The impact of diabetes-related complications on health care costs: results from the United Kingdom Prospective Diabetes Study (UKPDS)

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Introduction

The increasing number of interventions intended to prevent, delay or treat diabetic complications has been accompanied by a growing need to understand their economic implications. Here we report estimates of the direct medical costs associated with a set of clearly defined diabetic complications, using detailed clinical data from the United Kingdom Prospective Diabetes Study (UKPDS). The estimates support one part of the economic analysis required for researchers seeking to evaluate the costs and benefits of these interventions for patients with type 2 diabetes.

Many costing studies have documented the total burden of diabetes to the health system and society, with varying focus on the impact of diabetes related complications [1]. Although these cost of illness studies can be useful in outlining the scale of the problem, they are of little use for economic evaluation as they convey no information about the effectiveness or costs of interventions. An alternative approach has been to compare health care utilisation between patients with and without diabetes in case control studies [2, 3]. However, such studies shed little light on the cost impact of specific complications at the patient level, generally do not have validated clinical information, and are prone to sample selection problems associated with retrospective designs or administrative records. A small number of studies have reported results using patient level data, but only for specific endpoints or aggregated groups of endpoints [4, 5, 6], or over limited periods of time [7]. A recent study review of this literature concluded there are "… no recent papers that provide comprehensive patient-level cost estimates for the majority of relevant diabetic complications" [5]. This is a serious handicap for researchers interested in developing economic models of type 2 diabetes.

The purpose of this study is to address that deficiency. We use prospectively collected data from a large trial of therapies for diabetes, the UKPDS, and employ a regression based approach in order to estimate the short-term and long-term annual hospital and non-hospital costs associated with each of these complications after controlling for demographic variables. Our results provide robust estimates of the full hospital and non-hospital care cost impact of seven major macrovascular and microvascular complications of type 2 diabetes.

Participants and methods

Research setting and study population

The UKPDS was a large randomised controlled trial conducted from 1977 to 1997 in 23 participating centres in England, Scotland and Northern Ireland. A total of 5102 patients with newly diagnosed type 2 diabetes were recruited to the study, with a mean age at entry of 52.4 years (S.D. 8.8 years). 58% of the study population were men, and in ethnic composition 81% were Caucasian, 10% were Indian/Asian, 8% were Afro Caribbean, and 1% were from other ethnic groups. From this total, eligible patients were then randomised into blood glucose control and blood pressure control studies. Regardless of their allocation to a therapy group they attended UKPDS clinics at least every four months and participated for a median of 10.3 years in the study, generating up to 55,942 patient years of data for this analysis. Details of the main study design and main clinical results have been published elsewhere.[8]

Identification of clinical events

All patients attended UKPDS clinics every three or four months for the duration of the study. They were assessed during the visit to determine the occurrence of any clinical events or hospital episodes since the previous visit. Full clinical information on the

event was obtained, and this was presented to the UKPDS Endpoint Adjudication Committee where two clinical assessors independently classified the event into predefined categories based on the 9th revision of the International Classification of Diseases (ICD9) codes. If any disagreements could not be resolved by arbitration, the information was submitted to a panel of three assessors for a final decision.

Resource use data

Information on hospital inpatient stays was collated by each clinic based on patient interviews at every clinic visit, death records and hospital records. Where an inpatient stay had occurred, details were obtained from the relevant hospital of dates of admission and discharge, reasons for admission, and any major procedures undertaken. All hospital episodes were subsequently allocated to one of 40 national standard specialty codes [9] based on information from the hospital or assessment by a panel of two clinicians based on reason for admission, ICD code and/or procedures undertaken. In approximately 16% of cases (predominantly in the earliest years of the study) the length of stay was not recorded and so multiple imputation methods were applied to replace the missing data [10]. The variance was increased according to standard rules [11] to reflect the uncertainty surrounding the missing data. The cost of each episode of hospitalisation was estimated by multiplying the length of stay by the average cost of the respective specialty, based on an average of the Department of Health's NHS Trust Financial Returns (TFR2) for 1997/8 and 1998/9. Of the ten most frequently reported specialties the average cost per day ranged from £224 for gastroenterology to £534 for ophthalmology. Hospital episode costs were then aggregated into annual costs for each patient relative to entry into the study (which coincides with diagnosis of diabetes).

Information on non-inpatient health care resources was obtained using a different method. A cross-sectional survey of 3,488 UKPDS patients was conducted between January 1996 and September 1997, using a questionnaire distributed at clinic visits or by post to patients who did not attend clinics during the survey period. This survey recorded information on all home, clinic, and telephone contacts with general practitioners, nurses, podiatrists, opticians, and dieticians, and with eye and other hospital outpatient clinics over the four months prior to the survey. The total costs over this period were estimated by multiplying the number of contacts by unit costs for each type of contact, derived from UKPDS clinics and from published sources,[12] and the resulting total cost was then annualised.

Methods of analysis

We examine the relationship between health care costs and seven clinical event categories; myocardial infarction (MI); stroke, angina or ischaemic heart disease (IHD); heart failure; blindness in one eye; amputation and cataract extraction. Myocardial infarction and stroke are further subdivided into fatal and non-fatal events.[13] Table 1 lists these clinical events, the ICD codes or other criteria used to define them, and the number of first events in each category - that is, the number of patients who experienced one or more of that event. These numbers ranged from 828 first non-fatal myocardial infarctions to 67 first amputations.

Hospital inpatient costs are estimated for each of the seven complications. Previous studies of diabetes related complications have shown that their costs have a distinct profile over time [14]. To address this, we estimate both the immediate or acute impact of a diabetes-related complication (that is, the effect in the year the complication occurs) and the long-term impact (that is, the effect in all subsequent years) on inpatient costs.

The occurrence of complications also has an impact on non-inpatient costs as many patients will require subsequent care and rehabilitation. However, the cross-sectional nature of these data make it difficult to distinguish between the immediate and long-term impact on non-inpatient costs. In the analysis of non-inpatient costs we combine these time periods to estimate the impact of complications regardless of whether they occurred either in the same patient year or in any previous patient year of the study. For similar reasons we combine complications into two major groupings when estimating non-hospital costs: macrovascular complications (myocardial infarction, stroke, ischaemic heart disease, heart failure) and microvascular complications (blindness in one eye, amputation and cataract extraction). The coefficients and equations modelling non-inpatient costs are reported in Table 4.

Statistical methods

Health care cost data often have several characteristics that must be addressed through the use of appropriate statistical analysis. Typically, within a defined period of time (e.g. one year) a significant proportion of individuals have no contact with some types of health care providers and so incur no costs. However, amongst the individuals who do make use of health services, the distribution of costs is frequently highly skewed by the presence of a relatively small number of individuals accounting for a significant share of all costs. [15, 16, 17]

To estimate the cost of various complications we employ two-part models in our analysis. In the first part, logistic regression was used to model the probability of incurring some hospital costs within a single patient year time period. The dependent variable is set equal to one in any patient year an individual incurs costs. To determine

the impact of various clinical events on the probability of attending hospital we included indicator variables for each event and variables to adjust for current age, sex and duration of diabetes. In the second part, a Generalized Linear Model (GLM) was used to estimate the total hospital costs incurred, conditional on incurring any costs. The complications *amputation* and *cataract extraction* are treatments requiring hospitalisations rather than the diagnosis of a condition. We therefore assume that patients with these complications must attend hospital and exclude them from the first stage equation (i.e. the probability of attending hospital is set equal to one).

It is important to deal with the skew in the positive component of hospital costs, as some episodes with extremely high costs can overly influence the models parameters. Traditionally, log transformations have been adopted to deal with skewed costs, but recent methodological work suggests a GLM can be used to appropriately transform the data since they provide a wide variety of different transformations. [18] The model was therefore estimated on the transformed scale and the average cost conditional on having at least one hospital episode for each clinical event was then calculated after implementing the appropriate retransformation.

The coefficients attached to the variables included in the equations can be used to estimate the probability of having contact with a health care provider dependent on the patient's age, sex, and previous experience of diabetes-related complications. Examples are given in the results section to estimate the inpatient cost profile of an illustrative patient, and further details of statistical methods are given in the Appendix.

Results

Hospital inpatient costs

Table 2 reports the coefficients and standard errors for two regression equations relating to hospital inpatient costs. The first is a logistic regression modelling the annual probability of incurring some hospital inpatient cost, and the second a GLM to model the cost of hospitalisation conditional on that event occurring. Both equations include variables representing the patients' age and sex, and sets of indicator variables for the occurrence of diabetes related complications in the year in question, or in any previous year.

Table 3 reports an application of the logistic regression results, with age and sex set to reflect the mean values for the UKPDS study population (i.e. a male aged 52.4 years at diagnosis of diabetes), and with all results reported for the first complication only. The second column of the table shows the probability of incurring hospital inpatient costs. Patients who had no complications had a probability of incurring hospital inpatient costs in any single year of 0.06; that is, approximately 6% of patients who did not have any diabetes related complications in a given year nevertheless were admitted to hospital as an inpatient and consequently incurred some hospital costs. The immediate impact of a myocardial infarction is to greatly increase the probability of incurring hospital inpatient costs, to 74% for a fatal myocardial infarction and 80% for a non-fatal myocardial infarction. The approximately one-fifth of all non-fatal myocardial infarctions that do not incur any hospital inpatient costs in the year in which they occur probably includes patients not diagnosed as having had an MI until some subsequent investigation and those treated on a domiciliary basis. Similarly, a proportion of non-fatal strokes and instances of heart failure are not associated with inpatient costs in the year in which they occur, while IHD and blindness in one eye are primarily treated in a non-inpatient

setting. In years subsequent to the year in which any particular complication occurred, Table 3 shows that the probability of incurring hospital in-patient costs continues to be significantly higher than the 6% rate experienced by individuals who have not experienced any complication: for example, patients who have experienced a heart failure are predicted to have a 15% probability of incurring hospital inpatient costs in years subsequent to the year in which heart failure originally occurred. Only in the case of cataract extraction is this longer-term effect on hospital inpatient costs no higher than the rate experienced by patients who have not had a complication.

Column 3 of Table 3 shows the estimated mean hospital inpatient costs associated with each complication, conditional on some hospital inpatient costs being incurred. Thus, for the 80% of patients who incurred hospital inpatient costs in the year in which they had a nonfatal myocardial infarction, these costs averaged £5,104, while patients who experienced an amputation on average incurred hospital inpatient costs of £8,459 in that year. For all complications except fatal myocardial infarction and cataract extraction, these hospital inpatient costs are substantially higher than the £2,543 incurred on average by the 6% of patients with no complication who nevertheless were admitted to hospital as inpatients.

Finally, column 4 of Table 3 shows the product of columns 2 and 3: that is, the expected hospital inpatient costs associated with each complication. For example, someone who experiences a non-fatal stroke has a 35% probability of incurring hospital inpatient costs in the year the event occurred, the cost for these 35% of patients was £6,822 and so the expected or unconditional hospital inpatient costs associated with a non-fatal stroke is the product of these, or £2,367. Note that the 95% confidence intervals around these estimates are not symmetrical, due to the effects of retransformation.

Non-inpatient costs

Table 4 reports the coefficients and standard errors for two regression equations relating to non-inpatient costs. As with inpatient costs two regression equations are used first a logistic regression and secondly a GLM model. Table 5 reports an application of these logistic regression results, with age and sex set to reflect the mean values for the UKPDS study population (i.e. a male aged 52.4 years at diagnosis of diabetes), and with all results reported for the first complication only.

For patients with no complications the probability of incurring some non-inpatient costs is 76%. For patients with macrovascular complications this probability increases to 91% in the year the event occurs and 86% in subsequent years and patients with microvascular complications 79% and 83% respectively.

Second events

The results reported above give the costs associated with a diabetes-related complication when that is the first complication experienced. The question then arises whether the costs of second and subsequent complications are likely to be additive or multiplicative, and if multiplicative what ratio to use. This will be addressed in future work.

Discussion and conclusions

In this study we have reported the results of a regression analysis on a large and well-validated patient specific data set, and demonstrated that this approach yields plausible empirically based estimates of the hospital inpatient costs and non-inpatient health care costs associated with diabetes related complications. It is important to stress that these

are not simply the health care costs administratively allocated to an event - for example, the average cost of an inpatient admission for a non-fatal stroke - but rather are a robust statistical measure of the elevated health care costs associated with a complication, which may not be directly related to the event. Thus the hospital inpatient costs reported here for a non-fatal stroke will capture any inpatient stays directly associated with the stroke, but also the potential impact of the stroke on lengths of inpatient stay for other conditions. Application of these results should be made in a similar way, and should not be confused with the anticipated direct costs of specific procedures.

Our results indicate the substantial impact of diabetes related complications on hospital costs, especially concerning amputations and non-fatal stroke. These costs are immediate in that they elevate costs in the year in which the complication occurs, but they also have a permanent impact in that they raise the average hospital costs in all subsequent years. This could be due either to subsequent occurrences of the same event, or could be because patients with a history of complications may be more frail or compromised and have a greater propensity to require more hospitalisations of longer duration than those that have been free of complications.

It is interesting to compare our estimates with results from other sources such as specific costing studies or from reference costs, how in the United Kingdom few previous studies have reported cost estimates for diabetes-related complications. Our estimates indicate that the annual hospital costs for a fatal myocardial infarction are £1,567 (95% c.i.1279-1919) and for a non-fatal myocardial infarction are £5,104 (95% c.i.4486- 5806) which is greater than Department of Health reference cost for a finished consultant episode for a myocardial infarction with complications of £1,479 in general population. [19] Similarly, our estimates of £4,227 and £6,822 for a fatal and non-fatal

stroke respectively compare with an estimate of £5,000 per cerebrovascular event amongst patients with diabetes in a retrospective analysis of routine hospital records in the UK. [20] Again our estimate of the hospital costs associated with cataract extraction in the year it occurred - a mean of £1,553 (95% c.i. 1,278-1,888) - is higher than the Department of Health reference cost in 2000 for a phakoemulsification cataract extraction with lens implant of £877 for inpatients and £571 for out patients, [19] these reference costs being based on patients with and without type 2 diabetes. These comparisons tend to bear out previous research suggesting that cost analyses based on utilisation `labelled' to particular complications, particularly when based on routine data, will significantly underestimate the true incremental costs of complications of diabetes.[14]

We have not reported results for patients with end stage renal disease, due to the small numbers of patients (25 in the main UKPDS randomisation) with this complication at the end of the main follow-up period. Fortunately this is an area in which many "bottom-up" costing studies have been performed: data from one such large UK study suggest that the annual cost per patient (with and without diabetes) for all hospital costs associated with renal dialysis averaged £20,902 in 1996 prices, and also suggested that the presence of diabetes does not lead to a significant difference in treatment specific costs compared to non-diabetic patients [21], although it may lead to a lower probability of renal transplantation [22].

The figures we have reported are for first events. Clearly, those modelling diabetes are likely to wish to incorporate the costs of multiple events, and some issues arise on how to do this, given that these costs may well not be simply additive on the retransformed results. Addition prior to retransformation is equivalent to assuming an exponential

relationship when these costs are retransformed, and this may also be inaccurate. Even with the large number of observations at our disposal there are inadequate numbers of patients with multiple events to provide definitive results in specific categories: however we are working on comparisons of the costs of first and subsequent events taking into account case-mix changes, and hope this will cast some empirical light on the question. Meanwhile users may make their own assumptions on costing combinations of complications.

Although the randomised phase of the UKPDS finished in 1997, patient follow-up has continued and substantial additional information on complications and hospital inpatient costs will become available in the future. This will permit re-estimation and validation of the results reported here, allow the issue of estimating the costs of multiple events to be reconsidered, and create the possibility of incorporating other complications such as end stage renal disease into the analysis. Meanwhile, the results reported here provide robust evidence of the health care cost impact of specific diabetes related complications that has hitherto been unavailable. They should be of interest and use to other economists and health service researchers, particularly those wishing to assess within a modelling framework the costs of diabetes and the cost-effectiveness of interventions.

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Table 1: Diabetes-related complications included in the regression analysis, with diagnostic definitions and number of first events in each category

Category	Predefined diagnostic definitions	Number of first events used in analysis
Myocardial infarction (MI)	ICD9 Code 410	828
Stroke	Major stroke with symptoms that persist more than one month (ICD9 Codes 430 to 434.9 and 436)	271
Ischaemic heart disease (IHD)	ICD9 Code 411-414.9	319
Heart failure	ICD9 Codes 428 to 428.1	166
Blindness in one eye	ICD9 Code 369 to 369.9	163
Amputation	Major limb complications requiring amputation of digit or limb for any reason (ICD9 Codes 5.845 to 5.848)	67
Cataract extraction	ICD codes 5.143 to 5.146	297

Table 2: Regression equations to derive annual probability of incurring hospital costs, and costs of hospital care conditional on incurring a cost (5102 patients and 55,942 patient years)

Variable	Part 1 (logistic regression): Equation to derive annual probability of incurring hospital costs		Part 2 (GLM): Equation to derive annual cost of hospital care, conditional on costs being incurred	
	Coefficient	Standard error	Coefficient	Standard error
Age in years	0.017**	0.002	0.013**	0.002
Male (=1)	-0.108**	0.041	-0.106*	0.052
Event during year indicator:				
Fatal myocardial infarction	3.743**	0.137	-0.485**	0.107
Non fatal MI	4.091**	0.148	0.696**	0.067
Fatal stroke	4.108**	0.356	0.508	0.279
Non fatal stroke	2.087**	0.172	0.987**	0.136
Ischaemic heart disease	2.363**	0.133	0.627**	0.128
Heart failure	2.822**	0.191	0.508**	0.115
Blindness in one eye	1.330**	0.198	0.541**	0.204
Amputation	-	-	1.202**	0.253
Cataract extraction	-	-	-0.493**	0.134
History of event:				
Non fatal MI	0.809**	0.083	0.348**	0.076
Non fatal stroke	0.328*	0.134	0.155	0.141
Ischaemic heart disease	0.812**	0.083	0.405**	0.077
Heart failure	1.016**	0.135	0.477**	0.146
Blindness in one eye	0.471**	0.135	0.147	0.136
Amputation	0.309	0.216	0.358	0.207
Cataract extraction	-0.093	0.105	-0.316**	0.142
Constant	-3.607**	0.134	7.210**	0.122

* P<0.05; **P<0.01

History of event: refers to events that occurred in previous patient years

Table 3: Estimated probability of incurring some hospital inpatient costs, at UKPDS mean population values, by first diabetes related complication, during year of complication and in subsequent years

Complication	Mean (95% c.i.) probability of incurring some hospital inpatient costs	Estimated annual hospital inpatient costs (95% c.i.) conditional on cost being incurred (£s 1999)	Expected mean (95% c.i.) hospital inpatient cost of complication (product of probability and conditional cost) (£s 1999)
Column 1	Column 2	Column 3	Column 4
No complication	0.06 (0.06, 0.07)	£2,543 (2406, 2697)	£157 (145,170)
Estimates for the year in which the event occurred:			
Fatal MI	0.74 (0.68, 0.78)	£1,567 (1279, 1919)	£1,152 (941, 1396)
Non fatal MI	0.80 (0.75, 0.84)	£5,104 (4486, 5806)	£4,070 (3580, 4722)
Fatal Stroke	0.80 (0.67, 0.89)	£4,227 (2454, 7280)	£3,383 (1935, 5431)
Non fatal Stroke	0.35 (0.27, 0.43)	£6,822 (5255, 8858)	£2,367 (1599, 3274)
Ischaemic heart disease	0.41 (0.35, 0.48)	£4,760 (3736, 6064)	£1,959 (1476,2541)
Heart failure	0.53 (0.43, 0.62)	£4,227 (3431, 5208)	£2,221 (1690, 2896)
Blindness in one eye	0.20 (0.14, 0.27)	£4,370 (3219, 5933)	£872 (526, 1299)
Amputation	1	£8,459 (5220, 13706)	£8,459 (5295, 13200)
Cataract extraction	1	£1,553 (1278, 1888)	£1,553 (1320, 1855)
Estimates for each year subsequent to the year in which the event occurred:			
Non fatal MI	0.13 (0.11, 0.15)	£3,603 (3134, 4142)	£464 (377, 578)
Non fatal stroke	0.08 (0.07, 0.11)	£2,970 (2278, 3872)	£249 (166, 357)
Ischaemic heart disease	0.13 (0.11, 0.15)	£3,814 (3291, 4420)	£493 (392, 606)
Heart Failure	0.15 (0.12, 0.19)	£4,097 (3148, 5331)	£631 (403, 896)
Blindness in one eye	0.10 (0.07, 0.12)	£2,945 (2349, 3692)	£281 (189, 401)
Amputation	0.08 (0.06, 0.12)	£3,639 (2445, 5416)	£300 (154, 531)
Cataract extraction	0.06 (0.05, 0.07)	£1854 (1464, 2349)	£105 (80, 142)

Table 4: Regression equations to derive annual probability of incurring non-inpatient costs, and costs of non-inpatient care conditional on incurring a cost, (3460 patients)

Variable	Part 1 (logistic regression): Equation to derive annual probability of incurring non inpatient costs		Part 2 (GLM): Equation to derive non-inpatient costs conditional on costs being incurred	
	Coefficient	Standard error	Coefficient	Standard error
Age in years	0.023	0.005	0.003	0.003
Male (=1)	-0.604	0.098	-0.229	0.049
Event during year indicator:				
Macrovascular event	1.142	0.468	0.502	0.156
Microvascular event	2.181	1.014	0.292	0.193
History of event:				
Macrovascular event	0.720	0.170	0.358	0.072
Microvascular event	0.456	0.229	0.204	0.096
Constant	0.405	0.313	4.332	0.175

* P<0.05;**P<0.01

Table 5: Estimated probability of incurring some non-inpatient costs, at UKPDS mean population values, by first diabetes related complication, during year of complication and in subsequent years

Complication	Mean (95% c.i.) probability of incurring some non-inpatient costs in 4-month period	Estimated non inpatient costs (95% c.i.) conditional on cost being incurred in 4-month period (£s 1999)	Expected mean (95% c.i. annualised non-inpatient costs (£s 1999)
Column 1	Column 2	Column 3	Column 4
No complication	0.76 (0.74, 0.78)	£70 (66, 76)	£159 (150, 174)
Estimates for the year in which the event occurred:			
Macro vascular	0.91 (0.80, 0.96)	£116 (86, 158)	£315 (255, 393)
Micro vascular	0.97 (0.79, 1.00)	£94 (65, 138)	£273 (213, 342)
Estimates for each year subsequent to the year in which the event occurred:			
Macro vascular	0.86 (0.82, 0.90)	£101 (88, 116)	£258 (231, 297)
Micro vascular	0.83 (0.76, 0.88)	£82 (72, 104)	£204 (183, 249)

Statistical Appendix

Separate statistical analyses were employed in modelling the inpatient and non-inpatient costs. In the case of inpatient cost the data was characterized by repeated observations on each patients for the years they participated in the UKPDS. Given the structure of the data we used a random effects panel data models for both stages of the two-part model. In particular:

$$C_{it} = d X_{it} + m_i + n_{it}$$

where C_{it} are the total hospital costs for the i th patient ($i = 1..n$) in year t of the study ($t = 1,...,T$) and X_{it} is a vector of variables that influence costs including age, sex, indicator variables representing the occurrence of diabetes related complications. To estimate the immediate impact of complications we include an indicator variable that is set to one in the year that the event occurs. A second indicator variable is included to estimate the long-term effect that is set equal to one for all subsequent years while the patient is participating in the study. In the random effects model the error term is divided into two parts, m_i an unobservable individual specific effect independently identically distributed with zero mean and variance of s_m^2 (i.e. $m_i \sim \text{IID}(0, s_u^2)$ and n_{it} which denotes the remaining error term ($m_i \sim \text{IID}(0, s_n^2)$). In the first part a logistic regression is applied to the panel data and the predicted probability of incurring hospital costs:

$$\Pr(C_{it} > 0 \mid X_{it}) = \frac{\exp(a X_{it})}{(1 + \exp(a X_{it}))} \qquad (1.)$$

is estimated for each complication. In the second stage of the two-part model we use a GLM with a log link function on the assumption that:

$$E(C_{it} \mid C_{it} > 0, X_{it}) = \exp(b X_{it}) \qquad (2.)$$

Diagnostic tests [18] indicate that the gamma family should be used to specify the mean—variance relationship. Again the expected or mean costs were calculated for each complication conditional on having positive hospital costs. The overall estimate of hospital costs is then $\Pr(C_{it} > 0 \mid X_{it}) \times \exp(b X_{it})$ and the 95% CI are obtained through non-parametric bootstrapping involving 1000 replications. The analysis of non-inpatient costs is based similar approach, but was based on data from a cross sectional survey conducted towards the end of the trial. For methodological consistency we assign non-inpatient costs to the patient year in which the survey is conducted (denoted as year *s*) and employ the same two-part approach but with *t*=*s*.