Transition from children's to adults services for young people using health or social care

Appendix C3 – Economic report

Contents

1. Economics, Planned Modelling

1.1 Introduction

NICE guidelines make recommendations about health and social care practice based on a range of evidence. Recommendations for this topic, “Transition from children’s to adults’ services” is made in relation to specific review questions as set out in the scope. The economics work specifically makes recommendations about the cost-effectiveness of one intervention over an alternative intervention. The review questions where this type of evidence is likely to appear are as follows:

> Review question 4: What is the effectiveness of support models and frameworks to improve transition from children’s to adults’ services?
>
> Review question 5: What is the effectiveness of interventions designed to improve transition from children’s to adults’ services?
>
> Review question 7: How can the transition process (including preparing the young person, making the transfer and supporting them after the move) be managed effectively for those receiving a combination of different services?
>
> Review question 9: How can adult services support effective transitions for young people?

The other review questions, while relevant and important, did not provide evidence that allows a comparison of interventions that is essential for cost-effectiveness analysis.

1.2 Aim

This appendix sets out the economics work undertaken for this guideline.

The economics work is comprised of two main components. The first is the critical appraisal and review of existing cost-effectiveness literature and interpreting the results to make recommendations for the UK context. These can be found in Appendix C1 and C2 and these are not the focus of this appendix.

This appendix addresses the second component, which is to undertake ‘de novo’ economic modelling. The decision to undertake economic modelling depends on whether there is sufficient data and the analysis would generate new information about the intervention’s cost-effectiveness.

Specifically, this appendix discusses the two proposed economic analyses, how the decision was made, the results, and why it could not be used to support recommendations in this guideline.

The following section discuss the first proposed economic analysis, focusing on:

1. Care leavers with established familial relationships with their foster carers. Excludes individuals with placement instability, those placed with parents, secure units, children's homes and hostels. The interventions and comparators considered for inclusion is the "Staying Put 18+" program (Munro et al 2012) that allows care leavers the option to stay with their foster carers up until age 21. This intervention is compared to "standard" care leaver services available in England.

The subsequent section discusses the thinking behind the second proposed economic analysis, which is not a cost-effectiveness analysis.

2. The reason no cost-effectiveness analysis was undertaken was due to the lack of evidence. In the absence of cost-effectiveness work, discussions with the Guideline Committee determined that a 'costing the consequences' analysis of a particular population group would be useful to support research recommendations.

   In particular, it is a costing and quality of life analysis of the consequences of poorly managed diabetes. It is meant to provide a proxy estimate of the impact that poor transitions may have on individuals with diabetes. It was intended to support research recommendations by illustrating the magnitude of the consequences associated with poorly managed diabetes care that may occur during transition.

1.3 First proposed economic analysis

The first proposed economic analysis was agreed at the 5th guideline committee meeting. The proposed analysis aimed to estimate the cost-benefit and cost-utility of the 'Staying Put 18+' program compared to 'standard' transition services for care leavers (Munro et al 2012). Standard care leaver services typically include continued support from the leaving care personal, which can also include housing arrangements funded through social services (Munro et al 2012, p.101).

The perspective of the analysis would be that of the NHS and personal social services. The study only measured individuals' outcomes in relation to education, employment, and training however we planned on linking these outcomes to physical and mental health outcomes, QALYs, and monetary benefits.

While the study's internal validity was poor due to the lack of a robust comparator group, it was thought that data from other sources could be used to create a hypothetical comparator group.

After exploring the available literature, the data was found to be inappropriate for use in the model. Therefore, no analysis could be undertaken as the results would be unreliable for making recommendations. The following

section discusses the alternative data sources searched and their limitations to explain the rationale for not undertaking further analysis.

To address the lack of a comparator group, national English statistics on care leaver outcomes were explored. However, there were severe limitations in using this data because populations were different: the Staying Put program excluded vulnerable young people (individuals were not considered eligible if they had placement instability as they approached adulthood or who were placed with parents, in secure units, or in children's homes or hostels) (Munro et al 2012, p.25). The available national statistics include the whole population of care leavers and do not distinguish outcomes for the specific group that was eligible for the Staying Put 18+ program. Therefore using the national average, inclusive would bias the analysis. While it may have been possible to conduct a threshold analysis, ultimately, it does not change the fact that it is unclear whether the intervention is more effective than standard care leaver services. For this reason, it was not useful to continue the proposed economic analysis.

1.4 Second proposed economic analysis

The second proposed economic analysis is not a cost-effectiveness analysis. After investigating the suitability of the available evidence base (effectiveness and cost-effectiveness papers), there were several reasons why cost-effectiveness analysis could not be conducted which are described, in turn, in this section For further detail on these studies' interventions and samples, refer to Section 3 in the Full Guideline.

1. The evidence for this analysis was of poor quality in respect to internal validity and a lack of clarity around the intervention's effectiveness. The evidence came from the following studies :
    - Hagner (2012) (–, ++)
    - Prestidge (2012) (–, ++)
    - Nakhla (2009) (–, ++)
    - Cadario (2009) (–, ++)
    - MacDonald (2009) (+, +)
    - Certo (2003) (–, ++)

2. Where one study (Huang, 2014, US study, ++/+) did find positive results, these were in intermediate outcomes. The specific intermediate outcomes that improved included "Disease management", "Health-related self-efficacy", and "Patient-initiated communication. Additional economic analysis would be useful where these could be linked to final health outcomes. However, we anticipated it would be unlikely to find data to support such links to final health outcomes to support a cost-utility analysis.

3. In another instance, (Betz, 2010, US study, +/+) the quality of the evidence was good, but the intervention demonstrated no benefit. Therefore, no new information would be generated in conducting economic analysis.

4. In another study, (Bent, 2002, UK study, +/++) the quality of the evidence was good, the intervention demonstrated benefit, but the evidence on cost-effectiveness was available and there was no need for additional economic analysis. Furthermore, there was not a significant amount of uncertainty associated with results to warrant further economic analysis.

5. The Guideline Committee did not consider the specific intervention itself to be a priority for analysis (Lee, 2011, US study, +/+). Specifically, the Guideline Committee wanted to emphasise that the intervention needs to be delivered in a way that is understandable to the individual rather than to emphasise and recommend the intervention specifically.

1.5 Conclusion

As there were no suitable evidence for a cost-effectiveness analysis, the Guideline Committee proposed an analysis that 'cost the consequences' of a poor transition. This was decided at the 7th Guideline Committee. The Guideline Committee believed that by drawing attention to the potential economic consequences it would convince commissioners to pilot innovations in service models.

While it is not possible to directly draw conclusions about poor transitions without a comparator group, it might be possible to approximate consequences by estimating the consequences of 'poor management' more generally. This would provide a baseline to assess the potential for interventions to reduce poor management and understand the drivers of poor outcomes and high costs associated with it.

Several service user groups were prioritized based on data availability. These included individuals with Type 1 Diabetes, individuals using mental health services, and individuals with learning disabilities and challenging behaviour. Given the time constraints, the most readily available data was identified for individuals with Type 1 Diabetes. The corresponding work can be found in Appendix 2, "Costing the consequences of poorly managed Type 1 diabetes among adolescents at transition age (15-19 years old).

2. Costing the consequences of poorly managed Type 1 diabetes among adolescents at transition age (15-19 years old).

2.1 Aim

This analysis attempts to cost the consequences of poorly managed Type 1 Diabetes (T1D) among adolescents at transition age (between ages 15-19). The aim is to estimate both the short-term and long-term impacts through mapping the trajectory of complications rates and their associated costs and QALY losses. This information is intended to support research recommendations and to stimulate innovation in service delivery because the transition period may be a time of suboptimal management of T1D. This work, which estimates QALY losses, costs and rates of complications can help to support future cost-effectiveness work, but is not itself a cost-effectiveness analysis.

2.2 Background

Diabetes is a life-long condition. There are two types of diabetes – type 1 and type 2. T1D is usually known as juvenile diabetes because it mainly develops in children and adolescents (97% of individuals under age 18 are diagnosed with T1D) (Diabetes UK, 2012, p. 7). In England there are 25,069 individuals aged 19 registered with a pediatric diabetes unit in 2013/14 (NPDA, 2015, pp. 15,17). In a one-year period, the number of individuals between ages 15-19, the range at which a transition might occur, is around 7,619 (NPDA, 2015, pp. 15,17).

Glycemic levels (HbA1c) are the standard clinical indicator for monitoring whether T1D is managed well. Glycemic levels less than 58 mmol/mol indicate excellent glycaemic control and levels greater than 80 mmol/mol indicate poor control, as advised by NICE guidelines (NPDA, 2015, p. 5). Good control of T1D requires intensive daily self-management, education, and training (Elliot, et al., 2014, p. 848).

Is it important to have good diabetes control?

Poor management of T1D can lead to a range of health complications; some of which occur immediately and some that develop over time (Chiarelli & Marcovecchio, 2011, p. 203).

The immediate complications are diabetic ketoacidosis (DKA, caused by hyperglycemia – where blood glucose levels are too high) or hypoglycemia (when blood glucose levels are too low). DKA almost always leads to a hospital admission, while usually only severe hypoglycemic events lead to an acute admission (Elliot et al 2014).

Consistently high HbA1c levels indicate poorer control and can contribute to longer-term complications (NPDA, 2015). These include final outcomes like chronic kidney disease including established renal failure (development of nephropathy), blindness (due to retinopathy), limb amputations and skin ulcers (due to vascular disease and neuropathy), stroke, heart attack, and congestive heart failure (due to cardiovascular disease). These outcomes are costly to the

healthcare system and result in significant QALY losses. Not everyone will experience these complications if they receive treatment to prevent deterioration.

What is the possible impact of good diabetes management during the transition period?

Well-managed diabetes during the transition period can have sustained benefits post-transition. There is evidence from the DCCT / EPIC longitudinal comparative study that sustained, well-managed diabetes control contributes to 'metabolic memory'. That is, a history of good glycemic control leads to lasting effects on lowering the risk of complications even if glycemic control in subsequent years are not as optimal.[1] These effects apply to both adolescents and adults, but effects wane over time.[2]

Overall, the implication is that the benefits of the transition period can be sustained even after the intervention ends.

2.3 Methods

Search strategy and inclusion criteria

Bibliographic searching was conducted to identify epidemiological studies. Our inclusion criteria were samples with diabetes diagnosed in childhood (before age 18). We were mainly interested in evidence from England (complication rates, QALYs, costs) but drew on evidence from other countries where information was not available. It is important to note that this is not a comprehensive or systematic review and therefore there is potential that we may have missed evidence.

Data sources and limitations

Ideally, the estimation of total costs is based on healthcare resource use associated with a cohort of individuals at age 15-19 followed up until death. No such studies were identified.

Instead, various longitudinal and cross-sectional studies were available but only reported health outcomes rather than both outcomes and service use. However, using other literature it is possible, on the basis of outcomes only, to estimate total costs. A further limitation is that some of our sources only reported outcomes at the end of the study period, as a cumulative rate, which means we could not estimate the ongoing costs of care. Therefore we costed outcomes if they were associated with one-off treatment costs. However, these may also be underestimates because it is unclear whether more than one treatment is needed.

[1] This was evidenced in a comparison of complication rates between former intervention and control groups four and ten years after the study ended despite similarities in glycemic levels between groups (White et al 2010, p. 1244, p.1248).

[2] Overall, effects were stronger for the adult sample (mean age at baseline = 27, range 18-39) compared to adolescents (mean age at baseline = 15, range 13-17) (White et al 2010, p.1247). Part of the reason for stronger effects for adults is due to better levels of glycemic control during the intervention and post-intervention period compared to adolescents (79% of the difference can be explained by the better controlled glycemia).

The cost estimates are also limited in that we could not capture the potential for these complications to have knock-on effects on other service use, for example, the potential for increased outpatient and specialist healthcare visits for maintenance.

Furthermore, the studies we found did not measure all of the important complications. For example, we do not have rates (and therefore costs) of neuropathy that results in ulcers or amputations or rates of retinopathy leading to severe visual impairment or rates of nephropathy leading to kidney disease or kidney failure. These events are themselves relatively rare during the transition age, but do have significant cost implications when they occur.

On the whole, our total cost estimates are underestimates.

Likewise, estimates of total QALY losses are underestimates. This is either due to a lack of information on the duration of QALY losses or a lack of information more generally.

Costing approach

The perspective of the analysis is that of the NHS. Costs and QALY estimates were drawn from published sources in the UK, mostly drawing on those published sources identified in the Sheffield Type 1 Diabetes Policy Model (Thokala, et al., 2013). Other costs were taken from NHS reference costs 2013/14. The costs supplied in the Sheffield paper are intended to allow the addition of costs across all complications, and therefore do not double-count costs (this is because these are direct treatment costs associated with the complication). Likewise, costs not taken from the Sheffield model are also associated with direct treatment costs and do not double-count costs. All costs used in this report are inflated to 2013/14 prices.

2.4 Results

Total costs that we were able to identify (see below) amount to £9.94 million, for ages 15-38. This is an under-estimate. The components of these costs are summarized below.

Immediate complications for ages 15-24, where available, amount to £9.5 million as a result of an inpatient admission due to DKA, hypoglycemia, and unknown diabetes related cause. Total QALY losses between ages 15-24 due to hypoglycemic and DKA inpatient admissions between ages 15-22 years old amount to -5.89 QALYs (of which -5.48 QALYs are attributed to DKA and -0.41 QALYs due to hypoglycemia).

While it was not possible to capture costs associated with neuropathy, we could capture QALY losses associated with clinically confirmed neuropathy between ages 15-22 years old (-17.43 QALYs).

The remaining costs stem from nephropathy (micro and macro albuminuria) between ages 15-18 (£0.06 million) and at age 23, retinopathy (£0.0314 million). Costs as a result of cardiovascular disease amount to £0.353, at age 38

(undiscounted). For all these outcomes it was not possible to calculate QALY losses.

With respect to age-specific mortality, rate ratios for males and females in the age group from 15-34 were 3.9 and 6.6 times higher than the general population (National Diabetes Audit, 2015).

To aid readability, the details of the analysis are postponed until the Appendix in section 6, “supporting evidence” and instead the following section, section 5, provides a discussion and summary of the issues in estimating the final figures.

2.5 Discussion

We attempted to estimate the consequences of costs and QALY losses associated with the poor management of T1D among adolescents that may undergo transition to adult services, usually between the ages of 15-19.

Our findings are more robust for the immediate costs. This is because they were drawn from a recent national English survey and comprehensively measured all of the possible immediate outcomes. However, the estimates are somewhat limited and might be underestimates because costs could not be calculated on the impact of these complications on the use of non-acute care service use (i.e. primary or specialist health services). However, these costs may not be as large as those involved in the provision of acute care services. Therefore, we are more comfortable that the costs associated with the immediate outcomes have been, for the most part, adequately captured but not complete.

Findings for medium and long-term costs are much less robust due to the lack of data in several aspects. These limitations are summarized in the following paragraphs and are also summarized in Table 1 below.

First, not all major outcomes could be captured for the analysis. This includes neuropathy-related complications such ulcers, and amputations. There was also a lack of information on retinopathy-related complications such as severe visual impairment and nephropathy-related complications including kidney disease or kidney failure. This means that neither the costs nor QALY losses associated with these complications were included in our analysis.

Second, even for the outcomes that were available, there were still other shortcomings. For example, we could only find data on complications over a very short time horizon. For clinically confirmed neuropathy, data were available for ages 15-22. For micro and macro albuminuria, data were only available for ages 15-18. For retinopathy, data were available only at age 23.

Third, even in instances where outcomes were available, in some cases it was not possible to measure all the costs associated with the complication. For example, we could not include the pharmaceutical costs related to pain management due to clinically confirmed neuropathy, however, we were able to estimate QALY losses.

Where there were longer-term measurements, for example, cardiovascular outcomes, these were only provided as point estimates at age 38 and therefore we could not measure the ongoing maintenance costs nor capture the impact that these may have on the use of primary and secondary health care services.

Table 1 – Comprehensiveness of our estimates of total costs and QALY losses associated with diabetes-related complications

<table>
<tr><th colspan="4">Short-term complications</th></tr>
<tr><td>Included in calculations?</td><td>DKA</td><td>Hypoglycemia</td><td>Other emergency admissions for diabetes with unknown cause</td></tr>
<tr><td>Costs</td><td colspan="3">Ages 15-24
£9.5 million (acute care admissions)</td></tr>
<tr><td rowspan="2">QALYs?</td><td colspan="2">Ages 15-24</td><td rowspan="2">Not included</td></tr>
<tr><td>-5.48 QALYs</td><td>-0.41 QALYs</td></tr>
</table>

<table>
<tr><th colspan="4">Medium/Long-term complications: Neuropathy</th></tr>
<tr><td>Included in calculations?</td><td>Ulcers</td><td>Amputations</td><td>Clinically confirmed Neuropathy and pain management</td></tr>
<tr><td>Costs</td><td colspan="3">No</td></tr>
<tr><td>QALYs?</td><td colspan="2">No</td><td>Ages 15-22
-17.43 QALYs</td></tr>
</table>

<table>
<tr><th colspan="5">Medium/Long-term complications: Nephropathy</th></tr>
<tr><td rowspan="2">Included in calculations?</td><td rowspan="2">Micro albuminuria</td><td rowspan="2">Macro albuminuria</td><td colspan="2">End stage renal disease</td></tr>
<tr><td>Dialysis</td><td>Transplant</td></tr>
<tr><td>Costs</td><td colspan="2">Ages 15-18
£66,500 (pharmaceuticals & diagnostic tests)</td><td colspan="2">No</td></tr>
<tr><td>QALYs?</td><td colspan="4">No</td></tr>
</table>

<table>
<tr><th colspan="2">Medium/Long-term complications: Retinopathy</th></tr>
<tr><td>Included in calculations?</td><td>Severe retinopathy or Macular edema requiring treatment (laser or photocoagulation)</td></tr>
<tr><td>Costs</td><td>Cumulative rate when measured at age 23 years
£31,400 (laser or photocoagulation procedures)</td></tr>
<tr><td>QALYs?</td><td>No</td></tr>
</table>

Medium/Long-term complications: Cardiovascular				
Included in the estimate of costs and QALY losses?	Non-fatal myocardial infarction	Coronary artery disease w. catheter proven stenosis	Silent myocardial infarction	Angina
Costs	Cumulative rate when measured at age 38 years £353,500	No		
QALYs?	No			

A fourth limitation is that the estimates do not control for important factors that can affect complication rates apart from the individual's quality of managing diabetes at transition age. For example, this applies to our estimates on cardiovascular disease at age 38: we do not know what percentage of the sample had these outcomes as a result of poor management during post-transition versus during the transition period. Likewise, for all outcomes, it is unclear how much of the complication rates are attributed to poor diabetes management prior to the transition period.

A fifth limitation is that results are mainly based on US data. We can only make assumptions but cannot be sure of the generalizability of these data to the UK context. Furthermore, these studies are based on older data, adding another limitation to generalizability.

Even with these limitations, our findings on the short-term complications are relatively robust. The short-term complications are considerable and were based on robust, recent, and national English data.

However, the estimates on the medium and long-term complications associated with poor management in adolescence are lacking and less robust. While there is evidence that good and sustained management of diabetes in adolescence can have a positive albeit diminishing impact in later life it is much more difficult quantify this on costs and QALY losses due to the lack of data.

In spite of the limitations with the available data, positive developments are underway - the NPDA are expanding data collection to measure outcomes and processes for individuals transitioning from children's' to adult services and this is due in June 2016 (NPDA 2015, p.59).

2.6 Bibliography

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3. Supporting evidence

Several sources of data were used to estimate the complication rates, QALY losses, and unit costs. The epidemiological studies that provided data on specific complications are provided in section 3.3. The data used to estimate health state utility losses associated with the complications are presented in section 0. The following section, 3.5, presents the unit costs used to estimate total costs associated with complications. Section 3.6 provides information on the epidemiological studies' design and population characteristics. The last section, 3.7, provides a summary of the epidemiological studies used in the analysis.

The following sections provide a step-by-step description of methods used to estimate the consequences of immediate complications (section 3.1) and the medium/long-term complications (section 0).

3.1 Estimating consequences of immediate complications

The National Pediatrics Diabetes Audit (NPDA) provides prevalence data on acute care admissions associated with a primary diagnosis of DKA, hypoglycemia, or unknown cause for age groups 15-19 and 20-24. The data come from a national English audit of all 177 pediatric diabetes units. The data for ages 15 to 19 covers 7,619 individuals. There are smaller numbers of individuals between ages 20 to 24 covered in the audit (approximately 36 individuals) as most have transitioned to adult diabetes units (NPDA, 2015).[3] However, when estimating costs for ages 20-24, we assume a population size similar to those aged 15-19 (7,619 individuals). Therefore, the estimated population size for ages 15-24 is 15,238. The prevalence of each complication (DKA, hypoglycemia, or unknown cause) for both males and females combined for ages 15-24 years is 42.8%, 3.2%, and 16.6% respectively.[4] We multiply these rates by the population size, resulting in a total of 6,522 admissions due to DKA, 488 admissions due to hypoglycemia, and 2,530 admissions due to an unknown cause. NHS reference costs were multiplied by each admission to estimate total costs. We used a weighted average of NHS reference costs. This was based on whether the admission was elective or non-elective, the level of complication, and length of stay (long, short, and excess). The categories used for DKA, hypoglycemia, and 'unknown' were, respectively, "Paediatric Diabetes Mellitus, with Ketoacidosis or Coma", "Diabetes with Hypoglycemic Disorders", and "Paediatric Diabetes Mellitus, without Ketoacidosis or Coma". We used the mean weighted average, which was estimated to be £980 for a DKA admission,

[3] NPDA (2015, p.15) provide the English population size with Type 1 diabetes for ages 0-19, totaling 25,069 individuals. While the NPDA report does not report the number of individuals between ages 20-24 covered in the audit, it is possible to calculate based on the reported total population size between ages 0-24 (25,105 individuals). We subtracted the 0-19 estimate (25,069) from the 0-24 population size (25,105 individuals) to find that there are 36 individuals between ages 20-24 covered in the audit.

[4] The NPDA prevalence estimates we use are per 100,000 diabetes population. The NPDA present estimates for both admissions with and without a first time diagnosis (defined as within 10 days of a diagnosis). Our estimates are only based on those without a first time diagnosis.

£719 for a hypoglycemic admission, and £1,107 for an admission without DKA, coma, or hypoglycemia. These estimates are provided in Table 2.

Table 2 – Ages 15-24, male and female, hospital admissions associated with a primary diagnosis

Prevalent population with Type 1 diabetes	Complication	Prevalence rate	Admissions	Mean NHS reference cost	Total cost (millions) **
Ages 15-24* = 15,238	DKA	42.8%	6,522	£980	£6.3
	Hypoglycaemia	3.2%	488	£719	£0.35
	Unclear diagnosis	16.6%	2,530	£1,107	£2.8
*In the audit, 36 individuals are covered, however, the number we use in our calculation assumes the cohort size is the same as ages 15-19. ** Total costs for ages 20-24 may not be robust because of the small sample available for ages 20-24. Source: NPDA (2015)					

What is interesting to note is that there is potential for lower DKA rates if we refer to a well-known long-term RCT conducted between 1983/89 and 1993 in a 29 multi-center study in the USA and Canada (the Diabetes Control and Complications Study, DCCT). This study found that intensive control (defined as multiple, at least 3 daily insulin injections with frequent daily blood glucose monitoring) compared to standard care was able to reduce DKA rates by approximately 50%, but there was some trade-off in that it increased the rate of hypoglycemic events by 2.5 times (DCCT, 1993).[5] Results from 1993 in North America may not be generalizable to current context in England. According to expert opinion, current practice continues to improve and good management would probably be associated with less hypoglycemic events. However, significant hypoglycemic events still occur in those with poorly managed diabetes. Furthermore, evidence from adult studies including young adults indicate that good management need not need not increase the risk of hypoglycemic events (McEwan et al 2007, Elliot et al 2014).

Total QALY losses due to immediate complications

Two studies were identified that provided estimates of QALY losses associated with a severe hypoglycemic event. No studies were found for DKA. Utility losses from a severe hypoglycemic event with hospitalization were between -0.15 and -0.16 (Walters et al 2006; Nordfeldt & Jonnson 2001).[6]

The weighted average inpatient of stay for a severe hypoglycemic event is around 1.98 days. We took the average of the two sources, a disutility of -0.155, and multiplied it by the weighted average inpatient stay of 1.98 days. Per admission, this results in a utility loss of -0.309. As a proportion of an entire year,

[5] In the DCCT study, cumulative rates of DKA leading to an acute care admission for intervention and control groups were 19% and 32% respectively, and for hypoglycemic events, 13.6% and 5.4%, respectively (DCCT, 1993).

[6] These estimates are not from the UK; one was from the US and the other from Sweden, the former with an unclear sample composition, the latter with an adolescent sample. Both used different measurement tools, the former, the Hypoglycemia Fear Survey, and the latter, the EuroQoL 5-D. More information on the samples are provided in the appendix.

this represents a loss of -0.00084 QALYs. Multiplying this by the population affected, 488 individuals, for years 15-24, results in a total loss of 0.41 QALYs.[7] Our calculation assumes that there is immediate hospitalization after the event and that there is immediate recovery once hospitalization ends.

If we assume a hypoglycemic event and a DKA event have similar disutilities, multiplying a disutility of -0.155 to a weighted average inpatient stay of a DKA event of 1.61 days results in a per admission utility loss of -0.249. As a proportion of an entire year, this represents a loss of -0.00068 QALYs. Multiplying this by the population affected, 6,522 individuals, for years 15-24, results in a total loss of 5.48 QALYs.

Due to the lack of information on the nature of an unknown admission we do not assume that severe hypoglycemic events would have a similar disutility.

Total QALY losses due to all immediate complications are underestimates. The following estimates are presented in

Table **3**.

Table 3 – Ages 15-24, male and female, QALY losses associated with immediate complications

Prevalent population with Type 1 diabetes	Complication	Prevalence rate	Admissions	Weighted average inpatient stay**	Disutility ***	Total QALY losses ****
Ages 15-24* = 15,238	DKA	42.8%	6,522	1.98	-0.155	5.48
	Hypo-glycaemia	3.2%	488	1.61	-0.155	0.41
	Unknown	16.6%	2,530	1.63	unknown	unknown

*In the audit, 36 individuals are counted, however, the number used in our calculation assumes the same cohort size as ages 15-19.
** In some cases inpatient stay was presented as "N/A", where such was the case we assumed an average of 1 inpatient day.
*** No disutility data identified for DKA events. We assume similar disutility to severe hypoglycaemia.
**** Total QALY losses for ages 20-24 may not be robust because of small sample for ages 20-24.
Source: NPDA (2015) and NHS reference costs (2014)

[7] We use the mean of the two utility scores in our calculation, 0.155 = (0.15 + 0.16)/2.

3.2 Estimating the consequences of medium/long-term complications

Neuropathy, Retinopathy, Nephropathy, Cardiovascular disease
Four distinct epidemiological studies were identified, two from England[8] and two from the USA/Canada[9] on which we base our estimates of complication rates for any given age.

Neuropathy
No data were available from UK sources. The only available information came from the DCCT studies as a cumulative rate at age 15 (at baseline) and age 22 (at follow-up). Clinically confirmed neuropathy at baseline and follow up were 2.6% and 5%, respectively. Without information on the rate at which neuropathy increases in the sample, we take a conservative approach in estimating QALY losses. We assume that, for ages 15-22, the rate is constant at 2.6% for each year. Given that we knew the population affected between ages 15-19 amounted to 7,619 individuals, we assumed there was an equal distribution for each year, amounting to 1,524 individuals. In this way we estimated that between ages 15-22, approximately 12,190 individuals have Type 1 diabetes, and 2.6% would be affected with neuropathy, amounting to 317 individuals.

Unit costs for clinically confirmed neuropathy are not clear, but may incur pharmaceutical costs related to pain management. Costs were available for an adult sample (Currie et al 2003) but these were not the direct costs associated with neuropathy, rather these were wider NHS costs (such as overall outpatient and inpatient services), which is affected by other factors (other morbidities) and therefore we did not use this in our analysis.

Health state utility losses associated with clinically confirmed neuropathy is -0.055 QALYs[10] based on a sample of N=784 individuals in the USA (Coffey et al 2002). We did not identify estimates from the UK in our search. As neuropathy is an ongoing state, we assume this is a continuous reduction for each year with neuropathy. Assuming a constant rate of individuals affected, this results in a loss of -17.43 QALYs between ages 15-22. These are provided in Table 4.

In our search of the evidence, no data was found for rates of amputations and ulcers. Therefore, we were unable to provide estimates of any cost related to neuropathy.

Table 4 – Ages 15-22, male and female, QALY losses associated with clinically confirmed neuropathy

Prevalent population with Type 1 diabetes	Complication	Prevalence rate	Affected population	Disutility	Total QALY losses
Ages 15-22 = 12,190	Neuropathy	2.6%	317	-0.055	-17.43
Source (DCCT 1994)					

[8] Amin et al 2008, Bryden et al 2001
[9] DCCT studies (DCCT 1994, Nathan et al 2009, White et al 2010) and Orchard et al 2003, 2010
[10] Using the Quality of Well Being index, based on a sample of individuals diagnosed with type 1 diabetes prior to age 30, mean age 35 (range 25-44), 55% female.

Nephropathy

The NPDA 2013/14 audit also provides data on the rate of complications for stage 3 and 4 of nephropathy between ages 15-18 (micro and macro albuminuria). There are some limitations in that data is missing for between 22-33% of the sample, so it is unclear how rates of complications would change. Furthermore, the calculation does not take into account the (small) proportion of people with established renal disease (stage 5 of nephropathy) who are on dialysis or who have had a transplant – both of which are costly from the healthcare system perspective and result in significant QALY losses.

The rate of individuals with micro or macro albuminuria for each year between ages 15, 16, 17, and 18 is 6.8%, 8.5%, 7.8%, and 8.1% respectively, representing a total rate of 31.2% for this cohort of individuals. There are approximately 6,095 individuals with Type 1 diabetes between ages 15-18.[11] Multiplying these rates by the population size amounts to a total of 1,902 individuals affected with micro or macroalbuminuria.

Our estimates of costs for micro and macro albuminuria are based on published figures identified in the Sheffield model. These costs stem from pharmaceuticals and diagnostic tests. The Sheffield model estimates that costs for macro and micro albuminuria are similar, with ongoing costs of £35, using 2013/14 prices. For this cohort of 1,902 individuals affected between ages 15-18, this amounts to a total cost of £66,500. These are conservative estimates, as they do not take into account that some individuals will continue to remain on these medications beyond age 18 to prevent deterioration; however, some individuals will return to normal albuminuria (but we do not have these data).

QALY losses associated with macro albuminuria are available but the NPDA data provide prevalence figures for micro and macro albuminuria combined. Therefore, we do not provide estimates of QALY losses. This is in Table 5.

There are estimates from longitudinal studies of the cumulative rates of these complications (as well as for end-stage renal disease) but it is unclear when these events occurred and therefore make it difficult to estimate total costs. However, we do provide this information in the appendix (section 3.3).

Table 5 – Ages 15-18, male and female, Total costs associated with micro or macro albuminuria

Prevalent population with Type 1 diabetes	Complication	Prevalence rate	Affected population	Unit cost	Total Costs
Ages 15-18 = 6,095	Micro or macro albuminuria	31.2%	1,902	£35	£66,500
Source (NPDA 2015)					

[11] Given that we knew the population affected between ages 15-19 amounted to 7,619 individuals, we assumed there was an equal distribution for each year, amounting to 1,524 individuals.

Retinopathy

NPDA estimates provide information on the results of screening exams in terms of normal or abnormal findings. However, these do not help in estimating costs. We present costs based on rates of recorded treatment, defined as laser treatment or photocoagulation, based on epidemiological studies at a mean age of 22 and 23.

The percentage of individuals receiving laser or photocoagulation at a mean age of 22 is between 6.0% and 5.5%[12], and is 4%[13] of individuals at a mean age of 23. Our estimates of total costs associated with retinopathy are based on the conservative estimate, 4%, provided at age 23. Assuming a prevalent population of 1,524 individuals at age 23, this affects around 61 individuals.[14]

Our estimates of costs for retinopathy are based on published estimates identified in the Sheffield model. Unit costs for laser treatment, inflated to 2013/14 prices is £516. Altogether, total costs at age 23 amounts to £31,400 as a result of laser treatment only. Our estimates are based on the assumption that there is one treatment, but it is unclear whether individuals received more than one. This is in Table 6.

No information was available on QALY losses associated with these outcomes (which is usually at the stage of moderate to severe retinopathy and macular edema).

Table 6 – Age 23, male and female, total costs associated with retinopathy

Prevalent population with Type 1 diabetes	Complication	Prevalence rate	Affected population	Unit cost	Total Costs
Age 23 = 1,524	Retinopathy requiring treatment (laser or photocoagulation)	4%	61	£516	£31,400
Source (Bryden et al 2001)					

Cardiovascular disease

Only one epidemiological study from the USA followed up individuals to age 38. 82% of individuals did not have cardiovascular disease, 8% had angina, 3.5% with non-fatal myocardial infarction, 0.7% with silent myocardial infarction, and 2% have coronary artery disease with catheter proven stenosis >50%.

While these conditions may be associated with increased healthcare costs and utility losses, again, without information on timing of the event, our estimates for

[12] Estimates are based on the DCCT studies from the USA and Canada, reflecting results for control and intervention groups, respectively.
[13] Estimates are taken from a smaller epidemiological study in England (Bryden et al 2001).
[14] Given that we knew the population affected between ages 15-19 amounted to 7,619 individuals, we assumed there was an equal distribution for each year, amounting to 1,524 individuals.

costs are based on one-off direct treatment costs and we do not attempt to estimate QALY losses. Therefore, we only provide cost estimates for non-fatal myocardial infarction.

Costs for non-fatal myocardial infarction are based on published estimates identified in the Sheffield model, estimated at £6,628, inflated to 2013/14 prices. Assuming a prevalent population of 1,524 individuals at age 38, this affects around 53 individuals, resulting in a total cost of £353,500.[15] This is in Table 7.

Table 7 Age 23, male and female, total costs associated with retinopathy

Prevalent population with Type 1 diabetes	Complication	Prevalence rate	Affected population	Unit cost	Total Costs
Age 38 = 1,524	Non-fatal myocardial infarction	3.5%	53	£6,628	£353,500

[15] Given that we knew the population affected between ages 15-19 amounted to 7,619 individuals, we assumed there was an equal distribution for each year, amounting to 1,524 individuals.

3.3 Epidemiological studies used in estimating medium/long-term consequences

3.3.1 Nephropathy

Figure 1 – Cumulative rate of micro albuminuria

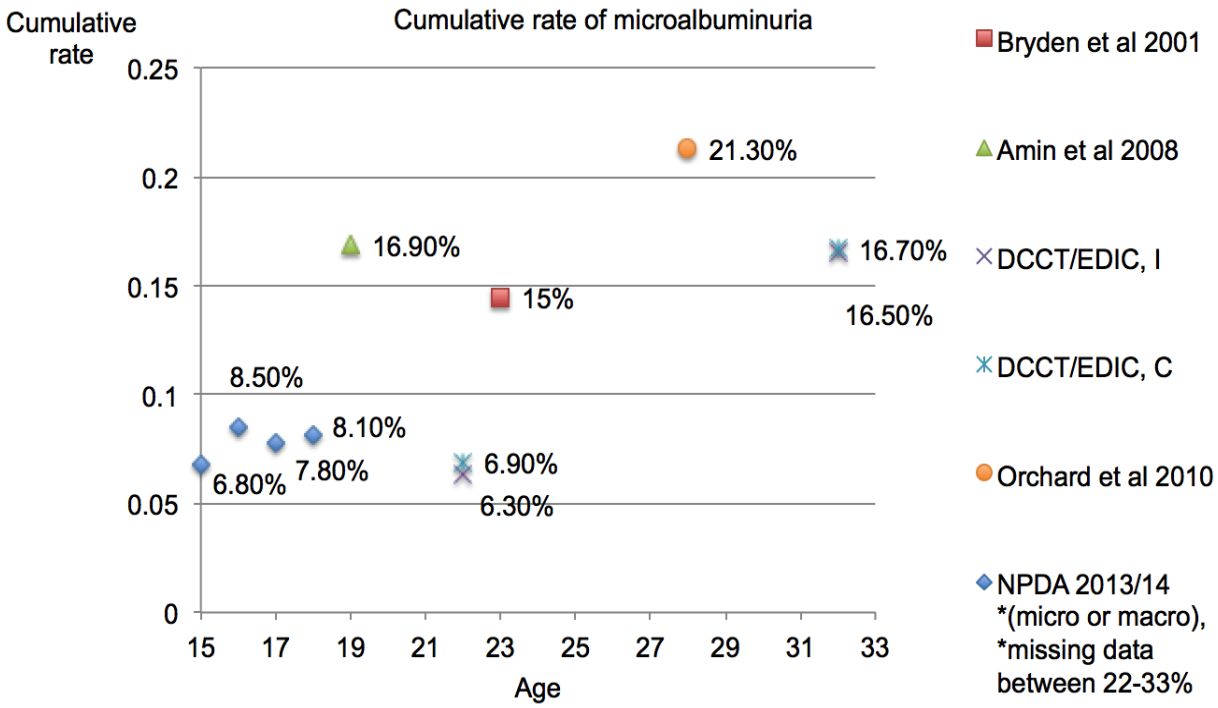

Table 8 – Cumulative rates of micro albuminuria

Micro albuminuria		
Mean age	**Cumulative rate**	**Source**
15 16 17 18	6.80% 8.50% 7.80% 8.10%	**NPDA 2013/14 (Rates are for micro and macro albuminuria combined and between 22-33% of the data is missing).
22	20.7% and 20.8%	Control, Intervention groups DCCT/EDIC, USA & Canada, White et al 2010
38	21.3%	Orchard et al 2003, USA

Figure 2 – Cumulative rate of macro albuminuria

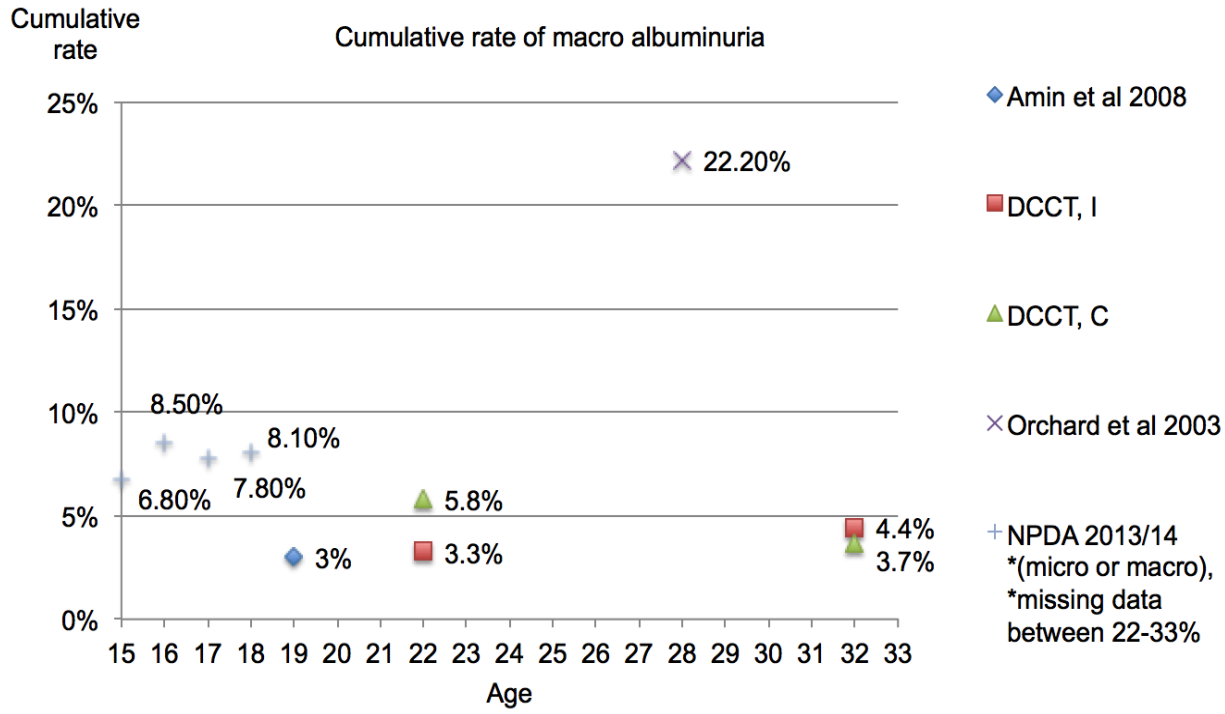

Table 9 – Cumulative rates of macro albuminuria

Macro albuminuria		
Mean age	**Cumulative rate**	**Source**
15 16 17 18	6.80% 8.50% 7.80% 8.10%	**NPDA 2013/14 (Rates are for micro and macro albuminuria combined and between 22-33% of the data is missing).
19	3%	Amin et al 2008, England
22	4.9% and 5.6%	Control, Intervention groups DCCT/EDIC, USA & Canada, White et al 2010
38	22.2%	Orchard et al 2003, USA

3.3.2. Nephropathy and end stage renal disease

Table 10 – Cumulative rate of nephropathy and end stage renal disease

End stage renal disease		
Mean age	**Cumulative rate**	**Source**
38	3.2%	Orchard et al 2003, USA

3.3.3. Retinopathy

Figure 3 – Cumulative rate of micro aneurysms

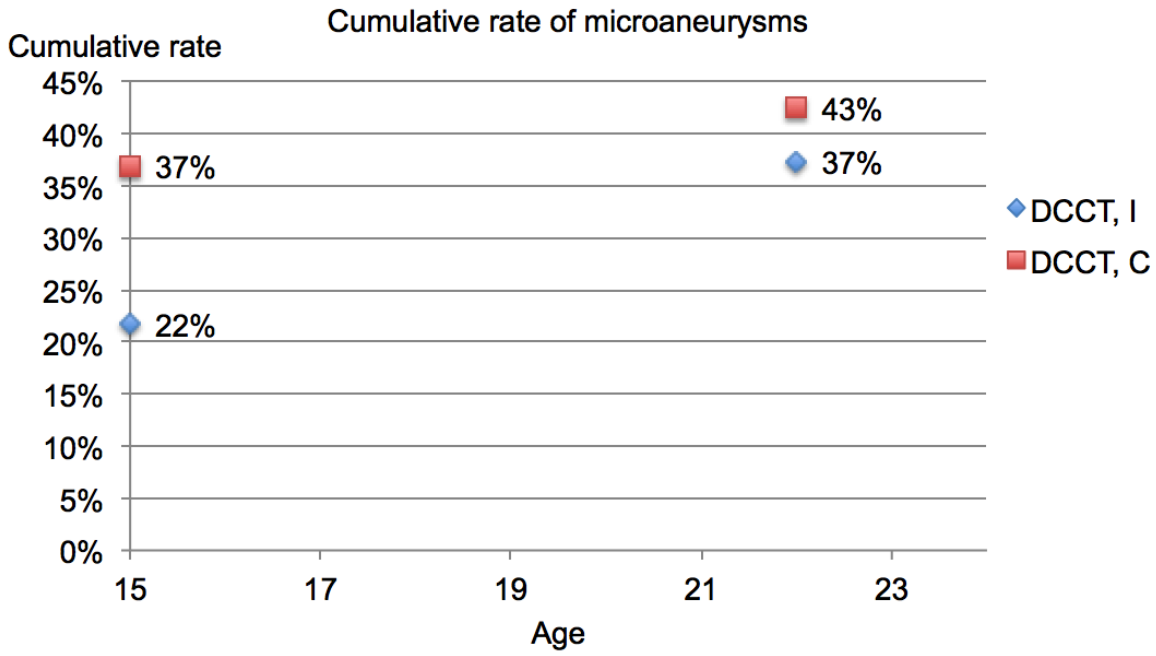

Figure 4 – Cumulative rate of mild non-proliferative retinopathy

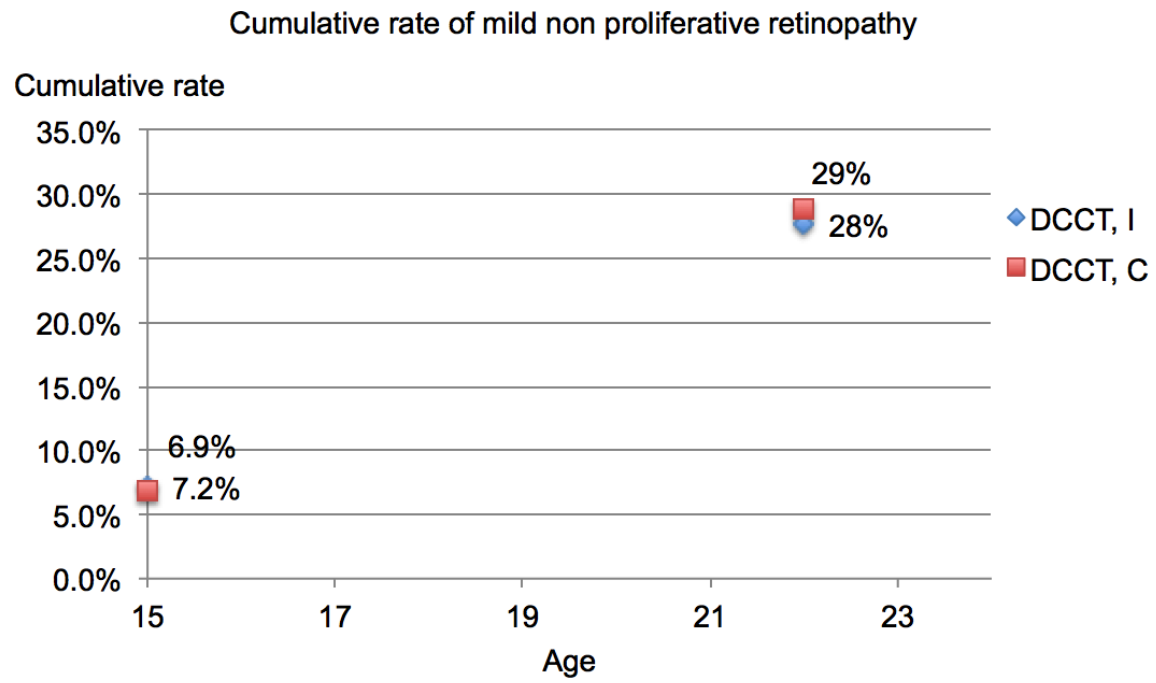

Figure 5 – Cumulative rate of mild moderate or severe retinopathy

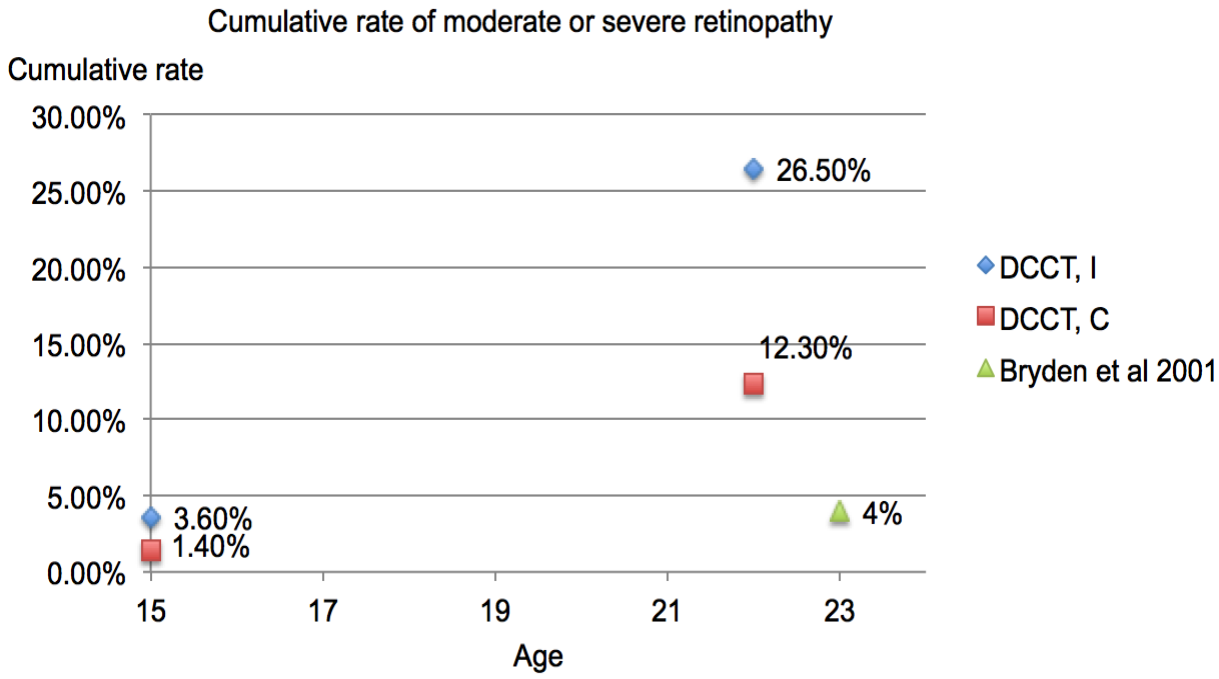

Table 11 – Cumulative rate of retinopathy: mild moderate or severe

Cumulative rate at age (mean age)	Age 15		Age 22		Age 23
Source	Control	Int.	Control	Int.	England Bryden et al 2001
	DCCT study, USA & Canada White et al 2010				
Micro aneurysms only	21.7%	37%	37.4%	42.5%	NA
Mild non proliferative retinopathy	7.2%	6.9%	27.7%	28.8%	NA
Moderate or severe retinopathy	3.6%	1.4%	26.5%	12.3%	4% (Requiring laser treatment)
Total, photocoagulation			6.0%	5.5%	NA
Photocoagulation, scatter, for severe retinopathy			4.8%	4.1%	NA
Photocoagulation, focal, for macular edema			1.2%	1.4%	NA

3.3.3. Cardiovascular disease

Table 12 – Cumulative rate of cardiovascular disease

Cardiovascular disease	Mean age 38, cumulative rate
Source	Orchard et al 2003, USA, Pittsburgh
None	82%
Angina	8%
Non-fatal MI	3.50%
Silent Q-wave MI	0.70%
CAD catheter proven stenosis >50%	2%

3.4 Health state utility losses

	Disutility 1	Disutility 2	Source 1	Source 2
Short term complications				
DKA	Not avail.	Not avail.		
Hypoglycaemia (hospitalisation)	-0.16	-0.15	Walters et al 2006	Nordfeldt & Jonnson 2001
Any hospitalisation	Not avail.	Not avail.		
Retinopathy				
Micro aneurysm	Not avail.			
Mild retinopathy	Not avail.			
Moderate to severe retinopathy	Not avail.			
Nephropathy				
Macro albuminuria	-0.017		Coffey et al 2002	
Dialysis	-0.023		Coffey et al 2002	
Neuropathy				
Clinically confirmed neuropathy	-0.055		Coffey et al 2002	
Cardiovascular disease				
CHF	-0.058		Coffey et al 2002	
Angina	-0.09		UKPDS	
MI	-0.058		Coffey et al 2002	

3.5 Unit costs

	Mean unit costs	Source	Components
Short term complications, Average inpatient stay			
DKA, hospitalisation	£980	NHS reference costs	NHS acute care inpatient costs
Hypoglycaemia, hospitalisation	£718		
Unclear cause, hospitalisation	£1,107		
Medium/Long-term complications			
Retinopathy			
Laser therapy	£516	Sheffield 2013, from McEwan et al 2007	Direct costs of laser therapy
Nephropathy			
Micro albuminuria	£35		Costs of diagnostic strips & pharmaceuticals
Macro albuminuria	£35		
Cardiovascular disease			
Myocardial infarction	£6,628	Sheffield 2013, from UKPDS	Acute care costs

3.6 Study information

Study	Study design	Recruitment method	Follow up duration, Time period	Baseline & follow-up sample size	Age at baseline & follow-up	Diagnosis of T1D
NPDA 2014 or 2015 England	Retro-spective audit (177 Paediatric Diabetes Units)	Representative Audit of all 177 paediatric diabetes units in England + linkages to Hospital Episode statistics.	For 2014: 2011-2012 For 2015: 2013-2014.	N=23,925 individuals with T1D in England	Survey of children of all ages (Ages 0-24 years). Most individuals in survey are younger than 19 years.	Unclear
Bryden et al (2001) England Oxford	Longitudinal cohort study using clinical notes and interviews (Radcliffe Hospital)	Representative Register of the outpatient paediatric diabetes clinic at John Radcliffe Hospital, Oxford, UK. It is the only clinic, serving children and adolescents with T1D and almost all children with T1D are known to the clinic, whether or not they attend regularly (P.1536).	Follow up duration = 8 years Time period = ?	Baseline N = 76 43 male, 33 female Follow up N= 65 individuals 39 male, 26 female	Baseline Mean age = 15 (11–18), Duration w. diabetes = 7.5 yrs Mean age at diagnosis = 7.5 yrs Follow-up Mean age = 23 (20-28) Duration w. diabetes = 16.3 yrs (3.5) male = 15.7 yrs (2.9) female	Diagnosed before 18. At least 1 year with diagnosis (inclusive sample age was btwn 11-18).
Amin et al 2008 England Oxford-shire health authority	Longitudinal prospective study (Oxford Regional Prospective Study)	Seems to be representative. Diabetes register used in the Bart's-Oxford (BOX) geographic area (p.495-6).	Follow up duration = 10 yrs Time period = 1986-97	Baseline, N=479 (55% males), Follow-up = N=463 (55% males), Drop-out rate = 9.8%	Baseline Mean age = 8.8 yrs (SD=4) Duration w. diabetes = ? Mean age at diagnosis = ? Follow-up Mean age = 19 Duration with diabetes = 16.3 (3.5) male, = 15.7 (2.9) female	Diagnosed before 16. Between 1986 and 1996 (p.1039)
DCCT research group 1994 USA & Canada, multi-centre study (29 centres)	Prospective longitudinal comparative study (subgroup analysis on adolescents)	Unclear representativeness. This is a RCT, which has inclusion and exclusion criteria.	Follow up duration = 7.3 years Follow up period = 1983-1993	Baseline & Follow-up N=195	Baseline Mean age = 15 (13-17) Duration w. diabetes = 5 years Mean age at diagnosis = 10 yrs Follow-up Mean age = 22 Duration with diabetes = 12.4 yrs	At least 1 year with diagnosis
White et al 2010	Same as above	Same as above	Follow up duration = 17.3 yrs Follow up period = 1983-2005	Follow-up N= 156	Follow-up Mean age = 33	Same as above

Orchard et al (2003) USA, Pitts-burgh, Penn-sylvania	Historical prospective cohort study (Pittsburgh Epidemiology of Diabetes Complications Study)	Representative of Allegheny County. Participants of the Pittsburgh EDC study, recruited from children's hospital of Pittsburgh registry of T1D, which is representative of the Allegheny County population	Follow up duration = 10 years Follow up period = 1950-60	Baseline N=658 eligible, N=603 patients available after excluding individuals with CAD at baseline (1986-1988) Follow-up N = 603	Baseline Mean age = 28 (8-47), Duration w. diabetes = 19 years (7-37), Mean age at diagnosis = 9 Follow-up Mean age = 38 years	Diagnosed before 18. 1950 - 1980
Orchard et al 2010	Same as above	Same as above	Follow up duration = 20 years Follow up period = 1960-80	Same as above	Follow-up Mean age = 48 years	Same as above
Norfeldt & Johnson (2001) Sweden Uni-versity Hospital of Link-oping, Oster-götland County	Prospective 12 month survey	Poor reporting, unclear representativeness. Authors say that the sample was a "complete geographic patient population of a smaller University City and its surrounding district. We therefore consider the socio-economic data to be representative for the rest of Sweden." (p.140)	Follow up duration = 1 year Follow up period = ?	Baseline & Follow-up, N=129	Baseline & Follow-up, Median age = 11.9, Mean age = 11.8 (range 2.2-18.4) Duration with diabetes, median = 3.8 years, Duration w. diabetes, mean = 4.3 (0.1 - 15.3) Mean/median age at diagnosis = 8 years old	Before age 19 (had diabetes for at least 1 year) (p.138).
Coffey 2002 USA, Mich-igan, multi-centre study	Cross sectional survey.	Not representative. Individuals were drawn from tertiary referral clinics. Individuals were purposefully oversampled in order to obtain large enough sample size for more rare health outcomes.	Follow up duration = Less than 1 year (survey)	Baseline & Follow-up, N=784	Baseline & Follow-up, Mean age = 34.5 years Duration w. diabetes = 20 years Mean age at diagnosis = 14.5	Before age 30 yrs.
Walters et al (2006) Aus-tralia	Cross sectional survey	Unclear. N=85 type 1 diabetics who complete a Hypoglycaemia Fear survey and questions relating to frequency and severity of hypoglycaemic events. N=122 people from general population to evaluate health states using TTO methodology.	Follow up duration = Less than 1 year (survey)	Baseline & Follow-up, N=85 type 1 diabetics and N=122 people from general population to evaluate health states	Unclear	Unclear

3.7 Studies assessed and type of data reported and used in our analysis

<table>
<tr><th></th><th>Other hospital admission</th><th>Hypo-glycemia hospital admission</th><th>DKA hospital admission</th><th>Neph-ropathy</th><th>Retin-opathy</th><th>Neuropathy</th><th>Cardiovascular</th></tr>
<tr><td>NPDA 2014 or 2015
Adolescent sample</td><td></td><td></td><td></td><td></td><td colspan="3">The report only measured screening for these risk factors and did not measure final outcomes so we could not use it in our analysis.</td></tr>
<tr><td>DCCT 1994
Adolescent sample</td><td rowspan="9">Not measured</td><td></td><td></td><td></td><td></td><td></td><td>Not used in our analysis. There were no final outcomes. There were only intermediate outcomes like lipids and blood pressure.</td></tr>
<tr><td>Bryden 2001
Adolescent sample</td><td>Not reported clearly so we did not use it.</td><td></td><td>Not well reported (definition was unclear)</td><td></td><td>Not measured.</td><td>Not used in our analysis. There were no final outcomes. There were only intermediate outcomes (Hypertension).</td></tr>
<tr><td>Amin 2008
Adolescent sample</td><td>Not measured</td><td>Not measured</td><td></td><td>Not measured</td><td>Not measured</td><td>Not measured</td></tr>
<tr><td>Orchard 2003
Adolescent sample</td><td>Not measured</td><td>Not measured</td><td></td><td>Not measured</td><td>Not measured</td><td></td></tr>
<tr><td>Orchard 2010
Adolescent sample</td><td>Not measured</td><td>Not measured</td><td></td><td>Not measured</td><td>Not measured</td><td>Not measured</td></tr>
<tr><td>Norfeldt & Johnson 2001
Adolescent sample</td><td colspan="6">Only used for QALYs.</td></tr>
<tr><td>Coffey 2002
Adult sample</td><td colspan="6">Only used for QALYs.</td></tr>
<tr><td>Walters 2006
Unclear sample</td><td colspan="6">Only used for QALYs.</td></tr>
</table>

Notes

indicates data was available and was included in the analysis.