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Requisite models for strategic commissioning: the example of type 1 diabetes

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Requisite models for strategic commissioning: the example of type 1 diabetes

Abstract

A developing emphasis of health care reforms has been creating organisations with responsibilities for strategic commissioning of services for defined populations. Such organisations must set priorities in aiming to meet their populations' needs subject to a budget constraint. This requires estimates of the health benefits and costs of different interventions for their populations. This paper outlines a framework that does this and shows how this requires modelling to produce estimates in a way that is transparent to commissioners, of requisite complexity to produce sound estimates for priority setting using routinely available data. The example illustrated in this paper is an intervention that would improve glucose control in the English population with type 1 diabetes. It takes many years for a change in glucose management to deliver maximum benefits; hence the intervention is not good value-for-money in the short run. We aim to give a more strategic view of the costs and benefits modelling costs and benefits in a steady-state model which suggests that the intervention is good value-for-money in the long run.

Keywords: resource allocation, population health, DALYs, QALYs, commissioning, strategic purchasing, type 1 diabetes, microvascular complications, intensive glucose control.

Requisite models for strategic commissioning: the example of type 1 diabetes

Introduction

Cost-effectiveness analysis (CEA) and disease modelling have grown apace in the hope of informing policy formation, however many authors have questioned their actual contribution to the development and implementation of policies [1-5]. This paper develops a framework for CEA and cost-effectiveness analysis to provide information for organisations responsible for strategic commissioning of health services for defined populations and illustrates its use by modelling intensive glucose control in type 1 diabetes in England. Strategic commissioners (or purchasers) have emerged in reforms of health care, which are required to assess needs of populations, determine the optimal way of meeting these needs, and accordingly contract with providers of different services. This is currently the task of Primary Care Trusts (PCTs) in the National Health Service (NHS) in England [6] and Local Health Integration Networks (LHINs) in Ontario [7]. The second section of this paper outlines the framework we have developed to help strategic commissioners set priorities. The third section illustrates how this framework was used in modelling type 1 diabetes. The final section discusses the results and implications of our framework for disease modelling.

Framework of analysis

The mainstream evaluation framework in economic evaluation for priority setting is that of Quality-Adjusted Life Years ([8, 9]; see [10, 11] for a review of proposed, albeit less widespread alternatives). A Quality-Adjusted Life Year (QALY) is a year weighted for quality of life, with a weight of one for perfect health and zero for death. QALYs are used to compare alternative interventions and to prioritize cost-effective interventions for funding. The cost-effectiveness of an intervention is measured by the ratio between its added value in terms of health benefits and its incremental cost compared to an alternative, the "incremental cost-

effectiveness ratio" or simply "cost/QALY". Interventions with a lower cost/QALY represent better value for money because a smaller investment is needed to produce a unit of benefit or, alternatively, more QALYs can be achieved per unit spent. A different measurement tool that raised a heated debate is the concept of Disability-Adjusted Life Years (DALYs) to estimate the Burden of Disease (BoD) in a population [12-17]. DALYs are a form of summary measures of population health and combine information on mortality and morbidity (for a review of alternative measures see [18]) and consist of the sum of Years of Life Lost (YLLs) from premature mortality and Years Lived with a Disability (YLDs), in which each year of life is weighted for disability with a weight of zero for perfect health and one for death. These different approaches have subsequently been developed to converge to produce information on costs and benefits of interventions in the population in terms of reductions in BoD measured in DALYs [19-21], or gains in health, measured in QALYs [22-25].

Beside common serious methodological, ethical and empirical problems [10, 18], each approach, as originally developed, was subject to different limitations as bases for setting priorities. The methodology of Cost/QALY was designed for marginal analysis: it does not distinguish interventions of low cost and low benefit from those of high cost and high benefit; does not tell us whether the bulk of resources are being currently used effectively [26, 27]; nor the number of people affected by an intervention. The value of reporting on the scale of the intervention has been highlighted by Murray and Lopez [17]: "If there are fixed assets, other than disposable dollars, limiting the feasible combinations of interventions that can be delivered – real-world examples include the attention of senior Ministry of Health decision-makers or the political commitment of government leaders –, then these should be devoted not just to the most cost-effective interventions but to those cost-effective interventions with the potential to effect substantial improvements in population health status'. The standard approach to estimating BoD in DALYs, however, gives estimates of that which exists given the current delivery of health care, and hence is best described as the 'current' BoD. Estimates of the current BoD in DALYs are of no value in themselves, nor a good guide on the potential benefit from an intervention. Hollinghurst *et al.* [28] estimate the current BoD and the potential benefits from interventions in the South West of England. Estimates varied greatly across different diseases and showed that, although the current BoD of heart diseases was higher than that of depression, the DALYs that are potentially avoidable by improving treatment of depression were much more than those of improving treatment of heart diseases. To set priorities using DALYs, we require information on benefits and costs, but to interpret the relationship between DALYs and costs, we need to distinguish between estimates of three different components of BoD [28-30]: (i) DALYs 'avoided' from the current delivery of health care which with their costs indicate cost-effectiveness of current practice; (ii) DALYs 'avoidable' through improving treatment

(coverage, appropriateness or compliance) which need to be put alongside estimates of their costs to indicate potential cost-effectiveness of changing practices; and (iii) DALYs that are 'unavoidable' and cannot be reduced given current evidence, and are hence irrelevant to assessments of setting priorities among available interventions.

To set priorities for populations we require methods that draw on both cost/QALY and DALYs by applying the framework of cost-effectiveness to populations in order to estimate the 'avoidable' burden of disease [29]. The concept of 'avoidable' burden of disease builds on the idea of using 'avoidable mortality' to assess the use of resources among different health care services [31-33] and combines it with DALYs to estimate both mortality and morbidity avoidable through an intervention. This has been the common basis for three different recent sets of studies: cost-effectiveness of treating mental illness in Australia [34]; WHO's project for *Choosing Interventions that are Cost Effective* [21, 27, 35]; and estimates of NHS productivity that sought to estimate gains in QALYs for the population of England [23-25, 36].

To deal with costs and health benefits occurring at different points in time, manuals of cost-effectiveness recommend the use of a common discount rate, but acknowledge that theory and empirical evidence on the relationship between interest rates and rates of time preference is unsettled. For strategic commissioners, the cost-effectiveness of a health intervention based on its derived present value is difficult to interpret and use: they are allocated annual budgets and cannot easily translate results from economic evaluation on the financial impacts in the short and in the long term. This is nicely illustrated by intensive glucose control for type 1 diabetes. This is because, although some evidence suggests that over the patient's lifetime this is more cost-effective than conventional care [37-40], its funding will cause an immediate increase in costs and delayed benefits. This paper proposes a different approach by measuring impacts on population health and on the commissioner's budget in the short- and long-run.

Modelling type 1 diabetes

The Disease and Interventions

Diabetes mellitus is one of the most common chronic diseases and the diabetic population in England is estimated to be about 2.2 million [41]. Of these, 2 million have type 2 diabetes, which is characterised by insulin resistance and usually diagnosed in the middle aged or elderly; and about 170,000 have type 1 diabetes, which is characterised by an absolute deficiency of insulin and is usually of rapid onset.

The evidence is that only a minority of people with type 1 diabetes have blood-glucose concentrations below the recommended levels (Figure 1) [42]; there is a well-known association between poor glucose control and the development of microvascular complications, i.e. eye, kidney and nerve damages that could lead to blindness, dialysis and amputation [40, 43, 44] hence, these people are expected to develop complications. A large longitudinal study has shown, however, that it is possible to reduce the levels of glucose concentration by providing intensive and personalized advice on insulin doses, diet and exercise and that, over time, this leads to a significant reduction in microvascular complications [40, 43, 44]. There is also some evidence that the intervention is cost-effective according to standard economic evaluation both in type 1 [37-40] and in type 2 diabetes [e.g. 45, 46]. However, microvascular complications are progressive, appear after several years after the onset of diabetes and tend to degenerate over time. The typically degenerative nature of these complications poses a particular challenge in designing policies for these patients: those who already have moderate complications will have limited benefits from intensive glucose therapy, as the damage is already present and cannot usually be reversed; the full benefits are for those who receive intensive glucose control from the early stages of their diabetes only, but there are long time lags between the start of the therapy and its benefits in terms of reduced complications.

----------*Figure 1 Proportion of type 1 diabetes population with glucose levels within the recommended level, by age group*----------

Modelling requirements of our framework

Our framework required estimates of the BoD from type 1 diabetes that is 'avoidable' through intensive glucose control by modelling the relationships between better glycaemic control and: reduced risks of developing renal, eye or neural complications; and slower progression from mild to severe stages after the onset of the complication; and lower mortality rates. We required estimates of the current BoD and that which is 'avoidable' from in terms of:

- Deaths;
- Years of Life Lost (YLLs) – the residual life expectancy at the age of the 'avoidable' death according to local life tables; and
- Years Lived with a Disability (YLDs) using disability weights developed by the Dutch Disability Weight study [47];

- DALYs (the sum of YLLs and YLDs), with and without discounting, using a 3.5% discount rate [48].

We also required estimates of average annual net costs of:

- expenditure each year, for the whole of the diabetic population, drugs, equipment; monthly specialist visits and measurement of HbA_{1c} , less

- savings due to intensive glucose control from reductions in the costs of treating the sequelae of diabetes, renal disease (including dialysis), eye disease, and diabetic foot (including amputation).

We also required estimates of the short- and long-run impacts of intensive glucose control:

- over the next five years, assuming a policy in which intensive glucose control was introduced for all patients regardless of the stage of their disease, in which we modelled changes in the current population from aging and death, but omitted births (this is known as a 'closed population model'); and

- in the long run, in a future 'steady state', in which all patients would have intensive glucose control at the onset of the disease, in which we modelled a population cohort of new cases of different ages and simulated changes over time by assuming that the total size and age distribution of the population was stable.

Although five years was an arbitrary choice, it reflects a period between the immediate and long run and corresponds to the time horizon recommended for strategic planning in the English NHS (supplemented by yearly reviews) and is similar to the Ontarian 4-year typical time horizon with yearly reviews. The steady state scenario gives indications of the expected annual health benefits and costs for a stable intervention and has been used in the past to evaluate services with long time lags as diabetes [49, 50].

To compare the health benefits with the net cost of the intervention, we attached a monetary value to life. We assumed a theoretical equivalence between a year of life in full health and a year of life free of disability [51] and used the putative threshold of the National Institute for health and Clinical Excellence, which on average judges cost-effective a health intervention that costs less than £30k per QALY. We ran a sensitivity analysis on the value of health benefits.

In this paper we investigate the adequacy of a simple disease model within our framework of analysis. To be useful for informing strategic commissioning, we required a transparent, simple model, using routinely-available data, that would produce approximate estimates that would

indicate orders of magnitude for comparison with other interventions within and across different diseases at the population level. Most of the diabetes models that have been developed understandably focus on type 2 diabetes (based on the pioneering work by Eastman and colleagues [45, 52]), but some like the Archimedes, the CORE or the EAGLE model are designed for both type 1 and 2 [53-55]. We tested the adequacy of our model through validation, sensitivity analysis and comparing results with those from more sophisticated models. The model we developed is requisite for our purpose and parsimonious [56, 57].

We modelled diabetes as a Markov chain, which makes the simplifying assumption that the probability of transition from disease state A to disease state B does not depend on the patient's history before arriving in state A. However, the incidence of microvascular complications correlates significantly with diabetes duration [58]; we divided the population in 5-year age groups to allow the use of a different set of transition probabilities for each one. The probability of death is dependent both on age and degree of severity of complication. The incidence of complications and their progression rates vary with age, but as there are no routinely available data on these, we assumed no incidence of microvascular complications before the age of 15 and lower incidence rates in young adults compared to older ones. The specifications for the two models are outlined in Figure 2. A description of the key assumptions and an evaluation of the data are given in Tables 1 and 2. We estimated the BoD: from higher mortality (deaths and YLLs) from all causes; and disability (YLDs) associated with microvascular complications, diabetic nephropathy, retinopathy and diabetic foot; but not from acute diabetic events (ketoacidosis), non-fatal myocardial infarctions, non-fatal strokes and coronary revascularisations. Although we did not model patients with cerebrovascular complications explicitly, deaths caused by these complications are accounted in the YLLs from all causes.

The model can be run for any local population and we have used it for England, ten different PCTs in the South-East of England and two PCTs in central London. However, the demographic differences across these PCTs did not have a significant impact on the relative magnitude of results. In this paper we discuss estimates for the population of England.

----------Figure 2 Base structure of the model for diabetic nephropathy (left) and diabetic retinopathy & diabetic foot (right)----------

----------Table 1 Main model assumptions----------

First five years

The model of the first five years tracked 100 birth cohorts, i.e. the population from ages 0 to 99 over five consecutive years. The distribution by age of the initial population was that in England in 2003. Estimates of BoD in DALYs were calculated by equation (1):

(1) $DALYs = YLLs + YLDs =$

$$= \sum_{i=1}^{5} e^{-ri} \sum_{j=0}^{99} \sum_{s=0}^{k} A(i,j,s) * \mu'(i+j,s) \int_{1}^{L(i+j+1)} e^{-rt} dt +$$

$$+ \sum_{i=1}^{5} e^{-ri} \sum_{j=0}^{99} \sum_{s=0}^{k} A(i,j,s) * w(s) * e^{-r} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

where:

- i is the index for the years over which the model is run;
- j is the index for the cohorts (j is the initial cohort age);
- s is the index for the degree of severity of the condition;
- r is a discount rate. The model was run with r=0 (which corresponds to no discounting) and with r=3.5% (giving discounted values);
- $A(i,j,s)$ is the number of the population with diabetes at stage s in year i of cohort j;
- $\mu'(i+j, s)$ is the *excess* mortality rate from type 1 diabetes with degree of severity s for the jth cohort in year i (by which time the members of this cohort will be $[i+j]$ years old);
- $L(i+j)$ is the residual life expectancy of the jth cohort in year i. (we assume that L is residual life expectancy based on local life tables for someone $i+j$ years old);
- $w(s)$ is the disability weight associated with degree of severity s.

At the core of the model, was the system of difference equations that model the evolution of two populations, A and N. $A(i, j, s)$ was the population with type 1 diabetes in degree of severity s,

N(i, j) was the population without type 1 diabetes (both constituted the *j*th cohort in the *i*th year of modelling).

The population with type 1 diabetes in the *j*th cohort in the *(i+1)*th year of modelling [*A(i+1, j, s)*] was derived from populations with type 1 diabetes [*A(i, j, s)* and *A(i, j, s-1)*] and without type 1 diabetes [*N(i, j)*], in the *j*th cohort in the *i*th year of modelling, and estimated by equation (2):

$$A(i+1,j,s) = A(i,j,s)\left[1-\gamma_s(i+j,s+1)-\mu(i+j,s)\right]+$$

$$+A(i,j,s-1)\gamma_s(i+j,s-1)+N(i,j)\left[\alpha(i+j,s)\right] \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

for all *j* (0 to 99) and for all *i* (1 to 5) where:

- $\gamma_s(i+j,s+1)$ is the transition probability from stage *s* to *s+1;*
- $\mu(i+j,s)$ is the death rate from type 1 diabetes in stage *s* for the *j*th cohort in year *i* (and is equal to age-specific mortality rate for the population without the condition, $\lambda(i+j)$, plus the excess mortality rate from type 1 diabetes with degree of severity *s* in year *i* of the cohort *j*th, $\mu'(i+j, s)$);
- $\gamma_s(i+j,s-1)$ is the transition probability from stage *s-1* to stage *s;*
- $\alpha(i+j,s)$ is the incidence rate of new cases of type 1 diabetes at stage *s* from population *N*, where $\sum_s \alpha(i+j,s) = \alpha(i+j)$.

The population without type 1 diabetes in the *j*th cohort in the *(i+1)*th year of modelling [*N(i+1, j)*], was derived from the population without type 1 diabetes in the *j*th cohort in the *i*th year of modelling [*N(i, j)*], were and estimated by equation (3):

$$N(i+1,j) = N(i,j)\left[1-\alpha(i+j)-\lambda(i+j)\right] \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (3)$$

for all *j* (0 to 99) and for all *i* (1 to 5) where:

- $\alpha(i+j)$ is incidence rate of new cases with type 1 diabetes for the jth cohort in year i;
- $\lambda(i+j)$ is death rate for of the population without type 1 diabetes in year *i*.

The model required estimates of the initial populations without and with type 1 diabetes: *N(0,j)* and *A(0,j)*. These were derived using data on the 2003 population in England [59] and prevalence estimates published by Harvey *et al.* [60]. We did not find data on the distribution of the population with type 1 diabetes (*A(0,j)*) in terms of degrees of severity by age of renal and eye complication. We estimated these distributions by generating a hypothetical birth cohort of 100,000 persons and simulating their aging, deaths and progression to and through diabetes over 100 years. The dynamic of the hypothetical cohort was modelled with a Markov-chain model that used the same transition probabilities of the main model presented in this paper. We assumed that the proportion of diabetic patients with degree of severity *s* at period *t* of the hypothetical cohort simulation was representative of the proportion of diabetic patients aged *t* in the current English diabetic population. We subject the resulting initial condition to validation.

Figure 2 outlines the progression of type 1 diabetes in the stages of nephropathy (left panel) and retinopathy (right panel). The stages of nephropathy are:

- microalbuminuria, i.e. an increased concentration of the protein 'albumina' in the urine;
- macroalbuminuria, i.e. overt proteinuria or 'clinical nephropathy', and
- end stage renal disease (ESRD).

Each of these stages is also associated with increased mortality rates, mainly due to cardiovascular disease [61-64]; and these are particularly high for macroalbuminuria [65, 66]. The progression of retinopathy to blindness is also associated with a higher mortality rate compared to the non-diabetic population. The effect of glycaemic control was modelled through transition probabilities γ, which are lower for diabetic patients under intensive glucose control compared to conventional care, which means there is a slower progression of the disease to and through microvascular complications (see Appendix).

The retinopathy model also estimated the BoD from ulcers, sores and amputation using the incidence rates of these complications associated with different degrees of retinopathy [67] (see Appendix). The Diabetes Control and Complications Trial (DCCT study) does not report the reduction in lower extremity amputation rates. We built on the association between degrees of severity in retinopathy and lower extremity amputation [67]. We made two assumptions: first, poor glucose control is an underlying cause of both diabetic retinopathy and diabetic foot; second, the association between degree of severity of retinopathy and diabetic foot is the same in the intensive glucose control and in the conventional treatment group (keeping constant the provision of other treatments, e.g. laser treatment). For instance, the 4-year incidence of lower extremity amputation is 7.8% in patients with proliferative diabetic retinopathy (PDR).

However, fewer people have PDR with intensive glucose monitoring and control than with conventional therapy. The model we built did not model neuropathy and diabetic foot explicitly and would be unsuitable to measure the impact of other specific interventions (e.g. changes in laser therapy).

There are interdependencies among all complications that cannot be represented in a simple spreadsheet model like ours (to represent them, the CORE model builds on fourteen sub-models and the Archimedes model generates the biology of a virtual patient directly rather than modelling distinct health states). We combined the nephropathy and retinopathy/diabetic foot models to estimate YLLs and YLDs from type 1 diabetes as follows:

- YLLs based on deaths from the nephropathy model, because albuminuria is the best predictor of all-cause mortality in type 1 diabetes [65]. These deaths includes those from macrovascular complications such as myocardial infarctions and strokes;
- YLDs from the nephropathy model (for macroalbuminuria and ESRD);
- YLDs from the retinopathy-diabetic foot model (for uncomplicated type 1 diabetes, moderate and severe visual impairments, sores, ulcers and lower extremity amputation.

The current BoD and health gains from reduced non-fatal macrovascular complications have not been estimated here.

The steady-state

The model of the steady-state estimated the BoD of type 1 diabetes for one year with a set of initial conditions $A(j,s)$ based on the age specific profile of a hypothetical birth cohort modelled over 100 years using again equations (2) and (3) for modelling transitions in the population with and without type 1 diabetes. The differences from the model for the first five years are the assumptions that: the size of the population does not change (as those who die are replaced with individuals of the same age); and that the hypothetical cohort has received intensive treatment from the onset of type 1 diabetes, and hence has also been subject to lower transition probabilities from the onset of the disease. In this model, the number of diabetic patients in each age group is the same as in the initial population of the model for the first five years, but they all have blood glucose under the recommended level and fewer of them have developed complications. The 'steady state' model reflectes the delay between the intervention and its full benefits, estimating the reduction in burden of disease *as if* the current diabetic population was subject to treatment from the onset of diabetes and does not take into account recent predictions

of increasing future incidence rates [41]. It therefore underestimates the likely future burden of disease. The initial population of the steady state model is a stable population, where everybody has blood glucose below the recommended level. At the end of the year the population progresses according to transition probabilities characteristic of diabetic patients with glycaemic control.

Estimates of BoD in DALYs were estimated by equation (4) (using the same notation as equation (1)):

$$DALYs = YLLs + YLDs =$$

$$= \sum_{j=0}^{99}\sum_{s=0}^{k} A(j,s) * \mu'(j,s) \int_{1}^{L(j+1)} e^{-rt} dt + \sum_{j=0}^{99}\sum_{s=0}^{k} A(j,s) * w(s) * e^{-r} \quad \text{.....(4)}$$

Data

As most death certificates of diabetic patients do not report diabetes as a cause of death, official statistics that report causes of mortality are unreliable for diabetes. So we estimated mortality from diabetes using mortality rates from longitudinal studies [63, 65] and prevalence data from Harvey et al [60]. We estimated the presence and degree of severity of complications using the best evidence we could find, including studies conducted in the US or the Netherlands. A systematic review of the evidence, although needed and valuable, was beyond the scope of this paper. Details on the assumptions needed to deal with missing data are given in the last column of Table 2.

----------*Table 2 Data sources and assumptions on missing data*----------

The benefits of intensive glucose control are the difference between estimates of BoD with and without the intervention. In the absence of evidence on the level of disability from co-morbid conditions (e.g. retinopathy and nephropathy affecting the same person), we assumed that the disability from renal complications could be meaningfully added to the disability from eye and

foot complications, that is, for instance, the disability of a patient with both nephropathy and severe retinopathy contributes 0.29+0.43 YLDs (0.72 YLDs). For comparison, this means that a year spent with diabetic nephropathy and severe visual impairments would have the same disability weight as, e.g., schizophrenia with several psychotic episodes and some permanent impairments, or a year of a child/adolescent in permanent stage with complex not curatively operable congenital heart disease. Patients with all three complications at the highest degree of severity would contribute 0.91 YLDs (0.29+0.43+0.19).

Our estimates of the potential net gain in output from intensive glucose control are based on estimated unit costs as outlined in Table 3 and Table 4.

----------*Table 3 Cost of monitoring glucose levels and prescribing insulin*----------

These costs assume the definition of intensive glucose control as it occurred in the original longitudinal study consisted of administration of insulin at least three times a day (or with an insulin pump); insulin dosage, dietary intake and exercise adjustment according to results of self-monitoring of blood glucose; self-monitoring of blood glucose at least four times per day; monthly measurement of HbA_{1c}; monthly visit at the diabetic centre; and specialist calls during the month to review regimens. We ran three sensitivity analyses of our estimates of costs. First, we replaced monthly clinic visits with telephone calls from a specialist nurse, which is a more realistic assumption of what might happen outside research conditions and does not appear to reduce health benefits [68]. Second, we assumed the use of insulin pumps rather than multiple daily injections (although there is some evidence that insulin pumps are clinically more effective than multiple daily injections, most of the benefit is in terms of hypoglycaemic events or practical convenience and would not significantly affect microvascular complications). Third, we allowed for the cost of treating a diabetic patient to be about 30% higher than a non-diabetic one and about 27% above the average cost for the general population [69].

----------*Table 4 Cost of treating microvascular complications*----------

Results

Health gains

Table 5 and the following Figures report annualised estimates for various measures of reductions in BoD and gains in DALYs.

The yearly estimates of the current BoD from type 1 diabetes in England was about 2,000 deaths; 66,000 YLLs and 34,000 YLDs; 100,000 undiscounted and 63,000 discounted DALYs. In the first five years and the steady state the estimated benefits from intensive glucose control are reductions in the BoD of about: 10 and 400 deaths; 300 and 11,000 YLLs; 1,200 and 11,000 YLDs; and 1,500 and 24,000 undiscounted DALYs; and 1,200 and 18,000 discounted DALYs. These are underestimates of the benefits as they do not include reductions in BoD from acute diabetes events (ketoacidosis), non-fatal myocardial infarctions, non-fatal strokes and coronary revascularisations, and this qualification also applies to our estimates of the monetary valuation of these benefits.

----------Table 5 Burden of Disease and its reduction through intensive glucose control in the first five years and in the steady-state----------

Figure 3 shows the BoD in undiscounted DALYs from type 1 diabetes and the estimated reductions in the first five years and in the steady state from intensive glucose control. This shows that much of the current BoD from type 1 diabetes is unavoidable even with 100% compliance with intensive glucose control. Figure 4 to Figure 7 show the distribution by age group of deaths, renal and eye diseases and amputations for the first five years and in the steady state. All these Figures bring out the common message that the benefits of intensive control appear to be much greater in the long run than the short run.

----------Figure 3 Estimates of BoD (undiscounted DALYs) from type 1 diabetes and reductions in the first five years and steady state from intensive glucose control----------

----------Figure 4 'Avoidable' deaths through intensive glucose control in the first five years and in the steady state by age at the beginning of the intervention----------

----------Figure 5 'Avoidable' cases of overt proteinuria and end-stage renal disease through intensive glucose control in the first five years and in the steady state by age at the beginning of the intervention----------

----------Figure 6 'Avoidable' cases of severe visual disorders through intensive glucose control in the first five years and in the steady state by age at the beginning of the intervention

----------Figure 7 'Avoidable' cases of amputation through intensive glucose control in the first five years and in the steady state by age at the beginning of the intervention----------

Net costs and net gains in output

We estimated that:

- the annual cost to prescribe, monitor and treat microvascular complications of diabetes type 1 in England is currently about £380m (most of which is spent on monitoring the disease, prescribing insulin and treating renal complications (Table 6));
- the introduction of intensive monitoring increases the cost of insulin prescribing and monitoring by £350m and reduces the annual costs of complications by £20m in the first five years; and by £370m and £100m respectively in the steady state;
- reductions in costs for eye diseases are mainly realized in the short run (£8m compared with long-run savings of £12m);
- reductions in costs for renal complications are mainly realized in the long run (£84m compared with short-run savings of £13m).

----------Table 6 Annual costs and savings (negative figures) from intensive glucose control in the first five years and the steady state----------

The estimates of costs and savings of intensive glucose control in the long run are of what these would be in a year: i.e. we have not examined these using discounting. If the savings were discounted, these would be negligible because of the long time lags between the start of incurring the costs of intensive glucose control and making these savings from reduced use of health services. In our estimates, the expected savings from reduced complication do not offset the increased cost for monitoring and prescribing. There is, however, evidence that these costs

can be reduced. It is not necessary to have monthly visits to the diabetic clinic: a telephone discussion with a specialist nurse three times a week to adjust insulin dose and diet to the observed glucose levels was successful in reducing HbA_{1c} below the recommended level at six months [68]. This practice would reduce the extra costs to about £270m and hence extra net costs to about £180m in the steady state.

We used these costs in Table 7, which gives results from comparing costs and benefits in the short and in the long run. This shows that the net cost of intensive glucose control in the short run are about six times larger than the monetary value of the health benefits. If the intervention were to be introduced and sustained over its run-in period, however, the monetary value of health benefits would be three times the net cost of the intervention.

----------*Table 7 Net gain in output in the first five years and in the steady state*----------

Model validity

Assessing the validity of our model is difficult, because routinely available data usually refers to type 1 and type 2 diabetes combined (even when these labels are used, most patients belong to an 'unspecified' type of diabetes). The available combined figures are likely to be a reflection of prevalence and incidence rates of diabetes type 2, which is about 90% of the diabetic population and is not representative of the population with type 1. In fact, type 1 typically has a much younger onset compared to diabetes type 2 and the duration of diabetes is one of the main risk factors of complications. Where data on type 1 diabetes exist, usually either there is no breakdown by age, or data are not for England, or they are not routinely available and hence could not be used as input for our initial condition. We now discuss how we compared the prevalence of complications resulting from our initial condition with data from the literature.

Diabetic nephropathy

Table 8 compares prevalence rates of renal complications by degree of severity in our model and in the literature. Our estimates are generally consistent with data from empirical analysis, although we might overestimate the prevalence of end stage renal disease. The Renal Registry in England estimates that 30,000 people are receiving renal replacement therapy (including those who received a kidney transplant) and 5,000 started renal replacement therapy in 2002 [70]. Our model estimates that there are about 6,000 people with End Stage Renal disease and 1,000 new cases per year among patients with type 1 diabetes which would correspond to about 16% and 20% respectively of all patients receiving renal replacement therapy. This might be an

overestimate and we will indicate the health benefits and cost component separately for ESRD in the result section for transparency.

----------*Table 8 Prevalence rates of renal complications*----------

Diabetic retinopathy

Estimates of diabetic retinopathy for the population with type 1 diabetes vary greatly. A recent literature review on prevalence reports rates between 0 and 84% for diabetic retinopathy in general; and between 1.1% and 25% for Proliferative Diabetic Retinopathy [71]. We report in Table 9 the prevalence of diabetic retinopathy in the WESDR study (which we used as a basis of our model) and the estimated prevalence based on the model by Davies *et al.* [72] who used the same dataset. Table 9 shows that our estimates are reasonable, once we assume the WESDR data can be used for England. Furthermore, the 9-year cumulative incidence of background diabetic retinopathy in our model is 81%, which is similar to estimates from the EAGLE model (77%), which also uses the WESDR study [73].

----------*Table 9 Prevalence rates of eye complications*----------

Diabetic foot

Health Episode Statistics (HES) report a total of 10,700 finished consultant episodes (FCEs) of amputation, including traumatic amputations and procedures associated with diabetic foot such as amputation of stumps. Our model predicts about 1,300 cases of amputation a year in the population with type 1 diabetes (toe and foot amputation) which would correspond to about 12% of all amputation procedures conducted in England (including diabetes type 2 and non-diabetic patients). From the publicly available HES data we could not identify what proportion of the total FCEs referred to people with type 1 diabetes. Results for diabetic foot are reported separately from those of renal and eye complications for transparency.

We compared our results with 4-year incidence rates of amputation and sores/ulcers in Moss et al. (1992) and show results in Table 10. Our prevalence estimates are based on the work by Moss and, as one should expect, the incidence rates correspond. It is reassuring, however, to observe consistency in the overall incidence rate (last column in Table 10), which is an output of our model and our assumptions on those with different severities of retinopathy.

We did not find data on prevalence or incidence of diabetic foot for the population with type 1 diabetes in England to validate the diabetic foot model externally. Our model, however, estimates an annual incidence of 2.8% for sores/ulcers and 0.7% for amputation, which is similar to 2.1% and 0.6% mean national incidence rates for type 1 diabetes in the Netherlands [74].

----------*Table 10 4-year incidence rates of sores/ulcers and foot/toe amputations* ----------

Intensive glucose control

We compare our model estimates on the relative risk of renal and eye complications with those in the DCCT study and in other diabetes models from the literature in table 11. Our model is consistent with the other studies in estimating the reduction in retinopathy and might slightly overestimate the reduction in renal complications by 15%. This overestimate does not have a significant impact on the estimate of the 'avoidable' Burden of Disease, which is mainly determined by a reduction in eye complications. The cost of renal complications, however, is the principal component of the savings in treating complications in the intensive care scenario in the steady state. Assuming a 15% lower savings from fewer renal complications, however, would not have an impact on the order of magnitude of our results: the net loss in the first five years would be unaffected and the net gain in the steady state would reduce from £350m to £330m.

Table 11 also reports estimates in the reduction of neuropathy, but our model does not model these complications explicitly. The relative risk in 9-year incidence of sores/ulcers and amputation in the intensive glucose control scenario is 0.95 and 0.91 which is much lower than the 0.47 relative risk of neuropathy at clinical examination in the DCCT study. A reduction in neuropathy does not imply an equivalent reduction in diabetic foot, however, the relatively small reduction in diabetic foot estimated in our model compared to the relatively high reduction in neuropathy indicates that we might have underestimated the 'avoidable' burden of disease.

----------*Table 11 Estimates of the risk reduction in 9-year incidence from microvascular complications* ----------

Costing

The estimate of the current, annual cost of monitoring, prescribing and treating microvascular complications amounts to about £2,300 per patient. This is broadly consistent with a recent estimate of the total healthcare cost of treating people with type 1 diabetes in the UK by Currie *et al.* [75]. The annual healthcare cost of participants in their survey spent about £3,200 a year, including treatment and prevention of macrovascular complications such as stroke and myocardial infarction.

Our estimate for the current cost of treating renal complications and diabetic foot are also in line with other estimates of the cost for type 1 diabetes in the UK. The estimate of £175m for nephropathy is consistent with Gordois *et al.* [76] estimate of £152m (range £125-230m); the estimate of £8m for *incident* cases of diabetic foot seems consistent with the £35m (range £16-61m) of *prevalent* cases of diabetic peripheral neuropathy [77].

Sensitivity analysis

Our estimates of health benefits assume that the transition probabilities and mortality rates observed in longitudinal studies, in which the participants were generally between adolescence and middle age [40, 43, 44, 78-82], apply to the type 1 diabetes population in England, and the confidence interval estimates of mortality rates in older cohorts are particularly wide [63]. To test the robustness of the model to these assumptions, we estimated the effects of excluding from the analysis all people older than 75 years. As this reduced these estimates by about one per cent, we concluded that they are robust to our assumptions of transition probabilities and mortality rates of older cohorts.

A crucial assumption in our estimates of the impacts of intensive glucose control is that there is compliance at levels comparable to those of the DCCT study. There is a linear relationship between the proportion complying and the reduction in BoD in DALYs. Figure 8 shows the estimated relationship for the steady-state model: a 1% increment in the proportion receiving intensive treatment and complying as in experimental conditions corresponds to a reduction of 240 DALYs (or 180 discounted DALYs).

----------*Figure 8 Estimates of annual BoD in undiscounted DALYs from type 1 diabetes in the steady state from 0 to 100% proportion of population complying with intensive glucose control*----------

Another assumption worth testing is that of offering intensive glucose monitoring to all patients, including children and adolescents. On one hand, DCCT researchers were cautious about the

use of intensive glucose monitoring in children because of the increased risk of hypoglycaemic events. On the other, the low proportion of adolescents with glucose concentration below the recommended level might signal the rebellion against parental or medical authority suggesting the possibility of very low compliance rates with intensive treatment. Our model, however, assumes that most microvascular complications arise after the age of 15 (with the exception of ulcers which we assume occurs at any age and amputation which we assume occurs only in people older than 30) and excluding these age groups from the analysis would not significantly impact on the estimates of health benefits: the estimate of the 'avoidable' burden of disease offering intensive glucose control only to people aged 20 or older is just 0.1% lower both in the short run and in the steady state. This result should be interpreted with caution because our Markov chain assumes that the incidence of microvascular complications from the age of 15 (or 30 for amputation) is independent from glucose concentrations maintained in childhood and we did not find evidence to support or dismiss this assumption. Clearly, however, the exclusion of children and adolescents from intensive glucose monitoring would have an impact on costs. The sensitivity analysis shows that the reduction in costs by providing intensive treatment only to patients who are 20 years old or older is 50m in the short run and 60m in the steady state which would imply a lower loss in net output in the first five years (£170m compared to £220 in the base case) and a higher net gain in output in the steady state (£410m compared to £350 in the base case).

To test the robustness of our cost estimates, we also assumed the use of insulin pumps to replace the base case assumption of multiple daily injections. There is growing interest in the use of insulin pumps as an alternative treatment to manage diabetes. In comparison with multiple daily injections, insulin pumps improve quality of life in terms of their higher efficacy on controlling glucose concentration, of reducing incidence of adverse events (i.e. hypoglycaemic events) and their flexibility of lifestyle. However, they are not currently considered cost-effective because of their higher cost [83]. If all patients use insulin pumps (using the average annual cost from Colquitt *et al.* [83]), the incremental cost of insulin prescribing and monitoring would be £515m in the short run (annualized figure over first 5 years) and £547m in the steady state. This would consistently lower the net gains from Table 7; however, although this is an extreme and unrealistic assumption, the results would still be a loss in the short run (£470m net loss in output) and a gain in the steady state (£75 net gain in output).

We also assumed a cost of acute care (inpatient and outpatient) 27% higher than the national average cost [69]. Under this scenario, the estimate of the total current cost of insulin and microvascular complication increases from £370m to £515m per year; the increase in spending from intensive glucose monitoring reduces from £250m to £210m and from £180m to £105m in

the first five year model and in the steady state respectively assuming telephone discussion with a specialist nurse rather than monthly visits to the diabetes clinic; from £330m to £285m and from £270m to £190m in the first five years and in the steady state model assuming monthly visit as in the original DCCT study. This is as expected because the higher cost of acute care increases the savings from treating microvascular complications, and this determines a lower net loss in the short run (£170m compared to £220m in the base case assuming monitoring with nurse on the phone) and a higher gain in net output in the steady state (£430m compared to £350m in the base case).

We ran a sensitivity analysis on the cost of peritoneal haemodialysis, assuming the use of continuous ambulatory peritoneal dialysis (CAPD) instead of continuous cyclic peritoneal dialysis (CCPD) which is cheaper although currently not considered cost-effective [84]. The resulting reduction in cost does not significantly affect results (£169m current cost vs. £162 in base case; same reduction in short run; 76m reduction nephropathy cost in steady state vs. £79 base case cheap or £84 base case DCCT).

Finally we tested the monetary value of health benefits with two sensitivity analyses. First, we use a lower figure of £20,000 as advocated by part of the literature [e.g. 85]. Second, we used the health benefits using the value of a statistical life (HM Treasury, 2003). Both sensitivity analyses confirm a net loss of more than £200m (£230 and £240 respectively) in the short run and a net gain above £180m in the steady-state (£180 and £260 respectively).

Discussion

This paper aimed to explore how disease models could be used in setting priorities for strategic commissioning for populations. To set priorities using evidence, it is essential to estimate impacts of interventions at the level of populations, but this can only be done by disease modelling. An obstacle to the use of such models is that they are often highly complex, demand rich sources of data, and take a long time to develop. We have described the development of a parsimonious transparent model of the size and timing of costs and benefits of intensive glucose control in the type 1 diabetes population, which has produced approximate estimates that are adequate for priority setting as shown by validation and sensitivity analysis. This paper has shown, that:

- The current BoD from type 1 diabetes disease from microvascular complications and premature mortality is about 100,000 DALYs of which one third is attributable to low quality of life and two thirds to premature death. This is an underestimate of the current

burden of disease from diabetes type 1, because it does not include disability due to acute diabetic events (ketoacidosis), non-fatal myocardial infarctions, non-fatal strokes and coronary revascularisations.

- Introducing intensive glucose control, in the short run, will almost double the spend for monitoring glucose, prescribing insulin and treating microvascular complications but have small effect in reducing the burden of disease (a 1-2% reduction).

- Introducing intensive glucose control, in the long run, reduced the BoD by about 30%: with this being approximately equally divided into benefits from lower mortality and lower morbidity. The lower cost of treating complications in the long run will still not offset the increased cost of monitoring and insulin prescribing (50% higher than conventional care); however, the value of the health benefits more than compensates the increase in costs.

The study also highlighted inadequacies in the data that are routinely collected in England: chronic diseases, such as diabetes, are frequently not reported on death certificates thereby masking the impact of long term consequences; there are significant gaps in data on the type of diabetes, age of the patient, duration of diabetes, presence of complication with degree and duration, sex and current treatment regime. In England many of these data are in principle available for purchase from the General Practice Research Database that offers a sample of about 7,500-8,000 type 1 diabetes patients, that is about 4.5% of the total type 1 diabetes population [63, 64]. These data ought to be collected in disease registers to support evidence-based policy making. An initiative that has the potential to provide this information in England is the current national Programme for IT in the NHS, *Connecting for Health*.

The final point concerns the approach to modelling illustrated by this paper. In setting priorities, information on costs and benefits in the short and long run for options for type 1 diabetes is obviously insufficient. We have applied our approach to a number of different interventions: suicide prevention, treatment of depression, prescribing of statins to reduce cholesterol, and various options for the prevention and treatment of strokes [86]. In all this work, it seems to us that relatively simple models, similar to that in this paper described for type 1 diabetes have been adequate in making comparisons for setting priorities for strategic commissioning. Indeed we see the key next step as not the development of more complex models for each of these but developing a simple method to generate adequate estimates for the wide range of interventions that must be considered by strategic commissioners.

Appendix

Model parameters

------- Table A1, A2, A3, A4 and A5 about here ----------

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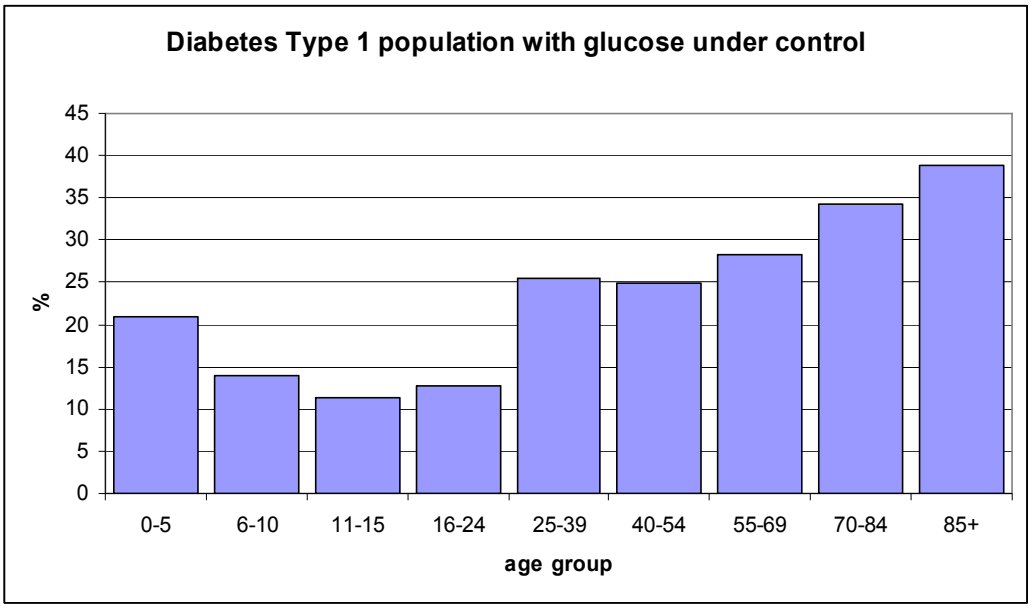
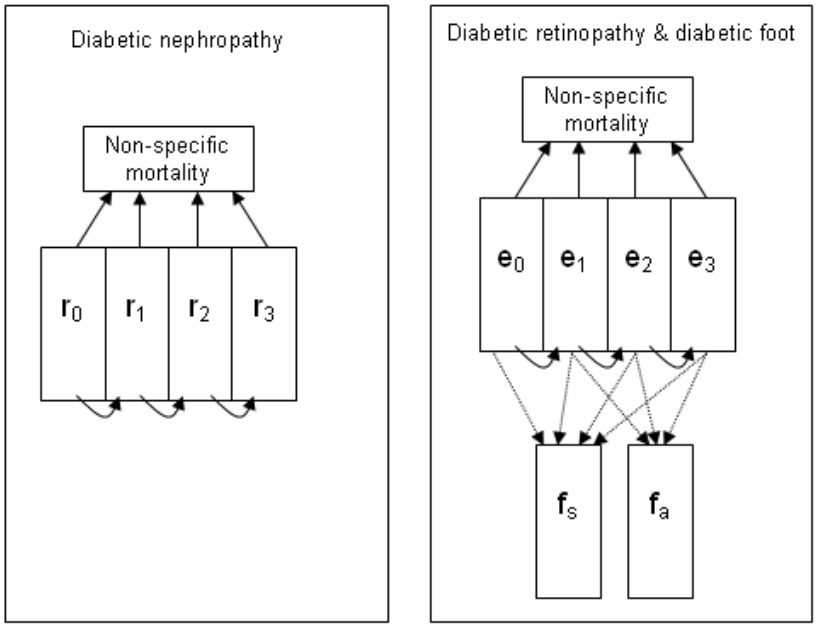
Figures

Figure 1 Proportion of type 1 diabetes population with glucose levels within the recommended level, by age group



Source:(National Clinical Audit Support Programme, 2005), data breakdown provided upon request by NHS – Health and Social Care Information Centre

Figure 2 Base structure of the model for diabetic nephropathy (left) and diabetic retinopathy & diabetic foot (right)



Diabetic nephropathy model	
r_0	Normo-albuminuria
r_1	Microalbuminuria (urinary albumin excretion ≥40 mg/24 hr)
r_2	Macroalbuminuria or overt-proteinuria (urinary albumin excretion ≥300 mg/24 hr)
r_3	End-Stage-Renal-Disease (ESRD)
Progression	Diabetic patients move through disease states according to annual transition probabilities. See table A3 in Appendix 2.
Mortality	All-cause mortality.
Diabetic retinopathy	
e_0	No retinopathy
e_1	Background diabetic retinopathy (BDR)
e_2	Proliferative diabetic retinopathy (PDR)
e_3	Severe visual loss
Progression	Diabetic patients move through disease states according to annual transition probabilities. See table A4 in Appendix 2.
Mortality	All-cause mortality.
Diabetic foot	
f_s	Sores /Ulcers
f_a	Amputation

DALYs	**YLDs +**	Years lived in each state *s* weighted for the disability associated with the state.
	YLLs	Years of Life Lost to premature (excess) mortality attributable to diabetes[1].

[1] Deaths in the diabetic population are caused by 'normal' mortality, i.e. mortality rate as in the non-diabetic population, and 'excess' mortality due to diabetes. Only 'excess' mortality generates Years of Life Lost (YLLs) for the Burden of diabetes estimate.

Figure 3 Estimates of BoD (undiscounted DALYs) from type 1 diabetes and reductions in the first five years and steady state from intensive glucose control

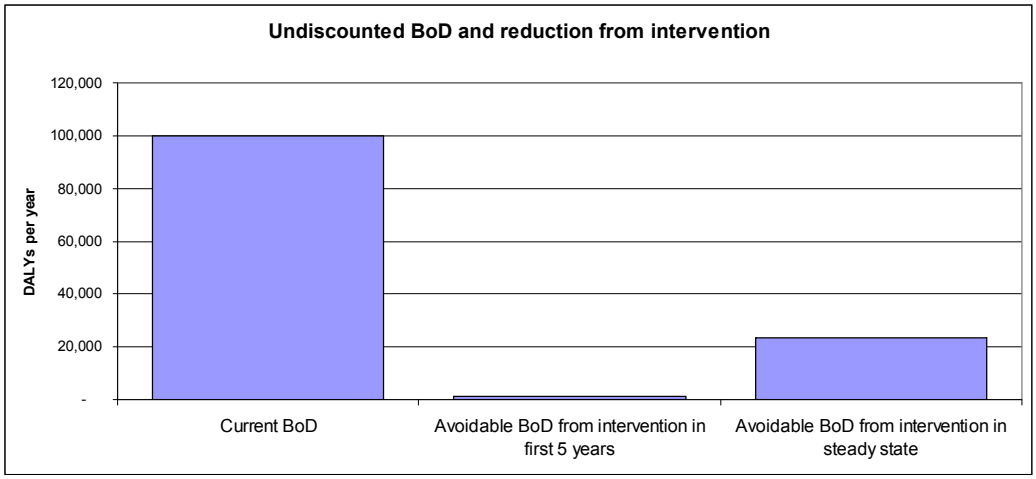


Figure 4 'Avoidable' deaths through intensive glucose control in the first five years and in the steady state by age at the beginning of the intervention

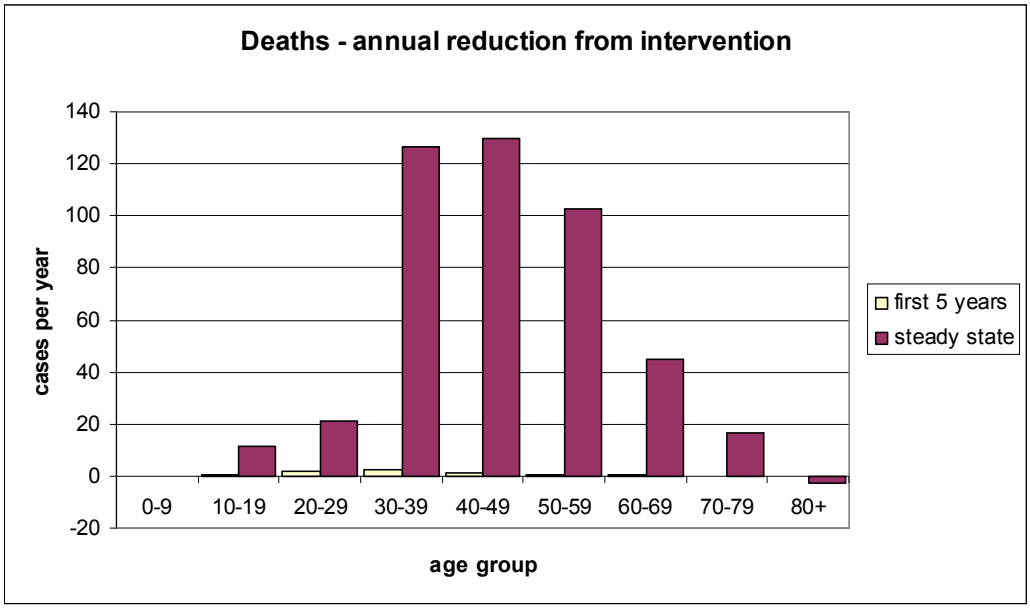


Figure 5 'Avoidable' cases of overt proteinuria and end-stage renal disease through intensive glucose control in the first five years and in the steady state by age at the beginning of the intervention

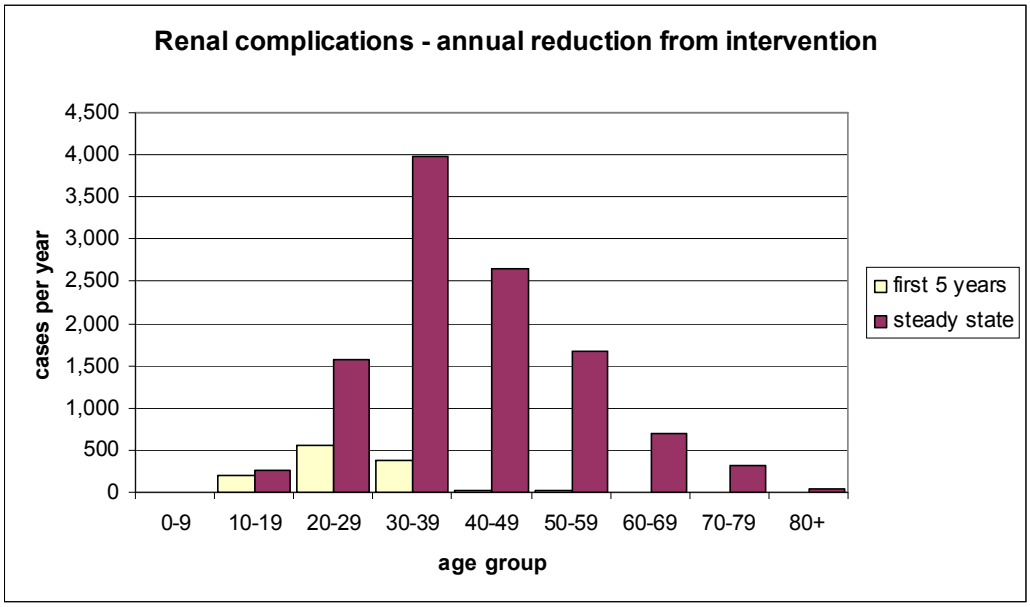


Figure 6 'Avoidable' cases of severe visual disorders through intensive glucose control in the first five years and in the steady state by age at the beginning of the intervention

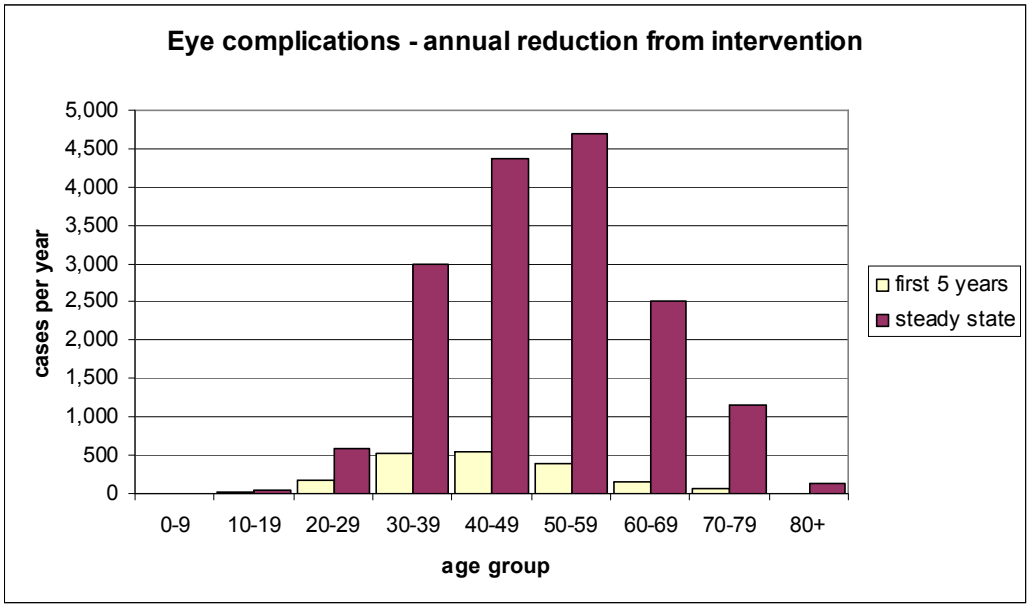


Figure 7 'Avoidable' cases of amputation through intensive glucose control in the first five years and in the steady state by age at the beginning of the intervention

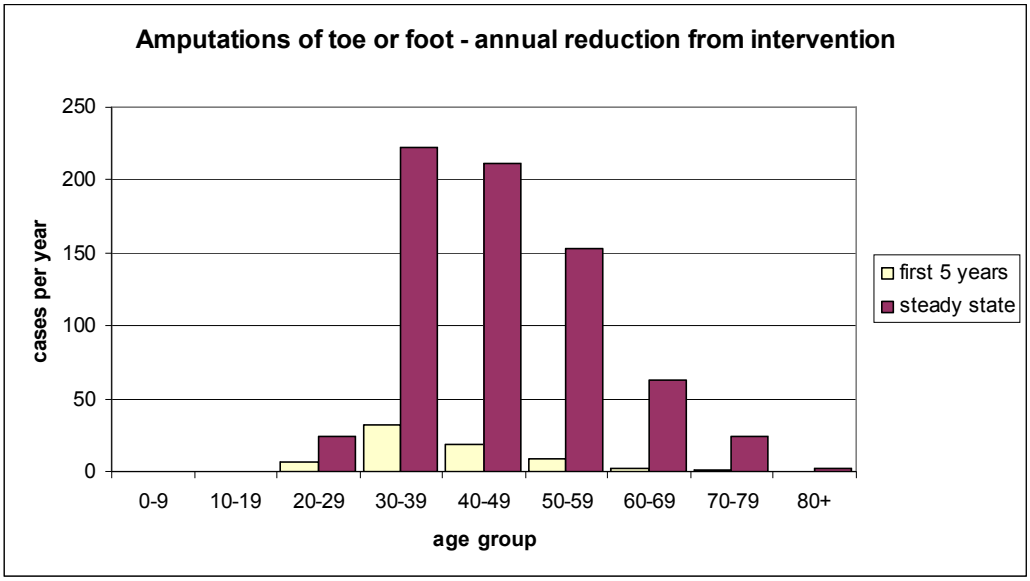
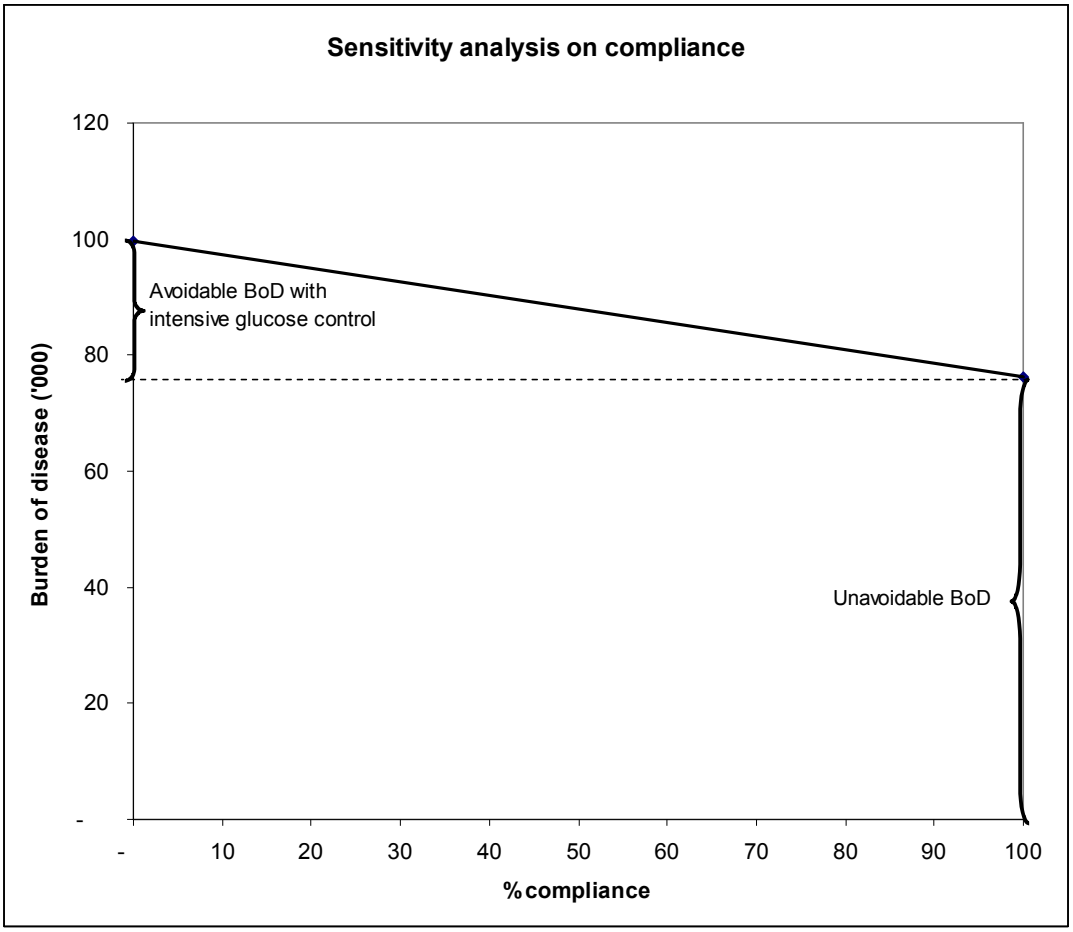


Figure 8 Estimates of annual BoD in undiscounted DALYs from type 1 diabetes in the steady state from 0 to 100% proportion of population complying with intensive glucose control.



Tables

Table 1 Main model assumptions

Assumption	**Justification**
The transition probabilities from state *i* depend only on being in state *i* and not on the history before arriving in state *i*.	This is the standard simplifying assumption in modelling stochastic processes and is the basis of Markov chain models that are widely used in modelling progression of disease and is common practice for modelling diabetes. To relax this assumption we divide the population in 5-year age groups and use a different set of transition probabilities for each one if data was available.
Same rates apply to men and women.	With the exception of myocardial infarction complication rates are similar in men and women (National Clinical Audit Support Programme, 2005).
Under the intervention scenario, all the diabetic population is subject to intensive treatment.	This reflects NICE recommendations to maintain $HbA_{1c} \leq 7.5\%$ in all diabetic patients, but will overstate the benefit of the intervention. We used sensitivity analysis on compliance rates to test this assumption.

Table 2 Data sources and assumptions on missing data

Information	Source	Description/Evaluation	Assumptions on missing data
Incidence α	(National Clinical Audit Support Programme, 2005)	This is an overview of diabetes and diabetes care in England. Coverage is partial: about 22% of eligible PCTs, GP practices and Hospitals registered; about 34% of paediatric units.	It gives data for 0-16 years old. We assumed diabetes onset is before age 35 using the incidence rate for 0-16 also for people 17-35 years old. This assumption implies a slight overestimate of the burden of diabetes in the model for the first five years. We made the standard assumption that all Type 1diabetic patients are diagnosed.
Current population with Type 1 Diabetes by age group *A(0,j)*	(Harvey *et al.*, 2002, Diabetes UK, 2004b, a, Health and Social Care Information Centre, 2004); details for (Health and Social Care Information Centre, 2004) provided by NHS – Health and Social Care Information Centre	(Diabetes UK, 2004b) gives estimates for the 17,000 children with Type 1 Diabetes which are based on audited data of about 10,000 children. (Diabetes UK, 2004a) estimates the diabetic population but in wide age bands. (Health and Social Care Information Centre, 2004) is the QOF data at GP level (carefully audited as the basis for the new GMS contract) and reports the total number of diabetic patients in the surgery (but lacks details on type of diabetes and age). (Harvey et al., 2002) reports age-specific prevalence estimates of Type 1 Diabetes for the County of Clwyd in North Wales.	There is no single definitive source of audited prevalence data of Type 1 Diabetes for all age groups. We used the (Harvey et al., 2002). This assumes that the estimates are representative for England.

Information	Source	Description/Evaluation	Assumptions on missing data
Number of people by degree of severity *s*	(Klein *et al.*, 1989b, a, Klein *et al.*, 1989c, Diabetes Control and Complication Trial, 1990, 1993, Klein *et al.*, 1994, Diabetes Control and Complication Trial, 1996, Rossing *et al.*, 1996, Brailsford *et al.*, 1998, Klein *et al.*, 1998, Davies *et al.*, 2001, Niessen, 2002, Soedamah-Muthu *et al.*, 2006a)	These data do not refer to the English population and some are ten years old. Most of these sources report transition probabilities based on longitudinal studies but the original dataset of the study is not available. Data are usually reported for the whole population in the study or for wide age groups.	We needed to make some heroic assumptions to generate the initial distribution of diabetic population across degrees of severity of renal and eye disease complications. We used our model to generate a sample population of 100,000 susceptible and projected it over 100 years. We assumed that the proportion of people in each degree of severity for each age was representative of the current population of that age. We applied these proportions to the *A(0,j)* as estimated above.
Transition probabilities in nephropathy (excluding mortality rates)	(Diabetes Control and Complication Trial, 1990, 1993, 1996, Niessen, 2002)	(Niessen, 2002) developed Markov chain models of diabetes complications, also on the DCCT study . The DCCT study was a major, multi-centre study of 1,441 diabetic patients in the US, lasted nine years. The study quantifies the effect of intense treatment on progression in microvascular sequelae. These data do not refer to the English population and some are ten years old. They report transition probabilities based on longitudinal studies but the original dataset of the study is not available. Data are usually reported for the whole population in the study or for wide age groups.	We assumed that the transition probabilities apply to the current diabetic population in England.
Mortality rates in nephropathy model	(Diabetes Control and Complication Trial, 1996, Rossing *et al.*, 1996, Soedamah-Muthu *et al.*, 2006a)	(Rossing et al., 1996) is a cohort study of a 10-year observational follow up of 939 adult patients with insulin dependent diabetes in Denmark. (Soedamah-Muthu et al., 2006a) gives all cause mortality rates from the General Practice Research Database. This is a reliable source of data of for England, based on a 7-year longitudinal study of 7,713 patients with Type 1 Diabetes .	We used an average between (Diabetes Control and Complication Trial, 1996, Rossing *et al.*, 1996). The aggregate mortality rate is similar to that in (Soedamah-Muthu et al., 2006a), which could not be used directly because does not specify complications severity.

Information	Source	Description/Evaluation	Assumptions on missing data
Transition probabilities in retinopathy (including mortality rates)	(Klein *et al.*, 1989b, a, Klein *et al.*, 1989c, Klein *et al.*, 1994, 1998, Davies *et al.*, 2000, Davies *et al.*, 2001)	The DCCT study had a high degree of uncertainty on its incidence estimate for retinopathy because only a small group of participants who did not have retinopathy at baseline stayed in the study for 9 years (Mount Hood 4 Modeling Group, 2007). We used another study on the progression of retinopathy in our model, the Wisconsin Epidemiologic Study of Diabetic (WESDR) Retinopathy following Davies *et al.*(2000). WESDR data do not refer to the English population and are fifteen years old. They report transition probabilities based on longitudinal studies but the original dataset of the study is not available. Data are usually reported for the whole population in the study or for wide age groups.	We assumed that the transition probabilities apply to the current diabetic population in England.
Incidence rates of amputations, sores or ulcers	(Moss et al., 1992)	(Moss et al., 1992) provide 4-year incidence rate of amputation and sores or ulcers by characteristics of the population, including the presence and degree of severity of diabetic retinopathy ($p<.0001$)	We assumed that the incidence rates from each degree of retinopathy apply to the current diabetic population in England.
Mortality rates non diabetic population	(Soedamah-Muthu et al., 2006a)	Data about the non-diabetic population refers to a control group matching the diabetic population under study and is not representative of the general non-diabetic population.	We used (Soedamah-Muthu et al., 2006a)'s age-specific mortality rates for the population with Type 1 Diabetes to generate the expected deaths in one year. We subtracted this data from the total number of deaths from all causes per age group as in (Office of National Statistics, 2003) and derived mortality rates for the non-diabetic population.
Disability weights	(Stouthard *et al.*, 1997)	The disability weights were estimated by the Dutch study that developed disability weights applicable to developed countries.	In the absence of disability weights in the presence of co-morbid conditions we assumed that the weights are additive.

Table 3 Cost of monitoring glucose levels and prescribing insulin

Item	unitary cost	Conventional treatment		Intensive treatment*	
		items per year	annual cost per diabetic patient	items per year	annual cost per diabetic patient
lancets	£0.07	730	£51	1,278	£89
glucose test stripes	£0.87	730	£633	1,278	£1,107
glucometer	£40.00	0	£11	0	£11
insulin	£0.26	730	£190	1,278	£332
insulin syringes	£0.15	730	£110	1,278	£192
insulin pen	£15.00	0	£4	0	£4
diabetes clinic visits	£106.00	1	£106	12	£1,272
nursing staff	£34.00	-	£-	9	£295
total			£1,105		£3,303

*When we run the model replacing monthly visit with specialist nurses on the phone, we change the intensive treatment assuming one annual visit at the clinic and three telephone conversations per week of 10 minutes each with the specialist nurse, for a total cost of intensive treatment of £2,726 per patient per year; when we tested the cost implications of using insulin pumps, we used the average annual cost of the pump and consumables (including savings from reduced use of insulin) from a recent Health Technology Assessment study (Colquitt *et al.*, 2004) assuming monitoring was provided through telephone conversation with a specialist nurse, for a total annual cost of £4,333 per patient per year.

Table 4 Cost of treating microvascular complications

Degree of severity	Data source	conventional care		intensive care[#]	
		cost 1st year	cost following years	cost 1st year	cost following years
microalbuminuria	(Gordois et al., 2004)	£44[a]	£44[a]	£44[a]	£44[a]
macroalbuminuria	(Gordois et al., 2004)	£4,215[a,b,c]	£4,215[a,b,c]	£3,791[a,b]	£3,791[a,b]
End Stage Renal Disease - dialysis	(MacLeod *et al.*, 1998, Mowatt *et al.*, 2003, Department of Health, 2004a, Gordois *et al.*, 2004)	£21,152[d]	£21,152[d]	£21,152[d]	£21,152[d]
End Stage Renal Disease - transplant	(Department of Health, 2004a)	£18,727[e]	£240[e]	£18,727[e]	£240[e]
Background Diabetic Retinopathy	(Department of Health, 2004a)	£89	£55	£-	£-
Proliferative Diabetic Retinopathy visits	(Department of Health, 2004a)	£89	£55	£-	£-
Laser treatment	(Department of Health, 2004a)	£602	£-	£602	£-
PDR cost	visit + laser treat at onset	£691	£55	£602	£-
Severe vision loss (blind one eye)	(Clarke et al., 2003)	£872	£281	£872	£281
Sores/ulcers	(Department of Health, 2004a)	£162[f]	£45[f]	£162[f]	£-
Amputation	(Department of Health, 2004a)	£6,248[g]	£73[g]	£6,248[g]	£73[g]

[#] The cost in the intensive treatment scenario is lower because we assumed that the monthly visit at the diabetes clinic is a substitute for routine follow-up visits after complications. When we run the model with the less expensive intervention we used the costs reported under 'conventional treatment' also for the intensive treatment scenario

[a] ACE inhibitor (Captopril 25mg, 4/day)

[b] epoetin alfa (3,000U, 3/week)

[c] four outpatients clinic visits per year

[d] £24,960 annual cost for hospital haemodialysis (20.5% of cases), £21,000 for haemodialysis in satellite units (20.5% of cases), £19,300 for home haemodialysis (1% of cases), £17,828 peritoneal dialysis COPD (22% of cases). Number of cases are those reported in Annual report of Renal Registry (Ansell *et al.*, 2003).

[e] cost of transplant and four post-transplant visits in first year; one post-transplant visit per year thereafter

[f] treatment for skin disorder followed by yearly podiatrist visits

[g] average cost of amputation (elective and non elective) weighted by number of Finished Consultation Episodes in first year and cost of orthopaedic follow up visit thereafter.

Table 5 Burden of Disease and its reduction through intensive glucose control in the first five years and in the steady-state

	Burden of disease with current care (current BoD)		**Short term burden reduction from intensive glucose control (100% compliance)**		**Steady state: burden reduction from intensive glucose control (100% compliance)**
	First 5 years (annualized)	First year only (sensitivity analysis)	First 5 years (annualized)	First year only (sensitivity analysis)	
Deaths ('000s)	2	2	0.01	0	0.4
Monetary value of deaths (£m)	2,300	2,300	9	0	440
YLLs ('000s)	66	65	0.3	0	11
YLDs from renal complications ('000s)	8*	7	0.2	0	3**
YLDs from eye complications ('000s)	23	23	0.9	0.3	8
YLDs from diabetic foot ('000)	3	1#	0	0	0.4
YLDs total ('000)	34	31	1.2	0.3	11
DALYs ('000s) (undiscounted)	100	96	1.5	0.3	23.5
DALYs ('000s) (discounted)	63	64	1.2	0.3	17.8
Monetary value of DALYs averted (discounted, £m)	1,900	1,900	35	9	535

* of which 2 from ESDR
** of which 1 from ESDR
# incident cases only, hence annualized figure for first 5 years is higher

Table 6 Annual costs and savings (negative figures) from intensive glucose control in the first five years and the steady state

	Conventional care (current spend) in £ m		Intensive glucose control assuming monthly visit at diabetic clinic as in original DCCT study		Intensive glucose control replacing monthly visits with more frequent telephone supervision by specialist nurse	
	In first year	In first five years (annualized)	First five years: change in expenditure (annualized) in £ m	Steady state: change in expenditure in £ m	First five years: change in expenditure (annualized) in £ m	Steady state: change in expenditure in £ m
Insulin prescription and glucose monitoring	187	175	+ 349	+ 373	+257	+275
Treatment of nephropathy	175	169	- 13	- 84	-6	-79
Treatment of retinopathy	14	14	- 8	- 12	-2	-9
Treatment of diabetic foot	8	8	- 0.5	- 4	-0.5	-4
Expenditure	383	366	+ 328	+ 272	+249	+182

Table 7 Net gain in output in the first five years and in the steady state

	Intervention in first five years in £m	**Intervention in the steady state in £m**
Monetary value of DALYs averted (at £30k per DALY, discounting YLLs)	30	530
Extra costs	250	180
Gain (loss) in output	**(220)**	**350**

Table 8. Prevalence estimates of renal complications by severity.

	Normo-albuminuria prevalence	Micro-albuminuria prevalence	Macro-albuminuria prevalence	End Stage Renal Disease prevalence
Model estimates (conventional care)	57%	28%	11%	4%
(Harvey *et al.*, 2001; n=1,297; Wales, UK)	61.4%	At 15-29 years duration: 27.2%; Below 5 years duration: 14%	11%	1.8%
DARTS (2001)	n/a	n/a	n/a	1%
Finne *et al.* (2005) (n=20,005; Finland)	n/a	n/a	n/a	Cumulative incidence at 20 years from onset = 2.2%; at 30 years from onset = 7.8%

Table 9. Prevalence estimates of eye complications by severity.

	No retinopathy	Background Diabetic Retinopathy	Proliferative Diabetic Retinopathy	Severe visual loss (including blindness)
Model estimates (conventional care)	26%	40%	23%	8%
(Klein *et al.*, 1984; US)	30%	46% (of which 17% severe non-proliferative diabetic retinopathy)	14%	9%
(Davies *et al.*, 2001)	20%	49%	30% (25% PDR and 5% untreatable)	

Table 10. 4-year incidence rates of sores/ulcers and foot/toe amputation.

4-year incidence of sores/ulcers				
	In patients with no retinopathy	In patients with mild or moderate retinopathy	In patients with PDR	All patients
Model estimate (conventional care)	5.6%	9%	18.7%	11.5%
Moss *et al.* (1992)	5.8% (n=273)	9% (n=440)	18.3% (n=166)	9.5% (n=879)
4-year incidence of amputation				
	In patients with no retinopathy	In patients with mild or moderate retinopathy	In patients with PDR	All patients
Model estimate (conventional care)	0%	1.4%	8%	3%
Moss *et al.* (1992)	0% (n=273)	1.4% (n=440)	7.8% (n=166)	2.2% (n=879)

Table 11 Estimates of risk reduction in 9-year incidence of microvascular complications (source: Mount Hood 4 Modeling Group, 2007)

	DCCT study	Our model	EAGLE model	CORE model	Archimedes model
Microalbuminuria	0.59	0.68	0.61	0.54	0.53
BDR	0.27	0.33	0.90	0.37	0.32
Neuropathy	0.47	n/a	0.29	0.39	n/a

Table A1 Parameters shared by the renal and eye disease model: mortality rate of the non-diabetic population and incidence rate of diabetes

age	λ	α
under 1	5.457821	0.000149
1_4	0.237416	0.000149
5_9	0.101432	0.000149
10_14	0.119732	0.000149
15_19	0.327034	0.000149
20_24	0.493336	0.000149
25_29	0.547027	0.000149
30_34	0.718174	0.000149
35_39	0.966249	0
40_44	1.506267	0
45_49	2.376491	0
50_54	3.811951	0
55_59	5.864163	0
60_64	9.851112	0
65_69	15.91389	0
70_74	26.90164	0
75_79	46.63052	0
80_84	76.82135	0
85+	172.5086	0

Table A2 Incidence rates of sores/ulcers and amputation

Degree of severity of retinopathy	**Incidence of sores and/or ulcers**	**Incidence of lower extremity amputation**
No retinopathy	1.45%	0%
Mild or Moderate retinopathy	2.25%	0.35%
Proliferative Diabetic Retinopathy	3.66%	1.95%

Table A3 Transition probabilities in the renal disease complication model

	Excess mortality				Transition probabilities: Intensive glucose control			Transition probabilities: Conventional care		
age	$\mu'(s_0)$	$\mu'(s_1)$	$\mu'(s_2)$	$\mu'(s_3)$	$\gamma_{0->1}$	$\gamma_{1->2}$	$\gamma_{2->3}$	$\gamma_{0->1}$	$\gamma_{1->2}$	$\gamma_{2->3}$
under 1	0.006092	0.008683	0.011820	0.000000	0	0	0	0	0	0
1_4	0.005047	0.006595	0.008166	0.000000	0	0	0	0	0	0
5_9	0.005020	0.006541	0.008071	0.000000	0	0	0	0	0	0
10_14	0.005024	0.006548	0.008084	0.000000	0	0	0	0	0	0
15_19	0.005065	0.006631	0.008229	0.000000	0.022	0.02	0.05	0.034	0.06	0.05
20_24	0.005099	0.006697	0.008345	0.030809	0.022	0.02	0.05	0.034	0.06	0.05
25_29	0.005109	0.006719	0.008383	0.030755	0.022	0.02	0.05	0.034	0.06	0.05
30_34	0.005144	0.006787	0.008503	0.030584	0.022	0.02	0.05	0.034	0.06	0.05
35_39	0.005193	0.006886	0.008676	0.107831	0.022	0.02	0.05	0.034	0.06	0.05
40_44	0.005301	0.007103	0.009054	0.107291	0.022	0.02	0.05	0.034	0.06	0.05
45_49	0.005475	0.007451	0.009664	0.106420	0.036	0.03	0.05	0.057	0.03	0.05
50_54	0.005762	0.008025	0.010668	0.145978	0.036	0.03	0.05	0.057	0.03	0.05
55_59	0.006173	0.008846	0.012105	0.143926	0.036	0.03	0.05	0.057	0.03	0.05
60_64	0.006970	0.010440	0.014896	0.176940	0.036	0.03	0.05	0.057	0.03	0.05
65_69	0.008183	0.012866	0.019140	0.195137	0.036	0.03	0.05	0.057	0.03	0.05
70_74	0.010380	0.017261	0.026831	0.184149	0.036	0.03	0.05	0.057	0.03	0.05
75_79	0.014326	0.025152	0.040641	0.164420	0.036	0.03	0.05	0.057	0.03	0.05
80_84	0.020364	0.037229	0.061775	0.134229	0.036	0.03	0.05	0.057	0.03	0.05
85+	0.039502	0.075503	0.128756	0.128756	0.036	0.03	0.05	0.057	0.03	0.05

Table A4 Transition probabilities in the eye disease complication model

	Excess mortality				Intensive glucose control			Conventional care		
age	$\mu'(s_0)$	$\mu'(s_1)$	$\mu'(s_2)$	$\mu'(s_3)$	$\gamma_{0->1}$	$\gamma_{1->2}$	$\gamma_{2->3}$	$\gamma_{0->1}$	$\gamma_{1->2}$	$\gamma_{2->3}$
under 1	0.0015	0.005	0.033186732	0.0331867	0	0	0	0	0	0
1_4	0.0015	0.005	0.025356124	0.0253561	0	0	0	0	0	0
5_9	0.0015	0.005	0.025152148	0.0251521	0	0	0	0	0	0
10_14	0.0015	0.005	0.025179598	0.0251796	0	0	0	0	0	0
15_19	0.0015	0.005	0.025490551	0.0254906	0.039	0.02544	0.01855	0.13	0.048	0.035
20_24	0.0015	0.005	0.025740004	0.02574	0.039	0.02544	0.01855	0.13	0.048	0.035
25_29	0.0015	0.005	0.025820541	0.0258205	0.039	0.02544	0.01855	0.13	0.048	0.035
30_34	0.0015	0.005	0.026077261	0.0260773	0.039	0.02544	0.01855	0.13	0.048	0.035
35_39	0.0015	0.005	0.026449374	0.0264494	0.039	0.02544	0.01855	0.13	0.048	0.035
40_44	0.0015	0.005	0.027259401	0.0272594	0.039	0.02544	0.01855	0.13	0.048	0.035
45_49	0.0015	0.005	0.028564737	0.0285647	0.039	0.02544	0.01855	0.13	0.048	0.035
50_54	0.0015	0.005	0.030717927	0.0307179	0.039	0.02544	0.01855	0.13	0.048	0.035
55_59	0.0015	0.005	0.033796245	0.0337962	0.039	0.02544	0.01855	0.13	0.048	0.035
60_64	0.0015	0.005	0.039776668	0.0397767	0.039	0.02544	0.01855	0.13	0.048	0.035
65_69	0.0015	0.005	0.048870835	0.0488708	0.039	0.02544	0.01855	0.13	0.048	0.035
70_74	0.0015	0.005	0.06535246	0.0653525	0.039	0.02544	0.01855	0.13	0.048	0.035
75_79	0.0015	0.005	0.09494578	0.0949458	0.039	0.02544	0.01855	0.13	0.048	0.035
80_84	0.0015	0.005	0.140232025	0.140232	0.039	0.02544	0.01855	0.13	0.048	0.035
85+	0.0015	0.005	0.2837629	0.2837629	0.039	0.02544	0.01855	0.13	0.048	0.035

Table A5 Disability weights

Health state	**Disability weight (95% C.I)**	**Health state description in disability weight source**	**Corresponding EQ 5D+ classification**	**Source**
No complications	0.07 (0.047-0.094)	"Uncomplicated diabetes mellitus"	111111 (90%), 112221 (10%)	Stouthard *et al.* 1997, p.73
Macroalbuminuria and ESRD	0.29 (0.201-0.380)	"Diabetes mellitus with nephropathy"	112121 (80%), 113231 (20%)	Stouthard *et al.* 1997, p.73
Moderate retinopathy (BDR, non severe PDR)	0.17 (0.073-.278)	"[Diabetes mellitus with] moderate [vision disorders] (i.e., great difficulty reading small newspaper print, some difficulty recognizing faces at 4m. distance"	112121	Stouthard *et al.* 1997, p.75
Severe retinopathy	0.43 (0.339-0.521)	"[Diabetes mellitus with] severe [vision disorders] (i.e. unable to read small newspaper print, great difficulty or unable to recognize faces at 4m. distance)"	123121	Stouthard *et al.* 1997, p.75
Sores, ulcers and Lower extremity amputation	0.19 (0.128-0.255)*	"[Diabetes mellitus] with neuropathy"	111111 (75%), 222221 (20%), 222331 (5%)	Stouthard *et al.* 1997, p.73

*the global burden of disease study uses 0.3 for foot amputation and 0.102 for toe amputation (Murray and Lopez, 1996); there is no disability weight for amputation in the paper by Stouthard *et al.* (1997) which we used as the main source for weights in our study. The 0.19 weight for neuropathy in the Stouthard *et al.* paper is an average across different degree of severity and we use it both for sores/ulcers and amputations.