and services-producing activities of households for own use (used to value caregiving time spent on instrumental activities daily living (IADL) in the sensitivity analysis, replacement cost approach)	45.56[c] (USD1.34)[d]	Ministry of Labour. The report of survey on labour's essential expenditures for efficiency improvement in the industrial sector. Bangkok: Ministry of Labour; 2014.

[a] Inflated from 2009 to 2017 year price levels using public transportation services consumer price index

[b] Inflated from 2015 to 2017 year price levels using medical-care consumer price index

[b] Inflated from 2014 to 2017 year price levels using medical-care consumer price index

[d] Average market exchange rate in 2017: USD1 = THB34.1008

Remarks: All direct medical costs were taken from the hospital's database, while other direct non-medical costs (e.g. paid domestic helps and nursing-home placement) were obtained directly from caregiver's responses in the RUD instrument.

Abbreviations: THB, Thai baht; USD, United States dollar; BADL, basic activities daily living; IADL, instrumental activities daily living; RUD, resource utilization in dementia

eTable 2 Evaluations of the impact of disease-severity measures (cognitive, behavioral and functional status) and other variables on patient's and caregiver's HR-QoL

Variables	Health-related quality of life	
	Patient[a] β (SE)	Caregiver[b] β (SE)
Cognitive status (MMSE score)	-	-
Behavioral status (NPI score)	-0.002 (0.001)**	-
Functional status (DAD score)	0.005 (0.001)***	-
Patient's age	0.001 (0.002)	-
Female patient (vs. male)	0.016 (0.030)	-
Charlson Comorbidity Index (CCI)	-	-0.009 (0.005)*
Caregiver's age	-0.002 (0.001)*	-0.000 (0.001)
Female caregiver (vs. male)	-	-0.032 (0.022)
Spousal caregiver (vs. non-spousal caregiver)	0.098 (0.048)**	-
Self-rating (vs. informant rating)	0.137 (0.035)***	-
Constant	0.409 (0.148)	0.767 (0.045)
Bootstrap-corrected calibration coefficient	0.871	0.179

[a] Estimates were derived from the multivariable generalized linear model with Gaussian distribution and identity link after the modified Park's test.

[b] Estimates were derived from the multivariable generalized linear model with inverse Gaussian distribution and identity link after the modified Park's test.

***, **, * denotes significance at 1%, 5% and 10% levels, respectively.

Remarks: The modified Park's test basis: (1) if the variance function was constant, the test would suggest the Gaussian family; (2) if the variance is proportional to the mean, the test would suggest the poison family; (3) if the variance is proportional to the square of the mean, the test would suggest the Gamma family; and (4) if the variance is proportional to the cube of the mean, the test would suggest the inverse Gaussian or Wald family.

Abbreviations: AD, Alzheimer's disease; USD, United States dollar; β, beta-coefficient; SE, standard error; MMSE, mini-mental state examination; NPI, neuropsychiatric inventory; DAD, disability assessment for dementia; CCI, Charlson comorbidity index

eTable 3 Disaggregated annual costs of AD care per patient by different levels of cognitive status, among patients living in nursing homes

Cost categories [mean (95% CI)] (2017 USD)	Mild (n = 0)	Moderate (n = 2)	Severe (n = 2)	p-value[a]	All patients (n = 4)
Direct medical costs					
- Outpatient visit	-	335.49	262.24	0.848	298.86
	(-)	(59.26-661.72)	(34.34-490.13)		(46.80-550.93)
- Inpatient visit	-	-	-	-	-
	(-)	(-)	(-)		(-)
- Emergency visit	-	25.68	-	-	12.84
	(-)	(0-51.36)	(-)		(0-51.36)
- Medication	-	1,483.26	2,246.64	0.487	1,864.95
	(-)	(784.35-2,182.18)	(1,535.54-2,957.75)		(1,133.81-2,602.19)
- Out-of-pocket	-	651.01	5,278.47	0.539	2,964.74
	(-)	(246.33-1,055.69)	(0-10,556.94)		(184.75-8,181.63)
- Total	**-**	**2,495.45**	**7,787.34**	**0.547**	**5,141.40**
	(-)	**(1,899.31-3,091.59)**	**(1,569.88-14,004.81)**		**(2,032.67-14,004.81)**

Cost categories [mean (95% CI)] (2017 USD)	Mild (n = 0)	Moderate (n = 2)	Severe (n = 2)	p-value[a]	All patients (n = 4)
Direct non-medical costs					
- Transportation	-	106.67	71.29	0.658	88.98
	(-)	(43.76-169.58)	(52.26-90.33)		(55.40-149.77)
- Nursing-home placement	-	4,626.57	7,037.96	0.418	5,982.26
	(-)	(4,574.67-5,278.47)	(5,278.47-8,797.45)		(4,750.62-7,917.70)
- Total	**-**	**5,033.24**	**7,109.25**	**0.412**	**6,071.25**
	(-)	**(4,618.43-5,448.05)**	**(5,368.80-8,849.70)**		**(4,993.61-7,999.29)**
Indirect costs (informal care)	**-**	**115.80**	**2,038.06**	**0.519**	**1,076.93**
	(-)	**(92.63-138.96)**	**(0-4,076.12)**		**(57.90-4,076.12)**
Total costs	**-**	**7,644.49**	**16,934.66**	**0.370**	**12,289.57**
	(-)	**(6,610.38-8,678.60)**	**(10,419.58-23,449.73)**		**(8,161.54-23,449.73)**

[a] p-value for comparison of differences in means between moderate and severe groups (Welch's unequal variances t-tests)

Remarks: 95% CI based on bias-corrected and accelerated bootstrapping

Abbreviations: n, number of patients; USD, United States dollar; 95% CI, 95% confidence interval

Appendix 2 The hospital-specific cost-to-charge ratio in 2017

We contacted Faculty of Medicine, Ramathibodi Hospital to request for the hospital-specific cost-to-charge ratio in 2017, which is necessary for estimating costs in our study. Personal communication with the hospital is provided below:

คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล
๒๗๐ ถนนพระราม ๖ แขวงทุ่งพญาไท เขตราชเทวี กทม. ๑๐๔๐๐
โทร. (๐๒) ๒๐๑-๑๐๐๐

Faculty of Medicine Ramathibodi Hospital, Mahidol University.
270 Rama VI Road, Ratchathewi, Bangkok 10400, Thailand
Tel. (662) 201-1000

February 13th, 2019

To Whom It May Concern,

Re: The specific cost-to-charge ratio of Ramathibodi Hospital in 2017

We have received an inquiry from researchers regarding the specific cost-to-charge ratio (CCR) of Ramathibodi Hospital in 2017. In order to support the research conducted in our institute, we would like to provide necessary information as follows:

According to Ramathibodi Hospital's Profit and Loss Statement in August 2017, the Net Profit Margin, which is the percentage of profit that the hospital produces from its total revenue, was 5.62%. The Net Profit Margin can be used to derive the hospital specific CCR, which should be equal to 1 - (5.62%) or 0.9438.

Yours faithfully,

Oraluck

Dr.Oraluck Pattanaprateep

Business Intelligence Development Team, Faculty of Medicine, Ramathibodi Hospital

Appendix 3 Sample size determination

This study aimed to investigate associations between costs, health related-quality of life (HR-QoL) and multiple disease-severity indicators. We, therefore, calculated sample size in order to yield sufficient power (power = 0.80; alpha = 0.05) for multiple correlation analyses. It has been suggested that the minimum number of subjects of 50+8m, where m refers to number of predictors, is required [1]. Predictors that potentially have a relationship with costs and HR-QoL include (1) cognitive status score, (2) behavioural status score, (3) functional status score, (4) age of AD patients, (5) gender of AD patients, (6) whether AD patients use psychotherapeutic agents, (7) age of caregivers, (8) gender of caregivers, and (9) whether patient-caregiver relationship is spousal [2-5]. Thus, the number of subjects should be no less than 122. Together with the consideration of receiving incomplete data from 20% of participants, we expected to enrol at least 153 patient-caregiver dyads.

References

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2. Turongkaravee S, Chaikledkaew U, Chansirikarnjana S. The cost of home-base care for Thai elderly with dementia in a Thai University hospital. Bangkok: Mahidol University; 2008.
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Appendix for Chapter 4

Appendix 1 Supplementary tables

eTable 1 A dataset of Thai patients with AD

No.	Age	Gender[a]	Use of PSY[b]	AD duration	CCI	MMSE	NPI	Age_CG	Gender_CG	Spousal[d]
1	83.57	2	1	4.0	3.0	14	4	62.00	2	0
2	71.97	2	1	8.5	1.0	9	33	42.50	2	0
3	77.69	1	0	5.0	6.0	21	3	79.00	2	1
4	85.00	2	0	3.3	2.0	13	12	61.00	1	0
5	78.50	1	0	3.0	2.0	21	0	72.00	2	1
6	91.65	2	1	10.0	4.0	0	2	55.00	1	0
7	91.26	2	0	6.0	0.0	7	19	59.00	2	0
8	77.61	1	0	3.4	1.0	18	20	29.00	2	0
9	88.14	1	0	15.0	2.0	17	2	58.00	2	0
10	89.17	2	0	9.0	2.0	4	28	62.00	2	0
11	66.98	2	1	13.0	1.0	0	22	68.00	1	1
12	81.89	2	1	1.0	2.0	9	40	20.00	2	0
13	78.95	2	0	3.5	4.0	19	4	54.00	1	0
14	78.89	1	0	12.0	3.0	0	20	40.00	2	0
15	81.00	1	0	8.0	2.0	10	7	75.00	2	1
16	83.90	2	1	2.0	2.0	18	9	58.00	2	0
17	82.87	2	0	2.0	3.0	23	4	60.00	2	0
18	89.73	2	1	4.2	3.0	17	1	57.00	2	0
19	79.95	2	0	8.0	1.0	16	21	53.00	1	0

No.	Age	Gender[a]	Use of PSY[b]	AD duration	CCI	MMSE	NPI	Age_CG	Gender_CG	Spousal[d]
20	70.55	2	1	2.0	1.0	2	38	70.00	1	1
21	90.44	2	1	5.5	3.0	7	25	66.00	2	0
22	88.02	2	0	10.0	1.0	10	32	50.00	2	0
23	93.26	2	1	2.6	1.0	23	17	54.00	2	0
24	88.88	2	0	2.0	1.0	0	10	63.00	1	0
25	79.61	2	1	2.0	1.0	19	21	46.00	2	0
26	80.93	2	0	1.0	2.0	21	0	62.00	1	0
27	67.60	2	1	2.0	1.0	19	2	67.00	1	1
28	83.19	1	0	10.0	5.0	26	0	63.00	2	0
29	76.98	2	1	2.0	4.0	9	7	49.00	2	0
30	83.64	1	1	7.0	5.0	4	1	53.00	2	0
31	63.93	2	1	4.0	2.0	6	23	69.00	1	1
32	85.42	1	1	6.2	7.0	16	25	68.00	1	0
33	84.10	2	1	5.2	1.0	8	18	46.00	2	0
34	88.89	1	0	5.5	5.0	15	11	55.00	2	0
35	68.56	2	1	7.5	1.0	0	50	78.00	1	1
36	83.33	1	0	1.0	3.0	25	3	40.00	2	0
37	86.69	1	0	3.0	1.0	15	8	63.00	2	0
38	92.75	2	1	2.0	3.0	4	9	70.00	2	0
39	90.36	2	1	3.5	1.0	13	10	64.00	2	0
40	78.09	2	0	0.5	2.0	17	14	51.00	2	0
41	78.37	2	1	5.0	1.0	24	0	35.00	2	0
42	79.96	2	1	3.0	1.0	14	19	45.00	2	0

No.	Age	Gender[a]	Use of PSY[b]	AD duration	CCI	MMSE	NPI	Age_CG	Gender_CG	Spousal[d]
43	88.86	1	1	2.0	2.0	13	16	74.00	2	1
44	74.63	1	1	2.0	1.0	23	4	68.00	2	1
45	90.74	2	0	3.0	1.0	15	11	44.00	2	0
46	84.20	2	1	5.0	1.0	18	16	60.00	2	0
47	92.57	2	0	10.0	2.0	10	30	57.00	2	0
48	79.12	2	0	3.0	1.0	17	5	48.00	2	0
49	80.37	2	1	7.0	1.0	8	74	52.00	2	0
50	89.98	2	1	8.0	3.0	6	28	70.00	2	0
51	74.28	2	0	7.0	1.0	0	0	33.00	2	0
52	86.71	2	1	20.0	1.0	0	15	63.00	2	0
53	84.08	2	1	2.0	2.0	25	3	53.00	2	0
54	80.62	2	1	5.0	4.0	15	22	52.00	2	0
55	73.60	2	1	7.0	1.0	11	1	75.00	1	1
56	78.82	2	1	12.0	1.0	6	60	50.00	2	0
57	78.06	1	0	6.0	2.0	25	4	40.00	2	0
58	69.75	2	1	4.0	1.0	17	0	44.00	2	0
59	90.03	2	0	3.0	1.0	6	6	70.00	2	0
60	92.78	1	0	5.1	1.0	17	6	24.00	2	0
61	89.21	2	1	5.5	1.0	6	14	59.00	2	0
62	77.05	1	1	3.0	3.0	27	6	73.00	2	1
63	91.36	2	1	6.5	1.0	6	10	60.00	2	0
64	75.63	1	1	3.6	1.0	15	5	36.00	2	0
65	62.21	2	1	1.0	2.0	15	12	66.00	1	1

No.	Age	Gender[a]	Use of PSY[b]	AD duration	CCI	MMSE	NPI	Age_CG	Gender_CG	Spousal[d]
66	70.65	1	1	3.2	2.0	23	11	60.00	2	1
67	86.48	2	1	7.0	1.0	14	9	60.00	2	0
68	88.12	2	1	4.0	1.0	14	30	53.00	2	0
69	70.52	2	0	2.0	3.0	16	3	73.00	1	1
70	81.25	1	0	2.0	1.0	22	2	71.00	2	1
71	78.16	2	0	3.0	4.0	13	9	50.00	1	0
72	82.34	2	1	10.0	1.0	4	29	50.00	2	0
73	89.98	2	0	6.0	3.0	3	14	60.00	2	0
74	92.15	2	1	5.0	1.0	0	43	59.00	2	0
75	75.08	2	0	8.0	1.0	19	3	42.00	2	0
76	65.89	1	1	13.0	1.0	0	12	67.00	2	1
77	87.72	2	1	3.0	1.0	8	12	67.00	2	0
78	86.58	2	1	8.0	1.0	0	4	50.00	2	0
79	81.23	1	0	3.9	7.0	18	0	63.00	2	1
80	74.00	1	1	8.0	2.0	19	10	39.00	1	0
81	75.39	2	1	2.0	2.0	23	2	65.00	2	0
82	79.49	2	0	2.0	2.0	24	1	87.00	1	1
83	86.06	2	0	15.0	1.0	9	6	59.00	2	0
84	72.21	2	1	3.0	6.0	2	44	45.00	2	0
85	72.06	2	0	1.0	1.0	16	4	41.00	1	0
86	82.91	2	0	2.0	1.0	18	6	44.00	1	0
87	88.62	1	1	10.0	9.0	16	1	39.00	1	0
88	67.25	1	1	7.0	1.0	2	14	67.00	2	1

No.	Age	Gender[a]	Use of PSY[b]	AD duration	CCI	MMSE	NPI	Age_CG	Gender_CG	Spousal[d]
89	66.89	2	0	1.0	1.0	23	0	38.00	1	0
90	89.36	2	1	4.0	5.0	7	22	39.00	2	0
91	87.08	2	1	11.0	1.0	5	17	67.00	2	0
92	87.18	1	1	3.0	1.0	19	5	58.00	1	0
93	91.58	1	0	8.5	1.0	9	4	53.00	2	0
94	84.38	1	0	7.0	1.0	0	23	73.00	2	1
95	74.77	2	1	5.0	1.0	1	8	19.00	1	0
96	75.14	2	1	1.0	2.0	21	6	45.00	2	0
97	79.12	2	1	2.0	4.0	24	1	74.00	2	0
98	80.26	1	1	3.0	1.0	13	1	78.00	2	1
99	79.67	2	1	7.0	1.0	2	30	50.00	2	0
100	79.89	1	0	6.0	3.0	16	13	72.00	2	1
101	65.17	2	1	10.0	2.0	10	22	67.00	1	1
102	80.97	1	1	6.0	1.0	0	14	34.00	2	0
103	70.03	2	0	10.0	1.0	0	10	58.00	2	0
104	82.09	1	0	6.0	5.0	8	20	70.00	2	1
105	72.21	2	0	7.0	1.0	25	26	50.00	2	0
106	70.06	2	0	5.0	1.0	14	2	72.00	1	1
107	83.10	2	0	10.0	1.0	0	12	41.00	2	0
108	78.51	1	1	15.0	1.0	20	8	48.00	1	0
109	87.16	2	0	4.0	1.0	18	14	67.00	2	0
110	71.79	1	0	3.0	4.0	20	4	38.00	1	0
111	80.69	2	1	4.0	3.0	21	6	50.00	2	0

No.	Age	Gender[a]	Use of PSY[b]	AD duration	CCI	MMSE	NPI	Age_CG	Gender_CG	Spousal[d]
112	79.50	1	0	3.0	4.0	24	1	70.00	2	1
113	90.20	2	1	6.0	1.0	3	41	68.00	2	0
114	90.17	2	0	6.0	2.0	7	11	63.00	2	0
115	87.12	2	1	2.0	1.0	10	47	38.00	2	0
116	76.34	2	1	3.3	1.0	13	17	41.00	2	0
117	80.71	1	1	3.0	2.0	18	5	50.00	1	0
118	60.79	2	1	7.0	1.0	0	24	64.00	2	0
119	86.80	2	1	6.0	0.0	5	8	42.00	2	0
120	66.55	2	1	4.0	2.0	12	38	55.00	1	1
121	81.09	2	1	8.0	0.0	0	30	45.00	2	0
122	62.89	2	1	4.0	1.0	3	31	42.00	2	0
123	85.85	1	0	3.0	11.0	15	11	72.00	2	1
124	88.89	2	1	3.0	1.0	10	12	55.00	2	0
125	83.89	1	1	4.0	3.0	20	5	52.00	1	0
126	83.25	1	0	2.0	4.0	20	0	57.00	2	0
127	76.10	2	1	2.0	2.0	1	60	52.00	2	0
128	69.40	1	0	2.0	1.0	25	0	39.00	2	0
129	82.12	2	1	5.0	2.0	4	32	58.00	2	0
130	71.74	2	1	3.0	2.0	2	4	44.00	2	0
131	73.52	2	0	2.3	3.0	20	2	46.00	2	0
132	81.91	2	1	8.0	1.0	9	6	57.00	2	0
133	83.12	2	0	3.0	3.0	13	1	50.00	2	0
134	74.16	2	0	5.0	1.0	1	7	54.00	1	0

No.	Age	Gender[a]	Use of PSY[b]	AD duration	CCI	MMSE	NPI	Age_CG	Gender_CG	Spousal[d]
135	70.81	1	1	3.0	1.0	21	10	40.00	2	0
136	79.75	2	1	1.5	1.0	15	35	70.00	1	0
137	82.32	1	1	3.0	1.0	22	5	83.00	2	1
138	63.00	2	1	3.0	1.0	20	9	28.00	2	0
139	84.02	2	1	3.0	1.0	23	6	51.00	2	0
140	67.89	2	1	2.0	3.0	16	22	71.00	1	1
141	68.62	2	1	1.0	2.0	15	7	43.00	2	0
142	78.24	1	1	1.0	1.0	19	28	55.00	1	0
143	70.82	2	1	1.5	1.0	16	2	41.00	2	0
144	72.56	2	1	2.7	1.0	13	14	50.00	1	0
145	93.48	2	1	5.0	3.0	14	13	62.00	1	0
146	66.76	2	1	0.4	0.0	20	10	39.00	2	0
147	71.30	2	1	1.0	1.0	22	6	33.00	2	0
148	85.01	2	0	1.0	1.0	25	1	45.00	2	0

[a] Gender: 1, Male; 2, Female

[b] Use of PSY: 0, No; 1, Yes

[c] Spousal: 0, No; 1, Yes

Abbreviations: PSY, psychotherapeutic agents; AD, Alzheimer's disease; CCI, Charlson comorbidity index; MMSE, mini-mental state examination; NPI, neuropsychiatric inventory; CG, caregiver

eTable 2 Cumulative probability table for predicting time to treatment discontinuation for donepezil

Time to treatment discontinuation for donepezil (years)	Cumulative probability
0	0
0.0027	0.0029
0.0055	0.0088
0.0082	0.0177
0.0110	0.0236
0.0137	0.0265
0.0164	0.0295
0.0192	0.0324
0.0219	0.0383
0.0274	0.0472
0.0329	0.0501
0.0383	0.056
0.0411	0.0649
0.0438	0.0678
0.0465	0.0708
0.0479	0.0737
0.0548	0.0796
0.0575	0.0855
0.0602	0.0885
0.0657	0.0914
0.0685	0.0973
0.0767	0.1003
0.0780	0.1032
0.0821	0.1268
0.0849	0.1298
0.0904	0.1327
0.0958	0.1357

Time to treatment discontinuation for donepezil (years)	Cumulative probability
0.0985	0.1386
0.1068	0.1445
0.1082	0.1475
0.1095	0.1563
0.1123	0.1593
0.1150	0.1622
0.1177	0.1711
0.1232	0.1770
0.1369	0.1829
0.1396	0.1888
0.1451	0.1947
0.1478	0.1976
0.1533	0.2094
0.1588	0.2183
0.1615	0.2212
0.1643	0.2330
0.1780	0.2360
0.1807	0.2389
0.1834	0.2419
0.1862	0.2448
0.1917	0.2537
0.1971	0.2566
0.1999	0.2596
0.2026	0.2684
0.2053	0.2743
0.2108	0.2773
0.2163	0.2802
0.2272	0.2861
0.2230	0.2891
0.2327	0.2920

Time to treatment discontinuation for donepezil (years)	Cumulative probability
0.2355	0.3009
0.2409	0.3068
0.2464	0.3215
0.2519	0.3245
0.2546	0.3274
0.2601	0.3304
0.2628	0.3363
0.2656	0.3392
0.2683	0.3451
0.2711	0.3510
0.2738	0.3540
0.2765	0.3628
0.2847	0.3658
0.2902	0.3687
0.2957	0.3717
0.2984	0.3746
0.3012	0.3835
0.3039	0.3864
0.3066	0.3894
0.3094	0.3953
0.31760	0.4012
0.3203	0.4041
0.3231	0.4071
0.3244	0.4100
0.3258	0.4130
0.3313	0.4159
0.3422	0.4218
0.3450	0.4277
0.3504	0.4336
0.3559	0.4366

Time to treatment discontinuation for donepezil (years)	Cumulative probability
0.3641	0.4425
0.3751	0.4454
0.3778	0.4484
0.3806	0.4543
0.3860	0.4572
0.4052	0.4602
0.4134	0.4661
0.4162	0.4720
0.4216	0.4749
0.4244	0.4779
0.4271	0.4867
0.4381	0.4926
0.4463	0.4956
0.4518	0.4985
0.4572	0.5015
0.4709	0.5044
0.4764	0.5162
0.4791	0.5192
0.4819	0.5221
0.4846	0.5251
0.4956	0.5280
0.5038	0.5310
0.5092	0.5369
0.5175	0.5398
0.5202	0.5428
0.5229	0.5487
0.5257	0.5516
0.5339	0.5546
0.5394	0.5605
0.5448	0.5634

Time to treatment discontinuation for donepezil (years)	Cumulative probability
0.5531	0.5664
0.5558	0.5723
0.5585	0.5782
0.5695	0.5870
0.5722	0.5900
0.5777	0.5988
0.5859	0.6018
0.5941	0.6077
0.5969	0.6106
0.6023	0.6136
0.6133	0.6224
0.6215	0.6254
0.6242	0.6313
0.6297	0.6342
0.6379	0.6372
0.6461	0.6431
0.6544	0.6460
0.6598	0.6519
0.6653	0.6549
0.6708	0.6578
0.6899	0.6696
0.6982	0.6726
0.7009	0.6785
0.7036	0.6814
0.7064	0.6844
0.7118	0.6873
0.7201	0.6903
0.7228	0.6932
0.7255	0.6991
0.7420	0.7021

Time to treatment discontinuation for donepezil (years)	Cumulative probability
0.7502	0.7050
0.7611	0.7080
0.7639	0.7109
0.7693	0.7139
0.7885	0.7168
0.7967	0.7198
0.8159	0.7227
0.8542	0.7257
0.8680	0.7345
0.8706	0.7375
0.8734	0.7404
0.8761	0.7434
0.8898	0.7463
0.8980	0.7493
0.9035	0.7552
0.9199	0.7581
0.9418	0.7640
0.9500	0.7670
0.9528	0.7699
0.9555	0.7729
0.9583	0.7758
0.9610	0.7788
0.9637	0.7817
0.9719	0.7847
0.9802	0.7876
0.9993	0.7906
1	0.7906
10	1

eTable 3 Cumulative probability table for predicting time to treatment discontinuation for galantamine

Time to treatment discontinuation for galantamine (years)	Cumulative probability
0	0
0.0137	0.0127
0.0192	0.0380
0.0383	0.0506
0.0548	0.0633
0.0931	0.0759
0.0958	0.0886
0.1095	0.1013
0.1533	0.1139
0.1643	0.1266
0.1698	0.1392
0.2218	0.1519
0.2272	0.1646
0.2355	0.1772
0.2464	0.1899
0.2601	0.2025
0.2683	0.2405
0.2738	0.2532
0.3066	0.2658
0.3176	0.2785
0.3313	0.2911
0.3559	0.3165
0.3587	0.3291
0.3614	0.3418
0.3942	0.3544
0.3997	0.3671
0.4052	0.3797

Time to treatment discontinuation for galantamine (years)	Cumulative probability
0.4189	0.3924
0.4216	0.4051
0.4298	0.4177
0.4627	0.4430
0.5558	0.4557
0.5585	0.4684
0.5613	0.4810
0.5777	0.5063
0.5804	0.5190
0.5859	0.5316
0.5941	0.5570
0.6023	0.5823
0.6160	0.5949
0.6434	0.6076
0.6571	0.6203
0.6653	0.6329
0.7064	0.6456
0.7173	0.6582
0.7228	0.6709
0.7392	0.6835
0.7721	0.6962
0.8077	0.7089
0.8433	0.7215
0.8515	0.7342
0.8597	0.7468
0.8871	0.7595
0.9035	0.7722
0.9117	0.7848
0.9391	0.7975
1	0.7975

Time to treatment discontinuation for galantamine (years)	Cumulative probability
10	1

eTable 4 Cumulative probability table for predicting time to treatment discontinuation for rivastigmine

Time to treatment discontinuation for rivastigmine (years)	Cumulative probability
0	0
0.0082	0.0180
0.0100	0.0270
0.0164	0.0360
0.0219	0.0541
0.0274	0.0721
0.0383	0.0811
0.0438	0.0901
0.0465	0.0991
0.0493	0.1081
0.0548	0.1261
0.0602	0.1351
0.0685	0.1441
0.0739	0.1532
0.0821	0.1982
0.0876	0.2072
0.1013	0.2162
0.1287	0.2342
0.1643	0.2703
0.1780	0.2793
0.1930	0.2883
0.1971	0.2973
0.2053	0.3063
0.2272	0.3153
0.2327	0.3243
0.2409	0.3423
0.2464	0.3604

Time to treatment discontinuation for rivastigmine (years)	Cumulative probability
0.2683	0.3694
0.2875	0.3874
0.2984	0.3964
0.3066	0.4054
0.3313	0.4144
0.3504	0.4234
0.3943	0.4324
0.4162	0.4414
0.4545	0.4505
0.4764	0.4595
0.4791	0.4685
0.5038	0.4775
0.5092	0.4865
0.5120	0.4955
0.5147	0.5045
0.5284	0.5135
0.5503	0.5225
0.5585	0.5315
0.5695	0.5405
0.5722	0.5495
0.5777	0.5586
0.5969	0.5676
0.6160	0.5766
0.6242	0.5856
0.6297	0.5946
0.6461	0.6036
0.6708	0.6126
0.7009	0.6306
0.7118	0.6396
0.7310	0.6486

Time to treatment discontinuation for rivastigmine (years)	Cumulative probability
0.7392	0.6577
0.7529	0.6757
0.7693	0.6847
0.8049	0.6937
0.8159	0.7027
0.8214	0.7117
0.9035	0.7207
0.9062	0.7297
0.9363	0.7387
0.9418	0.7477
0.9665	0.7568
0.9802	0.7658
0.9993	0.7748
1	0.7748
10	1

eTable 5 Cumulative probability table for predicting time to treatment discontinuation for memantine

Time to treatment discontinuation for memantine (years)	Cumulative probability
0	0
0.0164	0.0059
0.0219	0.0178
0.0233	0.0237
0.0246	0.0355
0.0274	0.0414
0.0329	0.0473
0.0411	0.0769
0.0465	0.0828
0.0507	0.0888
0.0520	0.0947
0.0548	0.1006
0.0575	0.1124
0.0698	0.1183
0.0767	0.1243
0.0821	0.1479
0.0849	0.1538
0.0890	0.1598
0.0904	0.1657
0.0958	0.1716
0.1013	0.1775
0.1177	0.1834
0.1232	0.1893
0.1342	0.1953
0.1369	0.2071
0.1506	0.2130
0.1533	0.2249

Time to treatment discontinuation for memantine (years)	Cumulative probability
0.1643	0.2426
0.1780	0.2485
0.1807	0.2604
0.1917	0.2663
0.2108	0.2722
0.2190	0.2781
0.2272	0.2840
0.2300	0.2899
0.2409	0.2959
0.2437	0.3018
0.2464	0.3077
0.2519	0.3195
0.2656	0.3254
0.2738	0.3314
0.2765	0.3373
0.2793	0.3432
0.2820	0.3491
0.2875	0.3550
0.2957	0.3609
0.3012	0.3669
0.3053	0.3728
0.3066	0.3787
0.3340	0.3846
0.3368	0.3905
0.3450	0.3964
0.3532	0.4024
0.3559	0.4201
0.3641	0.4260
0.3696	0.4320
0.3833	0.4379

Time to treatment discontinuation for memantine (years)	Cumulative probability
0.3943	0.4438
0.3997	0.4497
0.4025	0.4556
0.4052	0.4615
0.4134	0.4734
0.4381	0.4793
0.4490	0.4852
0.4627	0.4911
0.4682	0.4970
0.4873	0.5030
0.5147	0.5089
0.5202	0.5148
0.5229	0.5266
0.5339	0.5325
0.5476	0.5385
0.5503	0.5444
0.5585	0.5621
0.5613	0.5680
0.5722	0.5799
0.5832	0.5917
0.5969	0.5976
0.6105	0.6036
0.6242	0.6095
0.6352	0.6154
0.6434	0.6213
0.6571	0.6272
0.6680	0.6331
0.6763	0.6391
0.6831	0.6450
0.6899	0.6509

Time to treatment discontinuation for memantine (years)	Cumulative probability
0.6927	0.6568
0.7118	0.6627
0.7255	0.6686
0.7283	0.6746
0.7310	0.6805
0.7365	0.6864
0.7666	0.6923
0.7693	0.6982
0.7885	0.7041
0.8049	0.7160
0.8241	0.7219
0.8405	0.7278
0.8487	0.7337
0.8515	0.7396
0.8597	0.7456
0.8734	0.7515
0.8789	0.7574
0.9035	0.7633
0.9418	0.7692
0.9473	0.7751
0.9610	0.7811
0.9665	0.7870
0.9802	0.7929
1	0.7929
10	1

eTable 6 Cumulative probability table for predicting time to hospital visits

Time to hospital visits (years)	Cumulative probability
0	0
0.0192	0.0068
0.0385	0.0068
0.0769	0.0270
0.0962	0.0270
0.1154	0.0270
0.1346	0.0135
0.1539	0.0473
0.1731	0.0135
0.1923	0.0203
0.2115	0.0270
0.2308	0.1081
0.2500	0.0811
0.2692	0.0338
0.2885	0.0473
0.3077	0.1351
0.3269	0.1689
0.3462	0.0338
0.3654	0.0676
0.3846	0.0338
0.4039	0.0203
0.4231	0.0068
0.4615	0.0270
0.4808	0.0068
0.5000	0.0068
0.5385	0.0068
1	1

eTable 7 Cumulative probability table for predicting death age of AD patients in Thailand

Death age	Cumulative probability for male AD patients	Cumulative probability for female AD patients
0	0.0000	0.0000
0.0001	0.0028	0.0023
1	0.0006	0.0005
2	0.0006	0.0005
3	0.0005	0.0005
4	0.0005	0.0005
5	0.0005	0.0005
6	0.0005	0.0004
7	0.0005	0.0004
8	0.0005	0.0004
9	0.0004	0.0005
10	0.0004	0.0005
11	0.0006	0.0005
12	0.0008	0.0005
13	0.0011	0.0006
14	0.0013	0.0006
15	0.0016	0.0006
16	0.0019	0.0007
17	0.0022	0.0007
18	0.0024	0.0007
19	0.0026	0.0008
20	0.0027	0.0008
21	0.0028	0.0008
22	0.0029	0.0009
23	0.0030	0.0009
24	0.0030	0.0009
25	0.0031	0.0009
26	0.0031	0.0010

Death age	Cumulative probability for male AD patients	Cumulative probability for female AD patients
27	0.0031	0.0010
28	0.0032	0.0010
29	0.0032	0.0010
30	0.0033	0.0011
31	0.0034	0.0011
32	0.0036	0.0011
33	0.0037	0.0012
34	0.0039	0.0013
35	0.0041	0.0013
36	0.0043	0.0014
37	0.0046	0.0015
38	0.0048	0.0016
39	0.0051	0.0018
40	0.0054	0.0019
41	0.0057	0.0021
42	0.0061	0.0023
43	0.0065	0.0025
44	0.0069	0.0027
45	0.0074	0.0029
46	0.0079	0.0032
47	0.0085	0.0034
48	0.0092	0.0037
49	0.0099	0.0040
50	0.0106	0.0044
51	0.0114	0.0048
52	0.0123	0.0052
53	0.0132	0.0057
54	0.0142	0.0063
55	0.0154	0.0070
56	0.0166	0.0078

Death age	Cumulative probability for male AD patients	Cumulative probability for female AD patients
57	0.0180	0.0086
58	0.0196	0.0096
59	0.0214	0.0106
60	0.0234	0.0118
61	0.0257	0.0132
62	0.0283	0.0148
63	0.0312	0.0166
64	0.0345	0.0187
65	0.0382	0.0211
66	0.0423	0.0240
67	0.0470	0.0273
68	0.0522	0.0313
69	0.0581	0.0359
70	0.0647	0.0412
71	0.0721	0.0474
72	0.0804	0.0543
73	0.0896	0.0620
74	0.0996	0.0704
75	0.1104	0.0796
76	0.1220	0.0896
77	0.1342	0.1001
78	0.1471	0.1114
79	0.1604	0.1232
80	0.1743	0.1357
81	0.1885	0.1490
82	0.2030	0.1629
83	0.2180	0.1777
84	0.2333	0.1934
85	0.2491	0.2100
86	0.2655	0.2276

Death age	Cumulative probability for male AD patients	Cumulative probability for female AD patients
87	0.2826	0.2462
88	0.3043	0.2686
89	0.3274	0.2926
90	0.3516	0.3183
91	0.3772	0.3456
92	0.4039	0.3746
93	0.4319	0.4052
94	0.4583	0.4348
95	0.4850	0.4651
96	0.5119	0.4958
97	0.5389	0.5267
98	0.5657	0.5574
99	0.8812	0.8812
120	1.0000	1.0000

eTable 8 Full details of base-case results by four different scenarios

Base-case results per patient	Healthcare perspective					Societal perspective				
	No AD treatment	**Donepezil**	**Galantamine**	**Rivastigmine**	**Memantine**	**No AD treatment**	**Donepezil**	**Galantamine**	**Rivastigmine**	**Memantine**
1. A universal treatment scenario (AD cohort with all disease-severity levels) without consideration of stopping the treatment when MMSE <10										
Hospital visit costs (THB)	49,551	52,246	50,098	50,173	50,179	52,081	54,824	52,792	52,632	52,532
Fixed costs (THB)	142,263	141,626	141,191	140,611	141,488	333,929	331,833	330,319	328,519	330,557
AD treatment costs (THB)	-	10,468	79,264	85,868	10,379	-	10,419	79,205	85,492	10,406
Unpaid caregiving costs (THB)	-	-	-	-	-	566,236	557,330	557,218	551,533	558,206
Total costs (THB)	191,813	204,341	270,553	276,652	202,046	952,246	954,406	1,019,533	1,018,175	951,701
Quality of life (QALYs)	2.494	2.517	2.501	2.523	2.496	2.491	2.506	2.495	2.512	2.485

Base-case results per patient	Healthcare perspective					Societal perspective				
	No AD treatment	**Donepezil**	**Galantamine**	**Rivastigmine**	**Memantine**	**No AD treatment**	**Donepezil**	**Galantamine**	**Rivastigmine**	**Memantine**
ICER (THB/QALY)	-	Not cost-effective (504,804)	Extended dominated	Not cost-effective (13,908,491)	Extended dominated	-	Cost-effective (138,524)	Extended dominated	Not cost-effective (11,029,657)	Less effective
2. A late treatment scenario (moderate and severe AD cohort: MMSE <20) without consideration of stopping the treatment when MMSE <10										
Hospital visit costs (THB)	48,224	51,031	48,915	48,963	48,935	51,468	54,349	51,996	51,975	52,023
Fixed costs (THB)	142,746	142,197	141,602	141,299	141,820	343,703	342,625	340,727	339,633	340,597
AD treatment costs (THB)	-	10,206	77,314	82,191	10,279	-	10,217	78,542	84,254	10,311
Unpaid caregiving costs (THB)	-	-	-	-	-	588,558	581,383	579,463	574,651	580,634
Total costs (THB)	190,970	203,433	267,831	272,453	201,033	983,729	988,575	1,050,728	1,050,514	983,566
Quality of life (QALYs)	2.237	2.257	2.241	2.255	2.238	2.249	2.266	2.252	2.267	2.244

Base-case results per patient	Healthcare perspective					Societal perspective				
	No AD treatment	**Donepezil**	**Galantamine**	**Rivastigmine**	**Memantine**	**No AD treatment**	**Donepezil**	**Galantamine**	**Rivastigmine**	**Memantine**
ICER (THB/QALY)	-	Not cost-effective (638,798)	Extended dominated	Extended dominated	Extended dominated	-	Not cost-effective (284,388)	Extended dominated	Not cost-effective (73,395,541)	Less effective
3. An early treatment scenario (mild AD cohort: MMSE ≥20) without consideration of stopping the treatment when MMSE <10										
Hospital visit costs (THB)	52,602	54,834	53,012	52,926	No indication	55,479	58,098	55,909	55,725	No indication
Fixed costs (THB)	141,087	139,714	138,972	137,113	No indication	308,315	305,140	302,778	296,618	No indication
AD treatment costs (THB)	-	11,305	83,357	89,897	No indication	-	11,185	83,335	91,037	No indication
Unpaid caregiving costs (THB)	-	-	-	-	No indication	503,797	495,573	492,384	485,353	No indication
Total costs (THB)	193,689	205,853	275,341	279,936	No indication	867,590	869,995	934,407	928,734	No indication
Quality of life (QALYs)	3.316	3.339	3.318	3.347	No indication	3.297	3.336	3.303	3.327	No indication

Base-case results per patient	Healthcare perspective					Societal perspective				
	No AD treatment	**Donepezil**	**Galantamine**	**Rivastigmine**	**Memantine**	**No AD treatment**	**Donepezil**	**Galantamine**	**Rivastigmine**	**Memantine**
ICER (THB/QALY)	-	Not cost-effective (520,076)	Extended dominated	Not cost-effective (9,475,619)	No indication	-	Cost-effective (61,652)	Extended dominated	Extended dominated	No indication
4. An early treatment scenario (mild AD cohort: MMSE ≥20) with consideration of stopping the treatment when MMSE <10										
Hospital visit costs (THB)	52,944	54,856	52,992	53,032	No indication	55,785	57,824	55,856	55,713	No indication
Fixed costs (THB)	140,543	139,799	138,798	137,641	No indication	305,944	303,681	302,642	296,772	No indication
AD treatment costs (THB)	-	10,549	75,662	88,146	No indication	-	10,494	75,187	88,656	No indication
Unpaid caregiving costs (THB)	-	-	-	-	No indication	501,009	495,086	493,460	486,730	No indication
Total costs (THB)	193,487	205,204	267,452	278,819	No indication	862,738	867,085	927,145	927,871	No indication
Quality of life (QALYs)	3.302	3.338	3.317	3.352	No indication	3.282	3.319	3.300	3.327	No indication

Base-case results per patient	Healthcare perspective					Societal perspective				
	No AD treatment	**Donepezil**	**Galantamine**	**Rivastigmine**	**Memantine**	**No AD treatment**	**Donepezil**	**Galantamine**	**Rivastigmine**	**Memantine**
ICER (THB/QALY)	-	Not cost-effective (331,160)	Extended dominated	Not cost-effective (5,084,057)	No indication	-	Cost-effective (116,835)	Extended dominated	Not cost-effective (7,512,676)	No indication

Abbreviations: AD, Alzheimer's disease; MMSE, mini-mental state examination; THB, Thai baht; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

eTable 9 One-way sensitivity analysis results by four different scenarios

Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**
1. A universal treatment scenario (AD cohort with all disease-severity levels) without consideration of stopping the treatment when MMSE <10															
Base-case analysis	952,246	2.491	-	954,406	2.506	Cost-effective (138,524)	1,019,533	2.495	Extended dominated	1,018,175	2.512	Not cost-effective (11,029,657)	951,701	2.485	Less effective
Treatment effects LCI	952,246	2.491	-	958,989	2.494	Not cost-effective (2,238,393)	1,021,811	2.489	Less effective	1,028,391	2.483	Less effective	953,694	2.480	Less effective
Treatment effects UCI	952,246	2.491	-	949,499	2.521	Not cost-effective (314,303)	1,011,377	2.517	Extended dominated	1,003,551	2.555	Not cost-effective (1,597,986)	944,588	2.505	Dominant (-530,711)

Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)
Treatment persistence 100%	944,467	2.465	-	943,496	2.695	Dominant (-4,212)	1,281,364	2.545	Extended dominated	1,224,580	2.764	Not cost-effective (4,089,402)	984,615	2.491	Extended dominated
HR for mortality LCI	1,032,399	2.674	-	1,033,876	2.690	Cost-effective (87,001)	1,101,101	2.677	Extended dominated	1,101,259	2.699	Not cost-effective (8,071,625)	1,031,836	2.670	Less effective
HR for mortality UCI	881,131	2.330	-	884,986	2.348	Not cost-effective (217,021)	946,947	2.335	Extended dominated	944,953	2.351	Not cost-effective (26,538,454)	882,354	2.328	Dominated
Hospital visit	939,243	2.491	-	940,710	2.506	Cost-effective (94,053)	1,006,344	2.495	Extended dominated	1,005,028	2.512	Not cost-effective	938,578	2.485	Less effective

Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)
costs -25%												(11,139,326)			
Hospital visit costs +25%	965,285	2.491	-	968,123	2.506	Not cost-effective (182,035)	1,032,742	2.495	Extended dominated	1,031,345	2.512	Not cost-effective (10,949,424)	964,845	2.485	Less effective
Fixed costs -25%	868,763	2.491	-	871,448	2.506	Not cost-effective (172,114)	936,954	2.495	Extended dominated	936,045	2.512	Not cost-effective (11,172,984)	869,062	2.485	Dominated
Fixed costs +25%	1,035,728	2.491	-	1,037,365	2.506	Cost-effective (104,934)	1,102,113	2.495	Extended dominated	1,100,305	2.512	Not cost-effective (10,886,330)	1,034,340	2.485	Less effective

Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**
AD treatment costs -25%	952,246	2.491	-	951,802	2.506	Dominant (-28,476)	999,732	2.495	Extended dominated	996,802	2.512	Not cost-effective (7,786,443)	949,099	2.485	Less effective
AD treatment costs +25%	952,246	2.491	-	957,011	2.506	Not cost-effective (305,524)	1,039,335	2.495	Extended dominated	1,039,548	2.512	Not cost-effective (14,275,871)	954,303	2.485	Dominated
Discount rates 0%	1,073,333	2.748	-	1,076,439	2.771	Cost-effective (136,335)	1,145,237	2.759	Extended dominated	1,143,466	2.777	Not cost-effective (10,390,417)	1,073,714	2.747	Dominated
Discount rates 6%	853,172	2.277	-	854,586	2.287	Cost-effective (146,962)	916,549	2.277	Extended dominated	915,510	2.292	Not cost-effective	851,890	2.268	Less effective

Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**
												(11,683,353)			
Time horizon 5 years	626,273	1.870	-	627,671	1.878	Not cost-effective (195,083)	686,573	1.867	Less effective	685,532	1.878	Not cost-effective (322,078,816)	625,341	1.861	Less effective
2. A late treatment scenario (moderate and severe AD cohort: MMSE <20) without consideration of stopping the treatment when MMSE <10															
Base-case analysis	983,729	2.249	-	988,575	2.266	Not cost-effective (284,388)	1,050,728	2.252	Extended dominated	1,050,514	2.267	Not cost-effective (73,395,541)	983,566	2.244	Less effective
Treatment effects LCI	983,729	2.249	-	992,047	2.256	Not cost-effective	1,052,475	2.248	Less effective	1,058,743	2.242	Less effective	984,385	2.241	Less effective

Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**
						(1,260,318)									
Treatment effects UCI	983,729	2.249	-	984,586	2.278	Not cost-effective (415,867)	1,044,072	2.272	Extended dominated	1,037,112	2.304	Not cost-effective (2,018,912)	977,428	2.261	Dominant (-539,120)
Treatment persistence 100%	970,805	2.219	-	982,643	2.410	Cost-effective (61,991)	1,301,854	2.285	Extended dominated	1,263,537	2.460	Not cost-effective (5,589,084)	1,011,482	2.240	Extended dominated
HR for mortality LCI	1,063,855	2.408	-	1,067,104	2.425	Not cost-effective (189,309)	1,132,128	2.410	Extended dominated	1,134,635	2.431	Not cost-effective (11,851,764)	1,064,693	2.405	Less effective

Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**
HR for mortality UCI	909,881	2.100	-	916,767	2.120	Not cost-effective (338,829)	976,238	2.106	Extended dominated	975,614	2.120	Extended dominated	911,684	2.099	Less effective
Hospital visit costs -25%	970,857	2.249	-	975,013	2.266	Not cost-effective (242,655)	1,037,711	2.252	Extended dominated	1,037,512	2.267	Not cost-effective (85,929,400)	970,542	2.243	Less effective
Hospital visit costs +25%	996,591	2.249	-	1,002,189	2.266	Not cost-effective (326,807)	1,063,709	2.252	Extended dominated	1,063,500	2.267	Not cost-effective (84,295,644)	996,553	2.243	Less effective
Fixed costs -25%	897,803	2.249	-	902,919	2.266	Not cost-effective (300,200)	965,546	2.252	Extended dominated	965,605	2.267	Not cost-effective (74,282,047)	898,416	2.244	Dominated

Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**
Fixed costs +25%	1,069,655	2.249	-	1,074,231	2.266	Not cost-effective (268,575)	1,135,910	2.252	Extended dominated	1,135,422	2.267	Not cost-effective (72,509,034)	1,068,715	2.244	Less effective
AD treatment costs -25%	983,729	2.249	-	986,021	2.266	Cost-effective (134,485)	1,031,093	2.252	Extended dominated	1,029,450	2.267	Not cost-effective (51,462,673)	980,988	2.244	Less effective
AD treatment costs +25%	983,729	2.249	-	991,129	2.266	Not cost-effective (434,291)	1,070,363	2.252	Extended dominated	1,071,577	2.267	Not cost-effective (95,328,409)	986,143	2.244	Dominated
Discount rates 0%	1,104,472	2.485	-	1,110,769	2.508	Not cost-effective (270,020)	1,176,115	2.492	Extended dominated	1,175,747	2.509	Not cost-effective	1,105,356	2.482	Dominated

Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)
												(75,085,335)			
Discount rates 6%	884,687	2.054	-	888,364	2.066	Not cost-effective (311,918)	947,741	2.053	Dominated	947,631	2.067	Not cost-effective (74,291,243)	883,674	2.046	Less effective
Time horizon 5 years	663,898	1.675	-	664,365	1.680	Cost-effective (91,978)	721,709	1.670	Dominated	723,673	1.684	Not cost-effective (13,925,504)	661,844	1.666	Less effective
3. An early treatment scenario (mild AD cohort: MMSE ≥20) without consideration of stopping the treatment when MMSE <10															
Base-case analysis	867,590	3.297	-	869,995	3.336	Cost-effective (61,652)	934,407	3.303	Extended dominated	928,734	3.327	Extended dominated	No indication	No indication	No indication

Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)
Treatment effects LCI	867,590	3.297	-	877,407	3.317	Not cost-effective (495,799)	940,088	3.288	Less effective	946,419	3.281	Less effective	No indication	No indication	No indication
Treatment effects UCI	867,590	3.297	-	861,153	3.359	Dominant (-104,198)	922,004	3.336	Extended dominated	909,569	3.391	Not cost-effective (1,490,598)	No indication	No indication	No indication
Treatment persistence 100%	860,257	3.269	-	813,924	3.620	Dominant (-131,896)	1,213,936	3.396	Extended dominated	1,101,382	3.760	Not cost-effective (2,055,679)	No indication	No indication	No indication
HR for mortality LCI	941,726	3.514	-	941,021	3.551	Dominant (-18,945)	1,010,807	3.521	Extended dominated	1,005,118	3.551	Not cost-effective (158,924,298)	No indication	No indication	No indication

Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**
HR for mortality UCI	801,263	3.102	-	805,187	3.141	Cost-effective (102,862)	868,092	3.110	Extended dominated	862,715	3.132	Extended dominated	No indication	No indication	No indication
Hospital visit costs -25%	851,920	3.295	-	849,333	3.321	Dominant (-100,985)	918,854	3.303	Extended dominated	914,637	3.332	Not cost-effective (5,776,794)	No indication	No indication	No indication
Hospital visit costs +25%	881,461	3.297	-	884,519	3.336	Cost-effective (78,433)	948,385	3.303	Extended dominated	942,665	3.327	Extended dominated	No indication	No indication	No indication
Fixed costs -25%	790,512	3.297	-	793,710	3.336	Cost-effective (82,004)	858,712	3.303	Extended dominated	854,579	3.327	Extended dominated	No indication	No indication	No indication

Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**
Fixed costs +25%	944,669	3.297	-	946,280	3.336	Cost-effective (41,301)	1,010,102	3.303	Extended dominated	1,002,888	3.327	Extended dominated	No indication	No indication	No indication
AD treatment costs -25%	867,590	3.297	-	867,199	3.336	Dominant (-10,039)	913,573	3.303	Extended dominated	905,974	3.327	Extended dominated	No indication	No indication	No indication
AD treatment costs +25%	867,590	3.297	-	872,791	3.336	Cost-effective (133,344)	955,241	3.303	Extended dominated	951,493	3.327	Extended dominated	No indication	No indication	No indication
Discount rates 0%	992,675	3.631	-	995,664	3.683	Cost-effective (57,254)	1,063,401	3.645	Extended dominated	1,056,430	3.673	Extended dominated	No indication	No indication	No indication

Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**
Discount rates 6%	766,106	3.019	-	768,092	3.047	Cost-effective (70,733)	829,598	3.017	Less effective	824,950	3.039	Extended dominated	No indication	No indication	No indication
Time horizon 5 years	508,822	2.531	-	507,075	2.533	Dominant (1,018,855)	570,042	2.519	Less effective	568,242	2.532	Extended dominated	No indication	No indication	No indication
4. An early treatment scenario (mild AD cohort: MMSE ≥20) with consideration of stopping the treatment when MMSE <10															
Base-case analysis	862,738	3.282	-	867,085	3.319	Cost-effective (116,835)	927,145	3.300	Extended dominated	927,871	3.327	Not cost-effective (7,512,676)	No indication	No indication	No indication
Treatment effects LCI	863,501	3.283	-	874,313	3.304	Not cost-effective (526,517)	919,684	3.294	Extended dominated	933,097	3.286	Extended dominated	No indication	No indication	No indication

Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**
Treatment effects UCI	863,341	3.284	-	858,291	3.347	Dominant (-79,988)	921,855	3.337	Extended dominated	910,580	3.396	Not cost-effective (1,064,399)	No indication	No indication	No indication
Treatment persistence 100%	850,537	3.241	-	824,935	3.525	Dominant (-90,158)	1,101,715	3.332	Extended dominated	1,074,823	3.700	Not cost-effective (1,428,997)	No indication	No indication	No indication
HR for mortality LCI	937,045	3.501	-	940,962	3.542	Cost-effective (95,054)	1,005,518	3.527	Extended dominated	1,005,778	3.556	Not cost-effective (4,572,311)	No indication	No indication	No indication
HR for mortality UCI	796,660	3.089	-	804,276	3.129	Not cost-effective (187,373)	861,042	3.106	Extended dominated	862,328	3.132	Not cost-effective	No indication	No indication	No indication

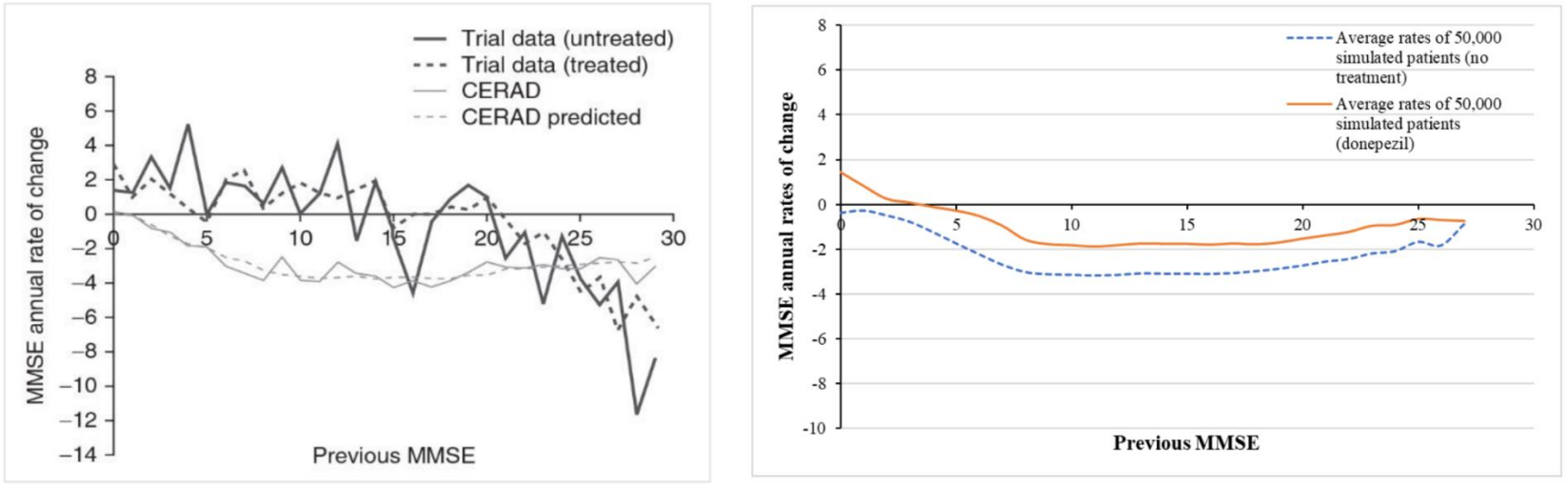
Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)
												(21,573,845)			
Hospital visit costs -25%	849,277	3.284	-	850,036	3.318	Cost-effective (22,492)	912,376	3.301	Extended dominated	915,567	3.332	Not cost-effective (4,433,758)	No indication	No indication	No indication
Hospital visit costs +25%	876,685	3.282	-	881,541	3.319	Cost-effective (130,544)	941,109	3.300	Extended dominated	941,799	3.327	Not cost-effective (7,447,219)	No indication	No indication	No indication
Fixed costs -25%	786,252	3.282	-	791,165	3.319	Cost-effective (132,035)	851,484	3.300	Extended dominated	853,678	3.327	Not cost-effective (7,726,168)	No indication	No indication	No indication

Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**	**Total costs (THB)**	**QALYs**	**ICER (THB/QALY)**
Fixed costs +25%	939,224	3.282	-	943,006	3.319	Cost-effective (101,634)	1,002,805	3.300	Extended dominated	1,002,064	3.327	Not cost-effective (7,299,183)	No indication	No indication	No indication
AD treatment costs -25%	862,738	3.282	-	864,462	3.319	Cost-effective (46,325)	908,348	3.300	Extended dominated	905,707	3.327	Not cost-effective (5,097,600)	No indication	No indication	No indication
AD treatment costs +25%	862,738	3.282	-	869,709	3.319	Cost-effective (187,344)	945,941	3.300	Extended dominated	950,035	3.327	Not cost-effective (9,927,751)	No indication	No indication	No indication
Discount rates 0%	987,588	3.615	-	992,271	3.664	Cost-effective (96,034)	1,054,741	3.641	Extended dominated	1,055,328	3.673	Not cost-effective	No indication	No indication	No indication

Analyses	No AD treatment			Donepezil			Galantamine			Rivastigmine			Memantine		
	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)	Total costs (THB)	QALYs	ICER (THB/QALY)
												(6,790,050)			
Discount rates 6%	761,515	3.005	-	765,569	3.032	Cost-effective (147,869)	823,465	3.015	Extended dominated	824,268	3.040	Not cost-effective (8,278,390)	No indication	No indication	No indication
Time horizon 5 years	499,384	2.503	-	505,696	2.531	Not cost-effective (229,807)	564,140	2.510	Extended dominated	566,767	2.528	Extended dominated	No indication	No indication	No indication

Abbreviations: AD, Alzheimer's disease; MMSE, mini-mental state examination; THB, Thai baht; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; and HR, hazard ratio; LCI, lower confidence interval; UCI, upper confidence interval

Appendix 2 Supplementary figures



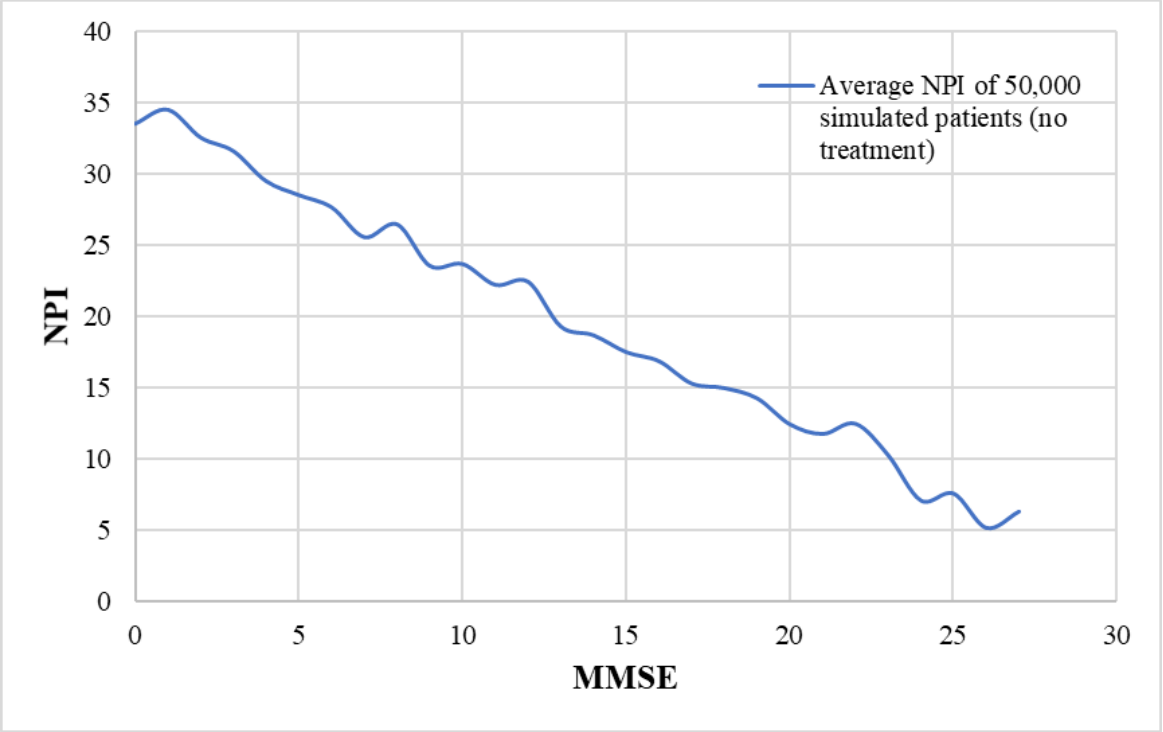
A. MMSE modelling from Getsios et al. (2010)

B. Simulated MMSE outputs from our model

eFigure 1 Model validation regarding simulation validity (face validity) [1] on cognitive status (MMSE)

Remarks: Getsios et al. (2010) modelled MMSE of untreated patients based on the CERAD registry. MMSE outputs of patients receiving no AD treatment from our simulation (a blue dotted line) were consistent with MMSE rates of change observed in the CERAD registry. In addition, MMSE outputs of patients receiving AD treatment (donepezil) from our simulation (an orange solid line: 100% treatment persistence was assumed) were also in agreement with actual MMSE rates of change in the donepezil trials for treated patients.

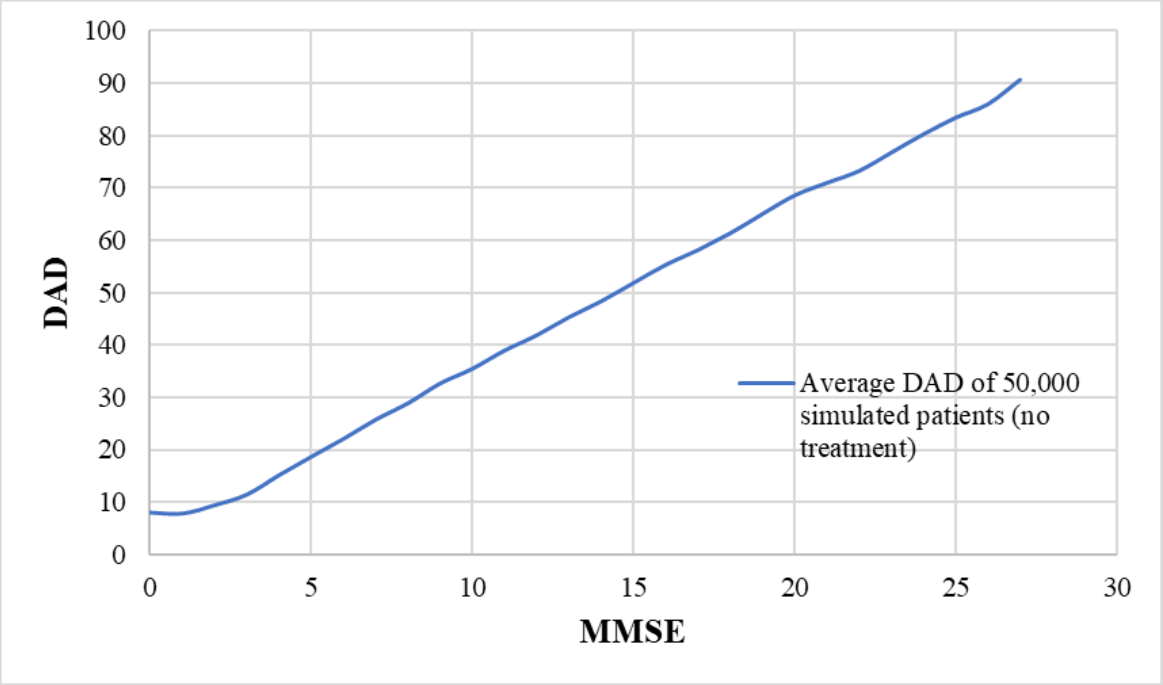
Abbreviations: MMSE, mini-mental state examination; CERAD, consortium to establish a registry for Alzheimer's disease



eFigure 2 Model validation regarding simulation validity (technical validity) [1] on behavioural status (NPI)

Remarks: As AD progresses to more severe stages (less MMES), neuropsychiatric symptoms become more problematic (more NPI), resulting in an inverse relationship between MMSE and NPI. Average NPI of 50,000 patients from our simulation showed a logical disease progression trend, which was consistent with the theoretical basis of the disease.

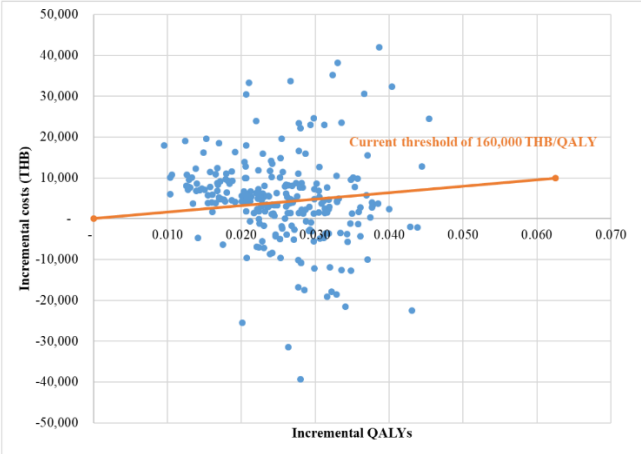
Abbreviations: MMSE, mini-mental state examination; NPI, neuropsychiatric inventory; AD, Alzheimer's disease



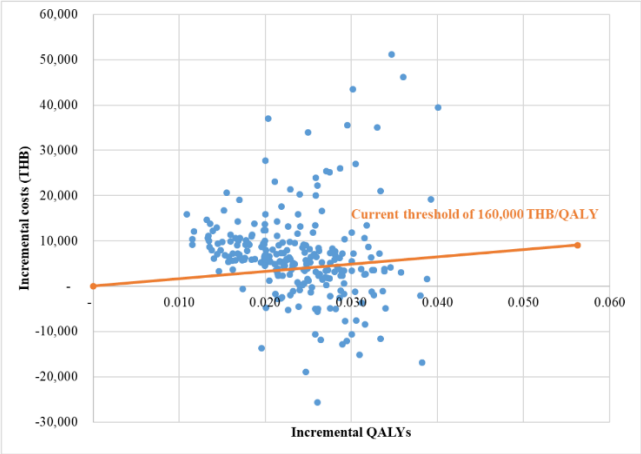
eFigure 3 Model validation regarding simulation validity (technical validity) [1] on functional status (DAD)

Remarks: As AD progresses to more severe stages (less MMSE), functional status is gradually deteriorated (less DAD), resulting in a direct relationship between MMSE and DAD. Average DAD of 50,000 patients from our simulation showed a logical disease progression trend, which was consistent with the theoretical basis of the disease.

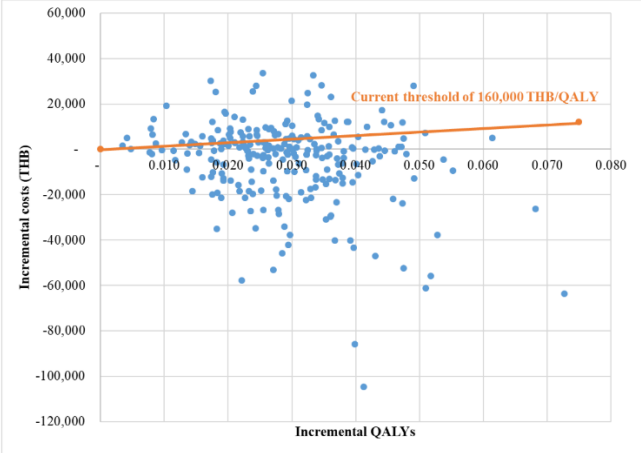
Abbreviations: MMSE, mini-mental state examination; DAD, disability assessment for dementia; AD, Alzheimer's disease



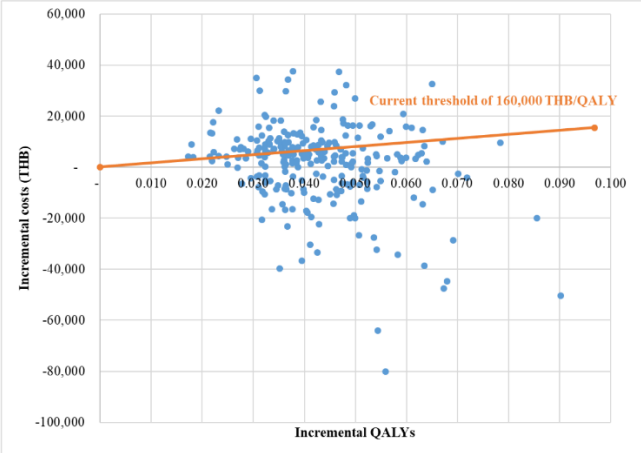
A. A universal treatment scenario without the stopping rule when MMSE <10



B. A late treatment scenario without the stopping rule when MMSE <10



C. An early treatment scenario without the stopping rule when MMSE <10



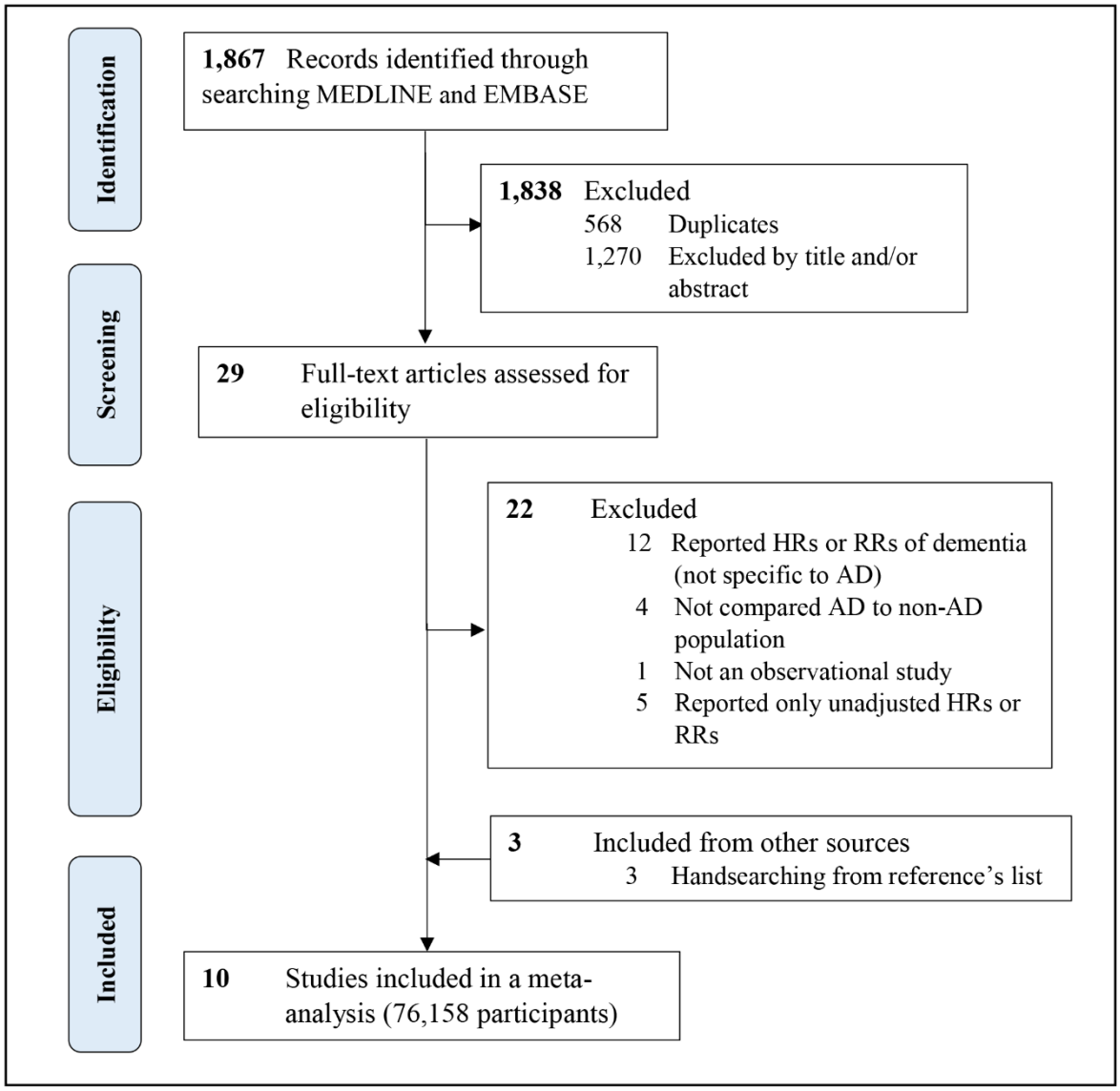
D. An early treatment scenario with the stopping rule when MMSE <10

eFigure 4 Cost-effectiveness scatterplots for donepezil under a societal perspective

Abbreviations: THB, Thai baht; QALYs, quality-adjusted life years; MMSE, mini-mental state examination

Appendix 3 A systematic review and meta-analysis for deriving hazard ratios for mortality associated with AD

In order to estimate hazard ratios for mortality associated with AD, we conducted a systematic review and meta-analysis. MEDLINE and EMBASE were searched for literature pertinent to risk of death associated with AD, from inception to 22 February 2019. A wide range of searching terms: (Alzheimer OR dementia OR neurodegenerative) AND (mortality OR death OR survival) was applied to each database to identify relevant studies. Through database searching, we identified 1,867 records from which 10 studies were included in our meta-analysis (**eFigure 5**), involving 76,158 participants from six countries across the world. Details of included studies are provided in **eTable 10**. A meta-analysis was done using 'metan' command in STATA (version 13.0, StataCorp, College Station, TX, USA). **eFigure 6** and **eFigure 7** illustrate a forest plot and its corresponding funnel plot, respectively. Overall, a pooled estimate of hazard ratios for mortality associated with AD was 2.13 (95% confidence interval: 1.80 to 2.47; I^2: 87.5%). Egger's (p-value: 0.315) and Begg's test (p-value: 0.210) indicated that there were no small-study effects in our pooled estimate. The estimate was then applied to adjust the age- and gender-specific mortality tables of general Thai population.



eFigure 5 PRISMA diagram

Remarks: Ten studies included in the meta-analysis are Oesterhus et al. (2014) [2], Lonnroos et al. (2013) [3], Wu et al. (2011) [4], Steenland et al. (2010) [5], Wilson et al. (2009) [6], Koedam et al. (2008) [7], Ganguli et al. (2005) [8], Fitzpatrick et al. (2005) [9], Tschanz et al. (2004) [10] and Jagger et al. (1995) [11]

Abbreviations: HRs, hazard ratios; RRs, risk ratios; AD, Alzheimer's disease

eTable 10 Details of included studies for the meta-analysis

No.	Author	Year	Country	Research type	N (All)	N (AD)	Age (years)	Follow-up duration (years)	Risk type	Adjusted for	Mortality wih AD compared to non-AD	LCI	UCI
1	Oesterhus R [2]	2014	Norway	Longitudinal cohort study	209	137	75.8	5.16	RR	Compared to the general sex- and age-matched population	1.50	1.30	1.70
2	Lonnroos E [3]	2013	Finland	Nested case-controlled study	56,041	28,093	79.7	4.75	HR	Crude	2.03	1.97	2.09
										Comorbidity	2.07	2.01	2.14
3	Wu XG [4]	2011	China	Longitudinal cohort study	2,788	NA	NA	7.25	HR	Potential covariates	2.52	1.96	3.24
4	Steenland K[a] [5]	2010	USA	Longitudinal cohort study	3,581	1,381	69	4.1	RR (Possible AD)	Race, sex and education	2.47	1.75	3.48
									RR (Probable AD)	Race, sex and education	2.73	2.07	3.60

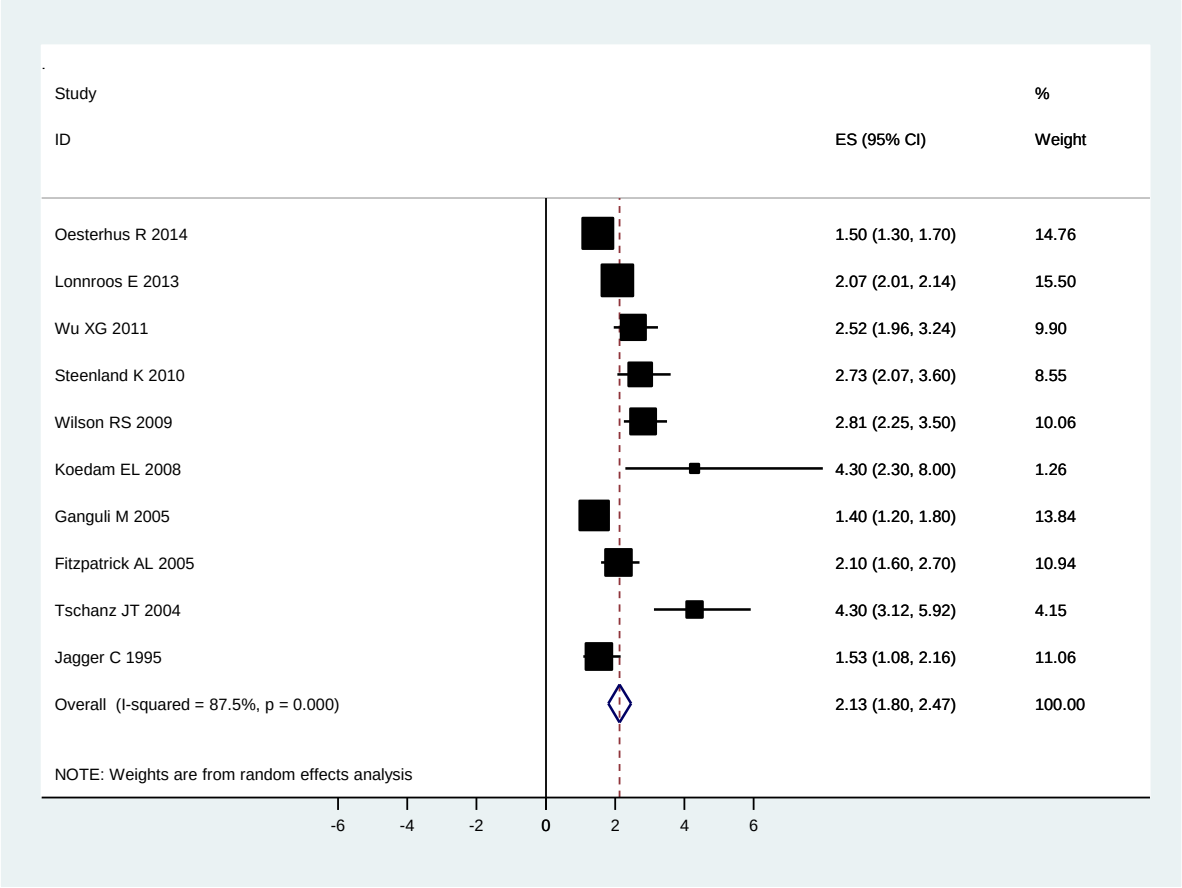
No.	Author	Year	Country	Research type	N (All)	N (AD)	Age (years)	Follow-up duration (years)	Risk type	Adjusted for	Mortality wih AD compared to non-AD	LCI	UCI
5	Wilson RS [6]	2009	USA	Longitudinal population-based observational study	802	296	80.1	10	RR	Age, sex and education	2.84	2.29	3.52
										Common chronic medical conditions (i.e. heart disease, diabetes mellitus and cancer)	2.81	2.25	3.50
6	Koedam EL [7]	2008	Netherlands	Cohort study	1,203	589	68.2	2.5	HR	Crude	5.60	3.00	10.50
										Age and sex	4.30	2.30	8.00
7	Ganguli M [8]	2005	USA	Prospective cohort study	1,670	348	73.4	15	HR	Unadjusted	2.60	2.20	3.10
									HR	Age and sex	1.70	1.40	2.00
									HR	Age, sex and comorbidities	1.40	1.20	1.80
8		2005	USA		3,602	245	75.1	6.5	HR	Unadjusted	3.00	2.30	3.80

No.	Author	Year	Country	Research type	N (All)	N (AD)	Age (years)	Follow-up duration (years)	Risk type	Adjusted for	Mortality wih AD compared to non-AD	LCI	UCI
	Fitzpatrick AL [9]			Prospective cohort study					HR	Age, gender and race	2.10	1.60	2.70
9	Tschanz JT[b] [10]	2004	USA	Prospective cohort study	4,683	207	75.4	5	RR (Age 65-74)	Covariates including education and APOE genotype	11.30	5.70	22.40
									RR (Age 75-84)	Covariates including education and APOE genotype	4.30	3.12	5.92
									RR (Age 85+)	Covariates including education and APOE genotype	2.12	1.50	2.90
10	Jagger C [11]	1995	UK	Prospective cohort study	1,579	377	81.8	6	RR	Age, sex and place of interview	1.53	1.08	2.16

[a] As this study used the same control (non-AD population) to derive RRs for possible and probable AD groups, only was the RR of probable AD group considered in our meta-analysis

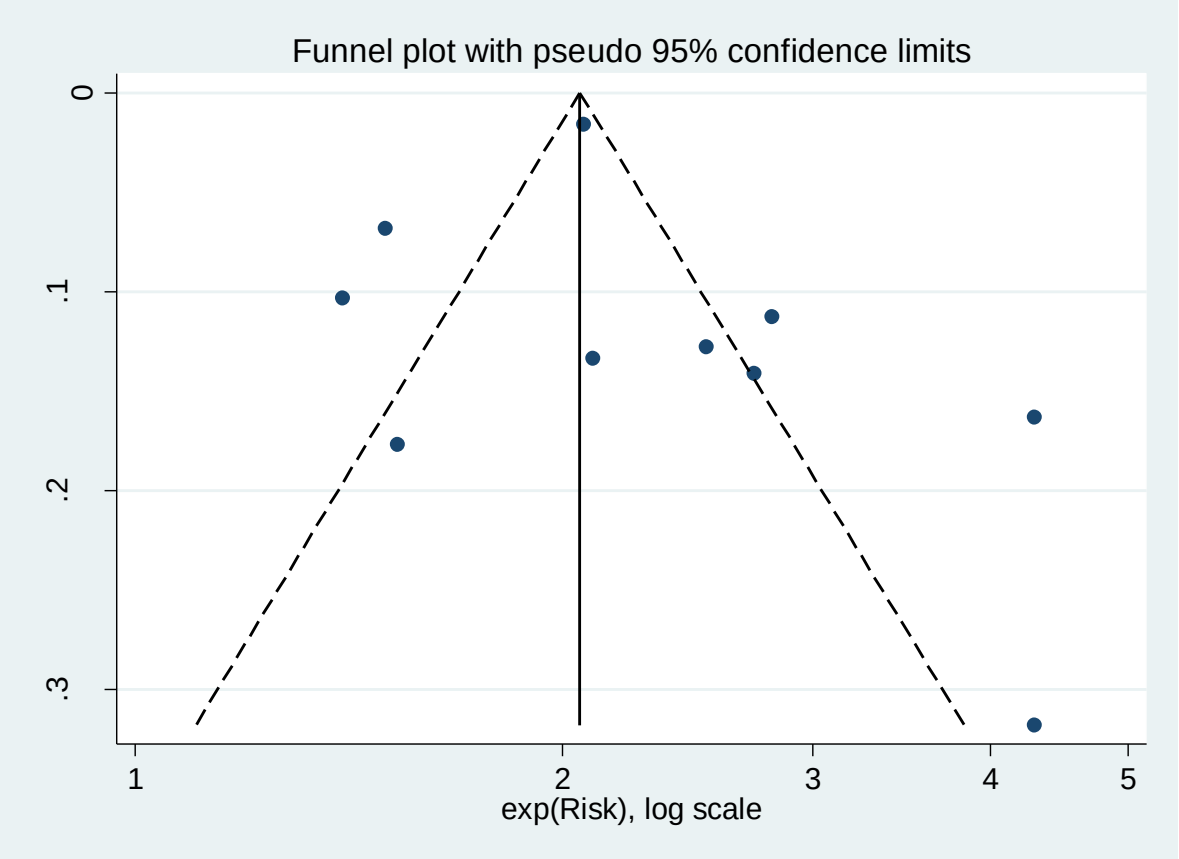
[b] Although this study used different control groups for each of RR estimates (by age groups), these RR estimates were not appropriate to be combined due to high within-study heterogeneity (I^2: 82.8%). As the median age of all included studies was 75.6 years, the RR of age group 75-84 years was chosen pool in the meta-analysis.

Abbreviations: N, number of participants; AD, Alzheimer's disease; RR, risk ratio; HR, hazard ratio; LCI, lower confidence interval; UCI, upper confidence interval; USA, the United State of America; UK, the United Kingdom



eFigure 6 Forest plot generated from the meta-analysis

Abbreviation: ES, effect size



eFigure 7 Funnel plot generated from the meta-analysis

Abbreviation: SE, standard error; and exp, exponential

Appendix 4 Discussion for one-way sensitivity analysis results

According to the one-way sensitivity analyses, five key determinants of the ICERs are identified. Four of the determinants are straightforward in interpretation. To illustrate, increases in treatment effects and treatment persistence, and decreases in HR of mortality associated with AD and AD treatment costs improve the cost-effectiveness results. However, decreasing the time horizon to 5 years leads to different results in different scenarios. Generally, shortening of the time horizon reduces the number of mild and moderate AD patients progressing to the severe stage. As severe AD patients are associated with higher costs, shorter time horizon should result in more cost-effectiveness findings. This logic can be seen in the late treatment and early treatment scenarios without the stopping rule. Nevertheless, the ICERs of the universal treatment scenario and the early treatment scenario with the stopping rule change towards the opposite direction. In the universal treatment scenario, the positive effect of shortened time horizon may not be able to overcome the influence of severe AD patients existing since the beginning of the simulation. Likewise, implementation of the stopping rule in mild AD cohorts potentially subsides treatment benefits, resulting in higher number of patients progressing to the severe stage, compared to the early treatment scenario without the stopping rule. Hence, the positive effect of shortened time horizon may not be sufficient to offset the influence of increased number of severe AD patients in this scenario.

Appendix 5 Monte Carlo Simulations and Model's Performance

During the developmental process of our model, the number of Monte Carlo simulations was varied in order to allow the model to perform stably and thereby produce accurate outputs. The mean total costs, along with the corresponding standard deviation (SD) and standard error (SE), of donepezil option were used to illustrate the effects of the varied number of Monte Carlo simulations on model's performance. Similar findings could also be achieved, if other parameters such as the mean health-related quality of life (HR-QoL) were used in replacement of the mean total costs.

eTable 11 shows the model's performance of 1st order Monte Carlo simulations. By increasing the number of simulated patients from 10,000 to 50,000, the SEs were reduced by more than half (55.3%). With this small SE in the simulation of 50,000 patients, we are 95% certain that population means are varied within ±1% of the means estimated from our model. Thus, we specified 50,000 patients for all of our 1st order Monte Carlo simulations.

When we decided the suitable number of 2nd order Monte Carlo simulations containing 50,000 simulated patients (**eTable 12**), the similar model's performance was observed [the SEs were reduced by more than half (54.9%)] when the number of replications had increased from 50 to 250. In addition, the probability of donepezil being cost-effective compared to no AD treatment also appeared to converge with the model of 250 replications. An increase in the number of replications beyond 250 may further improve the model's performance. However, concerning the time spent for executing an analysis (9.5 hours for 250 replications), we selected the 250 replications of 50,000 simulated patients as a practical approach.

All simulations were executed using an Intel® Xeon® CPU E5-2640 v4 @2.4 GHz with 32.0 GB installed memory (RAM).

eTable 11 Model's performance by the varied numbers of 1st order Monte Carlo simulation

Simulation parameters	Number of simulated patients (number of 1st order Monte Carlo simulations)				
	10,000	**20,000**	**30,000**	**40,000**	**50,000**
Time spent for executing an analysis	1 minute	2 minute	3 minute	4 minute	5 minute
Mean total costs of donepezil (THB)	949,100	951,343	953,507	949,100	954,406
SD (THB)	777,589	777,152	778,349	777,100	777,324
SE (THB)	7,776	5,495	4,494	3,885	3,476
Reduction in SE (%)	-	29.3	42.2	50.0	55.3

Abbreviations: THB: Thai baht; SD, standard deviation; SE, standard error

eTable 12 Model's performance by the varied numbers of 2st order Monte Carlo simulation based on 50,000 simulated patients

Simulation parameters	Number of replications (number of 2nd order Monte Carlo simulations) of 50,000 simulated patients				
	50	**100**	**150**	**200**	**250**
Time spent for executing an analysis	1.5 hours	3 hours	5 hours	7 hours	9.5 hours
Mean total costs of donepezil (THB)	886,670	1,005,452	947,799	988,703	948,405
SD (THB)	298,787	392,317	345,224	385,025	301,233
SE (THB)	42,255	39,232	28,187	27,225	19,052
Reduction in SE (%)	-	7.2	33.3	35.6	54.9
Probability of donepezil being cost-effective compared to no AD treatment (%)	44.0	51.0	40.7	45.5	45.2

Abbreviations: THB: Thai baht; SD, standard deviation; SE, standard error; AD, Alzheimer's disease

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