Modelling the cost-effectiveness of new medical technologies:

SPECT scans in diagnosing Alzheimer's dementia.

Christian Kronborg Andersen[1,2] and John Cairns[2]

Work in progress - please do not quote

Introduction

The cost-effectiveness of alternative strategies can be modelled at an early stage in the development of new medical technologies and as more information becomes available the model can be refined [1]. The objective of this study is to develop a model to compare the cost-effectiveness of two methods of scanning the brain using single photon emission computed tomography (SPECT) in diagnosing Alzheimer's disease.

Concerns have been raised in the literature that the use of models is liable to bias health policy decisions and that they sometimes are framed in a way that favours one strategy over another [2]. However, modelling is useful to identify key questions for further research [3] and to identify threshold values for variables below or above which a new technology is likely to represent good value for money [1].

For economic evaluation of new technologies, *life-years saved* or *quality-adjusted life-years (QALYs) gained* are more relevant outcome measures than intermediate clinical endpoints, such as reductions in blood pressure, in clinical trials. This is even more the case in economic evaluations of new diagnostic procedures where the endpoint for the clinical studies would be the number of patients identified. Unless the new diagnostic procedure is as effective as or more effective than the existing technology at the same or lower costs, economic evaluation needs to link the intermediate clinical endpoints to final outcomes such as QALYs gained. Furthermore, if the new diagnostic procedure is more effective than the existing practice, it may both affect the possibilities for successfully treating patients and the cost of treating these patients. For example, a new diagnostic procedure may be able to identify patients at an earlier stage of their disease than existing practice which may introduce the possibility of treating patients with less intensive treatments, or even more costly treatments. Thus, modelling is useful both to link intermediate clinical outcomes to final outcomes and to estimate long run cost consequences, either potential cost

[1]Institute of Publich Health, Health Econommic, University of Southern Denmark, Odense Denmark.

[2]Health Economics Research Unit, University of Aberdeen, Scotland, UK

savings or additional costs resulting from the intervention.

Another useful feature of modelling is the option to generalise results to other settings both in terms of generalising from clinical trials to routine practice and to generalise from one country to another [3].

Alzheimer's disease is a degenerative and fatal disease of the brain that advances by stages. The symptoms are losses of cognitive and emotional abilities that interfere with daily functioning and quality of life [4]. The prevalence of dementia ranges from below one per cent for persons less than 65 years old to more than 36 per cent for persons more than 95 years old [5]. Alzheimer's disease is the most prevalent of dementias accounting for about two thirds of dementia cases and is the main reason for the increased prevalence of dementia with age [6]. Drug treatment with donepezil is now available to patients with mild to moderate Alzheimer's disease. The drug is not curative, but studies have shown that it may delay the progression of the dementing process in a proportion of patients [7]. Donepezil is part of a group of pharmaceutical drugs that inhibits the breakdown of acetylcholine, which is an important neurotransmitter associated with memory. Other drugs are rivastigime and metriphonate. Cost-effectiveness studies of donepezil treatment suggest that the time patients spend in the severe stage of their dementia may be reduced by two to six months and that cost of donepezil treatment may be offset by a reduction in the costs of care compared with a no treatment alternative [8-12]. Experience from a Scottish region, that offers treatment according to a protocol developed for local use, shows that about half of the patients in donepezil treatment respond to the drug [13].

Diagnosis of Alzheimer's disease is problematic because there is no specific biological marker for the disease. Definitive diagnosis of Alzheimer's disease is by post-mortem examination of the brain tissue or through a brain biopsy [14]. Diagnostic criteria to identify possible or probable Alzheimer's disease have been developed which are reported to give 62% - 92% accuracy [4]. Lack of specificity of the criteria or the instruments used to evaluate the criteria may cause classification error, whereas lack of sensitivity may result in some patients remaining undiagnosed [14].

Single photon emission computed tomography (SPECT) imaging of the brain is a method to study the brain function. It can demonstrate some characteristic deficits that appear early in the course of Alzheimer's disease, and it has the potential to differentiate dementia from depression, which often has clinical overlap with dementing illnesses [15]. Nevertheless, its usefulness as a diagnostic test for Alzheimer's disease has been questioned in a number of studies reporting a range of values for the sensitivity and specificity of the test [16-19]. Traditional scan reporting uses visual inspection of the scan images

whereas a novel reporting method, Statistical Parametric Mapping (SPM), involves expressing SPECT scans as statistical maps based on reference scans from a normal population. It is anticipated that the SPM-based method will improve the early diagnosis of Alzheimer's disease compared with the traditional method.

Economic evaluations in Alzheimer's disease have mainly focused on the treatment of the dementia. However, as new diagnostic procedures and instruments are developed, economic evaluations are needed to guide decision making both in terms of healthcare policy and further research. These evaluations could be based on the models of the cost-effectiveness of drug treatment, which are mainly based on models, so called state-transition models or Markov models.

The basic idea of a state-transition model is that the patient at any time is in one of a finite set of health states, which are mutually exclusive and collectively exhaustive, and that changes form one state to another take place according to a set of transition probabilities over a discrete time period [20]. The model starts with an initial distribution of patients in different states of the disease. In Alzheimer's disease, a set of disease states can be defined by, for example, the Clinical Dementia Rating (CDR) scale or the Mini-Mental State Examination (MMSE) [21]. Attaching costs and quality-of-life weights to each state, it is possible to calculate the total cost and quality-adjusted life years (QALYs) of various treatment alternatives.

Four published studies of the cost-effectiveness of donepezil treatment use a state-transition model [8-11]. They all agree that donepezil treatment is a cost-effective and possibly cost saving even though some of their basic assumptions differ. First, the initial distribution of patients by disease state differs between the studies. Two studies [8;10] analyse various scenarios separately assuming all patients initiate donepezil treatment in a given state. An alternative to this approach assumes that the initial distribution on disease states is that observed in a clinical trial [11].

Second, the transition probabilities seems to differ significantly, mainly with respect to transitions to the *absorbing state*, dead, that it is impossible to leave once entered. Either mortality is included as a fixed rate [9;10] or severity specific mortality rates are used in the models [8;11]. The latter approach leads to the result that donepezil treatment has an effect on life expectancy even though there is no evidence from clinical trials that donepezil reduces mortality. In addition, three studies allow for transitions from a more severe state to less severe states [8-10].

Third, different measures of effectiveness are used in the studies either calculating the number of QALYs that are gained with donepezil treatment [8] or estimating reductions in the time patients spend in the severe state of their dementia [9-11]. Calculating QALYs for the treatment and no-treatment groups assuming that the transition probability to death differs by disease state causes a mortality effect on the difference in QALYs rather than a quality-of-life effect [8].

Fourth, the time horizon differs from eighteen months to five years. In addition, various assumptions are used on the duration of the drug effect because the clinical trials of donepezil treatment in patients with Alzheimer's disease lasted only 24 weeks. In one study the time horizon is equal to the duration of the drug effect which is judged to last for eighteen months by clinical experts [8]. The five years time horizon is used in three studies assuming that the effect of the drug lasts for 24 weeks only [9-11]. In the models this assumption is implemented by letting the transition probabilities differ in the first cycle of the state-transition model only, and thereafter, the transition probabilities for patients who are treated with donepezil are assumed to be equal to those of the patients who do not receive drug treatment. That is to assume that the progression of the dementia in patients who are treated with donepezil parallels the progression of untreated patients after six months treatment. In one study, the authors assume that the duration of the drug effect is that of the time horizon [11].

Methods and data

The framework

This study is a cost-effectiveness analysis in which costs and effects of the SPM-based method and the traditional scan reporting method are calculated and presented in a ratio of incremental costs to incremental effects [22]. The SPM-based method and the traditional scan reporting method are the programmes under consideration and the option of not scanning the patient is the comparator.

The study takes on the societal perspective. From this perspective all costs and outcomes are taken into account regardless of whom they affect. The study follows a cohort of patients for the duration of their lives, i.e. the time horizon is the patients' maximum life expectancy. Discounting future costs and outcomes at 5% per annum, we estimate total and incremental costs and outcomes. That is to adjust all costs and outcomes for differential timing and to present the costs and outcomes at their present value. All costs are reported in GBP (year 2000), and the outcomes used are quality-adjusted life years (QALYs).

The model

A decision tree is constructed to estimate expected costs and effectiveness of the SPM-based method, the traditional scan reporting method and the option of not scanning the patient [23;24] (Figure 1). The decision tree considers a patient who has completed examination and now is referred for a SPECT scan in order to identify patients suffering from Alzheimer's disease or alternatively to initiate drug treatment. The upper branch, *SPM*, represents the strategy of statistical mapping of the SPECT images, and the middle branch, *Traditional*, represents the traditional strategy of using visual inspection to analyse the images. The lower branch, *No SPECT*, represents the possibility of initiating drug treatment to all patients with suspected Alzheimer's disease without further examination with SPECT scanning.

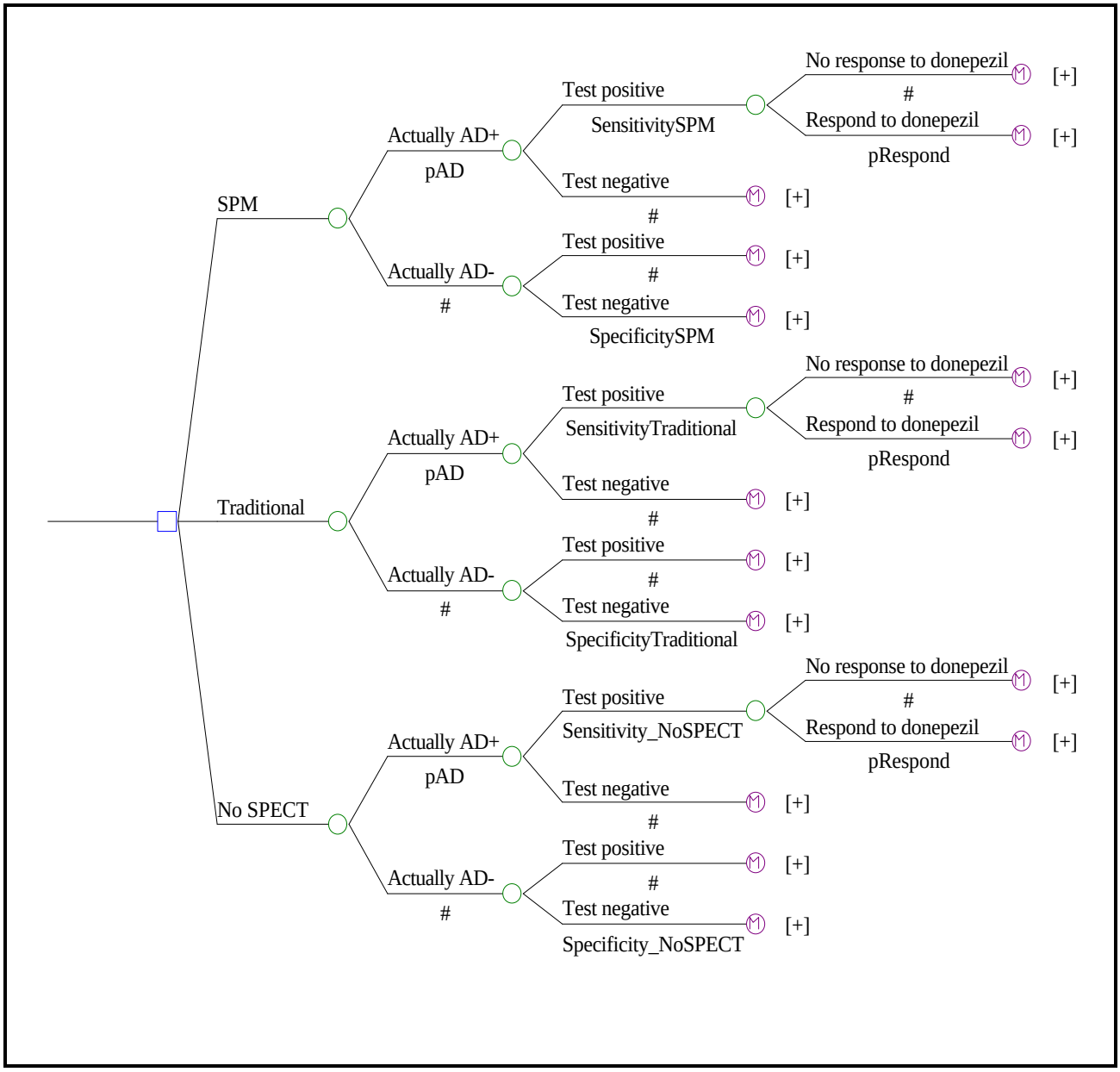

Figure 1 Decision Tree

For both the SPM branch and the Traditional branch as well as the No SPECT branch, there is an underlying and unknown probability that the patient actually suffers from Alzheimer's disease, p_{AD+}. This probability is the same for all strategies. Whether the patient actually suffers from Alzheimer's disease or not, there is a probability that the analyses of the SPECT scan test concludes that the patient is an Alzheimer's disease sufferer, i.e. *test positive*. If the patient actually is suffering from Alzheimer's disease, the probability of a positive test is the *sensitivity* of the tests. If the patient does not actually suffer from Alzheimer's disease, the probability of having a negative test result is the *specificity* of the test. (1 - sensitivity) represents the probability that the examination fails to identify a patient with Alzheimer's disease, and (1 - specificity) is the probability of falsely classifying a person as an Alheimer's disease patient.

If the patient is actually suffering from Alzheimer's disease there is an underlying and unknown probability that the patient will respond to treatment with donepezil, $p_{respond}$.

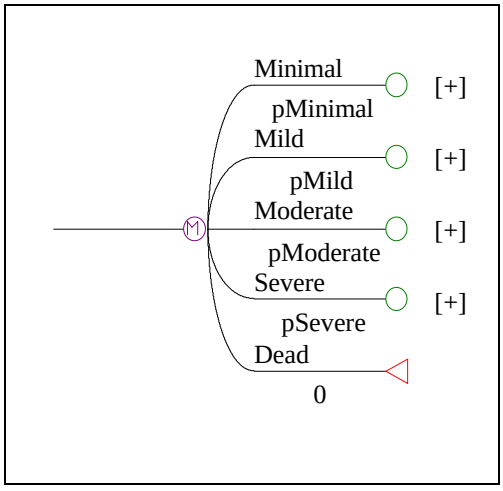

Figure 2 State-Transition Model

The long-term consequences in terms of costs and benefits of medical treatment are calculated with a state-transition model (Figure 2) [20;25;26]. States are defined by score intervals on the Mini Mental State Examination (MMSE), which is an instrument to measure a patient's cognitive ability [9]. Four states of Alzheimer's disease are defined in the model: minimal; mild; moderate; and severe (see table 1). A fifth state, dead, is defined as an absorbing state. Then, the state-transition model projects the progression of Alzheimer's disease patients into more severe disease stages using 6-month transition probabilities. The transition probabilities for Alzheimer's disease patients who receive donepezil are calculated by multiplying the transition probability with one minus the effectiveness of the drug [20]. The state-transition model starts with an initial distribution of patients assigned to different disease states,

$p_{minimal}$, p_{mild}, $p_{moderate}$ and p_{severe}. In each 6-month period there is a risk of dying, p_{Dead}.

As the patients cycle through the model, they accrue costs and quality-of-life weights associated with each state providing the basis for calculating expected costs and QALYs for each strategy.

Probabilities

Parameter estimates on the proportion of patients that actually suffer from Alzheimer's dementia; sensitivity and specificity of the diagnosis; the initial distribution on disease stage; transition probabilities; and mortality rates are obtained from the literature. Estimates of the drug effect are obtained from published journal articles from clinical trials of donepezil treatment in patients with Alzheimer's disease. Where a parameter estimate cannot be derived directly from the literature, the parameter estimate is based entirely on assumptions.

Six-month transition probabilities are estimated by the following formula where such probabilities are not directly available from the literature:

$$tp_{0.5} = 1 - (1 - tp_t)^{1/(t \times 2)}$$

where $tp_{0.5}$ is the 6-months transition probability and tp_t is the overall probability over time period t in years [20].

Costs

Direct costs include the value of all the goods, services, unpaid caregiver time and other resources that are consumed in the provision of an intervention or in dealing with the side effects of other current and future consequences linked to it [22].

Cost of SPECT scan

The cost of a SPECT scan is the cost of the staff and consumables used in carrying out the scan, cost of purchasing the scanner and other equipment, maintenance costs, room charges, administration, post, phones and other overheads to the department.

Information on resource use related to carrying out a SPECT scan is provided by consultants and physicists responsible for scanning patients. This includes information on the use of consumables and staff carrying out a scan, the number of brain scans per year, the proportion of the capacity used for brain SPECT scans and the length of time preparing and carrying out a scan.

The cost of a SPECT scan due to purchasing the equipment is estimated by annuitising the initial capital outlay of purchasing the scanner over its useful life and dividing this estimate by the number of brain scans that is carried out per year adjusting for the fact that the scanner is used for other imaging purposes than brain SPECT. Thus, the equivalent annual cost is multiplied by the proportion of the use of the scanner that is used for brain scans and divided by the total annual number of brain scans. The equivalent annual cost of purchasing the scanner is calculated with the following formula [27;28]

$$EAC = \frac{P - S(1+i)^{-n}}{A(n,i)}$$

where *EAC* is the calculated equivalent annual cost of purchasing the equipment, *P* is the cost of purchasing the equipment, *S* is the resale value of the equipment after n years in service, *n* is the total number of years that the equipment is used, *i* is the discount rate, and *A* is the annuity factor.

The annuity factor, A, is calculated with the following formula:

$$A(n,i) = \frac{1-(1+i)^{-n}}{i}$$

The annual maintenance cost of the scanner is allocated to a scan by multiplying the annual maintenance cost by the proportion of the scanner use that is used for brain SPECT and divided by the number of brain SPECT scans per year.

To allow for overhead costs, including porters, room charges, administration, post, phones and other overheads to the department, a proportion is added to the cost per scan. The initial capital outlays of purchasing the hardware and software requirements for SPM are allocated to a SPECT scan in the same way as allocating the purchasing cost of the scanner.

Cost of pharmaceutical treatment of patients suffering from Alzheimer's disease includes the cost of the drug and additional office visits to monitor the effectiveness of the drug, the dose adequacy of the dose and the presence of side effects. Other healthcare cost, cost of social services and unpaid caregiver time related to Alzheimer's disease are based on published estimates of the cost of Alzheimer's disease by degree of dementia.

Calculation of Quality Adjusted Life Years

Quality adjusted life years are calculated as a weighted sum of years lived where each life-year is weighted by their quality of life, utility weights [29;30]. The assumption is that a year in full health is valued 1, and years of life at less optimal health are weighted by a value less than one. Thus, it is as-

sumed that the quality of life for mildly demented patient is less than that of a nondemented person and that the quality of life for a mildly demented patient is higher than that for a moderately demented patient and so on. Utility weights associated with each state of the disease are obtained from the literature.

Since utility weights only exist for states of Alzheimer's disease defined by the Clinical Dementia Rating (CDR) scale, we assume that utility weights can be assigned to MMSE scores by mapping CDR scores to MMSE scores (Table 1).

Table 1 Disease severity and mapping scores on the mini mental state examination (MMSE) with scores on the clinical dementia rating (CDR) scale.[1]

Disease severity[2]	MMSE score	CDR score
Minimal	27 – 30	0.5
Minimal	21 – 26	0.5
Mild	15 – 20	0.5
Moderate	10- 14	1
Severe	< 10	2, 3, 4 and 5

note: 1) see Reisberg et al [21] 2) see Stewart et al [9].

Key assumptions of the model

We assume that donepezil treatment is not offered to patients who suffer from severe Alzheimer's disease. If a patient who actually suffers from Alzheimer's disease does not respond to the treatment, we assume that the patient receives the drug for three months before the patient discontinues treatment. Also, if a patient is falsely classified as an Alzheimer's disease sufferer and drug treatment is initiated, we assume that the patient receives the drug for three months before discontinuing treatment. Furthermore, donepezil treatment is assumed to include an extra office visit every six months.

For patients with Alzheimer's disease in moderate or less severe stages of the disease and who respond to drug treatment, we assume that the patient discontinues treatment for no other causes than disease progression into the severe stage. In patients who do not actually suffer from Alzheimer's disease and for whom donepezil treatment is initiated, we assume that drug treatment is discontinued after three months.

Data

Data input for the model are summarised in table 2. Based on epidemiological findings we assume that the proportion of patients that suffer from Alzheimer's disease is 67 % [6]. The sensitivity and specificity of the SPECT scan is derived from Jobst et al [31]. These estimates are used to estimate the sensitivity and specificity of the diagnosis based on the SPM-based SPECT scan method and without SPECT

scanning. We thus assume the sensitivity and specificity of the diagnosis using SPECT with visual inspection of the image is a result of increasing sensitivity and specificity of the diagnosis without SPECT by 18.7 % and 23.1 % respectively. Likewise, we assume that the SPM-based SPECT scan improves sensitivity and specificity by 6.7 % and 12.5 %, respectively, compared with visual inspection of the scan image.

Table 2 Data input for the model

Item		Estimate	Data source
Proportion actual AD sufferers		0.67	Andersen et al [6]
Sensitivity of diagnosis			
Without SPECT		0.75	Assumption
With Traditional SPECT		0.89	Jobst et al [31]
With SPM-based SPECT		0.95	Assumption
Specificity of diagnosis			
Without SPECT		0.66	Assumption
With Traditional SPECT		0.80	Jobst et al [31]
With SPM-based SPECT		0.90	Assumption
Initial distribution of patients by disease state			
Minimal		0.60	Assumption
Mild		0.35	
Moderate		0.05	
Severe		0	
6-months transition probabilities No donepezil			
From state	To state		
Minimal	Minimal	0.778	Stewart et al, 1998 [9]
	Mild	0.222	
	Moderate	0	
	Severe	0	
	Dead	Mortality	
Mild	Minimal	0.096	
	Mild	0.580	
	Moderate	0.307	
	Severe	0	
	Dead	Mortality	
Moderate	Minimal	0	
	Mild	0.166	
	Moderate	0.300	
	Severe	0.533	
	Dead	Mortality	
Severe	Minimal	0	
	Mild	0	
	Moderate	0	
	Severe	1	
	Dead	Mortality	
Mortality		0.13	Authors calulations from Østbye et al (1999) [32]
Proportion of patients that respond to donepezil		0.52	Hughes et al [13]
Effect of donepezil		0.4807	Jönsson et al (1999) [11]
Duration of drug effect		time horizon	Assumption

Table 2 (contimued) Data input for the model

Cost of SPECT scan		
Cost of purchasing SPECT scanner	330,000 GBP	Personal comunication
Resale value	0 GBP	Assumption
Annual maintenance cost	20,000 GBP	Personal comunication
The total number of years the scanner is in use	10 years	Personal comunication
Radiographer's time	45 minutes	Personal comunication
Nurse's time	20 minutes	Personal comunication
Consultant's time	5 minutes	Personal comunication
Physicist's time	5 minutes	Personal comunication
Salary radiographer	12.74 GBP/hour	Assumption
Salary Nurse	11.49 GBP/hour	Assumption
Salary Consultant	41.43 GBP/hour	Assumption
Salary Physicist	16.07 GBP/hour	Assumption
Cost of radiopharmaceutical	112 GBP/scan	Personal comunication
Overhead cost (proportion added on direct cost of scan)	20 %	Assumption
Cost of purchasing SPM hardware and software	500 GBP/year	Assumption
Additional physicist time due to SPM processing	60 minutes	Assumption
Proportion of scanner time used for brain SPECT	0.15	Personal comunication
Total number of brain SPECT scans per year	420 scans	Personal comunication
Transport cost	25 GDP/scan	Foster et al [x]
Cost of drug	104 GBP/month	Whole sale price
Cost of additional visits associated with donepezil treatment	32 GBP/visit	Neumann et al [8]
Costs of dementia by disease severity		
Minimal	4,117 GBP/year	Calculated from Jönsson et al
Mild	14,133 GBP/year	[11]
Moderate	20,280 GBP/year	
Severe	33,470 GBP/year	

Table 2 (continued) Data input for the model

Utility weights	Estimate	Data source
Minimal	0.73	Mapped on MMSE scores from Neumann et al [35]
Mild	0.73	
Moderate	0.69	
Severe	0.44	
Non-AD patients	0.73	Assumption
Discount rate (annual)		
Costs	0.03	Assumption
Outcome	0.03	

Transition probabilities are obtained from Stewart et al [9], where estimates of progression of cognitive impairment for persons not receiving any therapy for dementia are calculated from an epidemiological study, the Cambridge cohort study of frail elderly people. The mortality rate is calculated from Østbye et al [32] who report that 556 out of 739 patients with Alzheimer's disease have died within five years. This is equivalent to a half-year mortality rate of 0.13.

Based on a 24-week controlled trial of donepezil in patients with Alzheimer's disease, Jönsson et al [11] has calculated that the probability of moving to a more severe state of dementia is 48 % lower for patients who are treated with 10 mg donepezil per day when compared with patients who do not receive the drug.

The annual salaries for radiographers, nurses, physicists and consultants are assumed to be GBP 19,500, GBP 17,830, GBP 26660 and GBP 66,000 respectively. To these salaries we have added 16 % to allow for National Insurance and superannuation. To estimate an wage rate per hour we assume that staff work 48 weeks per year and that a number of hours of work per week are 37 for a radiographer, 37.5 for a nurse, 40 hours for a physicist, and 38.5 hours for a consultant.

Based on the parameter estimates in table 2, the cost of a SPECT scan is thus calculated to 190.27 GBP, and it is calculated that SPM adds 20.49 GBP to the cost of a scan. To cover community costs to transportation to the nearest SPECT scanner is assumed to average GBP 25 [34].

The cost of donepezil is estimated to GBP 104 per month, where the dose is 10 milligrams per day. The drug cost is estimated from the price of a packet with 28 tablets. The cost of extra office visits induced by donepezil treatment is calculated from Neumann et al [8] using an exchange rate of 0.68 GBP/USD. This estimate includes the cost of a visit for drug management.

Estimates on the cost of caring for demented patients is obtained from Jönsson et al [11] and calculated into GBP using an exchange rate of 0.074 GBP/SEK. These cost estimates include nursing home, home help and drugs (excluding donepezil).

Utility weights have been reported by Neumann et al [35] using the Health Utilities Index Mark II (HUI:2) in a cross-sectional study of 679 Alzheimer's disease patients and caregiver pairs where the

caregivers responded both as a proxy for the patients and for themselves. We have calculated the utility weight to severely demented patients that is defined by a MMSE lower than ten to 0.44 which is a weighted average of the utility weights as reported by Neumann et al [35].

Sensitivity analysis

Sensitivity analysis is carried out to reflect uncertainties in the numerical values of the parameters used as inputs in the model, that is *parameter uncertainty* [36]. Parameter uncertainty is analysed with one-way sensitivity analysis, where one variable is changed at a time, and multi-way sensitivity analyses, where two or more parameter values are changed at the same time.

First, we analyse the cost-effectiveness of the three strategies varying the assumption on the sensitivity and specificity of the tests without SPECT scanning of the patients before drug treatment is initiated. In addition, we analyse the cost-effectiveness of the three strategies varying the effect on the sensitivity and specificity of the tests due to SPECT scan with visual inspection of the scan, and the effect which is due to the SPM-based SPECT.

Second, we analyse the implications of varying the assumption of the characteristics of the patient cohort. This includes varying the proportion of patients who actually suffer from Alzheimer's disease, the initial distribution of patients by disease severity, and the quality-of-life weights, which are used to estimate QALYs.

Third, the effect of drug treatment is analysed both in terms of the effect on disease progression and duration of the drug effect. Fourth, we analyse the cost-effectiveness of the three strategies varying the discount rate and the assumption of overhead cost.

Finally, we analyse the consequences of allowing for increasing mortality rates with disease progression, and changing the transition probabilities between different states of the disease. For the later analysis, we use the transition probabilities which are calculated from Jönsson et al [11] in Appendix A. The increase in mortality by disease state is also based on calcultations in Appendix A.

Results

The average cost-effectiveness of the SPM-based SPECT scan is estimated to 16.157,17 GBP/QALY, that of the SPECT with visual inspection of the scan is estimated to 16.267,98 GBP/QALY, and the cost-effectiveness the option of not scanning patients before drug treatment is 16.523,71 GBP/QALY

(table 3). Thus, the traditional scan reporting method is dominated by the SPM-based method, and the option of not scanning is dominated by the traditional scan reporting method.

Table 3 Cost effectiveness of SPM-based SPECT scans versus Traditional SPECT scans.

Strategy	Costs (GBP)	QALYs	C*	Q*	C/ Q (GBP)
SPM	37,999	2,352			
Traditional	38,201	2,348	201.64	-0.004	(Dominated)
No SPECT	38,662	2,340	460.75	-0.008	(Dominated)

* C = change in costs; Q = change in quality-adjusted life-years (QALYs).

Sensitivity analyses of varying the assumptions on sensitivity and the specificity of the option of not scanning the patients before drug treatment is initiated shows that the SPM-based method remains the dominant strategy irrespective of the starting point of the sensitivity and specificity of the tests. However, estimates of the cost per QALY are more sensitive to the sensitivity of the diagnosis than to the specificity of the tests.

The sensitivity analysis of the effect of SPECT scanning with visual inspection of the scan shows a threshold value around 3.5%. That is, if SPECT scanning can improve the sensitivity of the tests from, for example, 75 % to 77.6 %, SPECT scanning dominates the option of initiating drug treatment to all patients. If the sensitivity of the test can be improved further by more than 0.2 %, the SPM-based strategy dominates the traditional SPECT scan reporting method and the option of not scanning. These threshold values vary little with the sensitivity and specificity of the tests without SPECT.

Varying the proportion of patients that actually suffers from Alzheimer's disease shows that the SPM-based strategy remains dominant over the traditional scan reporting method and the option of not scanning the patients before drug treatment is initiated. However, the cost per QALY estimate is highly sensitive to the proportion of Alzheimer's disease sufferers. The cost per QALY estimates are also highly sensitive to the assumption on the initial distribution by disease state, but it does not change the dominance of the SPM-based SPECT scan method over the two other strategies except in the case where all patients start in the severe state (Table 4).

The quality-of-life weights for different states of the disease influence cost-effectiveness but not the dominance of the SPM-based method over the two other strategies. In particular, the cost-effectiveness is sensitive to the quality-of-life weight assigned to patients who do not suffer from

Alzheimer's disease.

Table 4 Sensitivity analyses

Item		Cost per QALY (GBP) No SPECT	Traditional	SPM
Proportion Alzheimer's Disease				
0.50		12,099	11,949	11,862
0.75		18,669	18,378	18,235
1.00		25,646	25,185	24,975
Initial distribution of patients by disease state				
All start in minimal state		12,679	12,448	12,331
All start in mild state		21,534	21,255	21,116
All start in moderate state		31,293	31,083	30,970
All start in severe state		42,429	42,633	42,681
Proportion of patients that respond to donepezil				
0.30		17,058	17,126	17,058
0.70		15,946	15,601	15,434
Effect of donepezil				
0.30		17,429	17,351	17,297
0.50		16,422	16,161	16,029
0.70		14,667	14,880	15,335
Duration of drug effect				
6 months		18,447	18,429	18,339
12 months		18,045	18,052	18,021
18 months		17,708	17,736	17,755
24 months		17,428	17,473	17,533
60 months		16,157	16,281	16,524
Mortality rate				
0		21,165	20,725	20,527
0.32		11,687	11,737	11,714
0.50		10,073	10,281	10,303
Quality-of-life weights by disease state				
Minimal	0.73			
Mild	0.69			
Moderate	0.53			
Severe	0.34			
Non-AD	0.73	17,439	17,157	17,016
Quality-of-life weights Non-AD				
0		25,672	25,244	25,031

1		14,600	14,391	14,284

Table 4 (continued) Sensitivity analyses

Item	Cost per QALY (GBP) No SPECT	Traditional	SPM
Overhead cost to SPECT scan			
0	16,524	16,268	16,143
0.30	16,524	16,287	16,164
Discount rate			
0	17,133	16,861	16,726
0.05	16,159	15,934	15,817
0.10	15,371	15,187	15,085

The sensitivity analysis on the duration of the drug effect shows, that there is a threshold value of 13.8 months. Below this value, the option of not scanning the patients dominates the two other strategies, whereas duration that lasts longer than the threshold value makes the SPM-based SPECT scan the dominant strategy.

The result of the SPM-based SPECT scan method dominating the two other strategies is not changed by differences in the discount rate or changes in the overhead cost to the department where the scan is carried out.

The assumption on the mortality rate influences the cost-effectiveness of the three strategies, where a mortality rate above 0.30 causes the option of not scanning the patient to dominate the other two strategies. Furthermore, if we allow for increasing mortality with disease severity, there are no dominant strategies. For example, if the mortality rate for minimal and moderate demented patients is that of the patients who do not suffer from Alzheimer's disease, and the mortality rates of moderate and severe demented patients are 2.8 and 4.2 times higher respectively than the non-Alzheimer's disease group, the incremental cost-effectiveness ratio of SPECT scan over no scanning is 15,499 GBP/QALY, and the incremental cost-effectiveness ratio of SPM-based SPECT over SPECT with visual inspection is 9,121 GBP/QALY.

Using the state transition probabilities which are calculated from Jönsson et al [11], the incremental cost-effectiveness ratio of SPECT with visual inspection over no scanning of the patients is 25,037 GBP/QALY, and the incremental cost-effectiveness ratio of the SPM-based reporting method over the visual inspection method is 16,379 GBP/QALY (Table 5).

Table 5 Cost effectiveness of SPM-based SPECT scans versus Traditional SPECT scans using transition probabilities from Jönsson et al [11].

Strategy	Costs (GBP)	QALYs	C*	Q*	C/ Q (GBP)
No SPECT	34,322	2.916			
Traditional	34,638	2,928	316	0.012	25,037
SPM	34,727	2,934	89	0.005	16,379

* C = change in costs; Q = change in quality-adjusted life-years (QALYs).

Discussion

The objective of this study has been to develop a model to compare the cost-effectiveness of two methods of scanning the brain using single photon emission computed tomography (SPECT) in diagnosing Alzheimer's disease and to compare these methods with the option of not scanning the patients before drug treatment is initiated.

Based on this model, one tentative suggestion might be that even small changes in the sensitivity of the tests to detect Alzheimer's disease might be cost saving and, furthermore, improve patients quality-of-life. This conclusion seems very robust to changes in some of the parameter values that are used as inputs in the model. However, the sensitivity analyses of proportion of patients with Alzheimer's disease, their mortality, and the distribution by disease severity might reflect important characteristics of the patients that need to be examined more closely. For example, the mortality in the general population increases with age, and since a high mortality rate changes the dominance of the SPM-based SPECT scan to the option of not scanning the patients, this might suggest that SPECT scanning should only be undertaken selectively in more elderly patients as suggested by Foster et al [34] in their analysis of the use of CT scanning in dementia.

Furthermore, the differences in the probabilities of progressing to more severe states of the disease, which are observed in published studies of the cost-effectiveness of donepezil treatment in Alzheimer's disease, might also reflect differences in the characteristics of the patient cohort. The transition probabilities reported by Jönsson et al [11] suggest that the disease progresses at a slower rate than the transition probabilities used by Stewart et al [9] and O'Brien et al [10].

Generalisability is an important strength of modelling. In this study we have focused on modelling the

cost-effectiveness of SPECT scans in diagnosing Alzheimer's disease, but the model might easily be extended to assess the cost-effectiveness of diagnosing Alzheimer's disease in general where other diagnostic tools and instruments are used. With a general model of diagnosing Alzheimer's disease it is possible to assess the incremental costs and effect of including such new instruments in the test battery. Such a model would reflect actual clinical practice more than a model that only considers one diagnostic instrument.

A limitation of this study is, however, that we do not include the cost of unpaid caregiver time even though we carry out the analysis from the societal perspective. Studies of the cost of Alzheimer's disease have shown that one-third of the total cost of care for persons with severe Alzheimer's disease is costs of unpaid caregiver time, whereas the proportion of unpaid caregiver time cost of the total cost of care are more than 70 % in patients with mild to moderate dementia [37]. Thus, one consequence of delaying the dementing process might be that more cost is passed on to the patient's relatives.

Other major limitations of the study are that the data are obtained from various sources and based on assumptions where data are not available from the literature. First, regarding the quality-of-life weights used in the model. Since a clear relationship between MMSE score intervals and scores on the CDR scale is not available, bias might have been introduced in mapping the quality-of-life weights on MMSE scores from the CDR scale. Furthermore, the Health Utilities Index Mark II (HUI:2) used to derive quality-of-life weights to scores on the CDR scale has not been validated in Alzheimer's disease [8], and allowing patients who do not suffer from Alzheimer's disease to contribute to the calculations of QALYs might also have biased the results. Second, bias might have been introduced using costs from other settings than the one that is under consideration. This includes both the costs of caring for patients at different stages of Alzheimer's disease and the costs of additional office visits due to drug treatment. Third, a more subtle form for bias, that might have been introduced, is in the choice of which data sources to use. This is clearly seen from the sensitivity analysis of using different transition probabilities in the state-transition model. Thus, care should be taken when interpretating the results of this model.

The implications of the findings from this study are more with respect to further research than actual policy. The patient cohort, or the population, that the new technology is targeted to should be thoroughly described. This includes a description of the patients that do not actually suffer from the disease which the technology focuses on; in this case Alzheimer's dementia.

The assumptions about transition probabilities, in particular, seem to call for more research. By merging

data from different epidemiological studies, estimates on transition probabilities might be more representative. Such estimates would be highly valuable in revising existing models on the cost-effectiveness of donepezil treatment, and to evaluate new generations of the drug to delay or stop the dementing process. In the end, this would also be highly valuable in revising models to assess the cost-effectiveness of new technologies to detect Alzheimer's disease.

Further research should also focus on the inclusion of the other costs of diagnosing Alzheimer's disease. In the present study, as with the studies of the cost-effectiveness of donepezil treatment, the cost of the *core* tests in diagnosing Alzheimer's disease have not been included, e.g. blood tests to rule out other conditions known to affect cognitive functions. Also, other perspectives than the societal perspective should be considered in order to analyse whether administrative bodies have different incentives to initiate examination and drug treatment of the patients.

In conclusion, a model to compare the cost-effectiveness of alternative methods in diagnosing Alzheimer's disease can be developed. However, the results from such a modelling aproach should be interpreteted with care. The development of a model of the cost-effectiveness of SPECT scans in diagnosing Alzheimer's disease has highlighted the diversities in other models of the cost-effectiveness of donepezil treatment in Alzheimer's disease. This calls for more research on the impact of drug treatment on disease progression as well as the disease progression in patients who do not respond to drug treatment. Finally, it will be important to analyse the cost-effectiveness of interventions for Alzheimer's disease with varying patient characteristics because these might influence the results.

Acknowledgements

The Health Economics Research Unit (HERU) is funded by the Chief Scientist Office of the Scottish Executive Health Department (SEHD). This study received financial support from BIOMED:II. The views expressed in this paper are those of the authors and not necessarily those of the SEHD.

Reference List

1. Sculpher M, Drummond M, Buxton M. The iterative use of economic evaluation as part of the process of health technology assessment. J Health Serv Res Policy 1997;2:26-30.

2. Sheldon TA. Problems of using modelling in the economic evaluation of health care. Health Econ. 1996;5:1-11.

3. Buxton M, Drummond MF, van-Hout BA, et al. Modelling in economic evaluation: an unavoidable fact of life.

Health Econ. 1997;6:217-227.

4. Fratiglioni L. Classification and Diagnostics. In: Wimo A, Jönsson B, Karlsson G, Winblad B, eds. Health Economics of Dementia. Chichester: Wiley, 1998:3-12.

5. Hofman A, Rocca WA, Brayne C, et al. The prevalence of dementia in Europe: a collaborative study of 1980-1990 findings. Eurodem Prevalence Research Group. Int.J Epidemiol. 1991;20:736-748.

6. Andersen K, Lolk A, Nielsen H, Andersen J, Olsen C, Kragh-Sørensen P. Prevalence of very mild to severe dementia in Denmark. Acta Neurol Scand 1997;96:82-87.

7. Birks JS, Melzer D. Donepezil for mild to moderate Alzheimer's diesease (Cochrane Review).The Cochrane Library. 2000

8. Neumann PJ, Herman RC, Kuntz KM, et al. Cost-effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease. Neurology 1999;52:1138-1145.

9. Stewart A, Phillips R, Dempsey G. Pharmacotherapy for people with Alzheimer's Disease: A Markov-cycle evaluation of five years' therapy using Donepezil. Internationl journal of Geriatric Psychiatry 1998;13:445-453.

10. O'Brien BJ, Goeree R, Hux M, et al. Economic evaluation of donepezil for the treatment of Alzheimer's disease in Canada. J Am Geriatr Soc 1999;47:570-578.

11. Jönsson L, Lindgren P, Wimo A, et al. The Cost-Effectiveness of Donepezil Therapy in Swedish Patients with Alzheimer’s Disease: A Markov Model. Clinical Therapeutice 1999;21:1230-1240.

12. Small GW, Donohue JA, Brooks RL. An economic evaluation of Donepezil in the treatment of Alzheimer's Disease. Clinical Therapeutics 1998;20:838-850.

13. Hughes A, Coulter F, Gillespie R, et al. Anticholinesterases in the treatment of Alzheimer's Dementia - the first year's experience in Argyll & Clyde. Health Bulletin 2000;58:20-24.

14. Alloul K, Sauriol L, Kennedy W, et al. Alzheimer's disease: a review of the disease, its epidemiology and. Archives of Gerontology and Geriatrics 1998;27:189-221.

15. Small GW, Leiter F. Neuroimaging for Diagnosis of Dementia. J Clin Psychiatry 1998;59 (suppl 11):4-7.

16. Claus Jj, van Harskamp F, Breteler MM, et al. The diagnostic value of SPECT with Tc 99m HMPAO in Alzheimer's disease: a population-based study. Neurlogy 1994;44:454-461.

17. Bergman H, Chertkow H, Wolfson C, et al. HM-PAO (CERETEC) SPECT brain scanning in the diagnosis of Alzheimer's disease. J Am Geriatr Soc 1997;45:15-20.

18. Scheltens P, Launer LJ, Barkhof F, Weinstein HC, Jonker C. The diagnostic value of magnetic resonance imaging and technetium 99m-HMPAO single-photon-emission computed tomography for the diagnosis of Alzheimer's disease in a community-dwelling elderly population. Alzheimer Disease & Associated Disorders 1997;11:63-70.

19. Masterman DL, Mendez MF, Fairnbanks LA, Cummings JL. Sensitivity, specificity, and positive predictive value of technetium 99-HMPAO SPECT in discriminating Alzheimer's disease from other dementias. J Geriatr Psychiatry Neurol 1997;1997:1-15.

20. Briggs AH, Sculpher M. An Introduction to Markov Modelling for Economic Evaluation. PharmacoEconomics 1998;13:397-409.

21. Reisberg B, Franssen E, Souren L, Kenowski S, Auer S. Severity Scales. In: Wimo A, Jönsson B, Karlsson G, Winblad B, eds. Health Economics of Dementia. Chichester: Wiley, 1998:327-357.

22. Gold MR, Siegel JE, Russel LB, Weinstein MC. Cost-Effectiveness in Health and Medicine. New York:Oxford University Press, 1996:

23. Detsky AS, Naglie G, Krahn MD, Naimark D, Redelmeier DA. Primer on medical decision analysis: Part 1 - getting started. Med Decis.Making. 1997;17:123-125.

24. Keeler E. Decision trees and Markov models in cost-effectiveness research. In: Sloan F, ed. health care. Cambridge University Press, 1996:185-206.

25. Sonnenberg FA, Leventhal EA. Modeling Disease Progression with Markov Models. In: Wimo A, Jönsson B, Karlsson G, Winblad B, eds. Health Economics of Dementia. Chichester: Wiley, 1998:171-195.

26. Naimark D, Krahn M, Naglie G, Redelmeier DA, Detsky AS. Primer on medical decision analysis: Part 5 - working with Markov processes. Med Decis.Making. 1997;17:152-159.

27. Richardson AW, Gafni A. Treatment of capital costs in evaluating health-care programs. Cost and Management 1983;26-30.

28. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Second ed. Oxford University Press, 1997:

29. Kaplan RM. Utility assessment for estimating quality-adjusted life years. In: Sloan F, ed. Valuing health care. Cambridge University Press, 1996:31-60.

30. Garber AM, Weinstein MC, Torrance GW, Kamlet MS. Theoretical Foundations of Cost-Effectiveness Analysis. In: Gold MR, Siegel JE, Russel LB, Weinstein MC, eds. Cost-Effectiveness in Health and Medicine. New York: Oxford University Press, 1996:25-53.

31. Jobst KA, Barnetson LPD, Shepstone BJ. Accurate Prediction of Historically Confirmed Alzheimer's Disease and the Differential Diagnosis of Dementia: The use of NONCDS-ADRDA and DSM-III-R Criteria, SPECT, X-Ray CT, and Apo E4 in Medial Temporal Lobe Dementias. International Psychiatrics 1998;10:271-302.

32. Østbye T, Hill G, Steenhuis R. Mortality in elderly Canadians with and without dementia. A 5-year follow-up. Neurlogy 1999;53:521-526.

33. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Neurology 1998;50:136-145.

34. Foster GR, Scott DA, Payne S. The use of CT scanning in dementia. Internation Journal of Technology Assessment in Health Care 1999;15:406-423.

35. Neumann PJ, Kuntz KM, Leon J, et al. Health Utilities in Alzheimer's Disease. A Cross-Sectional Study of Patients and Caregivers. Med Care 1999;37:27-32.

36. Manning WG, Fryback DG, Weinstein MC. Reflecting Uncertainty in Cost-Effectiveness Analysis. In: Gold MR, Siegel JE, Russel LB, Weinstein MC, eds. New York: Oxford University Press, 1996:

37. Rice DP, Fox PJ, Max W, et al. The economic burden of Alzheimer's disease care. Health Aff.Millwood. 1993;12:164-176.