

## **Alternative Approaches to the Economic Evaluation of a Drug for Patients with Alzheimers Disease**

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**Abstract**

The increasing prevalence of Alzheimer's Disease (AD), and the costs of the drugs emerging for its treatment, together pose the question of how to evaluate these drugs in economic terms. We examine two approaches, first, an outline proposal [1] examining the requirements of a cost-effectiveness analysis of AD drugs; as it is defined, there exist severe problems in the areas of quality of life measurement, and international cost comparisons. Secondly, we discuss the common approach to economic evaluation of a series of papers [2-4] examining the value of AD drugs, presented to the Irish Centre of Pharmacoeconomics. Though the measurement problems and data collection requirements are fewer, it becomes clear that this approach also has its difficulties, mainly in respect of inter-country comparisons. An alternative approach, using an extended post-marketing surveillance trial, is suggested, and its relative value assessed.

## **The Economic Evaluation of a Drug for Patients with Alzheimers Disease**

### ***Introduction***

The concept of scarcity has been applied widely to health over the past twenty or so years; cost-effectiveness analysis (CEA) is now a recognised response to the need for some method of prioritising health budgets[5-7]. Prioritising requires comparison, and comparison requires measurement; it follows that much of health economics is concerned with measurement issues.

The problems of measuring health impacts and health costs can be difficult enough when the relevant variables are well-defined, and when the relationship between intervention and effect is understood. The general problems of evaluating mental health treatments[8] also apply to Alzheimer's Disease (AD); treatment and care of the mentally ill improves patient quality of life, rather than its length, there is "intrinsic uncertainty" surrounding the nature of the disease and the efficacy of treatment, and patients are cared for in a variety of settings, which complicates the measurement of costs. Despite the complexity of the measurement problems, the necessity for achieving the maximum health impact from the resources available is particularly pressing, given the emotional and resource burdens imposed by this disease, and its increasing incidence.

We consider two approaches to the achievement of cost-effectiveness analysis (CEA), as a basis for understanding the problems which need to be addressed. The first[1] is conventional enough, in relation to the accepted standards of CEA, but the nature of AD presents difficult obstacles. If conventional CEA is problematic, how has the value for money of AD drugs been demonstrated? We outline a common approach, of which [2], [3], and [4] are published examples.

There are important problems of principle in relation to the calculation of AD treatment cost-effectiveness. If they are not resolved, new drugs may not be approved, and important health gains may remain unrealised.

### **The first approach: applying CEA to Alzheimer's Disease[1]**

The weighing of costs against outcomes, usually from the point of view of society as a whole, requires the measurement of both on a consistent basis. The authors [1] examine costing issues, and the measurement of treatment effects.

### **Costing issues**

As is conventional in CEA, the authors advocate the perspective of society; rather than economise from the point of view of a health service, or of a third-party payer, such as a health insurance firm, all resources are itemised, as far as possible, to determine the resource cost of the different alternative treatments from society's point of view. We consider two issues, 1) the generalisation of direct costs between countries, and 2) the valuation of informal care.

#### *1) Generalisation of Direct Costs Between Countries*

The cost of treating and caring for AD patients includes drug prescriptions, hospital episodes, and community care. The authors note that the proportions of costs vary between countries; in one, the greatest proportion might be hospitalisation expenses, while in another, the largest proportion might be formal and informal community care. That is to say, the relationship between different resource inputs and health "outputs" (in economic terms, the health care production function) is fundamentally different between countries. This is another reason for careful consideration of international comparisons of cost-effectiveness. Rather than using a multi-national clinical trial to assess whether a drug is cost-effective, it might be more appropriate to either develop such a trial with sufficient numbers of respondents in one country, or split the multi-national trial, by grouping countries according to their type of production function. There are as yet no reports of production function classifications which would allow the latter course to be followed.

## *2) Valuation of Informal Care*

According to the authors, there exists no standardised method for measuring the amount of informal care, for example, for measuring in the same units all the different activities which informal care involves. They propose a “straightforward” questionnaire, as a practical solution, without giving many details of its design; how such a questionnaire is to be validated, and in particular, how cultural differences are to be taken into account, is not discussed.

It may be that a valid method of measuring the amount of informal care can be devised; the authors go on to discuss two methods for putting a value on each (standardised) hour of care, opportunity cost, and shadow-price, and express a preference for a shadow-pricing approach. It is not clear to us that the difficulties of one approach are appreciably less than the other; without a standardised measure of care, further discussion is not productive.

### **Measurement of treatment effects**

Firstly, the authors’ aim is to provide a “minimal framework.... with maximum applicability and international acceptability”[1], because evaluations are usually based on multi-centre international controlled trials. They note that the disease becomes evident in behavioural disturbances, and that hence the disease diagnosis and expression are considered to be determined by cultural factors. It follows that a standard questionnaire, applied in all the countries involved, will not be reliable, and they propose that a research plan to establish cost-effectiveness for AD drugs should include “a minimum number of well-accepted and internationally validated questionnaires and costing principles”[1].

This does not seem to solve the problem of the cultural determination of the diagnosis and expression of the disease. Unless the differences resulting from variations in culture can somehow be identified and measured, all questionnaires will be unreliable. Also, the well-rehearsed problems of extending the results of controlled trials to routine practice are not examined [9-12]; it is fairly well-known that the results of a randomised controlled trial (RCT) constitute the best representation of an intervention’s efficacy, not its effectiveness[5]. It follows that the reliance of the approach upon the RCT methodology may be misplaced.

Secondly, the authors consider quality of life [qol] as the only outcome variable, explicitly addressing the question, “how much is quality of life influenced by a health care programme?” They review the various qol instruments which could be used to assess this outcome for AD patients, and for their carers, and conclude that the “spine” of internationally valid instruments, with locally relevant “branches”, envisaged at the outset, cannot be operationalised. This is because validated translations of many instruments are not available, and because generic measures (such as the SF-36, or the Nottingham Health Profile) are often designed for completion by the patient, so that scores cannot be interpreted meaningfully if they are generated by a proxy. This excludes a large amount of recent qol development work. The authors do not resolve the important problems involved in assessing quality of life (qol) for AD patients, and neither of two more recent comprehensive reviews[13,14] identifies a “gold standard” measure.

Given their multi-national orientation, it is interesting that the authors consider only qol impacts as health outcomes. Qol is subject to greater variation than, say, cognitive functioning; a focus on the latter might make international comparisons more feasible, though reliability and validity remain difficult issues.

It is clear that, even for single country studies, there are serious difficulties in the way of measuring the qol impacts of AD drugs; the need for a reliable and valid measure is urgent, and a measure of cognitive functioning, such as the Mini-Mental State Evaluation Scale (MMSE), might be a reliable and reasonably valid measure of outcome in Ireland. This is the measure adopted by the studies (based on multi-national trials) to which we turn in the second section.

To conclude this section, the difficulties facing the usual CEA approach, of balancing outcomes measured in quality of life terms against costs measured from society's viewpoint, are quite extensive. Measuring qol does not appear to be feasible, either because instruments are developed for only one country, and have not been validated in their translated form(s), or because the instruments were not designed for completion by a carer. Also, cost definition and measurement is problematic, and cultural factors imply that AD care production functions vary between countries, in ways which have not been formally investigated.

### **The “economic evaluation” of AD drugs**

A CEA is a formal attempt to measure all the costs and outcomes associated with alternative treatments, so that they can be compared in terms of cost per unit of outcome, from the viewpoint of society as a whole. An “economic evaluation” is a more vague term, which implies the balancing of benefits against costs in a rigorous way, but without a commitment to the comprehensiveness of society's viewpoint. All of the studies examined by the Irish Centre of Pharmcoeconomics fall into this category, and we now describe their common approach.

#### ***The common approach of the studies***

- 1) Data collection: A multi-national randomised controlled trial is carried out, over a six month period, during which data is collected using the MMSE, at baseline, and at the end of the trial.
- 2) Cost Relationships: A secondary data source is available, which relates the cost of caring for AD patients to the level of their MMSE scores; this is based on the proportions of patients institutionalised, and the cost of care in institutions and in the community. The data usually comes from one country, and relates therefore to the production of care only in that country.
- 3) Modelling: The RCT data is used as a basis for extrapolation to between two and five years beyond the six-month trial, using either survival functions or a Markov analysis to determine the time spent by each patient at a particular MMSE level.
- 4) The drug is justified on the basis that there will be a reduction in the costs of care to the health service, or to society, because the drug reduces the amount of time spent in an institution, and increases the amount of time spent in the community.

We discuss a) the Mini-Mental State Examination Scale, b) modelling, and c) resource identification and measurement.

**a) The Mini-Mental State Examination Scale**

The MMSE is the chosen psychometric instrument for measuring health impact; we explained above why a measure of cognitive functioning might be more useful than a qol measure in the CEA of AD treatments. However, the validity of the MMSE instrument has been questioned; its positive and negative features have been listed[15] as:

- + high test-retest reliability
- + may be used for staging
- high rate of false positives in low education etc.
- low discrimination of normal ageing to very mild dementia
- low discrimination of moderate to severe dementia
- no patterning of deficits in varying cognitive domains
- predominance of verbal items, visuospatial abilities are poorly evaluated
- some ambiguities exist, which could be overcome

The same source reports findings [16] that the MMSE was valid in moderate to severe dementia, but less so in cases of mild dementia, mostly because of its sensitivity to variations in age, education, and cultural background. In a relatively homogeneous society, such as Ireland, these variations might be less important than in a multi-national trial.

## **b) Modelling**

A modelling approach [17-20] is appropriate, because trial data cover only a six-month period, while costs and benefits over the longer term are likely to be important. Also, AD is poorly understood and difficult to diagnose, so that clear entry to a trial through a defined sequence of events is not possible. It makes sense to specify clear assumptions about patient progress, for comparison with physician or clinical experience, rather than to leave progress beyond the trial completely undefined. The extension of outcomes beyond a trial period is explicitly recognised as a justification for modelling by the Australian pharmacoeconomic guidelines[6] and the Canadian guidelines encourage the use of models, provided that the assumptions are “stated explicitly and thoroughly tested with sensitivity analysis.”[7].

We are not prepared to comment here on the success or otherwise of the studies’ modelling procedures. In general terms, all models based on trial results still leave us ignorant of what actually happened to patients in the months and years that followed the trial.

## **c) Resource Identification and Measurement**

The studies do not resolve the problems of valuing carer time, discussed above. Patients with AD are cared for either at home or in institutions; if the drug reduces hospital care, it must increase informal care, to achieve its cost reductions. Other things equal, the greater the value placed on home care, the less cost-effective the drug will be. It is apparent that carers’ interests are directly opposed to those of taxpayers; detailed discussion is needed of how carers’ time should be valued.

In summary, the MMSE’s validity in multi-country studies is under question. While its validity may be adequate to an Irish study, this claim should be tested. Secondly, while modelling is a reasonable response to the problems of the CEA of AD treatments, careful attention needs to be paid to the assumptions necessary to extrapolate from a six-month trial. Finally, the valuation of informal care is the most important single issue in the area of resource identification and measurement.



## Discussion

Both of the approaches base economic evaluation on RCT results; the following conditions militate against an RCT-based approach to the CEA of Alzheimer's treatments:

- a) the diagnosis and expression of the disease are believed to be culturally determined
- b) its nature and progression are poorly understood
- c) patients are unable to communicate either symptoms or quality of life effects
- d) there is no consensus on the efficacy of any preparation to relieve symptoms or progression
- e) the relationship between costs and care outcomes is also culturally determined; in particular, local factors will determine whether patients are institutionalised or not.

It follows that efficacy is difficult to establish in the normal way, and it seems unlikely that prioritising drugs, on the basis of the balancing of effect against per unit cost, to achieve maximum health from a limited budget, will be feasible using international RCTs.

However, the scope for variation in the results could be reduced by confining a comparison of treatments to a single country, with a relatively homogeneous population (such as Ireland), and by confining the enquiry to cognitive functioning as an outcome measure. Any local trial would require the selection of the cognitive functioning measure best suited to this purpose; in what follows, we assume that the MMSE is selected.

The appropriate trial for measuring the impact on costs of different AD treatments may be an extended post marketing surveillance trial, including all licensed treatments for AD plus no treatment. Some of the problems discussed would remain, but such a trial might provide a set of data from a (relatively) homogenous population which would not only prove to be beneficial in the pharmacoeconomic evaluations of these drugs in the study country, but could be adapted for other countries if cultural differences could be mediated, using some further research on the translation process necessary between countries.

In brief, the trial proposed is designed to be as close to routine practice as possible; it has the following features:

*Patient Selection:* Diagnosis by GP of probable AD, plus a MMSE score of 30 or less, and presence of dedicated carer also willing to participate in the trial.

*GP Role:* Treatment and care, as in normal practice, with freedom to alter prescription if necessary.

*Duration:* Up to 24 months.

*Treatment Arms:* All licensed drugs for AD, plus no treatment

*Data Collection:* Initial: MMSE score; carer questionnaire including qol, medications, own GP visits, and health treatments; current AD treatment details; history of

previous AD treatment; approximate date of diagnosis of AD; details of participation in any other trials in the last 12 months

*Every 2 months* (by GP visit or by telephone contact): MMSE Score, carer questionnaire, and, as appropriate, date of institutionalisation, date of death, and reason for withdrawal

*At study end:* calculation of time to institutionalisation, duration of survival, MMSE scores profile, carer well-being profile from questionnaire scores.

Care production and cost would also be measured by estimating total number of respite care places, numbers of patients in institutions by end of the study, and their expected survival duration from institutional entry, consumption cost of care (that is, annual purchasing power minus subsistence cost), numbers of visits to GP by carers and patients.

### **Possible problems with the proposed trial**

It would be unethical to have a placebo arm, to introduce drugs blind (at any level) or randomly to control the treatment groups, because there is some evidence that the drugs are of benefit. Two years is a long time in the AD patient's expected survival of (approximately) five years, and the patient, GP, and/or carer should not be constrained from choosing the patient's treatment, in particular from changing the treatment if they wish to do so. It follows that a bias could be introduced in favour of a known treatment, and there could be significant differences in the number of patient receiving each treatment. Patients might also change between treatment arms, or move to a new licensed therapy, if a product was introduced during the course of the trial. As a result, it would be necessary to have sufficiently large numbers of patients participating in the trial to try to ensure that any of the problems mentioned above would not have a significant impact on the trial results.

Such a study would not prove that one drug was more efficacious than another, but it should demonstrate whether one drug lowered costs or not, when administered for up to two years under routine conditions.

**Conclusion**

The conventional approach to CEA, if based on a randomised controlled trial approach, is particularly difficult to apply to treatments of Alzheimer's Disease, and especially when the trial is carried out with centres in different countries. The evidence put forward for the effectiveness of drugs to treat this disease relies on RCT evidence plus modelling, and there remain important problems associated with this approach also. It may be more effective to carry out a cost-outcome study of AD treatments locally, and to apply foreign RCT results to it later, than to reason from foreign RCT results and cost-impact studies to the local situation.

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