

# **Quantifying uncertainty in long-term care costs following the introduction of new drug therapy: the importance of model choice in Probabilistic Sensitivity Analysis**

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## **Summary**

While economic evaluation methods addresses efficiency concerns, the related topic of affordability is also important for decision makers. Budget impact analysis is a proposed alternative method to address this question. Both methods are recognised by many national decision-making bodies, such as the National Institute for Clinical Excellence (NICE). However, in contrast to economic evaluation, there is little guidance on how to conduct budget impact analysis, nor has there been much research comparing different estimation methods.

Using Generalized Linear Model (GLM) estimation, this paper compares the results from different regression models to quantify the net costs of cholinesterase inhibitor therapy for Alzheimer's Disease (AD), inclusive of long-term care costs.

Three policy models were estimated: an "All Cohort" model that assumed all patients received therapy, irrespective of cognition, a "NICE Guidance 1" (NG1) model, where only those with a particular cognitive level commenced therapy and were withdrawn from therapy after another level of cognition was reached, and an alternative "NICE Guidance 2" (NG2) model where individuals with a certain level of cognition were treated until death. Probabilistic sensitivity analysis was employed for all models.

The results showed that there was a large difference in net costs between alternative modelling strategies. There was much greater uncertainty over whether therapy was cost saving using a multiplicative GLM model, relative to an additive model.

Further work is planned to develop further understanding of these results in order to assess the validity of the models. The results highlight the importance of the choice of modelling strategy in estimating cost impact, suggesting a need for further studies exploring the choice of modelling methods.

## **Work-In-Progress**

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## Introduction

Guidance from national agencies on resource allocation decisions in health care is increasingly relying on cost-effectiveness evidence. Whilst economic evaluation may assist in such decisions, it fails to provide information on whether a particular intervention is affordable. This is likely to be an important concern of local health care decision-makers responsible for guidance implementation, as no additional funds are made available to support implementation. Affordability questions are also likely to be a concern of national bodies, as there may be a positive relationship between affordability and guidance implementation.

Methods known as Budget Impact Analyses have been developed to address affordability questions (Chambers et al 2002). These are now being used in a number of countries to inform decision-making (Trueman et al 2001). The Australian Pharmaceutical Benefits Advisory Committee, the National Institute for Clinical Excellence (NICE) in the UK and the Sickness Funds Council in the Netherlands all recommend that health care system costs should be estimated in any reimbursement submissions.

In the UK, affordability is *not* held to be one of the criteria in the determination of whether new interventions should be provided using public funds. However, the most recent NICE guidance states that estimation of the net impact on the NHS (and Personal Social Services where appropriate) is required to enable effective national and local financial planning (NICE 2004). This suggests implicit recognition that affordability may be a contributory factor to the success or otherwise of the delivery of new interventions to patients. However, the guidance gives little information on the choice of analytical methods to undertake such estimation.

Previous estimates of budget impact within NICE Technology Appraisals Guidance have largely been undertaken using deterministic methods (see for example NICE 2001). It is unclear how reliable or uncertain these estimates are. However, with the development of probabilistic sensitivity analysis methods within economic evaluation, quantification of the uncertainty around budget impact estimates is also possible.

Previous national estimates of the cost implications associated with the provision of new treatments have been undertaken using deterministic approaches (Detournay et al 2002), cohort simulation methods (Wimo et al 1997; Fagnani et al 2004) or regression modelling techniques (Wimo et al 1998). Estimation using regression modelling must account for the statistical nature of cost data. Three characteristics of these data deserve special attention (Blough & Ramsey 2000). First, due to non-use of services, it is usual to find many zero observations. Second, the data are often highly right skewed. Finally, the assumption of homoscedasticity (constant variance) is often violated; that is, variability tends to increase as costs increase.

There is now a growing literature that has compared Ordinary Least Squares (OLS) methods with alternative estimation techniques using cost data (Lipscomb et al 1998; Diehr et al 1999; Andersen et al 2000; Kilian et al 2002). The choice between alternative techniques depends on the problem at hand. To deal with a large number of zeros, two-part models have been developed. In contrast, the problem of skewness and heteroscedasticity is often handled by a log transformation of the data. One drawback with this however is that inference is on the log scale, not on the original cost scale. In retransforming back to the original cost scale, biased estimates may be generated unless an appropriate heteroscedastic retransformation is applied (Manning 1998; Manning & Mullahy 2001).

An alternative approach to log transformation is the employment of a generalized linear model (GLM). These models explicitly account for heteroscedasticity whilst retaining the original cost scale. As there is no need to retransform the model, one advantage of GLMs is that the problems related to bias induced by retransformation are avoided. Further, these models directly accommodate skewness in the distribution through prior specification of an appropriate distribution.

Although the use of GLM estimation of cost data is growing, few studies have compared particular classes of GLM to OLS using untransformed data for predicting and extrapolating mean costs for a national population. This is a relevant consideration as in some circumstances it may be better to retain an additive scale (e.g. untransformed OLS or its GLM equivalent) instead of a multiplicative one (e.g. GLM on a log-link scale). Which scale is more appropriate is an empirical question that may be investigated by comparison of the plausibility of the respective cost estimates. Using Ordinary Least Squares (OLS) and Generalized Linear Model (GLM) estimation, this paper compares the results from both methods to quantify the net costs of cholinesterase inhibitor therapy for Alzheimer's disease (AD) to the NHS and personal social services in England and Wales.

## Methods

Estimates were produced using OLS and GLM regression models of the effects of therapy on disease progression and costs. The clinical effects of therapy on cognition were obtained from a systematic review of placebo-controlled trials of donepezil (Birks & Harvey 2004), observational data (Lopez et al 2002) and natural history studies (Mungas et al 2001; Neale et al 2001). The cost impact of the effects was modelled using cohort simulation. The cohort comprised the current population of people with AD in England and Wales, based on 2002 national population estimates (National Statistics, 2004) and AD prevalence rates (MRC CFAS 1998).

Costs of AD care were modelled as a function of age, gender, Mini-Mental State Examination (MMSE) score and Activities of Daily Living (ADL) score. Data for the regression estimates were obtained from a previous UK observational multi-centre study of resource use and costs that included older people with dementia (McNamee et al 1999). Treatment costs and other AD care costs were applied to the cohort over ten years, with or without cholinesterase inhibitor treatment. Based on previous guidance (NICE 2001), three policy models were estimated: an “All Cohort” model that assumed all patients with a diagnosis of AD received therapy, irrespective of MMSE level, a “NICE Guidelines 1” (NG1) model, where only those with a level of MMSE greater than 12 commenced therapy and were withdrawn from therapy when MMSE was no longer greater than 12, and an alternative “NICE Guidelines 2” (NG2) model where individuals with MMSE greater than 12 were treated until death. Baseline assumptions for model parameters are outlined in Table 1.

The sensitivity of the results to different model assumptions was explored using two approaches. First, to take account of parameter uncertainty, we undertook probabilistic sensitivity analysis. This involved taking repeated random draws from specific distributions of key parameters (MMSE and ADL baseline values, MMSE change per year, survival, regression coefficients). The correlation between parameters was modelled using Cholesky decomposition based on variance-covariance matrix values. Second, changes to other parameters were implemented on an individual basis using one-way sensitivity analysis (discount rate, treatment cost).

As previously outlined (see for example Blough & Ramsey 2000; Barber & Thompson 2004), the GLM is an extension of the traditional linear model. The two key components are a distribution function ( $F$ ) for the dependent variable and a link function ( $g$ ) to describe the relationship between covariates and the dependent variable. Let  $y_i$  equal the cost for individual  $i = 1 \dots n$  and  $\mu_i = E(y_i)$  equal the expected mean cost generated from the model. With  $K$  covariates, and letting  $x_{ik}$  be the  $k$ th covariate for individual  $i$ , the general structure is:

$$g(\mu_i) = x_i \beta, y_i \sim F$$

where  $x_i \beta = \beta_0 + \sum_{k=1}^K \beta_k x_{ik}$  and  $\beta_0, \beta_1 \dots \beta_K$  are the regression coefficients.

The standard OLS model is a GLM with an identity link function and gaussian (normal) distribution. The identity link means that covariates act additively on costs, with the coefficients describing the change in mean costs per unit change in a covariate.

Changing the distribution function but retaining the identity link function leaves

interpretation of the coefficients unchanged. Alternative functions to the identity link, such as the log, change the interpretation of the coefficients. A log-link would mean that covariates have a multiplicative effect on costs, with an anti-logged coefficient giving the *percentage* change in mean costs per unit change in a covariate.

Our modelling strategy is to compare a GLM with an identity-link function and gaussian distribution (i.e. untransformed OLS) with alternative GLMs that possess different link functions and distributions. We go on to demonstrate that a log-link function applied to a gamma or negative binomial distribution provides an appropriate specification within the GLM class:

$$\log(\mu_i) = x_i\beta, y_i \sim \text{gamma} / \text{negative binomial}$$

We therefore compare two sets of cost estimates, which we label as OLS and GLM for exposition. Regression estimates were performed in STATA version 8.2 and cost estimates were produced using EXCEL.

## Results

Under deterministic OLS analysis, for the All Cohort model, the mean discounted incremental care costs associated with cholinesterase inhibitor treatment were £550 million (2002/3 prices) over 10 years. On a per patient basis, this equated to £1792. Cholinesterase inhibitor acquisition costs were £851 million (£2,773 per patient over 10 years).

For the NG1 model, mean discounted incremental care costs were £115 million, or £597 per patient over 10 years. Acquisition costs of cholinesterase inhibitor treatment amounted to £233 million (£1,210 per patient over 10 years).

For the NG2 model, mean discounted incremental care costs were £298 million, or £1550 per patient over 10 years. Acquisition costs of cholinesterase inhibitor treatment totalled £449 million (£2,331 per patient over 10 years).

Probabilistic sensitivity analysis supported the findings from the baseline OLS deterministic models that treatment did not produce cost savings large enough to offset the costs of therapy (Figures 1 and 2). These models all produced estimates to within 3% of the deterministic analyses. The probabilistic models however provide additional information relating to the range surrounding the mean estimates (Figures 3-5).

Appendix 1 shows the performance of alternative GLM estimators. Based on low AIC values, amongst log-link versions there was little to choose between alternative distributional forms. A Park test value of 1.25 suggests that both the negative-binomial



and gamma distributions would be appropriate. Appendix 2 demonstrates that all of the models tend to over predict costs in the bottom half of the distribution, whilst under predicting costs in the top half of the distribution. Use of a GLM with coefficient estimates from the gamma and negative binomial models led to a considerable change in incremental costs. Table 2 shows that the deterministic GLM models produced incremental cost estimates that were between 15-23% *higher* than the OLS models, whilst the probabilistic GLM models were between 11-45% *lower* than the OLS models.

The greater difference between OLS and GLM estimation in probabilistic analysis gave rise to greater uncertainty within GLM over the probability that therapy was cost saving. With OLS, the probability that therapy was cost saving was less than or equal to 0.001. With GLM, this probability equalled 0.094, 0.212 and 0.096 for the All Cohort, NG1 and NG2 models respectively.

We also explored the sensitivity of the model results to changes in two parameters. The costs estimates varied quite considerably according to the different assumptions taken. The effect of a zero discount rate led to therapy being more costly in all models. For the OLS model, the rise of 11% was largest in the All Cohort model. For the All Cohort and NG1&2 OLS deterministic models respectively, incremental cohort costs rose to £609 million, £1117 million and £324 million (or £1984, £609, £1684 per patient respectively).

Relative to zero discounting, the effect of an increase in treatment costs to reflect 2 extra monitoring visits (Pakrasi et al 2003) was more important in magnitude. Assuming a cost of £127.30 per visit at 2002/3 prices (Clegg et al 2001), incremental cohort costs rose by approximately 50% in all OLS models to £794 million, £182 million and £427 million respectively (or £2586, £943 and £2217 per patient respectively).

## Discussion

The analyses in this paper suggest that the introduction of cholinesterase inhibitors for the management of Alzheimer's Disease is likely to lead to additional costs from the perspective of the NHS and personal social services in England and Wales. The estimated magnitude of these additional costs is partly dependent on treatment policies such as NICE guidance. The choice of modelling approach was also demonstrated to be important. For example, the probability that therapy was cost saving was considerably different in GLM estimation relative to OLS estimation.

The difference between the OLS and GLM models arises primarily from the way in which the cost coefficient estimates act on the dependent variable. One key difference is the use of the constant term in GLM estimation. Incorporation of this term produces greater variation in costs relative to the OLS model, because of the multiplicative nature of the model. This is further magnified as the effect of a change in MMSE on costs is dependent on the product of the constant term and the MMSE coefficient. As a result, the effect of different values for the MMSE coefficient on costs varies between the OLS and GLM specification. Relative to OLS, higher values for the MMSE coefficient in GLM led to much greater cost savings per MMSE point reduction. In the extreme, for the same value of MMSE coefficient, cost savings of £3000 per year per MMSE point reduction were obtained with GLM, relative to £600 per year for OLS. However, for GLM, these values were also very sensitive to relatively small changes in the intercept term. For example, a less than one point change in the constant term produces a reduction of over 50% in the cost effect of a one point MMSE reduction.

Where estimates are a linear function of covariates on the log-link scale, a previous study has noted that outliers can greatly affect GLM parameter estimates (Blough & Ramsey 2000). This suggests that probabilistic analysis using the multiplicative GLM is more sensitive to estimates that are less precise because of smaller sample size. This is not necessarily problematic if the values appear credible. However, for a one point reduction in MMSE, the higher values generated by GLM appear less credible than the lower values produced by OLS. For example, a value of £3000 per year per MMSE point reduction implies a saving of approximately 2 months in long-stay residential care, which has not been demonstrated in previous clinical trials (AD2000 Collaborative Group 2004).

For both OLS and GLM estimation, a vital question relates to the validity of the structural assumptions underlying both models and the quality of the data sources. All of the above models may be viewed as ‘conservative’, as they assume that the benefits of therapy are *maintained* over time. This is based on the current evidence available in the literature (Birks & Harvey 2004). A more ‘optimistic’ scenario assumes that the benefits of therapy *increase* over time. In other words, the difference in MMSE seen at the end of year 1 is not only maintained but increases over time. We also calculated cost estimates based on this assumption. As the focus of this paper relates to modelling methods, these results are not reported here. However, the different modelling methods did produce different results under this assumption. In particular, the GLM estimation using probabilistic methods led to mean cost savings.

In addition, some of the data sources used may no longer reflect current forms of care. The resource use and cost data are based on observational data collected between 1991 and 1995. Since that time, there have been a number of policy changes that have

affected the delivery of care for older people with dementia. This is partly addressed through the probabilistic analysis, although it remains unclear the extent to which this form of sensitivity analysis introduces too much noise into the estimates.

Although there is little national guidance from NICE on how to conduct estimates using Budget Impact Analyses, other guidance is available (Trueman et al 2001). One particular parameter that deserves some attention is a measure of the rate of adoption of new therapies. Estimation of this parameter requires some knowledge on demand elasticities. For example, introduction of a new treatment may substitute or complement existing treatments. In addition, there may be separate effects related to whether or not clinicians, patients and carers opt to choose the new therapy, given eligibility criteria. Further, there is likely to be clinical variability over the interpretation of eligibility criteria. In the absence of observational data on implementation patterns related to current NICE guidance over these therapies, the assumption taken in the estimations reported here is that there is full adoption.

It is perhaps however a topic for debate over whether such a parameter should be estimated at all. There may be some value for a national decision-making body such as NICE or the Department of Health, but it is more difficult to see the value for a local decision-maker. A more important question for them perhaps is which patient groups to prioritise if they cannot afford full adoption. Different rates of adoption could be modelled for this purpose. To inform decision-making however, this would of course require additional data on the gains to population health as well as calculation of cost implications.

In conclusion, it appears that there is a need for some form of cost estimation that relates to policy guidance decisions. The analytical approach to be taken to meet this need can take a variety of forms. This paper demonstrates methods that could be used to generate such estimates. As the estimates are sensitive to the modelling approach adopted, careful attention to model specification is required. Equally however, the validity of the model structure and data quality issues remains important to the estimation process.

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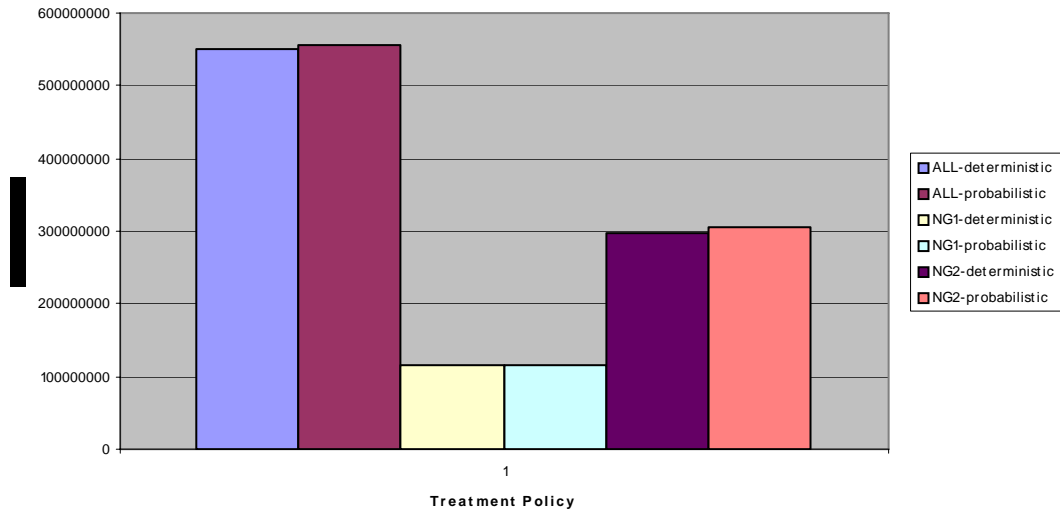
**Table 1 Model Assumptions and Parameters**

<b>Parameter</b>	<b>Value/assumption</b>	<b>Data Source</b>
Population of England and Wales aged 65 years or over in mid 2002	8,385,800	National Statistics (2004).
Prevalence of AD	50% of age & sex specific rates for dementia	MRC CFAS (1998).
Cohort distribution by baseline MMSE	Age & sex specific values from a minimum of 12.7 to a maximum of 18.6	McNamee et al (1999).
Cohort distribution by baseline ADL	Age & sex specific values from a minimum of 6.5 to a maximum of 13.8	McNamee et al (1999).
Cohort distribution by baseline costs per person per year	Age & sex specific values from a minimum of £1584 to a maximum of £14,457	McNamee et al (1999).
MMSE reduction per year without therapy	Age specific values from a minimum of 2 to a maximum of 3	Mungas et al (2001).
MMSE reduction per year with therapy	Age specific values from a minimum of 1.2 to a maximum of 1.8	Lopez et al (2002).
Therapy costs per person per year	£891	British National Formulary (2003).
Cost savings per person per year per MMSE point reduction (OLS)	£414	Regression estimates.
Cost savings per person per year per MMSE point reduction (GLM)	£343	Regression estimates.
Discount rate	3.5%	Treasury Green Book (2003).
Survival probability to 1, 3 and 5 years	Age, sex and time varying values from a minimum of 0.18 to 0.90	Neale et al (2001).

**Table 2 Comparison of OLS and GLM estimated incremental costs per patient over 10 years**

<b>OLS: Deterministic and Probabilistic values (£)</b>		<b>GLM: Deterministic and Probabilistic values (£)</b>		<b>OLS and GLM % difference</b>
ALL-deterministic	1792.103	ALL-deterministic	2107.001	0.175714
ALL-probabilistic	1810.262	ALL-probabilistic	1608.287	-0.11157
NG1-deterministic	596.7916	NG1-deterministic	736.5616	0.234202
NG1-probabilistic	607.3662	NG1-probabilistic	333.7527	-0.45049
NG2-deterministic	1549.592	NG2-deterministic	1785.023	0.151931
NG2-probabilistic	1591.395	NG2-probabilistic	1388.689	-0.12738

**Figure 1: Mean 10 year discounted incremental costs per cohort**



**Figure 2: Mean 10 year discounted incremental costs per patient**

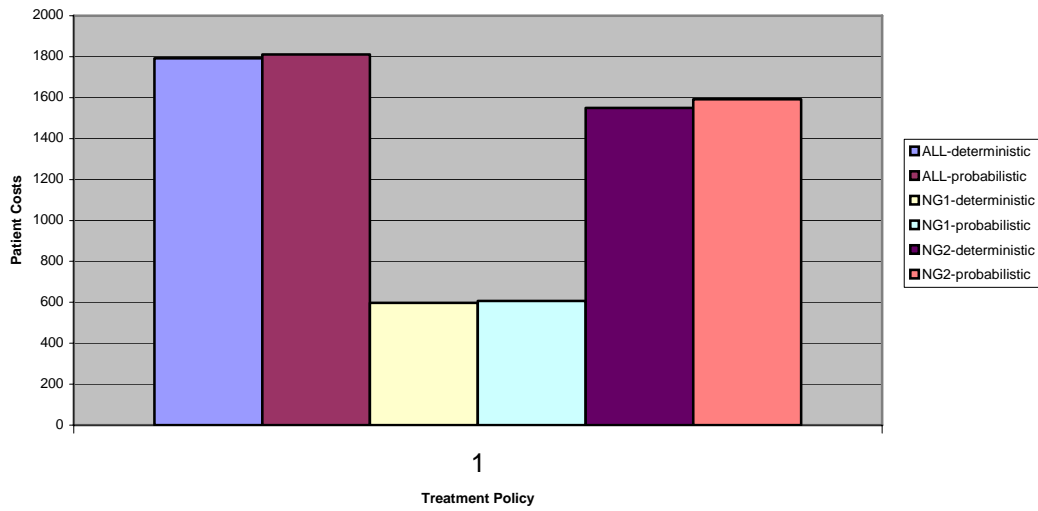


Figure 3: ALL COHORT - Discounted 10 year incremental costs per cohort

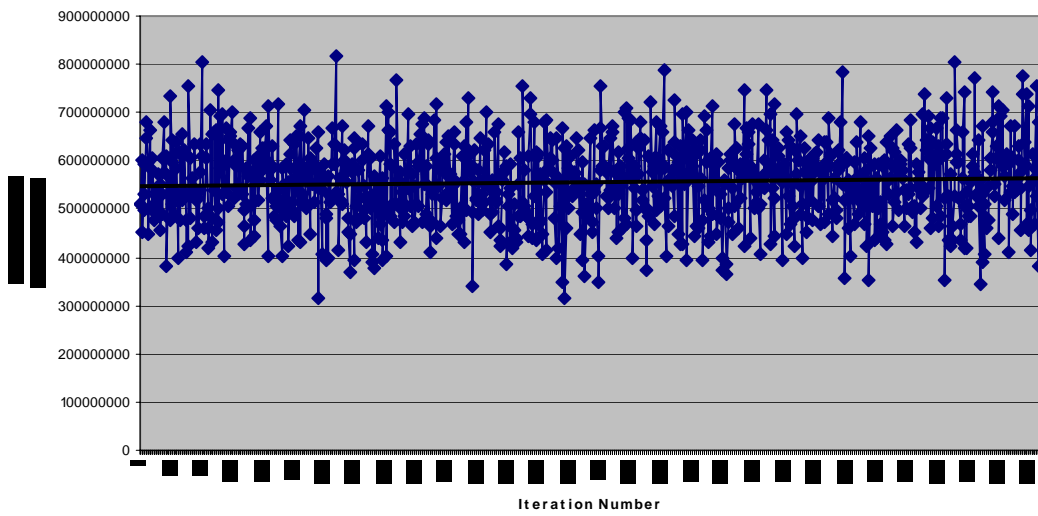


Figure 4: NG1 COHORT - Discounted 10 year incremental costs per cohort

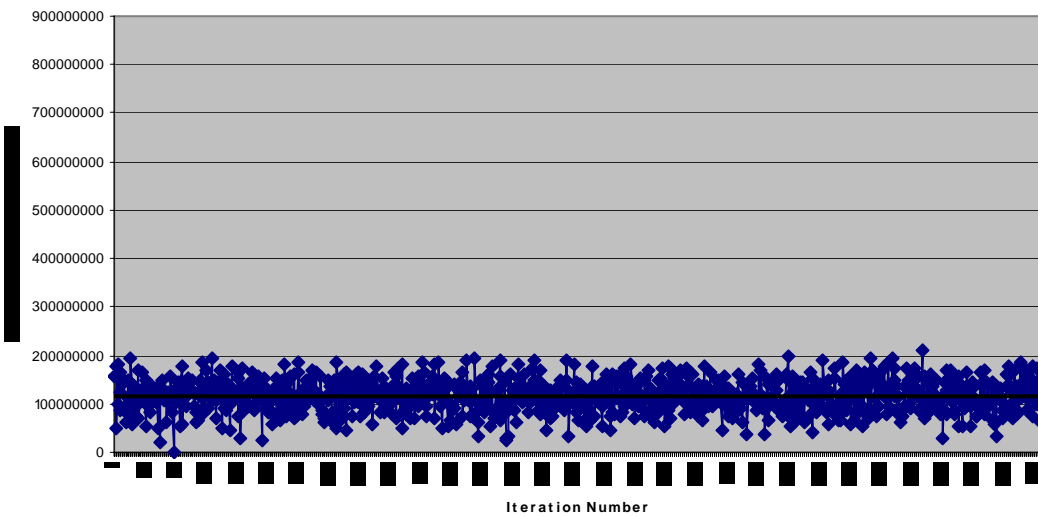
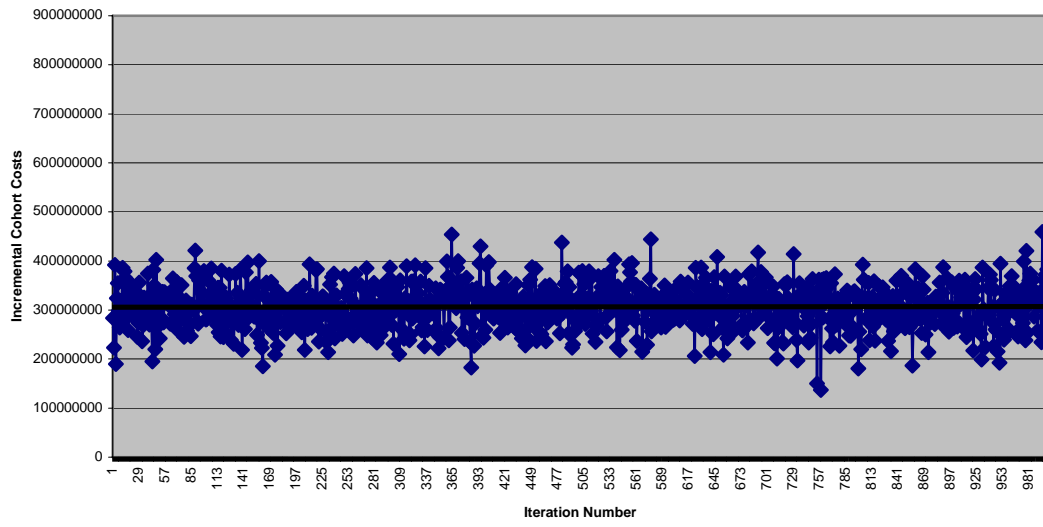


Figure 5: NG2 COHORT - Discounted 10 year incremental costs per cohort



## Appendix 1 Comparison of alternative GLM estimators

Model	Constant	Sex	Age	ADL	MMSE	AIC	Bias*
<i>Identity link</i>							
Gaussian	-1.13 (151.25)	-49.77 (22.60)	5.35 (1.66)	-9.98 (1.90)	-7.96 (2.46)	13.47	0.26
Poisson**	-	-	-	-	-	-	-
Gamma	-42.58 (0.00)	-10.88 (0.00)	1.82 (0.00)	-3.46 (0.00)	-0.94 (0.00)	1.16e+08	0.78
Negative binomial	231.47 (100.84)	-6.95 (12.32)	1.55 (0.94)	-7.62 (1.25)	-7.12 (1.53)	11.89	0.31
<i>Log link</i>							
Gaussian	2.88 (0.90)	-0.35 (0.12)	0.04 (0.01)	-0.06 (0.01)	-0.03 (0.01)	13.46	0.26
Poisson	3.72 (0.06)	-0.32 (0.01)	0.04 (0.00)	-0.06 (0.00)	-0.05 (0.00)	213.09	0.26
Gamma	4.37 (1.02)	-0.44 (0.16)	0.04 (0.01)	-0.06 (0.01)	-0.09 (0.02)	11.85	0.21
Negative binomial	4.37 (0.73)	-0.44 (0.12)	0.04 (0.01)	-0.06 (0.01)	-0.09 (0.01)	11.86	0.21

\*Computed as the absolute value of the difference between mean predicted and mean actual weekly costs divided by mean actual weekly costs

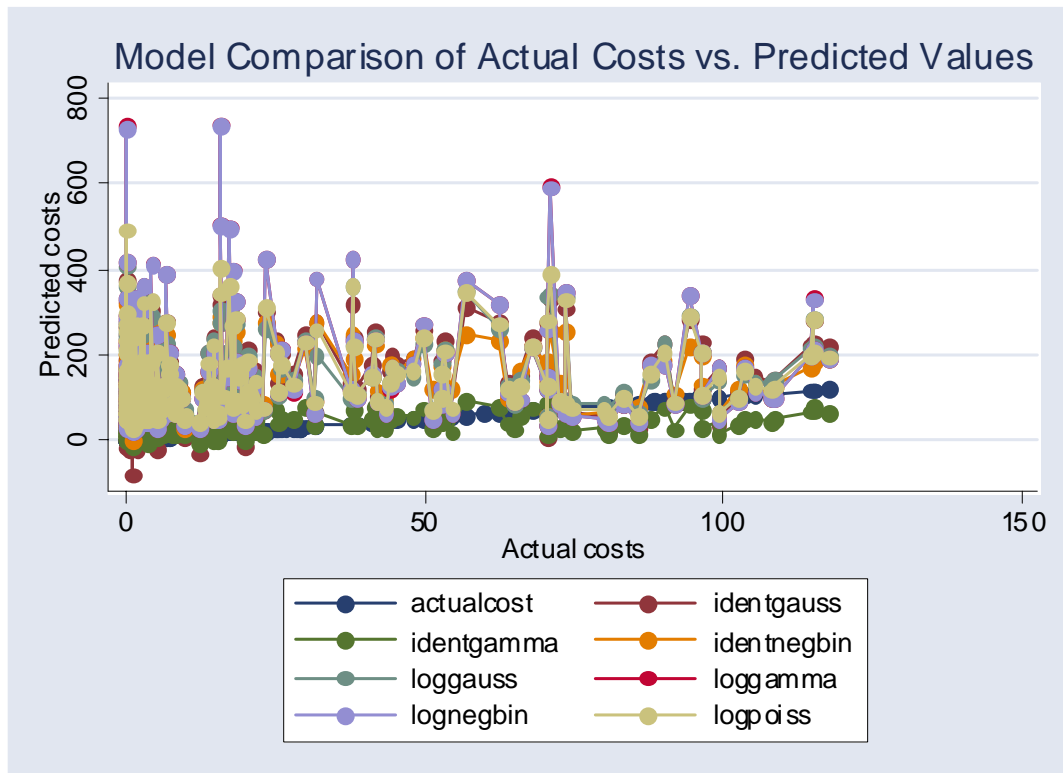
\*\*Convergence not achieved

Variable definitions: *Sex* (=1 if female, =0 if male); *Age* (years); *ADL* (Activities of Daily Living index, range 0-18, scored according to whether respondents required help (=0), have problems (=1) or have no difficulties with (=2) nine daily activities); *MMSE* (Mini Mental State Examination index, range 0-30, where values 0-10, 11-22 and 23-30 indicate severe, moderate to mild, and absence of cognitive impairment respectively).

Standard errors in parentheses.

## Appendix 2 Model comparison of predicted versus actual values

### Scheme 1 Model comparison for lower half of the actual cost distribution



### Scheme 2 Model comparison for upper half of the actual cost distribution

