

## ASSESSING HEALTH ECONOMIC OUTCOME IN ALZHEIMER'S DISEASE CLINICAL TRIALS

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**Abstract:** This paper reviews methodological considerations in collecting data on economic endpoints and conducting economic evaluation alongside clinical trials in Alzheimer's disease (AD).

### Purpose and role of economic evaluation

Economic evaluation is increasingly applied to establish the value-for-money with new medical technologies. Regulatory agencies in many European countries require economic data being submitted for new pharmaceuticals and review the cost-effectiveness of drugs already on the market, e.g. the Pharmaceuticals Benefits Board (LFN, Sweden) (1), National Institute for Clinical Excellence (NICE, United Kingdom) (2), Institute for Quality and Efficiency in Health Care (IQWiG, Germany) (3), and the Transparency Commission (France) (4). Cholinesterase inhibitors and memantine for Alzheimer's disease (AD) have been the focus of attention in recent reviews (5).

The purpose of economic evaluation is to inform decisions on the allocation of resources to different technologies so that the overall health benefits are maximised (6). The ability of this analysis to contribute to the efficient use of health care resources hinges on the quality of the underlying data on which the analyses are based.

### Uses of clinical trial data for economic evaluation

Economic evaluations often draw upon data from multiple sources, but clinical trials are commonly the source of data on the efficacy of the technology being evaluated. Increasingly, data on resource use and costs are collected alongside pivotal clinical trials (7-9). The proposition of conducting economic evaluation entirely based on data collected within the clinical trial gives attractive high internal validity and timeliness (10).

A number of factors however limit the possibilities for directly drawing conclusions about cost-effectiveness based on clinical trial results. Inclusion and exclusion criteria lead to non-representative samples of patients that have lower degree of co-morbidity than what would be expected. The care provided during the trial is different from standard care, and there is an issue of protocol-driven costs (11). Missing data and unbalanced drop-out lead to statistical issues in analysing trial data, as well as the pooling of data from multi-center and international trials (12, 13). The follow-up time is often inadequate to capture effects on relevant economic endpoints, and sample sizes are insufficient since power calculations are based on primary endpoints with lower standard deviations than

cost variables (14, 15).

Often, therefore, modelling is used to extrapolate from results on clinical parameters to the economic endpoints of interest. Models are simplified representations of disease processes, and models of Alzheimer's disease have been based on deterioration of cognitive function, loss of autonomy and need for full-time care (16-19). Models are populated by data from prospective or retrospective observational studies on disease progression, costs of care and outcome. By applying efficacy data from clinical trials in the disease model, the cost-effectiveness of different treatments can then be predicted. Modelling studies have been challenged for being overly simplistic and disregarding aspects of clinical importance, and for introducing untested assumptions with potential for investigator bias.

There is therefore a place for both within-trial analysis and modelling in economic evaluation, since the methods are to some extent complementary and possess different merits.

### Measuring resource use in AD drug trials

Resource utilisation in dementia care can be divided into medical care, community care and informal care. Since few patients are in working age, indirect costs for patients are often ignored. The main components of medical care are outpatient care, inpatient care and drug costs.

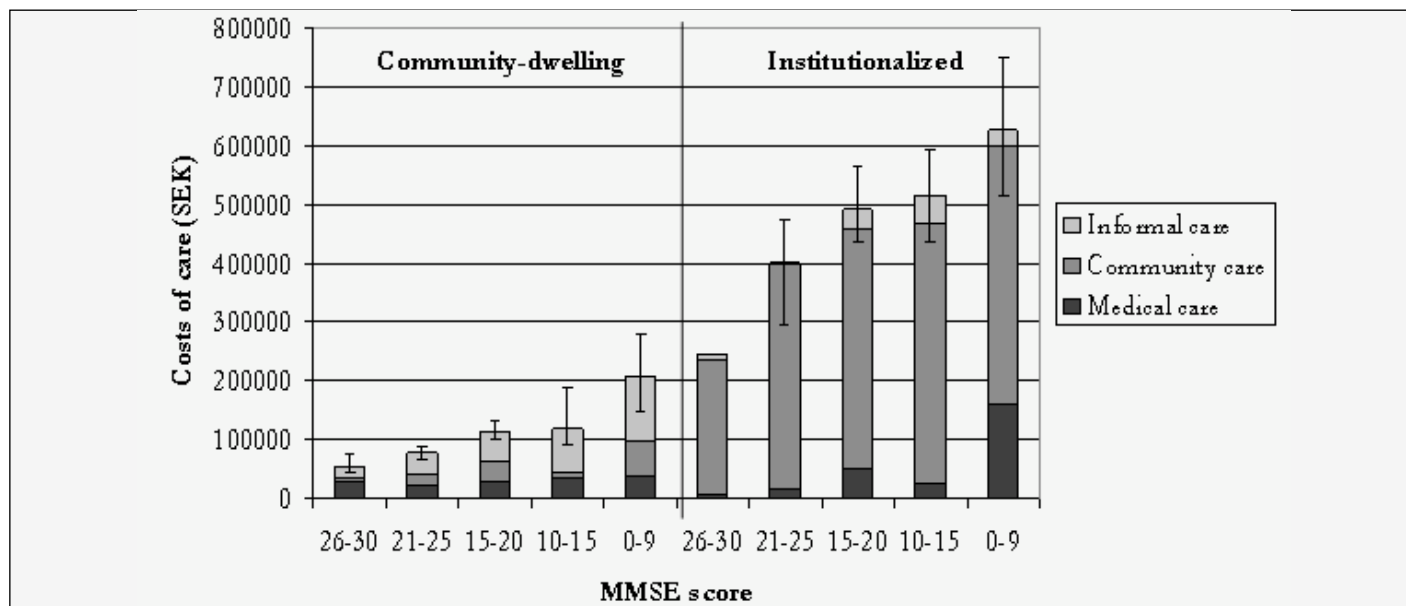
The costs of care for a patient with dementia is known to depend on a wide range of factors including care setting, presence of informal caregivers, cognitive function, ADL and instrumental ADL abilities, behavioural disturbances and comorbidities (20-24). Also the structure of care delivery differs between countries, as well as unit costs (prices). Figure 1 presents costs of care from a Nordic 12-month observational study (22).

This data demonstrates the increase in cost with progressing disease severity and institutionalisation. Also, costs are mainly centred in community care for institutionalised patients, and informal care costs are the largest share of costs in non-institutionalised patients.

Institutionalisation is an important milestone at which costs increase and the distribution of costs shifts from informal to formal caregivers. The definition of 'institution' can however vary between countries as well as the probabilities of

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**Figure 1**  
 Costs of care by MMSE score and care setting (patients from Sweden, Denmark, Norway and Finland, 2003).  
 1 € ≈ 9 SEK (22)



institutionalisation. Further, patients who are included in clinical trials typically have much lower probability of institutionalisation than . This means that the estimated absolute risk reduction in the trial may not be relevant to clinical practice, and statistical significance can be difficult to achieve even with large sample sizes and long follow-up time.

The Resource Utilization in Dementia (RUD) instrument was developed to capture the use of resources by demented patients in a clinical trial setting, which in a further step can be calculated into costs (25). RUD has been used in several studies and proven to be a powerful and comprehensive instrument (8, 26).

RUD and the shorter version RUD Lite (27) assesses both formal and informal resource use, making it possible to calculate costs from a societal perspective. RUD is administrated as an interview with the primary caregiver or other person with knowledge about the patient's situation. The validity and reliability of the RUD instrument has been

investigated both in a residential care setting and in community care by comparing responses to the RUD questions with actual observations of caregiving time (28). Both the complete RUD and RUD lite is available in several languages.

There are different ways of formulating questions about caregiver time, e.g. querying the respondent for resource use during a particular day or having the respondent report for a "typical" day during a certain period. Alternative approaches have different merits, which will vary depending on the data recorded (personal ADLs which are more stable over time, vs instrumental ADLs which vary more from day to day). The use of a caregiver diary can potentially improve data quality and reduce the risk of recall bias which can be a major limitation.

**Estimating costs of care**

Table 1 below shows results from three previous AD drug trials which collected data on informal care time.

**Table 1**  
 Informal care time and cost estimates in three AD drug trials

	Donepezil in mild to moderate AD (8)	Donepezil in moderate to severe AD (7)	Memantine in moderate to severe AD (9)
Cap on informal care per day	16 h	16 h	24 h
Method for valuing informal care	value of leisure time / average wage	Minimum wage	Average wage by age and gender
Value of informal care	102 SEK / h	6.85 Can\$ / h	9.18-23.65 US\$ /h
Average informal care (placebo)	1.96 h / day	4.6 h / day	15.2 h / day
Informal care cost (placebo)	8,886 US\$ / year	3,847 US\$ / 24 weeks	7,231 US\$ / month
Informal care cost (placebo), per day	24 US\$ / day	23 US\$ / day	241 US\$ / day

A common problem in recording the time spend on informal care activities is that some caregivers report time estimates that clearly are unrealistic, e.g. add up to over 24 hours per day. The maximum hours of care per day has therefore been capped at 16 or 24 hours per day. Depending on this assumption and also on the chosen principle for valuing informal care time the hourly cost and the total cost of informal care per day varies considerably between studies. Methodological consistency is important to assure comparability between studies.

### Outcome assessment

Quantifying health benefits is often a major challenge in economic evaluations. Cost-utility analysis, using quality-adjusted life-years (QALYs) as outcome measure, is widely applied in other disease areas; however application in AD is limited by difficulties in applying standard methods for utility assessment. Proxy-rated health utilities using the Health Utilities Index (29, 30) and the EuroQoL (31) have been shown to be reliable and correlated with measures of disease severity (32). However, patients consistently estimate their own health utilities higher than the proxy estimates and with less variability with disease severity, raising the issue of from whose viewpoint utilities should be measured.

Clearly, caregivers are also affected by the disease, to perhaps the same degree as the patient or more. Therefore incorporating effects on the lives of caregivers is an important challenge requiring both methodological development and further empirical studies (33).

### Statistical analysis

There is a fundamental difference between the objectives of clinical trials and the aims of economic evaluation. The purpose of a clinical trial is to investigate one or several hypotheses regarding the effect and safety of a treatment. For economic evaluation, however, the purpose is rather to provide the best possible estimate of the cost-effectiveness of the treatment. The focus is thus on estimation rather than hypothesis testing, since what is relevant for decision makers is to know the best estimate of the cost-effectiveness ratio and the uncertainty surrounding this estimate (34).

This has implications for the statistical analysis of cost-effectiveness data from clinical trials, which should focus on the joint distribution of costs and outcomes (35). Current best practice in the analysis of stochastic cost-effectiveness data includes presenting point estimates of cost-effectiveness ratios with the uncertainty expressed as acceptability curves. However this rarely followed in practice [36] and AD drug trials have to date not reported cost-effectiveness acceptability curves.

### Conclusions

Economic evaluation alongside AD drug trials is an important opportunity for gaining insight in the value of these drugs, but need to be complemented by modelling studies based on observational data from clinical practice. The RUD instrument has been widely applied to capture resource utilization data. There is no established standard for outcome assessment in AD trials however an ideal outcome should incorporate relevant effects on the lives of both patients and caregivers. Appropriate statistical analysis includes consideration of the joint distribution of cost and outcomes.

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