Clinical and cost-effectiveness of continuous subcutaneous infusion for diabetes: updating review

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This TAR updates the previous review, published as HTA 2004; vol 8: no 43.
Some of the information used comes from unpublished studies which are currently (5th August 2007) "academic in confidence". The relevant sections had been underlined and highlighted.

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The Aberdeen HTA group

The Aberdeen Health Technology Assessment Group is part of the Institute of Applied Health Sciences (IAHS), which is part of the College of Medicine and Life Sciences of the University of Aberdeen. The Institute of Applied Health Sciences is made up of discrete but methodologically related research groups. The HTA Group is drawn mainly from the Health Services Research Unit, Public Health, and the Health Economics Research Unit.

The HTA Group carries out independent health technology assessments (TARs) for the UK HTA Programme, which commissions TARs for NICE and other bodies, such as the National Screening Committee. In addition, a joint venture between the Health Services Research Unit at Aberdeen and the Medical Care Research Unit at Sheffield University informs the Review Body for Interventional Procedures Programme within NICE (ReBIP) ReBIP undertakes systematic reviews and establishes UK registries, where appropriate, to collect and analyse data on the efficacy and safety of selected procedures, and to produce an evaluation report.

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Glossary
From The Cochrane Library, Cochrane Metabolic and Endocrine Disorders Group Glossary

Carbohydrate

Sugars (such as glucose, fructose, lactose, sucrose, etc.) or molecules composed of many sugar units (such as starch). Carbohydrates are important as a source of energy in living organisms. All carbohydrates are eventually broken down to the simple sugar glucose, which can then take part in energy-producing metabolic processes.

Dawn phenomenon

The dawn phenomenon refers to rising blood glucose levels in the hours before breakfast, partly due to the effect of the previous day's insulin wearing off, partly to rises in levels of other hormones, notably growth hormone. It can be a problem to manage because if the previous evening's dose of insulin is increased, hypoglycaemia may occur during the night.

Diabetes mellitus

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Insulin is secreted by specialised cells in the pancreas (pancreatic ß-cells) in response to a rise in blood sugar levels. A consequence of this defect is chronic hyperglycaemia (that is elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism. The two most common types of diabetes are type 1 diabetes mellitus (see below) and type 2 diabetes mellitus (see below). There are also other less common types of diabetes mellitus (see below). Individuals with any of these conditions are considered to be diabetic.

Type 1 diabetes mellitus (formely insulin-dependent diabetes mellitus)

Type 1 diabetes mellitus is characterised by absolute or nearly absolute insulin deficiency, sudden onset of symptoms, severe elevation of blood glucose levels (hyperglycaemia), rapid acidification of the blood (see ketoacidosis), and death unless treated with insulin. The disease may occur at any age, but onset in childhood or adolescence is most common. In most cases, type 1 diabetes is caused by the immune system attacking the cells in the pancreas that produce insulin (auto-immune destruction of pancreatic ß-cells). Some signs of hyperglycaemia are a great thirst, a dry mouth, and a need to urinate often.

Type 2 diabetes mellitus (formerly non insulin-dependent diabetes mellitus)

Type 2 diabetes mellitus is characterised by relative insulin deficiency. The pancreas generally retains some ability to produce insulin, but this is insufficient for the body's needs, and the production of insulin usually falls progressively over time, so that insulin treatment is often required.

Additionally, people with this type of diabetes are often resistant to the actions of insulin. Autoimmune destruction of pancreatic ß-cells does not occur and ketoacidosis is rare. Type 2 diabetes mellitus is usually of slow onset and the risk of developing the disease increases with age, obesity and lack of physical activity.

Diabetic foot

Reduced sensation, ulcers and other impairments of the foot as a complication of diabetes, resulting from the disease causing impaired nerve function (neuropathy) and predisposing to vascular disease.

Gestational diabetes

Diabetes that appears during pregnancy and disappears after the birth of the baby.

Glucose

Physiologically, one of the most important basic sugar (carbohydrate) units. For example, starch is composed of many units of glucose.

Hyperglycaemia

Condition characterised by too high a level of glucose (sugar) in the blood, for example in cases where diabetes is out of control. It occurs when the body does not have enough insulin to turn glucose into energy, and/or store it, or cannot use the insulin it does have.

Hypoglycaemia

Abnormally low concentration of glucose in the blood, which can cause muscular weakness and incoordination, mental confusion, and sweating. If severe it may lead to hypoglycaemic coma. Hypoglycaemia most commonly occurs in diabetes mellitus as a consequence of relative insulin excess from insulin injection or insulin secretagogue therapy, associated with insufficient intake of carbohydrate, excess energy expenditure, and/or other blood glucose lowering agents such as alcohol. It is treated by administration of glucose or glucagon.

Insulin

Hormone secreted by special cells of the pancreas (pancreatic ß-cells) in response to blood glucose. It is involved in regulating blood glucose levels and promotes fuel storage.

Ketoacidosis

Complication of diabetes resulting from critical insulin deficiency with presence of elevated blood ketones. In uncontrolled type 1 diabetes, that is in the absence of insulin, the body starts to break

down fats for fuel. Ketone bodies are a metabolic by-product of fat metabolism and can be used as fuel by muscle and brain tissue. In diabetic ketoacidosis, ketone bodies accumulate and elevated levels can be found in blood and urine, leading to a dangerous acidification of the blood.

Nephropathy

Disease of the kidney. In diabetic nephropathy, damage to the kidneys occurs as a consequence of hyperglycaemia (see above), which induces damage of blood vessels leading to several phenomena, including impaired blood flow. Features include increased excretion of protein in the urine, increased blood pressure and declining kidney function. Severe diabetic nephropathy can lead to kidney failure and end-stage renal disease. Individuals with end-stage disease must rely on kidney dialysis, peritoneal dialysis or kidney transplantation to survive.

Neuropathy

Damage to nerves. High blood glucose levels in longstanding poorly controlled diabetes can damage nerves. A complication of diabetes, in some forms of which neuropathy plays a role, is the diabetic foot (see above).

Pancreas

Organ located behind the stomach. The exocrine pancreas secretes enzymes important in digestion. The endocrine pancreas produces two hormones vital for carbohydrate metabolism, insulin and glucagon.

Retinopathy

Disease of the retina (the light-sensitive layer at the back of the eye, onto which external images are projected). In diabetes, damage to blood vessels as a consequence of diabetes may lead to, for example, haemorrhages (bleeding) and retinal detachment, thereby causing impairment or loss of vision.

List of abbreviations

ADA	American Diabetes Association
AADE	American Association of Diabetes Educators
AETMIS	Agence D'Évaluation des Technologies et des Modes D'Intervention en Santé
AUC	Area under the curve
BMI	Body mass index
BNF	British National Formulary
CHQ-CF87	The Child Health Questionnaire
CORE	Center for Outcomes Research
CSII	Continuous subcutaneous insulin infusion
CVA	Cerebrovascular accident
DAFNE	Dose Adjustment for Normal Eating
DCCT	The Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
DOH	Department of Health
DQOL	Diabetes Quality of Life
DQOL-Y	Diabetes Quality of Life for Youths
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DQOLCTQ	Diabetes Quality of Life Clinical Trial Questionnaire
DSN	Diabetes specialist nurse
EDIC	Epidemiology of Diabetes Interventions and Complications Research Group
EQ-5D	EuroQol 5D
GP	General Practitioner
HbA_{1c}	Glycated haemoglobin
HTA	Health Technology Assessment
IAHS	Institute of Applied Health Sciences
ICT	Insulin conventional therapy
IHD	Ischaemic heart disease
IM	Intramuscular
INPUT	Insulin Pump Therapy – patient led support group
IIT	Intensive insulin therapy
ITT	Intention to treat
IPTSQ	Insulin Pump Therapy Satisfaction Questionnaire
IPWG	Insulin Pump Working Group
IQ	Intelligence quotient
IHD	Ischaemic heart disease
ITT	Intention-to-treat
IV	Intravenous
JDRF	Juvenile Diabetes Research Foundation
MAGE	Mean amplitude of glycaemic excursions
MDI	Multiple daily injections
NIH	National Institutes of Health
NICE	National Institute for Health and Clinical Excellence
NPH	Neutral protamine Hagedorn
NS	Not significant
OR	Odds ratio
PCT	Primary Care Trust
QALY	Quality adjusted life years
ReBIP	Review Body for Interventional Procedures Programme
RCT	Randomised controlled trial
RR	Relative risk
SSGCDY	Scottish Study Group for the Care of Diabetes in the Young
SDS	Standard deviation score

SE	Standard error
SED	Self-Efficacy for Diabetes Scale
SF-36	Short Form 36
SA	Short acting
TAPQoL	Pre-school children Quality of Life questionnaire
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TAR	Technology Appraisal Report
UKPDS	UK Prospective Diabetes Study
YHPHO	York and Humber Public Health Observatory

Summary

Background

Continuous subcutaneous insulin infusion (CSII) is a way of giving insulin. A small programmable pump with a reservoir of short-acting insulin is connected to a cannula under the skin by a narrow tube. The pump is set to deliver insulin at slow rates appropriate to the time of day, and can be adjusted by the user to accommodate reduced insulin needs during and after exercise, and to deliver a higher infusion rate to cover food intake. The rate can changed at any time by the user. For example, meal time doses are delivered by activation of a booster dose by the user.

CSII provides a form of intensified insulin therapy, and is part of a system of self-care which also includes home testing of blood glucose, self-adjustment of insulin dose, and care with diet. It is an alternative to multiple daily injections (MDI) of a combination of long acting and short-acting insulins, usually involving four or more injections a day.

In 2002, NICE issued guidance on the use of CSII, recommending restricted use in people with type 1 diabetes (T1DM) who could not achieve good control on MDI without problems with severe hypoglycaemia. It was not recommended in type 2 diabetes (T2DM). At that time, there were no randomised trials in children, or in adults with T2DM. There was little evidence in diabetic pregnancies, and that showed little difference from MDI. The guidance expected that only 1-2% of people with T1DM would become insulin pump users.

CSII is used in around 1% of people with T1DM in the UK, much less than the 10-20% in comparable countries in Europe or North America.

The aim of this report is to update the previous assessment report by reviewing evidence which has emerged since the last appraisal, and to take account of developments in alternative therapies, in particular the long-acting analogue insulins, which cause fewer problems with hypoglycaemia. And as Professor Amiel points out (personal communication, July 2007), we also have increasingly tight glycaemic targets, and an increasingly educated patient population who want to achieve these.

Methods

We carried out a systematic review of the literature and an economic evaluation. The primary focus in T1DM was on comparison of CSII with analogue-based MDI, but for completeness, trials of NPH-based MDI which had been published since the last assessment were identified and described in brief. In T2DM, all trials of MDI versus CSII were included, whether the long-acting insulin was analogue or not, because there was no evidence that in T2DM, analogue-based MDI was better than NPH-based

MDI. Some recent observational studies were reviewed for data on longer-term results, discontinuation rates and adverse events. Studies on quality of life were also included. Previous studies of the cost-effectiveness of CSII were reviewed.

Information on the patient's perspective was obtained from four sources: the submission from the pump users group, INPUT; interviews with parents of young children who were members of INPUT; from some recent studies; and from a summary of findings from the previous assessment report.

Economic modelling used the Center for Outcomes Research (CORE) model, through an arrangement with NICE and the pump manufacturers, whose submission also used the CORE model.

Results

Number of studies

In the last guidance, NICE commented on the need for trials of CSII against analogue-based MDI in T1DM. Unfortunately, only four trials have been done, some are very small, and only two have been published in full, of which one was only a pilot. The trials included 32 children and 81 adults.
For the comparison of CSII versus MDI in T2DM, we found four studies with 296 patients. There were eight new trials of older forms of MDI against CSII in T1DM, with 500 patients, although over half came from one trial. There are a large number of observational studies, mainly case series.

Clinical effectiveness

The benefits of CSII can include;

- Better control of blood glucose levels, as reflected in glycated haemoglobin, by reduction in swings in blood glucose levels, and in problems due to the dawn phenomenon
- Fewer problems with hypoglycaemic episodes, of which severe incapacitating hypoglycaemia is most important
- A reduction in insulin dose per day, thereby partly off-setting the cost of CSII
- Quality of life, including a reduction in the chronic fear of severe hypoglycaemia
- More flexibility of lifestyle – no need to eat at fixed intervals, more freedom of lifestyle, easier to participate in social and physical activity

Control of blood glucose

CSII versus analogue-based MDI in T1DM:

- One study in children and adolescents reported that HbA_{1c} was reduced by 1%.
- The studies in adults found no difference in HbA1c

CSII versus MDI in T2DM:

- In T2DM, there was little evidence that CSII was better than analogue-based MDI. In one study, a clinically significant difference in HbA_{1c} was reported but failed to reach statistical significance.
- A recent trial reported that CSII was better than NPH-based MDI.

CSII versus NPH-based MDI in T1DM – new trials:

- Of the eight new trials, three showed no difference in HbA_{1c}; four showed differences which were not statistically significant (though one showed a clinically significant difference of 0.5%), and the last showed a larger and statistically significant difference of 0.84%. Some had very small numbers of patients.

Observational studies:

There are far more observational studies available now than there were at the last review. They need to be interpreted with caution due to the greater risk of bias, but in general they report greater improvements in HbA_{1c} than reported in the trials.

- In all 18 studies in adults, there were reductions in HbA1c in adults and mixed age groups, ranging from 0.2% to 1.4%.
- 20 of 23 studies in older children and adolescents showed reductions ranging from 0.2% to 1.2%, and in 13 studies the reductions were statistically significant.
- The five studies in young children (under 7 years) reported decreases of 0.2 to 1.6%, with these being statistically significant in all but one small study (only 14 patients; reduction 0.2%).

Hypoglycaemia

CSII versus analogue-based MDI in T1DM:

- The trials in adults had too few patients, too short durations and too few severe hypoglycaemic episodes to be conclusive, but reported no significant differences in the frequency of severe hypoglycaemia.
- The trial in children reported a statistically significant drop in severe hypoglycaemia, but based on five episodes on MDI versus two on CSII.

CSII in T2DM

- None of the four trials reported a significant difference in hypoglycaemic episodes.

CSII versus NPH-based MDI in T1DM – new trials:

Again, most trials had small numbers. Five trials had under 30 patients.

- The trials which reported the number of severe hypoglycaemia events usually found about half the rate with CSII and with MDI.
- The biggest trial (which had more patients than all the rest put together) reported annual rates of severe hypoglycaemia of 0.2 per patient year on CSII and 0.5 on MDI.

Observational studies:
These reported considerable reductions in severe hypoglycaemia. This may reflect selection for CSII of people having particular problems with hypoglycaemia, but that would make them more applicable to routine care. Of 26 studies reporting comparable before and after data;

- 15 showed a statistically significant decrease in severe hypoglycaemic episodes
- five reported a statistically non-significant decrease
- three reported a decrease in episodes but did not report significance levels
- three did not report any episodes.

Patient evidence:
Several patients reported to us that they had found that the onset of hypoglycaemia was much slower on CSII than MDI, giving them more time to take preventive action and avoid severe hypoglycaemic events.

Reduction in insulin dose

CSII versus analogue-based MDI in T1DM:

- The study in children reported a reduction, from 0.7 units/kg/day on CSII to 0.6 units/kg/day on MDI, but this was not statistically significant.
- The only published trial in adults reported a significant drop by 24 weeks in the CSII group, from 0.7 units/kg/day before CSII to 0.4 units/kg.day after 24 weeks. The MDI group showed an insignificant rise, from 0.7 to 0.8 units/kg/day.
- The studies available only as abstracts gave no details.

CSII in T2DM:
No persisting differences in insulin dose were found.

Observational studies:
Eight studies in adults, 11 in older children and adolescents, and two in younger children, reported comparable data.

- Six of the eight adults studies reported a decrease in insulin dose, ranging from 2% to 27%.

- Of the 11 studies in older children and adolescents, 10 showed decreases varying in size from 3% to 32%, most statistically significant.
- There were no significant changes in two studies in the youngest children

Quality of life

CSII versus analogue-based MDI in T1DM:

- The two studies that reported quality of life outcomes found no differences.

CSII in T2DM:

- Of four RCTs, one study reported no difference and one reported a significant improvement in treatment satisfaction on CSII.

Observational studies:

Bias in observational studies is more of a problem with questionnaire-based results than with biochemical ones such as HbA1c and all results must be treated with caution. Of 48 observational studies, only nine reported on quality of life aspects. Study numbers were small, with at most 35 patients.

- One study in adult patients reported that they preferred CSII; another reported gains in quality of life.
- In older children and adolescents, three of four studies reported gains in various measures such as less worry, patient satisfaction, sleep quality, flexibility of meal times, better moods in children, and reduced impact of diabetes. But some reported initial worry, difficulties calculating insulin dose, and that it took from six weeks to nine months to feel confident.
- In children under 7 years, most families preferred CSII. In one study, parents reported quality of life gains; in another, children did not, but both had small numbers (15 and 14 children).

Other outcomes

- 15 observational studies reported the frequency of diabetic keto-acidosis. None reported a statistically significant increase; three reported statistically significant decreases.
- The trials reported no difference in weight gain between CSII and MDI. Most of the observational studies reported no significant weight change before and after CSII.

Pregnancy

There were no new trials. Observational studies in general showed that CSII achieved similar glycaemic control to MDI. Maternal and fetal outcomes were similar. One study reported more

diabetic ketoacidosis with CSII. A recently published Cochrane review noted that there was a dearth of good evidence.

The industry submission

The pump manufacturers submitted a joint submission. It used the Center for Outcomes Research (CORE) diabetes model. Three HbA1c scenarios were assessed, all for T1DM;

- A baseline HbA1c based on results from trials, with a reduction on CSII of [redacted] (AiC)
- A higher baseline thought to be more representative of levels in the UK, with a reduction of 1.3%
- An intermediate scenario with a reduction of [redacted]

All these scenarios assumed a severe hypoglycaemic episode rate of 15 per 100 person years.

The submission concluded that CSII in T1DM was cost-effective if the drop in HbA_{1c} was 0.9% or more. Some assumptions favoured CSII, including the cost of hypoglycaemic episodes, and the size of the reduction in insulin dose. The model also assumes that reductions in HbA1c with CSII are sustained. In other ways the industry submission may have under-estimated the benefits, for example by not including hypoglycaemic mortality, and not allowing for all the quality of life gains. However, some of the omissions are understandable given that some gains, for example in flexibility of lifestyle, or happiness of children, are not easily measurable, and do not fit easily into cost per QALY estimations.

There are only occasional deaths from hypoglycaemia, but because they often occur in young people, the number of life years lost can be considerable.

The industry submission did not examine the economics of CSII in type 2 diabetes. In practice, CSII would be considered only in people with T2DM who had progressed to intensive insulin therapy, and would have a beta cell failure status not far off those with T1DM. Treatment group is more relevant than type of diabetes.

The perspective of pump users

The submission from INPUT emphasised the quality of life gains from CSII, as well as improved control and fewer hypoglycaemic episodes. Our own small enquiry noted the difficulties which families of young children sometimes had in getting access to CSII, and the benefits gained.

Costs

The main cost of CSII is for consumables such as tubing and cannulae – about £1,800 to £2,000 a year. The cost of the pump, assuming four year life, adds another £430 to £720 per annumn.

The extra cost compared to analogue-based MDI, averages £1,700.

Cost-effectiveness.

A review of existing studies found three full papers and eight abstracts examining the cost-effectiveness of CSII compare to MDI. Most use the CORE model, and most found CSII to be cost-effective. They assumed a reduction in HbA1c of 1.2%. If CSII only resulted in an improvement of 0.5%, its cost-effectiveness was much poorer.

Modelling was carried out with varying assumptions about improvement in HbA1c, and reduction in severe hypoglycaemic episodes. With an improvement in HbA1c of 0.9% and a reduction in severe hypoglycaemic episodes of 50% (from a relatively low baseline severe hypo event rate of 19 per 100 patient years), the cost per QALY is about £38,000. If higher baseline severe hypoglycaemia rates are used, the cost per QALY falls, but only to about £36,500, because the CORE model is driven more by HbA1c than hypoglycaemia, and because the quality of life decrement from each hypoglycaemic event is of short duration.

The base case assumes average age of 40 at baseline. If we assume a younger starting age, of say 30, the cost per QALY falls to £34,000. The CORE model was not designed to run with children, and so the results of CSII started in childhood have not been modelled.

If the reduction in HbA1c is assumed to be only 0.6%, then the ICER rises to over £50,000. Conversely, if the reduction in Hba1c is 1.4%, then the cost per QALY falls to around £25,000.

A reduction in severe hypoglycaemia events can produce benefits in three ways. Firstly, the immediate disbenefits at the time of the episode are avoided. Secondly, the chronic fear of a recurrence is reduced or relieved. Thirdly, reduction in the fear of severe hypoglycaemia may allow more intensive therapy and lower HbA1c, hence reducing future complications. The second aspect has major implications for the cost per QALY which has not been factored into any of the above estimates. An annual quality of life increment of as little as 0.01 from reduced fear of hypoglycaemia would, because of the number of years of benefit, reduce the base case cost per QALY to about £29,000. An annual increment of 0.03 would reduce it to about £21,000 per QALY.

Patient selection

CSII is a form of intensive insulin treatment which requires commitment from patients, and is part of package of care and self-care, along with structured education, home self-testing of blood glucose, adjustment of insulin dose, and attention to diet and physical activity.

Diabetes clinics which provide a specialist CSII service have developed ways of selecting patients who would be most suitable for CSII.

Implementation

If CSII were to be made more widely available, education would have to be provided not just for patients (perhaps involving a course such as DAFNE (Dose Adjustment For Normal Eating), but also for health care professionals in centres which do not currently provide a pumps service.

Uncertainties

Some gains and losses in utility have not been quantified. The unquantified disutilities include;

- The fear of severe hypoglycaemia
- The possibility of cognitive impairment due to severe hypoglycaemia in some children who become diabetic when very young.

The gains which have not been quantified include non-health related benefits of CSII, such as greater flexibility of lifestyle, easier participation in social activities or school events trips, happier children, less disruption to family routines, and in mothers of young children with diabetes, less interrupted employment.

The costs per QALY in children have not been estimated.

Many of the trials are of short duration. It takes time to get the full benefit from CSII, for example by trying out different basal rate combinations, and short trials may under-estimate benefit.

Research needs

The need identified by NICE at the first appraisal of CSII, for adequate trials of CSII against analogue-based MDI, has not been met. Such trials should include children.

There should be a trial of CSII against the DAFNE package.

Automated systems for monitoring blood glucose levels are entering clinical practice, and there is potential to link with the insulin pumps.

There is a need for a large trial in pregnancy, in women with pre-existing diabetes, which in order to allow for using CSII to best effect, should start before conception.

The present economic model assumes an adult population, and we need a model developed which would allow use in children to be assessed.

Conclusion

Based on the totality of evidence, rather than just the randomised trials against best MDI, CSII provides some advantages over multiple daily injections;

- Better control of glucose levels as reflected in HbA1c, with the size of improvement depending on the level before starting CSII
- Fewer problems with hypoglycaemia
- Quality of life gains, such as greater flexibility of lifestyle

However this comes at an extra cost.

Chapter 1 Introduction

1.1 Diabetes

There are two main types of diabetes mellitus ("Mellitus" to distinguish it from a rarer disease called diabetes insipidus, which is not relevant to this review).

1.1.1 Normal blood glucose control

Glucose is the primary source of fuel for cells in the body. Carbohydrate in food is metabolised to glucose within hours of ingestion, and is absorbed from the blood into cells for use as fuel. Uptake of glucose into cells is regulated by the hormone insulin that is released from the pancreas in response to rising blood glucose levels. Insulin also regulates the use of glucose by cells, so if there is insufficient insulin, or if cells do not respond properly to insulin (insulin insensitivity or resistance), then glucose is not used efficiently by cells, either in terms of energy or storage.

1.1.2 Type 1 diabetes

In Type 1 diabetes mellitus (T1DM), formerly known as insulin-dependent diabetes, all or nearly all of the beta cells in the pancreas, which produce insulin, have been destroyed, usually by an autoimmune process. The cause is not known. People with T1DM have little or no ability to produce their own insulin, would die without insulin, and so have to inject insulin for the rest of their lives. T1DM usually starts in children or young adults, but it can have onset at any age. The incidence (number of new cases per year) has risen considerably over recent decades. Scottish data show that the rate in children has more than trebled over the last 30 years (Figure 1). The rise has been greater in the youngest age group, though absolute numbers are smaller (SSG, unpublished).

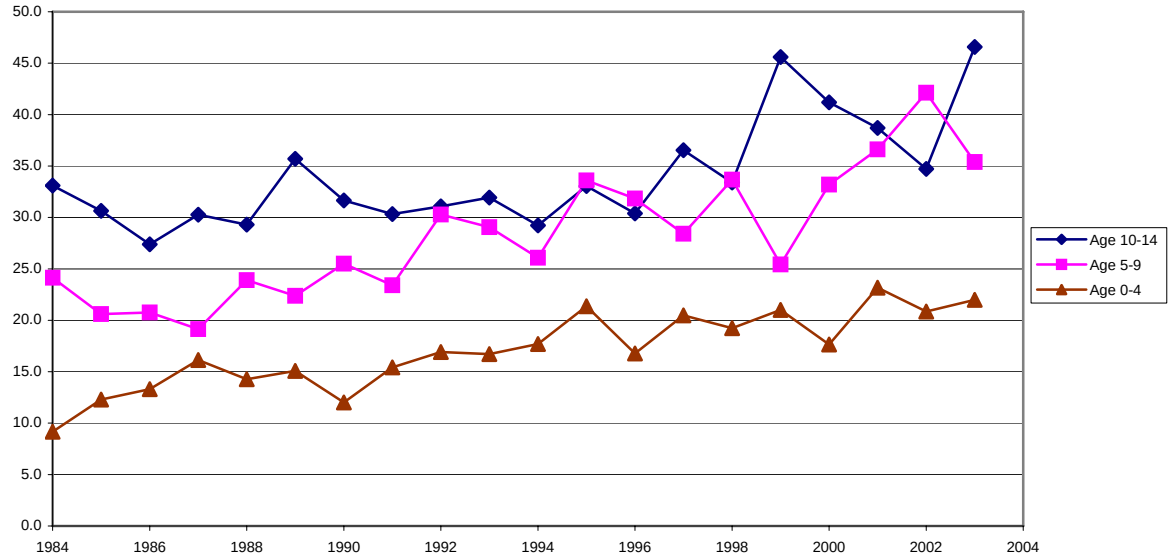


Figure 1: SSG incidence by age at diagnosis 1984-2003

Similar rises have been reported from Oxford Region by Wilson and colleagues.[1] The incidence of childhood diabetes (under age 15) rose from 17 per 100,000 in 1985-90 to 26.5 in 2003-4. The greatest increase was in the under five's, where the number who had diabetes by age five rose five-fold.

1.1.3 Type 2 diabetes

Type 2 diabetes (T2DM), formerly known as non-insulin-dependent diabetes or maturity-onset diabetes, comes on later in life than T2DM. It used to be seen almost exclusively in people over 45, associated with overweight or obesity, but with rising prevalence of obesity, it is now increasingly being seen at younger ages and even in children. Some ethnic groups such as South Asians have earlier onsets. The York and Humber Public Health Observatory (YHPHO) website (a very useful compendium of data on diabetes: www.yhpho.org.uk) estimates that the total prevalence of T2DM in England is 4.3%, though that includes people with undiagnosed diabetes.[2] (Some people with T2DM, perhaps 20%, have no symptoms and do not know they have it. Hence the current debate on screening, which is covered by another health technology assessment report.[3] The YHPHO estimated that the total prevalence of diabetes would rise by 15% between 2001 and 2010, with a 6% increase due to the ageing population and a 9% increase due to increasing obesity.[4]

T2DM usually starts with insulin resistance, related to overweight, with the pancreas producing more insulin than usual to overcome the resistance. Over time, the pancreas fails to produce enough,

insulin production falls, blood glucose rises further, and clinical diabetes ensues. In the UK Prospective Diabetes Study (UKPDS) patients' insulin production had fallen to about 50% of normal at the time of diagnosis.[5] Treatment starts with lifestyle measures, diet, weight loss and exercise, and if those fail, oral drugs are added. In most patients, T2DM is a progressive disease and over time, many patients will need insulin.[6] The UKPDS showed that just over half of patients initially randomised to sulphonylureas (an oral drug which stimulates pancreatic insulin production) had to switch to insulin by six years.[7] In a population-based study in Tayside, Scotland, 6% of patients with T2DM started insulin each year.[8] Most people with T2DM starting insulin nowadays probably start with a once-daily injection of a long-acting analogue, but over time, some will progress to multiple daily injections (MDI) in order to achieve good control.

Data from other studies have shown that many patients with T2DM are on insulin therapy. The Lothian Audit reported that 32% of people with T2DM are on insulin (McKnight J personal communication 2005).

1.1.4 Control, glycated haemoglobin and insulin treatment

The term control is a recurring one in diabetes. It refers principally to preventing blood glucose from going too high, but also applies to preventing it from going too low. High blood glucose is known as hyperglycaemia. Low blood glucose is called hypoglycaemia.

In the non-diabetic person, blood glucose is kept within a narrow normal range (about 4 to 5.6mmol/l) through the action of insulin and other hormones. The pancreas releases a little insulin throughout the 24 hours (known as basal insulin; about 0.5 to 1 unit per hour in adults) but production of insulin is swiftly and markedly increased with meals, going up 5-10 fold in the first 30 minutes. If blood glucose falls too low, counter-regulatory hormones are released and nervous system mechanisms are activated to increase it again. A key aspect is that the brain is dependent on glucose for energy. If blood glucose falls too low, brain function is impaired, as will be described later.

Control of blood glucose is measured in three ways. Firstly, blood glucose can be checked at any time by finger-pricking to produce a drop of blood, and testing it with a testing strip and blood glucose meter. This gives the glucose level at that time, but it may change quite rapidly after meals or either insulin or tablets. Secondly, longer-term control is measured by glycated haemoglobin, or HbA_{1c}, which reflects the average blood glucose over two to three months. HbA_{1c} has been a major advance in diabetes because by testing every three months, it gives an indication of how good control is. However, it provides an average, and that can reflect very tight control with little fluctuation in glucose levels, or poorer control with considerable fluctuation. At the risk of considerable

simplification, this can be illustrated by the averages of 4 and 8, and 2 and 10 – both 6. Thirdly, new devices can now provide frequent automated testing of interstitial tissue glucose, calibrated to reflect plasma glucose, and known as "continuous blood glucose monitoring". These devices are currently used more in research, but are coming into routine clinical practice in some clinics.

In T1DM, control is dependent on injected insulin, and unfortunately currently there is no insulin that can exactly mimic production by the normal pancreas. Even the latest rapid-acting insulins cannot achieve as rapid a rise after meals as the pancreas can, and nor can they achieve as rapid a fall. A key point is that natural pancreatic insulin release is regulated by the level of glucose in the blood in a way that injected insulin cannot be. A fall in blood glucose will switch off pancreatic insulin release but cannot affect injected insulin.

There are various forms of insulin, and various combinations, grouped by duration of action.

Short-acting insulin comes in three types. The oldest type is called regular or soluble; we will refer to it as short-acting (SA) soluble because some long-acting analogues are also soluble. The next type is short-acting analogue insulin, with three varieties on the market – aspart, lispro and glulisine. SA soluble starts acting within an hour of injection, peaks at two to four hours, and has some effect for up to eight hours. The SA analogues act a bit more quickly and do not last quite as long. They are therefore regarded as being closer in effect to pancreatic insulin than SA soluble insulin. However a Cochrane review [9] concluded that the advantages of SA analogues over SA soluble were minor – very little difference (0.1%) in glycated haemoglobin (HbA_{1c}) or total hypoglycaemic episodes, a greater (50%) but not statistically significant reduction in severe hypoglycaemic episodes ("hypos") in adults, but not adolescents, when used in multiple daily injections (MDI), but a greater difference (0.2%) in HbA_{1c}in patients on continuous subcutaneous insulin infusion (CSII). The improvement in HbA_{1c} with SA analogues rather than SA soluble in CSII, was reported to be 0.26% in a meta-analysis based on the last assessment report for NICE [10] and patient preference was also higher for analogues. The third type is inhaled insulin, appraised by NICE in 2006 (TA 113) and reviewed in another assessment report (monograph 2007/in press, expected August 2007).

Intermediate-acting insulins such as neutral protamine Hagedorn (NPH) or isophane start working in one to two hours, peak at about six to 10 hours, and have some effect for 16-18 hours. Unfortunately, the peaks may vary unpredictably from injection to injection, and hence from day to day.

Short and intermediate acting insulins can be mixed in the same syringe, and can be given as a premixed version twice daily. This is known as "conventional" insulin therapy. The newer long-

acting analogue insulins, glargine and detemir, are longer acting than NPH and have a long steady action, being sometimes called "peak-less".

In recent years, since the Diabetes Control and Complications Trial [11] showed that good control reduced the adverse effects of T1DM, there has been a move to more intensive insulin treatment. This consists of a combination of basal insulin using NPH (usually twice a day) or a long-acting analogue, with short-acting insulin at meal-times, usually called "bolus" insulin – hence the term "basal-bolus" regimens. These can be given in two ways – by MDI or by CSII via insulin pumps.

1.1.5 The history of continuous subcutaneous insulin infusion

The first studies of CSII delivered via insulin pumps came from Guy's Hospital, London in 1978 [12] and Yale in 1979.[13] CSII uses a small programmable pump with a fine tube connected to a soft plastic cannula (introduced by needle) which goes into the subcutaneous tissue under the skin, often in the abdomen. The needle is changed every two to four days. The aim of CSII is to try to approximate the insulin delivery profile more closely to the pattern of output behaviour of the normal pancreas, by providing continuously infused, low volume basal insulin for fasting periods and the delivery of increased rate boluses to cover meals. Only short-acting (soluble or analogues) insulin is used.

Lenhard and Reeves reviewed the literature in 2001 using Medline only.[14] They noted the rise in popularity of CSII after the introduction of pumps in the late 1970s and early 1980s, followed by a fall because of size, safety and efficacy concerns, followed then by a rise in usage after the publication of the DCCT study. They also noted that the newer pumps were smaller, more reliable and easier to use. They estimated that about 8% of all adults in North America with T1DM were using pumps. They concluded that there was good evidence for benefits in adults ("comparable or slightly superior to MDI"), and some in pregnancy, but that there was little good quality evidence in children.

Pickup and Keen, who were the originators of CSII, reviewed the history of and evidence base for CSII in 2002.[15] They noted the considerable world-wide use of pumps (over 200,000 patients) and the disproportionately low UK use. They concluded that on CSII, blood glucose and HbA_{1c} are similar or slightly lower than with MDI, that hypoglycaemia is much less frequent, and that ketoacidosis occurs at the same rate. They concluded that the proportion of patients who would be suitable is relatively small. In a complementary paper, Pickup and colleagues [16] carried out a meta-analysis of RCTs comparing CSII with MDI. They found that HbA_{1c} was about 0.5% better on CSII, but found that few studies reported hypoglycaemic episodes; none appeared to report effect on quality of life. The CSII group needed 14% less insulin.

The previous UK HTA report has been mentioned already and its summary is in appendix 1. The Agence D'Evaluation des Technologies et des Modes D'Intervention en Sante (AETMIS) from Quebec published a report in June 2005, comparing MDI with CSII.[17] It concluded that CSII might be indicated for a limited, selected group of people with T1DM, and cited various selection criteria, including;

- inadequate glycaemic control despite a trial of intensive insulin therapy
- recurrent, unpredictable severe hypoglycaemic episodes, nocturnal hypoglycaemia or hypoglycaemic unawareness, causing incapacitating anxiety and affecting the quality of life
- morning hyperglycaemic episodes (morning blood glucose level of 8 mmol/l or more)
- and for children, the above plus extreme insulin sensitivity (under 20 units of insulin per day).

At the time the report was written, glargine was not available in Quebec.

It is always interesting to know what treatments clinicians with diabetes choose for themselves. A survey of the American Association of Diabetes Educators and the American Diabetes Association (ADA) asked members if they had diabetes, and if so how they were treated.[18] About 6.4% of members had diabetes, of whom 72% had T1DM. The survey found that 96% of those with T1DM used an intensive insulin regimen, and that over half (60% of the AADE members with diabetes and 52% of the ADA ones) used an insulin pump.

Modern pumps

Modern pumps are small and lightweight compared to the early ones. The pumps are battery operated and hold enough insulin for several days, depending on daily need. The infusion rate can be programmed for both dose and timing. Different basal rates can be preset, for example overnight could be lower than during the day, or vice versa. Bolus boosts can be given starting just before meals (if analogue insulins are used), and infusion rates can be reduced during exercise. The newer pumps are more reliable[19] and may have alarms for empty cartridges, low batteries, occlusion of tubing and faulty electronics giving rise to less fear of undetected malfunction, which was a problem with some of the older pumps.

1.2 Complications of diabetes

Diabetes causes short and long-term problems. The short-term ones include acute metabolic upsets such as:

a) diabetic ketoacidosis (DKA): where insufficiency of insulin, often at a time of incidental other illnesses when the body needs more than usual, leads to disordered metabolism with the blood become more acidic than it should be (hence the "acidosis") due to accumulation of ketones (hence the "keto"). DKA is a medical emergency and can be life threatening. Mortality nowadays is very

low, from 0.15% to 0.31% in children in North America, the UK[20] and India[21] but higher at 4% in Danish adults.[22] However, it remains a serious threat.

b) hypoglycaemia: mild hypoglycaemia may only cause a feeling of hunger and sweating, quickly corrected by taking food or a sugary drink. However if it occurs during the night (nocturnal hypoglycaemia) it can reduce the amount and quality of sleep. More serious hypoglycaemia can mean that the diabetic person needs help in order to recover. "Severe hypoglycaemia" is usually defined by the need for assistance from another person, meaning that the diabetic person cannot recover without aid. Severe hypoglycaemia can lead to behavioural disturbances, unconsciousness, convulsions (similar to an epileptic fit) or death. In very young children with frequent or severe hypoglycaemic events there may be some impairment of intellectual function (see below).

The problems mentioned above refer to physical effects, but as has been pointed out by Cryer and colleagues,[23] there is also psychological morbidity;

"*At the very least, an episode of hypoglycaemia is a nuisance and a distraction. It can be embarrassing and can cause social ostracism. The psychological morbidity of hypoglycaemia includes fear of hypoglycaemia, high levels of anxiety and low levels of overall happiness."*

The longer-term adverse consequences of diabetes have been traditionally known as "complications" and are related to chronic hyperglycaemia. They include conditions due to damage to small blood vessels (microangiopathy) and larger ones (macrovascular disease):

- retinopathy – a disease of the eyes, which in the past has been the commonest cause of blindness in people of working age (macular degeneration is commoner in the elderly).[24]
- nephropathy – disease of the kidneys, which is one of the commonest causes of end-stage renal failure, leading to a need for renal dialysis or transplantation.[25]
- ischaemic heart disease (IHD) due to disease of the coronary arteries. People with diabetes have an increased risk of IHD.[26-29]
- stroke - due to disease of the arteries to the brain. The risk is increased three to four fold in T1DM.[27]
- amputations - due to a combination of damage to nerves (neuropathy) and to arteries in the leg. (For review see Boulton and colleagues 2005).[30] A Welsh study reported a relative risk for amputation of 32 in people with diabetes.[31]
- neuropathy – damage to the nervous system.

1.3 Intensified insulin therapy and better control of T1DM

Conventional insulin treatment usually means twice-daily combination of a short-acting and an intermediate acting insulin. Intensified insulin therapy (IIT) is a combination of more frequent doses of insulin, usually one injection of a long acting insulin a day (sometimes two) and three mealtime doses of short-acting, together with regular self-monitoring of blood glucose, self-adjustment of insulin dose, and care with diet. It requires commitment from an educated patient, and not all patients wish to move to intensified therapy. It is not just about taking insulin more often.

The DCCT in T1DM confirmed the benefits of intensified therapy, with MDI or insulin pumps, in achieving good control and thereby reducing the risk of complications.[11] It confirmed the results of smaller trials, summarised in the meta-analysis by Wang and colleagues (1993).[32] Since the DCCT, there has been increased emphasis on the importance of good control of blood glucose in reducing the risk of complications. The DCCT compared outcomes at an average follow-up of 6.5 years, between those randomised to intensive insulin treatment with multiple daily injections or CSII, and those randomised to conventional insulin regimens, usually two injections per day. In those who had no retinopathy (eye disease) at baseline, intensive therapy reduced the risk of retinopathy by 76% (95% CI 62-85): by six years, 7% of the intensive group and 265 of the conventional group had developed retinopathy.[11] The gap widened in later years.[33] In those who had some retinopathy at baseline, intensive therapy reduced progression by 54%, and reduced the need for laser photocoagulation therapy (a way of treating sight-threatening retinopathy) by 56%.

Intensive therapy reduced the appearance of microalbuminuria, a marker for diabetic renal damage, by 39%.[11]

The reduction in retinopathy was related to the improvement in HbA_{1c}, and applied across the whole range of HbA_{1c}. So a 10% reduction in HbA_{1c} gave a 39% decrease in retinopathy risk, whether the reduction was from 9.0% to 8.1% or from 8.0 to 7.2%.[34] The retinopathy risk increased as the HbA_{1c} increased, so the absolute risk reductions would be different. (For example, drops from 40% to 20% and from 20% to 10% are both 50% relative reductions but the former is a larger absolute reduction.)

The DCCT ended after 6.5 years, and the conventional group was advised to switch to intensive therapy. Within a year, the gap in HbA_{1c} levels had narrowed from the 1.8% seen in the trial, to 0.4%, and by five years there was no difference. But at seven years, the former intensive group continued to do better, for example with progression of retinopathy at about one third of the former conventional group, despite identical HbA_{1c}.[35] The reasons are not fully understood, but it may mean that once changes get beyond a certain point, progression is not halted by improving glucose control. This is seen in nephropathy (renal disease), which once established, progresses even if very good control of

blood glucose is achieved. One finding from the DCCT was that tight control was more effective if applied early in the disease. [36]

This phenomenon whereby early good control can reduce later complications even if control worsens has been called "metabolic memory" by the DCCT/EDIC investigators.[37] A recent review by Ihnat and colleagues (2007)[38] identified possible underlying biochemical mechanisms through which this could occur. If, to use Ihnat's words, "*hyperglycaemia can leave an early imprint in cells of the vasculature and of target organs, favouring the future development of complications*", then there are implications for diabetes care. One is that as Ihnat and colleagues say, "*the existence of the metabolic memory suggests that very early aggressive treatment of hyperglycemia is mandatory".*

Since the DCCT, there has been a move to intensified insulin regimens. A study of two cohorts of children in the USA by Svoren and colleagues [39], one enrolled in 1977 and the other in 2002, found that the proportion on three or more injections a day or CSII, increased from 65% in the earlier cohort to 85% in the later one. HbA_{1c} dropped by 0.3% but the incidence of severe hypoglycaemic episodes and emergency room visits also dropped, by almost 50% and 25% respectively.

Unfortunately, many patients with T1DM are poorly controlled, especially in childhood and adolescence. Two audits by the Scottish Study Group for the Care of Diabetes in the Young (SSGCDY) have examined control of hyperglycaemia as reflected by glycated haemoglobin. Following a pilot audit carried out in a few centres (Diabaud 1, unpublished), the first audit, Diabaud 2 (SSGCYD 2001),[40] reported that in 1997-99, the average HbAc1 was 9.1%. Only about 10% of children were achieving the current NICE guidelines target of 7.5% or less. Nearly all children were on two injections a day; only 25 were on intensive insulin regimens of four injections a day. The second audit, Diabaud 3 (SSGCDY 2006) was carried out in 2002-4.[41] It found that mean HbA_{1c} had not changed (it was 9.2%) and again only 10% reached the NICE guideline target. The number of children on more than two injections a day had risen to 51% but almost all were on a three-injection regimen, splitting the evening dose. MDI was still uncommon (2.3%) and pump use was rare.

The proportion of people with diabetes who have good control as reflected in HbA_{1c} has been increasing. The National Diabetes Audit 2004/5, reported in Diabetes UK's State of the Nation report 2006 found that in England 62% of people with diabetes reached the target of an HbA_{1c} of 7.4% or under; in Wales 61% did.[42] However, this means that 48% in England did not. For children, 84% did not achieve the target in 2004/5. Unfortunately the data, based on returns from general practices, do not give data for T1DM separately.

1.4 Treatment of T2DM with insulin

As mentioned above, T2DM is usually a progressive disease, and about a third end up on insulin. There has been reluctance amongst both patients and clinicians to switch from oral agents to insulin in T2DM, because good control is still usually not achieved, and because weight gain tends to follow insulin therapy.[43,44] Data submitted by Pfizer for the technology appraisal of inhaled insulin showed that many patients with T2DM with poor control on oral agents, remained on them for years before switching to insulin.[45] This may be changing for several reasons: the new GP contract with incentives for reaching HbA_{1c} targets; the evidence on the benefits of tighter control; the greater ease of switching to insulin with once-daily long-acting analogues. Gulliford and colleagues [46] noted that the impact of the Quality and Outcomes Framework target was seen in the proportions of patients whose HbA_{1c} was under 7.5%: 22% in 2000; 32% in 2001; 37% in 2002; and 57% in 2005.

For the purposes of this review, the relevant T2DM group is those who have progressed to the stage of needing intensive insulin therapy because of poor control and poor pancreatic beta cell function. Such therapy usually involves MDI, with a combination of long-acting insulin to provide a basal level of insulin throughout the 24 hours, supplemented with short-acting insulin at mealtimes.

1.5 Hypoglycaemia in T1DM

In the DCCT, intensification of insulin therapy was associated with a higher rate of hypoglycaemia.[11,47] Over an average follow-up of 6.5 years, 65% of patients in the intensive and 35% of those in the conventional groups had at least one severe hypoglycaemic episode. Those in the intensive group had 61.2 episodes per 100 patient years whereas those in the conventional group had 18.7 episodes per 100 patient years. The average number of severe hypoglycaemic episodes a year was low, but they may have a longer effect. As one of our expert advisers said;

"*Even though any single hypo event is short-lived in terms of its acute physiological effect, the psychological effect on many patients is not at all short-lived. It often has a profound effect so that the patient will do everything they can to avoid a recurrence. Many patients have a greater fear of hypos than of developing diabetes-related complications, and as a result will keep their blood glucose levels higher than recommended in order to avoid hypos. If they lost their fear of hypos, better glycaemic control could be achieved, resulting in a reduced risk for complications".*[48]

The NICE guidance on long-acting analogue insulins recognised that fear of hypoglycaemia was a significant factor;

"The Committee accepted that episodes of hypoglycaemia are potentially detrimental to an individual's quality of life. That is partly the result of an individual's objective fear of symptomatic hypoglycaemic attacks…" [49]

A review of hypoglycaemia and diabetes noted that patients were as worried about severe hypoglycaemia as about eye disease.[50] Nordfeldt and Ludwigsson [51] reported that patients (under the age of 19) who had had a severe hypoglycaemic episode within the previous year, had lower quality of life, and that they regarded hypoglycaemia as a bigger problem than long-term complications. Quality of life as measured by EQ-5D median was normal (1.0) in those who had not had a severe hypoglycaemic episode within the past year, but reduced (0.85) in those who had.

Fear affects not just patients but families. Clarke and colleagues (1998)[52] reported higher fear of hypoglycaemia amongst mothers of children with T1DM who had lost consciousness due to hypoglycaemia. They were concerned that this might cause harm in two ways: firstly, that the children's blood glucose levels might be allowed to run higher than desirable in order to avoid further hypoglycaemia; secondly, that maternal reluctance to allow the child to be separated might hinder normal psychosocial development. Hypoglycaemia can be more difficult to recognise in the under 2-year olds.

Streisand and colleagues (2005)[53] studied what they called "paediatric parenting stress" amongst parents of diabetic children aged nine to 17 years, most on intensive insulin regimens, and noted that fear of hypoglycaemia played a significant part in raising stress levels. (Parents of the 20% of children on pumps had lower stress levels, but confounding factors must have been operating, and we cannot conclude from this study that CSII reduces stress in parents.)

Hypoglycaemia has three adverse effects;

- the hypoglycaemic episodes themselves
- the fear of recurrence
- the long-term complications which result from allowing poorer control in order to avoid hypoglycaemia

1.5.1 Hypoglycaemic unawareness

Hypoglycaemia usually causes symptoms such as hunger, sweating, tremor, palpitations, or headache. Some of these are related to the activation of the autonomic nervous system which releases the hormones adrenaline and noradrenaline into the bloodstream. These warning symptoms alert the patient to the need to take action, such as taking sugar, in order to correct the hypoglycaemia.

Unfortunately, in some patients, these warning symptoms do not occur. This is called hypoglycaemic unawareness, which can be partial or complete. A review by Heller (2001)[54] noted that as many as a quarter of T1DM patients may have partial or total unawareness. In people with diabetes who are aware of impending hypoglycaemia, the nervous system activates and causes warning symptoms at plasma glucose levels of around 3.6 mmol/l, above the level at which cognitive impairment starts (around 3.0mmol/l). Those with hypoglycaemic unawareness have what Heller hypothesises to be a re-setting of the threshold for autonomic nervous system activation, so that the cognitive impairment (drowsiness, incoordination, confusion) starts before the warning symptoms do – which may make it impossible for the patients to help themselves.

Severe hypoglycaemia is three to six times commoner in people with hypoglycaemic unawareness. The cause is uncertain, but unawareness may be related to the frequency of previous hypoglycaemic episodes. Studies in which people with unawareness were helped to avoid hypoglycaemic episodes for several months, showed that awareness could be restored, with an apparent re-setting of the threshold, so that the level at which symptoms returned rose to above the level at which cognitive impairment happens (see Heller 2001 for review).[54] Nocturnal hypoglycaemia may contribute to hypoglycaemic unawareness, even when people sleep through the nocturnal hypoglycaemia.

1.5.2 Hypoglycaemia and cognitive impairment in children

1.5.2.1 The effects of hypoglycaemia

Under normal conditions, the brain is fuelled by glucose. It is well known that acute hypoglycaemia causes transient changes in brain function in diabetic adults, manifesting as neurobehavioural or cognitive changes, particularly in cognitive domains such as attention, information processing and both short and long-term memory.[55] However adult brains appear to suffer no obvious harm from moderate hypoglycaemia, and as reported by the DCCT/EDIC group,[56] even severe hypoglycaemia seems to have no long-term cognitive effects.

However, hypoglycaemia may have deleterious effects on the immature and developing brain of young diabetic children leading to permanent effects on brain function. A review by Gold and Frier (1995)[57] noted that;

- the IQs of diabetic children were lower
- their reading skills were on average lower
- cognitive impairment correlated with the frequency of severe hypoglycaemic episodes, and perhaps especially with convulsions
- the poorest performance was in those with onsets of diabetes under the age of five

The complexity of the issue is illustrated by research by McCarthy and colleagues in Iowa [58] They examined the academic performance and diabetes control in 244 children with diabetes, aged 8 to 18. Cognitive function was better if control, as reflected in HbA_{1c}, was better, but they note that this could mean that children with better academic skills were better at controlling their diabetes. Hospital admission, and hence time off school, could be a confounding factor. They noted that a group with good control but hospital admissions because of hypoglycaemia, had poorer academic scores, but this was a small subset (16 patients), making it difficult to draw firm conclusions

Northam and colleagues reported that, compared with non-diabetic controls, six years after disease onset 90 children with T1DM, onsets aged three to 11, performed significantly worse on measures of intelligence, attention, processing speed, long-term memory, and executive skills. Some differences were more marked in those with onset of diabetes under the age of four. Children with a history of hypoglycaemic seizures did worse.[59]

More recently, a study by Dahlquist and Kallen (2007) compared the school marks of 5159 Swedish diabetic children compared with a reference population of 1,330,968 non-diabetic children.[60] The mean of all marks obtained at the time of leaving compulsory education at the age of 16 was significantly lower for the diabetic children compared with the non-diabetic children (3.15 ± 0.01 vs 3.23, $p<0.001$). The maximum possible is not clear but may be five, in which case the difference between diabetic and non-diabetic children is only a few percent.) The largest difference was in children with onsets under the age of two, but this was not statistically significant, and duration would be a confounding factor. In several subjects (mathematics, Swedish, English, sports), the chance of a diabetic child getting high or pass marks was reduced compared to non-diabetic children.

Poor cognitive performance has been suggested to be related to the age of onset of diabetes, the extent of exposure to severe hypoglycaemic episodes, number of seizures and nocturnal hypoglycaemic episodes.[61] Desrocher and Rovet (2004) reviewed a number of studies of cognitive impairment in diabetic children, and noted that problems included;

- slower motor function
- visuospatial deficits
- memory deficits, for example recall of words
- reduced IQ, by 10-20 points

However, these deficits were mostly in children diagnosed under the age of four or five. Children diagnosed over five had no IQ deficit.[61]

Ferguson and colleagues (2005) reported that IQ and information processing ability were significantly poorer (p=0.03 and p=0.006 respectively) in 26 children who developed diabetes before the age of seven years compared with 45 children with later-onset diabetes.[62] They also reported structural changes in the brain in some early onset cases, with a reduction in volume of brain tissue.

1.5.2.2 Severe hypoglycaemia

To test the hypothesis that repeated severe hypoglycaemia, especially starting at a young age, may be detrimental to spatial memory function, Hershey and colleagues (2005) retrospectively studied a group of 103 people with T1DM aged six to 18 years that participated in three individual similar studies.[63] Participants were categorized according to the number of severe hypoglycaemic episodes they had experienced, and according to whether they had their first severe hypoglycaemic episode before or after the age of five. They found that, compared with non-diabetics and those diabetics who had fewer than three episodes of severe hypoglycaemia, having more than three episodes of severe hypoglycaemia was associated with significantly reduced performance in a computerised test of spatial memory ($p<0.01$), particularly in those subjects where age of onset of severe hypoglycaemia was <5 years ($p<0.001$). Long-delay (60s) spatial memory, requiring long-term memory and intact medial temporal function was significantly affected whereas no significant difference was seen in short (5s) delay spatial memory. Mean HbA_{1c} did not correlate with spatial memory performance. It is difficult to precisely measure the occurrence of severe hypoglycaemic episode due to the possibility of under-reporting or unrecognized episodes, particularly in younger children. The authors concluded that the developing brain of very young children may be more vulnerable than the brains of older children to the effects of severe hypoglycaemia on longer-term spatial memory.

Older children seem not to be at risk of cognitive impairment after severe hypoglycaemia. Wysocki and colleagues (2003) carried out a trial of intensive versus conventional insulin treatment, in 142 six to fifteen year old children in the US with T1DM, achieving follow-up HbA_{1c}s of 7.7% and 8.65% respectively.[64] They prospectively studied the frequency and severity of hypoglycaemia, and found that neither the occurrence nor frequency of severe hypoglycaemia was associated with a decline in IQ or measures of cognitive function over an 18-month period. Similar findings were evident for patients who had experienced hypoglycaemic seizures or coma, two pathological situations that could independently affect cognitive function. HbA_{1c} levels were also not associated with change in cognitive function. The authors acknowledged that sensitivity to the effects of severe hypoglycaemia may be greatest among children six years old or under who were not included in this study, and that the 18 month study duration may not be long enough to detect any differences that may emerge.

1.5.2.3 Conclusions

There is evidence of cognitive impairment in diabetic children with the youngest onsets. It is difficult to distinguish the components of the diabetes disease process that might account for this. Early onset of disease, episodes of severe hypoglycaemia, poor control, duration of diabetes, nocturnal hypoglycaemia and seizures are inextricably linked,[64] making it difficult to draw conclusions about the relative contributions. If hypoglycaemia in the youngest children can adversely affect cognitive function, a key aim of treatment will be to minimise the incidence of hypoglycaemic episodes.

1.6 Hypoglycaemia in T2DM

Although the overall incidence of severe hypoglycaemia is much lower in people with T2DM, there is less difference from T1DM in those with T2DM who are on insulin. Leese and colleagues in Tayside (2003) linked an area diabetes register with ambulance call-outs, accident and emergency attendances, and hospital admissions, for all hypoglycaemic episodes requiring NHS assistance.[65] The incidence of severe hypoglycaemia is shown in table 1.

Table 1: Incidence of severe hypoglycaemia requiring NHS resource use

Type of diabetes	Treatment	Incidence per 100 patient years (95% CI)
Type 1	Insulin	11.5 (9.4 – 13.6)
Type 2	Insulin	11.8 (9.5-14.1)
Type 2	Sulphonylurea tablets	0.9 (0.6 -1.3)
Type 2	Metformin or diet	0.05 (0.01- 0.2)

Therefore, treatment rather than type of diabetes determines the incidence of severe hypoglycaemia. The cost per episode was £375 (in 1997-8), spread as follows: ambulance service 31%; accident and emergency 14%; hospital admissions 55%. These costs do not cover all severe hypoglycaemic episodes because some would be managed at home by family members.

A later study from Tayside in adults only, recruited a random sample of patients and reported that the incidence of all hypoglycaemic episodes was 0.82 episodes per week in T1DM and 0.33 episodes per week in insulin-treated T2DM.[66] Only 10% of severe hypoglycaemic episodes in people with T1DM required medical assistance, compared to 33% of such episodes in people with T2DM.

Another, more recent UK study noted that hypoglycaemia was much less common in T2DM, but that was greater in those on insulin, and that it became more frequent over time.[67] (see Table 2).

Table 2: Self-reported hypoglycaemic episodes in T2DM, by treatment

Treatment	Mild hypoglycaemic episodes per person-year	Proportion having at least one mild hypoglycaemic episode per year	Severe hypoglycaemic episodes per person-year	Proportion having at least one severe hypoglycaemic episode
Tablets	1.9	39%	0.1	7%

insulin for less than 2 years	4.1	51%	0.1	7%
insulin for more than 5 years	10	87%	0.7	25%

1.7 The dawn phenomenon

The "dawn phenomenon" is characterised by rapidly rising blood glucose levels over the few hours before breakfast. It is usually caused by the combination of the declining effect of the previous day's insulin and a circadian rise in growth hormone levels, which make tissues less sensitive to insulin. It can be a problem to manage. If the previous evening dose of insulin is increased, that may cause troublesome hypoglycaemia in the middle of the night. Studies in which insulin infusions have been adjusted to maintain blood glucose at a constant level in people with T1DM have shown that the amount required between six and nine am is about double the amount needed between 12 midnight and 6am.[68] Measures to overcome the dawn phenomenon include increasing the previous evening dose of insulin or splitting the evening dose, with short-acting insulin taken at evening mealtime and intermediate acting insulin at bedtime. However, both may cause hypoglycaemia during the night, though this is less with the split dose. With CSII, different basal rates can be used, with an increase in the pre-breakfast hours, and the dawn phenomenon can be prevented.[69] In one study, CSII was used only during the night and the incidence of hypos was reduced by 32%, although this was carried out before the long-acting analogues were available.[70]

1.8 Quality of life

In the last assessment report, we sought comments from a number of users of insulin pumps. One point repeatedly made was that CSII made life much more flexible, with pump users being freed from the discipline of fixed mealtimes and activities. Comments are included in Chapter 4 of the last TAR, but included;

"*From my own perspective, the pump has allowed me to lead a full and active life where I control my diabetes rather than it controlling me. I have been able to travel extensively on business and for pleasure without worrying about changing time zones, strange local eating customs, and where/when the next meal might come from."*

and

"*Freedom, flexibility, pleasure and peace of mind on one's daily life, almost like being a non-diabetic, compared with the uncertainty of the MDI regime."*

and

"*I have experience of both injection (19 years) and insulin pump (6 years) therapy. I find pump therapy to be preferable as it gives me far more control of my insulin input and daily activities. I am now able to live a near normal lifestyle with better control of my disease."*

Interestingly, similar comments are made after DAFNE courses. The Diabetes Service in Aberdeen runs DAFNE courses. A book is kept for comments from participants at the end of each course, and we have seen it. Comments such as "I now control my diabetes rather than it controlling me" are common.

1.9 Indications for CSII

From the above sections, we can list possible indications for CSII;

- to improve control as reflected in glycated haemoglobin, with a view to reducing the risk of long-term complications
- to reduce problems with hypoglycaemia, in particular for people with hypoglycaemic unawareness, and possibly to prevent cognitive impairment in young children
- to prevent the dawn phenomenon
- to allow for more flexible lifestyles and activities, and improve non-health related quality of life.

1.10 The 2003 NICE guidance

1.10.1 TA 57

The TA 57 stated that;[71]

1.1 CSII is recommended as an option for people with type 1 diabetes provided that:

- *Multiple-dose insulin (MDI) therapy (including, where appropriate the use of insulin glargine) has failed; and*
- *Those receiving the treatment have the commitment and competence to use the therapy effectively*

1.2 People for whom MDI therapy has failed are considered to be those for whom it has been impossible to maintain a haemoglobin A1c level no greater than 7.5% (or 6.5% in the presence of microalbuminuria or adverse features of the metabolic syndrome) without disabling hypoglycaemia occurring, despite a high level of self care of their diabetes.

1.6 CSII therapy is not recommended for people with type 2 diabetes who require insulin therapy."

The evidence on which the first appraisal of CSII was based consisted of 14 trials in adults with T1DM, four in pregnancy and two in adolescents. There were no published trials in children. A few very short-term trials had been done in T2DM but not considered suitable for inclusion by the Assessment Group because they were mostly of short duration.

1.10.2 The comparator

At the time of the first appraisal the long-acting insulin analogue, glargine, had only recently become available. The other insulin of this type, detemir, was not. The Appraisal Committee had recently considered the use of glargine, and had noted that hypoglycaemia appeared to be less of a problem with glargine than with older basal insulins such as NPH, because it had a more prolonged action with an almost peak-less profile.[49] The Committee (para 4.3.6) considered whether MDI therapy using glargine would reduce the need for CSII, but concluded that there would be still be some need for it. The Committee (para 5.1) recommended that there should be a trial to compare the use of insulin glargine in MDI regimens with CSII, with particular focus on problems of hypoglycaemia and overnight control.

Searches carried out, in 2002, for the assessment report on glargine found 19 studies but only six had been published in full.[72] Time did not permit us to do a full review to update the evidence base for the long-acting analogues, compared to older insulins, but we carried out a search (May 2007) for studies published since 2002, which compared long-acting analogues with NPH or ultralente. Brief details are given in Table 3.

Table 3: Recent trials of long-acting analogues versus older basal insulin in T1DM

First author and year	Analogue	Comparator	Difference in HbA_{1c}	Difference in hypoglycaemia	Difference in nocturnal Hypoglycaemia	Difference in weight
Ashwell 2006 [73]	glargine	NPH	0.5% lower with glargine		44% lower with glargine	-
Chatterjee 2007 [74]	glargine	NPH	0.19% lower	ND	ND	ND
De 2005 [75]	detemir	NPH	0.04%		32% lower	lower with detemir
Dixon 2005 [76]	glargine	NPH	ND	fewer severe	fewer	BMI ND
Fulcher 2005 [77]	glargine	NPH	0.5% lower	Daytime similar	fewer	-
Hermansen 2004 [78]	detemir	NPH	0.22% lower	overall 21% lower	55% lower	1kg lower

Hershon 2004 [79]	glargine	NPH	ND	lower	-	-
Home 2004 [80]	detemir	NPH	0.18% lower	overall lower	53% lower	0.7kg lower
Home 2005 [81]	glargine	NPH	0.11% lower (NS)	Lower but NS (Severe 10.6% vs 15%)	Lower but NS	-
Kudva 2005 [82]	glargine	ultralente	0.02% lower	less	ND	-
Murphy 2003 [83]	glargine	NPH	0.4% lower (NS)	ND in symptomatic hypo	43% lower	
Pieber 2005 [84]	detemir	NPH	ND	ND	ND	1 kg lower
Porcellati 2004 [85]	glargine	NPH	0.4% lower	all hypos halved on glargine	--	
Russell-Jones 2004 [86]	detemir	NPH	-0.12% (NS)		26% lower	0.54kg lower
Schober 2002 [87]	glargine	NPH	NSD	SH reduced by 25% (NS)	Severe hypos reduced by 30% (NS)	
Standl 2004 [88]	detemir	NPH	ND	RR 0.71 NS	RR 0.7 NS	1.7kg lower
Vague 2003 [89]	detemir	NPH	ND	22% lower	34% lower	Lower

ND No difference; NSD No significant difference; SH Severe hypoglycaemia; BMI Body mass index; RR Relative risk

All these studies were in patients with T1DM. Dixon (2005)[76] recruited children under six years of age, Murphy (2003)[83] studied adolescents, and Schober (2002)[87] included children and adolescents. The other studies were in adults.

Several reviews have been done since the last assessment report on glargine. Mathieu (2004) concluded that compared to NPH MDI, detemir reduced the risk of hypoglycaemia, especially nocturnal, and gave equivalent or better levels of glycaemic control.[90] Peterson (2006) concluded that both detemir and glargine gave better glycaemia control, with similar or reduced hypoglycaemia.[91] For children, the Guidelines group of the International Society for Pediatric and Adolescent Diabetes concluded that the long-acting analogues had reduced day-to-day variability, and that the most marked effect was a reduction in hypoglycaemia.[92]

Two analyses by the CORE group estimated that detemir-based MDI was cost-effective in the UK, at a cost of £19,285 per QALY (Palmer and colleagues 2004; sponsored by Novo Nordisk)[93], and in the USA at a cost of $14,974 (Valentine and colleagues 2006).[94]

From the above brief review, and taking into account the NICE guidance on long-acting analogue insulins [49], we conclude that analogue-based MDI is somewhat better than NPH-based MDI in T1DM, and that it should be the comparator for CSII. Indeed, analogue-based MDI is often referred

to as "the poor man's pump". However, analogue insulins provide less flexibility, either a single basal rate over almost 24 hours, or two basal rates if given twice daily, whereas insulin pumps can be set to provide a range of basal insulins at different times of day and night. These can be pre-set, so that a patient can go to sleep with the pump set to provide different basal rates at different periods during the night.

1.10.3 Analogues in T2DM

The situation may be different in T2DM. A recent Cochrane review on the long-acting analogues versus NPH, concluded that there were no benefits in terms of HbA_{1c}, no statistically significant reduction in severe hypoglycaemic episodes (the odds ratios of 0.7 and 0.5 for glargine and detemir respectively looked promising, but had wide confidence intervals which overlapped with the no difference line), but that both total symptomatic hypoglycaemia and nocturnal hypoglycaemia were reduced. [95]

The NICE guidance (NICE 2002 TA 53) on glargine (detemir was not then available) concluded that (para 4.3.9) the cost-effectiveness of glargine in T2DM was "less well established" because of the lower frequency of hypoglycaemic episodes and hence the more limited scope for improvement. However, the guidance noted that there would be some people with T2DM who could benefit, such as those who had particular problems with hypoglycaemia, and those who would otherwise need twice daily NPH injections.[49]

So in T2DM, the advantages of long-acting analogues are insufficiently proven, given their increased cost, to make them the clear comparator to CSII, and we need to include NPH-based MDI as a comparator.

1.11 The last assessment report

The Summary of the last Assessment Report (Colquitt 2004) is included as Appendix 1 of this report, for convenience.[48] The Assessment Group concluded;

"*Control of diabetes consists of more than just control of blood glucose as reflected in glycated haemoglobin. Compared with optimised multiple injection therapy, CSII results in a modest but useful improvement in glycated haemoglobin, but its main value may be in reducing other problems such as hypoglycaemia and the dawn phenomenon, and in improving quality of life by allowing greater flexibility of lifestyle."*

The Assessment Group based their primary analysis on randomised controlled trials (RCTs), but noted several points. The first was that some of the RCTs were by then quite old, going back to 1982, and using older forms of insulin. The second was that some trials had used older pumps, now superseded. The third was that most trials reported less hypoglycaemia with CSII than with MDI, but the difference was less than seen in some observational studies.[96-99] The Assessment Group wondered if this was because the trials recruited unselected patients from clinics, whereas the observational studies included people having particular problems such as hypoglycaemic episodes.

The Assessment Group also noted that most trials did not report quality of life. It obtained information from pump users with the aid of a patient led support group (INPUT). These pump users reported considerable gains in quality of life, some because of reduction in hypoglycaemia, some because of increased flexibility of life and greater ability to cope with activities of daily life when day-to-day variations occurred. The Assessment Group noted that many of the gains were not in health-related quality of life, but were gains in "social" quality of life, which might not be picked up by the usual utility measures.

1.12 Use of CSII in the UK

Reasons for the low use of CSII in the UK were examined in the last assessment report. The low use is ironic given that the use of insulin pumps was pioneered in the UK, by Keen and Pickup.[12,69] Likely reasons noted in the last assessment report included:

- fear of DKA, which had been reported in some early experiences with pumps. If a pump fails for any reason, the body has no store of insulin and metabolic disturbance ensues rapidly. However in the DCCT there was no evidence of an increased risk of DKA in pump users [11] and this has been the experience of groups with extensive use of CSII in the UK,[100] Germany [101] and the USA.[102]
- lack of funding, or competition for funding for other desirable developments at a time when the incidence of T1DM has been rising. Anecdotal information following the NICE guidance suggest that some Primary Care Trusts (PCTs) are funding pumps at the lowest level suggested by NICE, of 1% of people with T1DM. NICE estimated that 1-2% of people with T1DM would use CSII (NICE 2003 Guidance 4.3.10).[71]
- manpower shortage, especially of diabetes specialist nurses (DSNs)
- the non-prescribability of pumps and associated consumables, such as the infusion tubing. What this means is that either the hospital or the patient has to pay for the pump and the tubing. In some places patients are funding CSII themselves, in other places the NHS is paying.

The submissions from both Diabetes UK and INPUT noted that there were also marked geographical differences in CSII provision in different parts of the UK.

1.13 The Insulin Pumps Working Group Report

The recent report of the Insulin Pumps Working Group, issued jointly by the Department of Health and Diabetes UK (DOH 2007) noted that;[103]

"*Collating this information, there is a consensus that several countries are now treating about 15-20% of people with type 1 diabetes by CSII (USA, Israel, Germany), and in most of the UK's European neighbours a substantial proportion (~10%) of people with type 1 diabetes use insulin pumps for routine management (France, Sweden and The Netherlands). In contrast, overall UK pumps usage is probably no more than 1% of people with type 1 diabetes and in some areas of the country, and in children, it is much less. Thus, the present uptake of CSII in the UK is dramatically lower than in most other countries of comparable economic standing and level of health care provision."*

The Insulin Pumps Working Group report was more about how to provide a pumps service, than about whether to provide it, or how much to provide – these being more within the remit of NICE. It noted that despite the 2003 NICE guidance, there was still "*unacceptable variation in access to CSII across the country"*

The report commented on research needs, and on some areas of uncertainty, including:

- the meaning of the term "failure of multiple dose injection therapy". It was suggested that NICE should consider additional guidance
- the NICE expectation that only 1-2% of T1DM patients would benefit from CSII was thought to be misleading
- indications other than the very limited ones in the current NICE guidance, including pregnancy and pre-conception; hypoglycaemia unawareness; needle phobia; painful neuropathy and autonomic neuropathy; quality of life gains, children
- use by people with T2DM

It also noted some issues for NICE to address in the review of the guidance, including:

- lack of clarity of the term "failure of MDI"
- the indication in the current guidance that only 1-2% of T1 patients were likely to benefit from CSII was thought to be misleading
- the indications in the 2003 guidance were very limited. Other possible indications suggested included;

- quality of life issues, including the number of injections daily required to achieve control, frequent sick days, marked glycaemic swings or dawn phenomenon, impaired exercise capacity, and difficulties with shift work or travel across time zones
- additional issues for children and parents, including school performance, inability to fully integrate into school life, behavioural issues eg meal times
- pregnancy including pre-conception control
- hypoglycaemic unawareness
- use in people with T2DM
- extreme insulin sensitivity

Some of these issues were raised in the patient perspectives chapter of the last assessment report.

1.14 Questions for this review

1.14.1 T1DM in adults and adolescents

The first question will be whether evidence has emerged since the last review on the use of CSII in people with T1DM. One issue will be the impact of glargine and detemir. Will hypoglycaemia be less of a problem than in the past, and if so will the need for CSII be reduced? The assessment report for the NICE appraisal of long-acting insulin analogues noted that most trials in T1DM showed no difference in HbA_{1c} but that there were fewer hypoglycaemic episodes with glargine. Hence, a key question for this assessment is how CSII compares with "best MDI" with long-acting and short-acting analogues, in T1DM. In the clinical effectiveness analysis, we will therefore consider separately any trials of analogue-based MDI versus CSII.

New trials of CSII against NPH–based insulin regimens will be briefly reported for completeness, but we note the findings of the last review that CSII is better than NPH-based MDI, and selected meta-analyses are reproduced in appendix 2.

An issue raised in the last assessment, and mentioned above, was whether the RCTs might under-estimate the gains in routine care. We will therefore examine the results in a number of observational studies. These are more susceptible to bias, but if the effect size is different from that seen in RCTs, that can be used in a sensitivity analysis in the economic assessment.

1.14.2 T2DM

The current guidance states that CSII is not indicated in T2DM, and there is very little use of it. The Insulin Pump Clinical Database data reported [redacted] The key question is therefore whether new evidence has emerged that supports the use of CSII in T2DM.

1.14.3 Children

Little could be said in the last appraisal on CSII in children because of a lack of evidence. However, a preliminary review of the literature shows that there are now trials of CSII in younger children.

1.14.4 Pregnancy

At the time of the last assessment report, there were a few trials of CSII versus MDI in pregnancy, which found little difference in results. Some trials found HbA_{1c} to be lower with CSII, by 0.2 to 1.1% but the differences were not statistically significant. The question for this review is whether any new evidence has emerged.

Chapter 2 Systematic Review of Clinical Effectiveness

2.1 Research questions

There are five sections in this chapter:

CSII versus best MDI

For the reasons outlined in the previous chapter, the key question is whether CSII is more effective than best MDI. For T1DM, that means MDI with short and long acting analogue insulins. However for T2DM, there is as yet no evidence that analogue-based MDI is superior to NPH-based MDI, and so we include both as comparators.[95] The first part of this chapter (2.2) therefore examines the RCT evidence comparing those two forms of therapy.

CSII versus older MDI

Studies included in the previous assessment report are not re-visited, but Appendix 2 includes some of the meta-analysis summaries from the previous report. Some new studies comparing CSII with older forms of MDI have been published since the last review. These are of less relevance to our key question but are summarised in Table 6 in section 2.6 for completeness.

Pregnancy

A specific section on new studies of CSII in pregnancy is included (2.7).

Observational studies

The last review noted that some observational studies reported greater benefit than the RCTs, and we speculated that these might be a closer guide to results in routine care. We therefore include a section on recent observational studies (2.8).

Other evidence

This includes;

- two studies on the use of CSII at night only
- some data from pump users on use of basal insulins
- an unpublished meta-analysis by Pickup and Sutton (academic in confidence)
- unpublished data on pump use and results from the Insulin Pump Clinical Database (also academic in confidence)

- data on quality of life aspects of pump use, from Barnard and colleagues (2007)
- notes on other relevant studies and reviews published since the last appraisal by NICE.[71]

2.2 CSII versus best MDI

The review adopted the methodological approach published by the NHS Centre for Reviews and Dissemination (York) Report No.4.[104]

Inclusion criteria

Intervention	CSII
Comparator	Best MDI – short and long-acting analogues for T1DM, and short and long acting analogues or NPH for T2DM
Population	T1DM and T2DM any age
Study design	RCT
Outcomes	Glycaemic control - HbA_{1c} (%) Blood glucose levels Quality of life Hypoglycaemia Insulin dose Weight/BMI

2.2.1 Search strategy

Sensitive searches of electronic databases were done in order to retrieve a wide range of different types of evidence and study designs. All bibliographic records retrieved were then manually screened for studies of interest. These included systematic reviews, randomised controlled trials, non-randomised trials, observational studies, and studies on economics, costs, quality of life and patient satisfaction.

The following sources were used to identify both published studies and meeting abstracts:

MEDLINE, 2002-June 2007; Embase, 2002-June 2007; Science Citation Index, 2002-June 2007 (limited to meeting abstracts only); Cochrane Library 2007 Issue 1; Contact with experts Reference lists; Industry submission; Web site of ADA (American Diabetes Association) for recent meeting abstracts from the 67th Scientific Session June 22-26 2007 Chicago ILL. Searches were limited to English language only.

Ongoing and recently completed studies were searched for using National Research Register 2007 Issue 2 and Current Controlled Trials June 2007.

Details of the search strategies used and a flowchart of studies identified for the clinical effectiveness sections are given in Appendix 3.

2.2.2 Identification of studies

Abstracts returned by the search strategy were examined independently by two researchers and screened for inclusion and exclusion. Full texts of the identified studies were obtained. Four researchers examined these independently.

2.2.3 Data extraction strategy

Two reviewers extracted data regarding study design and characteristics, details of the intervention and patient characteristics and outcomes into a specially designed form. Differences in data extraction were resolved by discussion, referring back to the original papers.

2.2.4 Quality assessment strategy

To assess the quality of the randomised controlled trials, the following criteria were used: (1) Method and description of randomisation; (2) Description of attrition/losses to follow up; (3) Specification of eligibility criteria; (4) Power calculation; (5) Robustness of outcome measurements; (6) Similarity of group participants at baseline; (7) Data analysis. Blinding was not used as a quality criterion in this report, as it is not possible to blind patients to the wearing of an insulin pump.

Overall study quality was rated as follows: A (all quality criteria met), B (one or more of the quality criteria only partially met), or C (one or more criteria not met).

2.3 CSII versus best MDI – quantity of research available

Four RCTs comparing CSII with analogue MDI were found in people with T1DM (two full publications Doyle 2004[105] and Thomas 2007[106] and two abstracts, Maran 2005[107], Bolli 2004[108]) .

Four RCTs in T2DM (full publications Berthe 2007,[109] Herman 2005,[110] Raskin 2003[111] and Wainstein 2005[112]) compared CSII with MDI, one using glargine based MDI and the others using NPH. This is a useful advance from the previous appraisal, when there were no trials of adequate duration in T2DM.

The eight trials (identified by first author and year) were as follow.

2.3.1. Type 1 diabetes

Doyle (2004)[105] recruited children and adolescents with T1DM, age range eight to 21 years. None had been on glargine or CSII before, and most were on conventional twice-daily insulins. Baseline HbA1c ranged from 6.5% to 11%.

Thomas (2007),[106] a pilot study, was a three-arm trial in adults with altered hypoglycaemia awareness and debilitating severe hypoglycaemia. One arm was analogue MDI, another was CSII, and the third (not further mentioned in this report) was of education and relaxation of glycaemic targets. None had been on analogues before, 15 (71%) were using human insulin MDI; five (29%) twice-daily biphasic insulin mixtures. Baseline HbA_{1c} was 8.6%.

Maran (2005)[107] was a small trial in 10 adults with T1DM who had been on CSII therapy for at least six months. Details are sparse but the aim was presumably to find out whether the advent of glargine based MDI means that patients on CSII could return to MDI. Mean baseline HbA_{1c} was 7.7%.

Bolli (2004)[108] recruited patients (ages not given) with T1DM naive to CSII and glargine in Italy, UK and France. Mean baseline HbA_{1c} was 7.7%. Details of treatment at recruitment are not given.

2.3.2. Type 2 diabetes

Herman (2005)[110] recruited people over 60 years in the USA. Mean baseline HbA_{1c} was 8.25%. They were on at least one injection of insulin a day, with or without oral agents.

Wainstein (2005)[112] recruited obese people (BMI 30-45 kg/m^2) with T2DM age range 30 to 70 years, who had not been well–controlled on two or more injections per day plus metformin. All had HbA_{1c} over 8.5%. Insulin dosage before the trial was over 1 unit/kg/day.

Raskin (2003)[111] recruited adults over 35 years (mean age 56) with T2DM, on at least one injection of insulin a day, with or without an oral agent. Mean baseline HbA_{1c} was 8.1%.

Berthe (2007)[109] recruited people aged 40 to 65 years with a BMI between 26 and 42 kg/m^2 and an HbA_{1c} level of $\geq$ 6.5% on two determinations to a randomised cross-over trial. The mean HbA_{1c} was 9.0%.

Raskin (2003) was funded by Novo Nordisk (who do not manufacture pumps). Thomas (2007) was supported by Sanofi-Aventis and Medtronic. Herman (2005) was funded by the ADA. Doyle (2004) was funded by NIH (National Institute of Health) and Juvenile Diabetes Research Foundation (JDRF)

with additional support from Medtronic. Berthe (2007) was supported by Ely Lilly France. No details were given of funding for the Bolli (2004), Maran (2005), or Wainstein (2005) trials. Table 4 gives further details of these trials.

Table 4: Summary of trials of CSII versus best MDI

Study ID	Study design	Sample size	Intervention	Comparator	Concurrent treatment	Setting	Length of treatment	Any differences in educational input
Type 1 diabetes								
Doyle 2004 [105]	RCT parallel (full publication)	32	CSII (aspart)	MDI (lispro and glargine)	None	Single centre US	16 weeks	CSII patients = 90 min pump training session and a 45 min follow-up 2 days later Glargine patients = 45 min training session for use of insulin pens for premeal aspart insulin. All other training and education equivalent
Thomas 2007[106]	RCT parallel	21 (14 for MDI vs CSII)	CSII (lispro)	MDI (lispro and glargine)	None	UK	24 weeks	Equivalent education and support to all was ensured throughout with a single additional training session for those randomized to CSII, confined to technical aspects of pump management.
Maran 2005 [107]	RCT crossover (abstract)	10	CSII (lispro)	MDI (lispro and glargine)	Not stated	Not stated Italy	4 months	None reported
Bolli 2004 [108]	RCT parallel (abstract)	57	CSII (lispro)	MDI (lispro and glargine)	Not stated	Multicentre Italy, UK, France	6 months	None reported
Type 2 diabetes								
Herman 2005[110]	RCT parallel (full publication)	107	CSII (previous insulin)	MDI (lispro and glargine)	None	Multicentre (2) US	12 months	None reported
Wainstein 2005 [112]	RCT crossover (full publication) analysed as parallel	40	CSII lispro	MDI (regular insulin or Humulin R and NPH or Humulin N)	Diet and metformin	Multicentre (7) Israel	18 weeks (first treatment period of a 48 week total duration)	None reported

Raskin 2003 [111]	RCT parallel (full publication)	132	CSII aspart	MDI (aspart and NPH)	None	Multicentre (14) US	24 weeks	None reported
Berthe 2007 [109]	RCT cross-over (full publication)	17	CSII lispro	MDI (lispro and NPH)	None	Multicentre (2) France	24 weeks (12 weeks on each treatment)	Patients were hospitalized for 24 to 48 hours at the beginning MDI period for 5 days and at the beginning of the CSII period, in order to receive individual education sessions including pump training sessions.

The issue about differences in educational input, usually not reported in these trials, is because the amount of education is potentially a confounding factor – if the CSII group gets more education, any difference observed may be due to that rather than the CSII. The Berthe trial design gives some concern.

2.4 Quality of included trials

2.4.1 Internal validity

2.4.1.1. Sample size

Details of study power were lacking in three of the four RCTs (one full publication and two abstracts) conducted in subjects with T1DM. Thomas and colleagues (2007) stated that as they were doing a pilot study no power calculations were performed. Studies in T1DM ranged in size from 10 participants (Maran 2005) to 57 participants (Bolli 2004). Of the studies conducted in subjects with T2DM, two (Wainstein 2005 and Raskin 2003) were appropriately powered for the primary outcome (change in HbA_{1c} %) under consideration. Power calculations were undertaken prior to recruitment in Herman (2005) but recruitment was terminated early due to the small effect size. Berthe and colleagues (2007) did not mention whether a power calculation was performed. Studies in T2DM ranged in size from 17 in Berthe 2007, to 107 in Herman (2005).

2.4.1.2. Randomisation

Doyle (2004) was the only study in T1DM that provided details of randomisation. It used a random number table in blocks of four and stratified patients according to sex and age. Block randomisation was also used in Herman (2005), whereas Raskin (2003) "randomised subjects to the lowest randomisation number with each centre to provide a treatment assignment for each centre that was as balanced as possible"; however, no criterion were used to stratify the 132 participants. Wainstein (2005) and Berthe (2007) provided no details of randomisation.

2.4.1.3. Similarity of groups at baseline

With the exception of the two studies presented in abstract form, (which did not provide details of baseline characteristics of participants), the CSII and MDI groups mostly appear well matched at baseline. Herman (2005) noted that there were more men in their CSII group and Berthe (2007) (a cross-over study) noted that the Group 2 patients (MDI then pump) were older by a mean of 7.8 years.

2.4.1.4. Protocol violations and other problems

Protocol violations were either not described in detail (Thomas 2005, Maran 2005 and Bolli 2004) or were small in number i.e. <5 (Doyle 2004, Wainstein 2005) and therefore unlikely to affect results. In contrast to the other studies, Herman (2005) described numerous technical and mechanical delivery problems in the delivery of both CSII and MDI interventions; these may have affected the results. Berthe (2007) admitted patients for 24 to 48 hours at the start of MDI and for five days at the start of CSII, for training, which introduces a bias in favour of CSII.

2.4.1.5. Attrition bias and intention to treat analysis

Three studies (Doyle 2004, Herman 2005 and Wainstein 2005) conducted ITT analysis and there were no obvious differences in drop-out rates or reasons for withdrawal between CSII and MDI groups. Thomas (2007) had no drop-outs. No details of analysis were reported in the two abstracts, (Maran 2005 and Bolli 2004) and Raskin (2003) only conducted analysis based on 127/132 (96%) of subjects who received treatment.

2.4.1.6. Detection bias

For practical reasons, none of the trials were blinded. HbA_{1c} is an objectively measured outcome but outcomes such as patient satisfaction may be more susceptible to bias.

2.4.2 External validity

HbA_{1c} was used as the primary outcome and a measurement of glycaemic control. Historically, HbA_{1c} has been used as a measure of glucose control. However, a key limitation of HbA_{1c} measurement is that it does not provide information regarding daily glucose variability. Daily glucose excursions are thought to affect the risk of complications in people with diabetes. All the RCTs reported HbA_{1c} levels; additional measurements of mean daily blood glucose, mean amplitude of glucose excursions and 8-point blood glucose profiles were also reported in some studies.

Most of the trials were done in countries other than the UK.

See Appendix 4 for full details of study quality assessment of the trials

2.5 Results

The following outcomes reported in the RCTs are summarised in this section:

1. Mean HbA_{1c} (%)
2. Blood glucose levels
3. Quality of life
4. Hypoglycaemia
5. Insulin dose
6. Weight

Details of all the trials are given in appendix 4. See Table 43 for details of the participant characteristics at baseline.

2.5.1 Mean HbA_{1c}

2.5.1.1. Type 1 diabetes

All four trials in people with T1DM compared HbA_{1c} (%) at baseline compared with end of study. Conflicting results were reported. Doyle and colleagues (2004), in the child and adolescent study, found that subjects on CSII for 16 weeks had a significantly greater reduction in HbA_{1c} than subjects on MDI (1% versus no change: $p<0.05$ between groups). In contrast, the other three studies (Maran 2005; Bolli 2004; Thomas 2007) reported no significant difference between groups. Doyle (2004) also that a greater percentage of subjects on CSII (50%) achieved the goal of having HbA_{1c} <7% by 16 weeks compared with 13% in the MDI group ($p<0.05$ between groups).

2.5.1.2. Type 2 diabetes

Four trials in people with T2DM measured HbA_{1c} levels as the primary outcome of interest. Three were parallel trials, and Berthe (2007) was a cross-over trial. All trials compared HbA_{1c} at baseline compared with end of study. Herman and colleagues (2005) did not compare differences between CSII and MDI but did report that HbA_{1c} was significantly reduced from baseline to end of study in both groups ($p<0.0001$). Berthe (2007) reported that HbA_{1c} decreased significantly more in patients at the end of the CSII period compared to end of MDI period. The other two studies (Wainstein 2005, Raskin 2003) reported no significant difference between groups; although both CSII and MDI reduced HbA_{1c} significantly between baseline and end of study ($p<0.05$).

Table 5: Glycated haemoglobin results

Study	HbA_{1c} (%) baseline	HbA_{1c} (%) End	Change from baseline (%)	P value from baseline	Difference between groups at end (MDI-CSII)	P value between groups
Type 1 diabetes						
Doyle 2004 [105]	CSII 8.2 ± 1.1 MDI 8.1 ± 1.2	CSII 7.2 ± 1.0 MDI 8.1 ± 1.2	CSII – 1.0 MDI no change	CSII p<0.02 MDI p = NS	0.9%	P<0.05
Thomas 2007 [106]	CSII 8.5 ± 1.9 MDI 8.6 ± 1	CSII 7.4 ± 1 MDI 7.6 ± 0.8	CSII – 1.1 MDI – 1.0	CSII p = 0.06 MDI = 0.04	0.2%	Not stated
Maran 2005 [107]	All 7.7 ± 0.7	CSII 7.2 ± 0.2 MDI 7.2 ± 0.2	Not clear	Not stated	No change	P =NS
Bolli 2004 [108]	CSII 7.7 ± 0.7 MDI 7.8 ± 0.6	CSII 7.0 ± 0.8 MDI 7.2 ± 0.7	CSII – 0.7 MDI – 0.6	Not stated	-0.1% (95% -0.5 to 0.3)	P = NS
Type 2 diabetes						
Berthe 2007 [109]	CSII 9.0 ± 1.6 MDI 9.0 ± 1.6	CSII 7.7 ± 0.8 MDI 8.6 ± 1.6	CSII –1.3 MDI – 0.4	Not stated	0.9%	P<0.03
Herman 2005 [110]	CSII 8.4 ± 1.1 MDI 8.1 ± 1.2	CSII 6.6 ± 0.8 MDI 6.4 ± 0.8	CSII – 1.7 ± 1.0 MDI – 1.6 ± 1.2	CSII p<0.0001 MDI p<0.0001	0.1%	Not stated
Wainstein 2005 [112]	CSII 10.2 ± 1.4 MDI 10.3 ± 1.2	CSII 7.9 ± 1.0 MDI 8.4 ± 1.3	CSII – 2.3 MDI – 1.9	CSII p= 0.01 MDI P = 0.01	0.5%	P = NS
Raskin 2003 [111]	CSII 8.2 ± 1.4 MDI 8.0 ± 1.1	CSII 7.6 ± 1.22 MDI 7.5 ± 1.17	CSII – 0.62 ± 1.11 MDI -0.46 ± 0.89	CSII p<0.05 MDI p<0.05	0.1%	P = NS

Therefore only two trials showed a statistically significant lower HbA_{1c} with CSII; Doyle 2004 in T1DM and Berthe 2007 in T2DM. Only two trials reported the proportions reaching targets. Doyle and colleagues noted that only three subjects met the American Diabetes Association target of HbA1c <7% at baseline; by 16 weeks, 8 of the 16 in the CSII group and 2 of the 16 in the MDI group had met the target.

2.5.2 Mean blood glucose levels

Mean daily blood glucose level was measured in all four RCTs in T1DM. Bolli (2004) reported no significant difference between groups in daily blood glucose levels. Doyle (2004) reported that fasting levels were the same on CSII and MDI but that meal-time levels were lower on CSII. Maran (2005) reported lower mean glucose levels in CSII (147mg/dl) compared with MDI (189mg/dl)($p<0.03$).

Thomas and colleagues (2007) reported median glucose levels and the results of CGMS for MDI and CSII groups at six months. Daytime median glucoses were similar at 7.6 and 7.8 mmol/l. Night-time median glucose was higher with CSII at 8.4mmol/l, but mainly because the MDI group spent on average 15% of time with hypoglycaemia (under 2.5 mmol/l) whereas the CSII group had very little hypoglycaemia, with 0.6% of glucose readings under 2.5 mmol/l. Neither group showed a significant change over the 24 weeks.

2.5.3 Glucose variability

Two studies (Bolli 2004 and Maran 2005) reported measures of glucose variability. Bolli 2004 reported no significant difference between groups in mean amplitude of glycaemic excursions (MAGE) at baseline and six months (CSII baseline 8 ± 2.4 to 6 months 6.4 ± 2.2 vs MDI baseline 7.6 ± 1.7 to 6 months 6.4 ± 2.1). Eight-point blood glucose profiles (coefficient of variation) measurements also revealed no significant differences between treatments at baseline and endpoint.

Maran (2005) reported glucose variability as area under the curve (AUC) >10mmol/l, time spent at glucose level >3.6 mmol/l and <10mmol/l, and time spent during night-time hours in glucose range >3.6 mmol/l and <10mmol/l. There was significantly less hyperglycaemia during CSII treatment compared with MDI (AUC >10mmol/l CSII end of study 9603 ± 3941 min vs. MDI 26445 ± 9390 min; $p<0.02$ between groups). By the end of the study, significantly more time was spent in the glucose range >3.6 mmol/l and <10mmol/l in the CSII group compared with MDI (CSII 1582 ± 212 minutes vs. MDI 769 ± 158 minutes; $p<0.02$ between groups). Similar results were reported for night-time glucose (CSII 298 ± 63 minutes vs. MDI 194 ± 51 minutes; $p<0.02$). These results do not quite fit with the lack of difference in HbA_{1c}, unless the MDI group had much wider variation around the mean.

Berthe (2007) used continuous blood glucose monitoring devices, and produced glucose profiles against a target on keeping glucose in the range 3.3 to 10mmol/l. The target was achieved for 44% of the time on conventional insulin therapy, for 54% on MDI and for 77% on CSII ($p= 0.0095$ for CSII vs MDI).

2.5.4 Quality of life

Two studies (Doyle 2004 and Thomas 2007) in people with T1DM reported quality of life outcomes. Neither study showed a significant difference in quality of life between CSII and MDI (measured using DQOL). In people with T2DM, Herman (2005) reported no significant difference in quality of life as measured by SF-36 and DQOLCTQ. However, Raskin (2003) reported a significant improvement in treatment satisfaction in CSII group compared with MDI ($p<0.001$).

See Table 44 in Appendix 4 for more details of quality of life and patient satisfaction outcomes in the trials.

2.5.5 Hypoglycaemia

All eight RCTs reported the occurrence of hypoglycaemia. Only two RCTs in people with T1DM (Doyle 2004 and Maran 2005) conducted a statistical analysis on the occurrence of hypoglycaemic episodes. Doyle 2004 reported that significantly fewer subjects with T1DM on CSII had severe hypoglycaemia episodes by end of study compared with MDI (CSII 2 episodes vs. MDI 5 episodes in four patients; $p<0.05$ between groups). In contrast, Maran (2005) (the smallest trial) reported no significant difference in hypoglycaemic reaction exposure between groups.

Bolli (2004) commented that severe hypoglycaemic episodes were too infrequent to allow meaningful comparison. The frequency of confirmed hypoglycaemic events/patients where blood glucose fell below 4mmol/l was similar in both groups at six months (CSII 41 events in 28 people vs. MDI 35 events in 29 people). There were only two severe hypoglycaemic events so no comparison of that was possible.

Thomas and colleagues (2007), with 21 patients followed for 24 weeks, reported that non-significant trends towards reduced incidence of severe and mild symptomatic hypoglycaemia were seen in the MDI and CSII groups in comparison with the third arm, the Education Group, but no difference between MDI and CSII. This may have been due to the very small numbers involved.

None of the four RCTs in people with T2DM reported a significant difference in hypoglycaemic episodes.

See Table 45 in Appendix 4 for more details of adverse events in each of the trials

2.5.6 Insulin dose

Doyle (2004) reported an insignificant difference – 0.6 unit/kg /day on CSII and 0.7 u/kg/day on MDI. Thomas (2007) reported the daily insulin dose at zero and 24 weeks. There was a non-significant

increase in the MDI group and a significant (P=0.01) decrease in the CSII group. Both groups started on 0.7 units/kg/day. The MDI group ended at 24 weeks on 0.8 unit/kg and the CSII on 0.4 units/kg. They did not test the statistical significance between MDI and CSII. The other two T1DM studies, both abstracts only, gave no results. In T2DM, no differences were found. Wainstein and colleagues (2005) noted a drop in the CSII group in the first period but it did not persist.

2.5.7 Weight

The only T1DM study that reported changes in weight was Thomas (2007), where both CSII and MDI showed a non-significant change. All the T2DM studies reported that there were no significant differences in weight changes between CSII and MDI.

2.5.8 Summary

Type 1

In the last Guidance, NICE commented on the need for trials of CSII against analogue-based MDI in T1DM. Unfortunately, few trials have been done, most are very small, and only two have been published in full, one of which was only a pilot.

One trial (Doyle 2004) reports that HbA_{1c} is significantly lower on CSII than on analogue-based MDI in children and adolescents. The other studies in adults report no differences in HbA1c.

In T2DM, there was little evidence that CSII was better than analogue based MDI . In one study, a clinically significant difference in HbA_{1c} was reported but it failed to reach statistical significance. The Berthe 2007 trial showed that CSII was better than NPH-based MDI.

2.6 New studies of CSII against NPH-based MDI in T1DM

The last assessment report [48] included a meta-analysis (reproduced in appendix 2) which showed that CSII gave a mean HbA_{1c} of about 0.6% lower than MDI, in T1DM. Most of the studies used regular soluble insulin in the pumps, and a switch to a short-acting analogue would give a further reduction of about 0.26%. Most of the basal insulin in those trials was NPH.

Table 6 below gives brief details of trials of CSII against NPH-based MDI in T1DM published since the last review. Some of the studies are small. Some show no differences, or differences that are not statistically significant. Those which do show significant differences favour CSII, and are thus in line with the last assessment report.

Table 6: New trials of CSII versus NPH-based MDI

Randomised trials			
Pump versus MDI with NPH in T1 diabetes			
FIRST AUTHOR, YEAR, TYPE OF STUDY	STUDY POPULATION, DURATION OF STUDY, TYPE OF INSULIN	RESULTS	SUMMARY
Cohen 2003 [113] Randomized crossover trial	N = 16 adolescents aged 14 to 18 years with T1DM of at least 2 years Duration: 6 months for each treatment Pump: Lispro MDI: NPH and regular insulin	HbA_{1c} (change from baseline): NS Pump:-0.43% MDI: +0.09% **Severe hypoglycaemia** (total number of events): NS Pump: 1 MDI: 4	HbA_{1c} 0.52% lower with CSII and fewer hypos, but neither statistically significant, probably due to small numbers
DeVries 2002 [114] Randomized, parallel-group trial	N = 79 adults aged 18 to 70 years with T1DM Duration: 16 weeks Pump: Aspart MDI: NPH and aspart	HbA_{1c} (change from baseline): Pump: -0.91 ±1.28% MDI: -0.07 ±0.70% Difference: 0.84% (-1.31 to -0.36) p=0.002 **Severe hypoglycaemia (**total number of events): NS Pump: 3 MDI: 6	HbAc1 0.84% lower on CSII. Difference in severe hypos NS
DiMeglio 2004 [115] Randomized, parallel-group trial	N = 42 children < 5 years with T1DM of at least 12 months Duration: 6 months Pump: Lispro MDI: Maintained pre-study insulin regimens (NPH=10, insulin IZS=2, glargine=1)	HbA_{1c} (change from baseline): NS Pump: -0.43% MDI: -0.09% **Severe hypoglycaemia** (total number of events): NS Pump: 1 Current therapy: 1	HbA_{1c} 0.34% lower with CSII
Fox 2005 [116] Randomized, parallel-group trial	N = 26 children aged 1 to 6 years with T1DM of at least 6 months Duration: 6 months Pump: NA MDI: NPH	HbA_{1c} (change from baseline): NS Pump: -0.19% Current therapy: -0.11% **Severe hypoglycaemia** (total number of events): NS Pump: 0 Current therapy: 1	No difference

Hoogma 2006 [117] Randomized controlled crossover trial	N = 272 adults aged 18 to 65 years with T1DM on MDI for at least 6 months Duration: 16 months Pump: Lispro MDI: NPH and lispro	HbA_{1c} (end of treatment): Baseline from graph CSII 7.66 MDI 7.61% Pump: 7.45% MDI: 7.67% p<0.001 CSII vs MDI **Severe hypoglycaemia** (events per patient year): p<0.001 CSII: 0.2 MDI: 0.5	Fewer hypos with CSII
Pozzilli 2003 [118] Randomized pilot study	N = 23 patients aged 12 to 35 years with T1DM, duration since beginning insulin therapy < 4 weeks Duration: 2 years Pump: Lispro MDI: NPH	HbA_{1c} (end of treatment): NS Pump: 6.3 ±0.5% ISIT: 6.2 ±0.5% **Hypoglycaemic episodes**: NS Data not given	No difference
Weintrob 2003 and 2004 [119,120] Randomized crossover trial	N = 23 patients aged 8 to 14 years treated with insulin for at least 2 years Duration: 3.5 months for each treatment Pump: Lispro MDI: NPH and regular insulin	HbA_{1c}**:** (change from baseline): NS Pump: 0.03 ±1.0 MDI: -0.23 ±1.0 Difference: 0.26% N/S **Severe hypoglycaemia** (number of episodes per patient per year): NS Pump: 0.13 (0.0 - 0.4) MDI: 0.39 (0.0 - 0.84)	No differences
Wilson 2005 [121]	N=19 patients aged <6 years with T1DM for at least 6 months Duration: 1 year Pump: 6 subjects (66%) used lispro MDI: At baseline, three (16%) subjects were using glargine, five (26%) were using ultralente, and 15 were using NPH at baseline (some subjects received both NPH and ultralente or glargine). Over the course of the study, the percentage of MDI subjects using glargine increased from 10% to 60% (P < 0.05).	HbA_{1c}: (change from baseline) Pump: -0.21 ± 0.67%, MDI: 0.04 ± 0.71 Difference: NS **Severe hypoglycaemia:** Pump: 1 episode MDI: 1 episode	No difference
NA: Data not available NS: Not significant.			

Summary

In terms of HbA_{1c}, three of the new studies show no difference between MDI and CSII; four show differences (0.52, 0.34, 0.25 and 0.26) which are not significant, and one shows a larger and statistically significant difference of 0.84%. The lack of statistical significance may sometimes be due to small numbers – the Cohen (2003) study reported what would be seen as a clinically useful difference (0.52%) but had only 16 patients.

2.7 Pregnancy and insulin pumps

Pregnancy results in an increased metabolic demand on the body, and presents a challenge to both diabetologists and pregnant women with diabetes in maintaining glucose control to prevent poor outcomes. Inadequate control, episodes of hypoglycaemic, and ketoacidosis, can all have detrimental effects both on the mother and developing fetus.

Diabetic pregnancies comprise three groups of women; those with T1DM or T2DM pre-pregnancy, and those with gestational diabetes, which refers to a temporary form of diabetes that comes on in pregnancy and goes away after birth. In some women, good control can be achieved with diet and exercise, but many require insulin to maintain adequate glycaemic control. Oral therapy with glibenclamide has also been used in recent years in the USA. Clinical guidelines recommend the optimal HbA_{1c} level for pregnant women with diabetes to be between 4 and 7 mmol/l.[122,123] (though in practice diabetes control in pregnancy is monitored by home testing of blood glucose because HbA1c changes too slowly for fine tuning of insulin dose).

Maintaining good glycaemic control is very important in pregnant women with diabetes as, compared with pregnant women in the general population, diabetic women have a higher rate of morbidity, miscarriage and stillbirth and their babies have a higher rate of congenital malformations.[124,125] A comprehensive picture of the outcomes associated with diabetic pregnancies is discussed in the 2007 Confidential Enquiry into Maternal and Child Health report.[126]

Diabetes in pregnancy requires regular maternal and fetal monitoring to ensure the best possible outcome for mother and child. Current care pathways for women with diabetes in pregnancy advocate that, ideally, all women with diabetes should be offered pre-pregnancy advice to achieve optimal control of diabetes (HbA_{1c} <7%) at least 3 months before conception. This reduces the congenital malformation rate. However, in practice many pregnancies are unplanned so achieving glycaemic control often becomes a post-conception goal.

The standard treatment of diabetes in pregnancy in the UK uses the MDI regimen to deliver insulin on a frequent, self-regulated basis. The increased requirement for close monitoring of glucose levels to prevent maternal and fetal compromise has resulted in some Trusts offering pregnant women with diabetes the option of using insulin pumps.

The assessment report for the first NICE appraisal on CSII noted four RCTs of CSII versus MDI in pregnancy.[48] These showed that HbA_{1c} was lower on CSII than MDI, but not statistically significantly so. Differences ranged from 0.2 to 1.1% lower. It concluded that there was then insufficient evidence that CSII is better than MDI in pregnancy. Since then, there seem to have been no further RCTs, but only a few observational studies, described here for completeness, though the usual caveats about observational studies should apply.

Two studies published in full (Lapolla 2003, Gimenez 2007) have retrospectively compared the outcomes of pregnancies of women with T1DM treated with either MDI or CSII using matched control study design.

Lapolla and colleagues (2003)[127] reported no significant difference in HbA_{1c} control between CSII (n=25) and MDI (n=68) both before and during pregnancy, although both groups progressively reduced their HbA_{1c} levels from first to third trimester (HbA_{1c} CSII trimester 1 7.4 ± 2.0 trimester 3 6.4 ± 1.2; $p<0.05$ MDI trimester 1 7.1 ± 1.3 trimester 3 6.3 ± 1.0; $p<0.05$). No significant differences were reported between groups in rate of maternal (eg hypertension, preeclampsia) or fetal complications (eg congenital malformations). The authors noted that, compared with those who received MDI, the CSII group had diabetes for a significantly longer duration (CSII 16.0 ± 7.9 years vs. MDI 11.6 ± 8.8; $p <0.04$ between groups), a significantly greater percentage had a planned pregnancy (CSII 52% vs MDI 25%; $p<0.026$ between groups), and significantly more women in the CSII group were White's class D ($p<0.02$ between groups) and significantly less were White's class B ($p<0.059$ between groups). The authors thus concluded that CSII "may be used both before and during pregnancy in more complicated patients in whom conventional intensive insulin treatment fails to achieve good metabolic control".

Similar results were reported by Gimenez and colleagues (2007) [128] in 58 women with T1DM who received either CSII or MDI. No significant differences in glycaemic control, maternal or fetal outcomes were reported between groups.

Four additional studies (one cohort study, two case series and a matched control study) published in abstract format compared the efficacy of insulin pumps in pregnant women with T1DM.[129-132]

Chen and colleagues (2006) compared 30 pregnant women with T1DM treated with CSII with 60 matched controls treated with MDI.[129] No between group differences were reported in maternal age, nulliparity rate, severity of diabetes, pre-pregnancy BMI and weight gain during pregnancy; however, the rate of DKA (CSII 13% vs MDI 2%; p = 0.04) and neonatal hypoglycaemia (CSII 35% vs 13%; p =0.01) were significantly higher in the CSII group. There were no other reported differences in pregnancy outcome between groups.

Cheng and colleagues (2006) evaluated a cohort of 688 women with T1DM and compared those managed with CSII (n=60) and MDI (n=628).[130] The CSII groups had significantly lower mean HbA_{1c} levels compared with MDI group (CSII 6.7% vs. 7.7%, p<0.001 between groups) and were significantly more likely to have an HbA_{1c} <6% (CSII 25% vs. 12.6%, adjusted OR 3.37 95% CI 1.08-10.5), although it is unclear at what period of the pregnancy the measurements were taken. The small number of women on CSII suggests that selection biases were be operating and the results should be discounted.

Kinsley and colleagues evaluated 43 pregnant women with T1DM treated with CSII (n=7), soluble insulin (n=18) or analogue (n=18). [131] Firm conclusions regarding glucose control could not be drawn from this study as HbA_{1c} in the CSII group was lower at baseline than in the other groups; however, the percentage of mean blood glucose readings <2.0mmol/l was higher in CSII compared with the other treatment groups at 14, 26 and 36 weeks (no statistical analysis provided). Total insulin dose was significantly lower in the CSII group compared with other treatments at 14 weeks and 26 weeks (p<0.05 between groups). No significant differences in maternal weight or birth weight were reported.

Jimenez and colleagues (2005) reported a case series of 36 pregnant women with T1DM on CSII over a six year period.[132] Compared with 169 women treated with MDI who had slightly lower baseline mean BMI there were no significant differences in glycaemic control, maternal outcomes or perinatal outcomes.

In summary, most studies conclude that CSII achieves similar glycaemic control to MDI regimens in pregnant women with T1DM. Maternal and fetal outcomes are similar between treatments. One study reported more DKA with CSII and another more hypoglycaemia. Since CSII gives no added benefit over MDI, but is more costly, this implies that it will not be cost-effective in diabetic pregnancies.

2.8 Observational studies reporting data before and after the initiation of CSII

2.8.1 Caveats

For assessing efficacy, RCTs are the gold standard. Observational studies usually provide poorer quality evidence than randomised controlled trials because there is a much greater risk of bias. For example, good results may be obtained because the recruits adhere better to therapy than most patients. Publication bias may be more of a problem, so that negative observational studies may be less likely to be published than positive ones. For that reason, observational studies are usually excluded from technology assessment reports and Cochrane reviews. However, in the last TAR on CSII, we noted that the reduction in hypoglycaemia was greater in some observational studies than in the RCTs.[48] We speculated that this might be because trials were unselective in their recruitment, whereas observational studies might selectively recruit people having particular problems. If so, it is possible that the observational studies will be a better guide to results in routine care. They may also be of longer duration and hence provide useful data on discontinuation rates and side-effects. It is also possible that patients will not become fully expert in pump use in short duration trials, in which case long-term follow-up might show better results. Some of the studies may give useful data on the training requirements for people starting CSII.

In this section, we give results from a group of observational studies. Some were comparisons of MDI and CSII, in matched groups or un-matched groups. Because of possible biases, and because we have evidence from RCTs, we have not used the comparative data, but have used only the CSII arms as case series. Nor have we attempted to be comprehensive.

2.8.2 Study characteristics

There were 48 observational studies; details are given in Tables 7, 8 and 9, for the different age groups. Twenty studies included adults (either adults only or mixed ages), 23 studies included children/adolescents and five studies included young children (aged ≤7 years).

Studies were conducted in a variety of countries most commonly in the USA (n=20) and Europe. Three studies were conducted in the UK.[133-135] Other studies were set in Australia, New Zealand, Canada and Israel.

The observational studies incorporated a variety of study designs – surveys, audits, before and after studies with and without control group (matched and unmatched), prospective and retrospective data, primary data, patient records and national registers.

Sample size ranged from eight to 2702. The majority of studies had a sample size of <50. In the adult/mixed age groups, the duration of follow-up ranged from 11.5 months to 13 years, the majority being one to two years. In the children/adolescent groups, follow-up ranged from six months to five years, majority of studies one to two years. Among younger children, four studies had a follow-up of one year and one study of a mean 30 months.

2.8.3 Reasons for starting CSII

Reasons for starting CSII were not reported in 13 studies. All but a few studies included poor metabolic control (including frequent hypoglycaemic episodes and the dawn phenomenon) as a reason for starting CSII.

Among adults and mixed age groups, planning for pregnancy or during pregnancy [135-138]and the desire for a more flexible lifestyle [135,136,139-141] were commonly cited reasons. Patient preference was included as a reason in four studies.[136,142] Other less commonly cited reasons included: quality of life,[136] low insulin requirements, hypoglycaemia unawareness,[139] diabetic complications,[143] participation in study,[137] allergy to insulin,[138] gastroparesis,[135] and lipodystrophy.[135]

Among children and adolescents, commonly cited reasons were: request of patient or parents [144-151] and the desire for a more flexible lifestyle.[144,152-154] Less common reasons reported included hypoglycaemia unawareness,[152] quality of life,[152] early onset of diabetic complications,[155] too much work with multiple injections,[145] and problems with injections.[145,153,155]

2.8.4 Selection of patients for CSII

Many of the studies gave details of how patients were selected for CSII. Among adult and mixed age studies, patients were selected if already on MDI,[133,134,141,156,157] and showed willingness and ability to master intensive management features of CSII.[98,158] In Pickup (2005), patients who showed poor compliance or psychological problems were considered unsuitable for pump therapy.[133]

Among studies including only adolescents and children, patients and families needed to demonstrate the desire and ability for intensive management.[144,147,149,152,153,155,159] Two studies reported that patients were already on MDI (Sulli 2003,[155] Berhe 2006[160]) and two studies reported requiring prior documentation of adequate blood glucose testing.[154,161] Other inclusion criteria included good parental supervision (Garcia-Garcia 2007[162], Litton 2002[159]), minimum duration of diabetes,[162,163] daily insulin

requirement more than 0.75 U/kg.[162] One study reported that patients were excluded if in the honeymoon phase.[160]

2.8.5 Education and support for CSII

Seventeen studies did not report details of education and support A few studies reported identical educational and support programmes for both CSII and MDI groups (Cersosimo 2002,[164] Pickup 2005,[133] Garcia-Garcia 2007,[162 163])

Several studies described intensive training/education of participants and their families.[98,135,139,141,142,147,149-157,159-161,165-169] Some training programmes included the use of a dummy saline pump.[149,152,153,166]. Initiation of pump therapy involved a period of admission to clinic or hospital in a few studies.[147,153,166]

Intensive ongoing support was often provided, including initial frequent visits and telephone contact,[147,151,153,156,160,161,167] and 24 hour nurse on call or telephone support.[135,159,161,169]

Table 7: Observational studies on CSII - Adults/mixed age groups

First Author Year Country Study type	Age group Sample size	Reasons for starting on pump	Duration of follow-up	Notes – including selection criteria and training (where reported)
Bruttomesso 2006 [136] Italy Survey	Mean age 39 years (range 4 to 85). n=2702	Main reason: poor metabolic control under intensified insulin treatment. Other reasons included desire for pregnancy, wish for more flexible lifestyle, correction of dawn phenomenon, reduction in hypo emergencies and improve quality of life; in very few cases CSII was started at patient's request or for the presence of low insulin requirements (no % given).	Mean 3.9 years for adults and 2.4 years for children	Survey of 145 clinics
Cersosimo 2002 [164] [Abstract] USA Before and after study comparing CSII and MDI	Mean age 37 years n=35	NR	2 years	Multidisciplinary comprehensive education programme patients were offered to intensify glycemic control using either pump or multiple injections.
D'Annunzio 2005 [139] [Abstract] Italy Before and after study	Aged 15 to 29 years n=15	Suggested to highly motivated patients with brittle disease (n=8), hypoglycaemic unawareness (n=1), pregnancy (n=4) or need for more flexible lifestyle (n=2)	18 months	Training period about CSII management, both in normal conditions or during physical activity or intercurrent illnesses; a strict self-monitoring of diabetes was mandatory.
Fahlen 2005 [156] Sweden Before and after comparing CSII and glargine using retrospective data	Mean age 40.8 (SD 12) years n =563	Patients were generally selected for the therapies due to persistently high HbA_{1c} or unstable blood glucose values, despite prolonged efforts to improve glycaemia.	Median 25 months	Patients using multiple dose injections were included prior to starting on either CSII or glargine. The basic education in MDI was the same for both groups, however, the use of the pump is an additional educational tool. Initially, the visits of patients starting on CSII were more frequent, but there was no difference in the time interval between visits after 6 months.

Garg 2004 [170] USA Retrospective controlled comparison of pump vs glargine using electronic database parameters	Mean age 33 years n=216	NR	Mean 11.6 months	Training: NR
Hunger-Dathe 2003 [165] Germany Case series/audit	Mean 36 years (range 11 to 71) n=250	NR	Mean 1 year	Patients who participated in a structured treatment and teaching programme
Jankovec 2005 [143] [Abstract] Czech Republic Before and after using retrospective data from national register	Mean age 38 years All adults n=1051	Poor glycaemic control (69.5%), diabetic neuropathy (22.8%) and repeated hypo (21.2%)	Mean 4.71 years	Data from national register
Lepore 2004 [157] Italy Parallel group study	Mean age 38 years n=24	Poor metabolic control (HbA_{1c} >8% in previous year)	1 year	All patients had been treated with MDI (regular or lispro insulin before each meal plus NPH as basal insulin) for at least 1 year before the study. One arm of CCT. Patients received instructions on the use of insulin infusion pumps in an out-patient basis.
Linkeschova 2002 [140] Germany Before and after	Mean age 33 years (SD 11) (range 17-66) n=103	Optimization of metabolic control and improvement of flexibility of life style in 60 patients, and prevention of severe hypoglycaemia in 43 patients	Mean 1.8 (SD 1.2) years	Prior to CSII, all patients had been on conventional intensified insulin therapy with 2 injections of NPH insulin (in the morning and at bed-time) and preprandial injections of regular human insulin.

Nimri 2006 [142] Israel Before and after using patient file data	• prepubertal: (median age 5.4, range 1.6-8.6 years) n=23 • adolescent: (median age 13.7, range 9-17 years) n=127 • young adult (median age 22.8, range 17-40 years) n=129 Total n=279	Poor glycaemic control, recurrent hypoglycaemic episodes, and patient preference.	Mean 2.4 (SD 1.8) years. Range 1-6 years.	Only patients <40 years included in the study. Pump therapy preceded by a training program for the patients and their parents. Program consisted of 3 sessions. It covered principles and mechanics of pump therapy, insertion- site care, carbohydrate counting, and insulin bolus dosing.
Norgaard 2003 [137] Denmark Survey and data collection from patient records.	Mean age 48 years n=142	Data for 117 patients: participation in study (24%); poor control and complications of DM (22%); poor control but no DM complications (18%); motivated to CSII (11%); pre-pregnancy (10%); other / no data (15%).	Mean 13 years	Survey of endocrinology departments to determine the attitudes of chief consultants to CSII. Data collection from CSII records.
Pickup [133]2005 UK Before and after study	Mean age 39 years (SD 9.9) n=27	Disabling hypoglycaemia during intensive injection treatment. and whose glycaemic control was unaltered by a median 5 months' renewed MDI.	Median 17 months	After initial consultation, patients were entered into a pump assessment programme attempting to optimise glycaemic control with MDI. Those in whom glycaemic control did not improve on re-optimised multiple injections and were otherwise suitable for pump therapy were treated with CSII. Patients initially referred but considered unsuitable for pump therapy because of poor compliance, psychological problems or improvement on optimised injections (n=3) were not offered a trial of insulin pump therapy. Dietary instruction included carbohydrate counting and lifestyle advice, including advice diet, exercise and alcohol, and was essentially identical for the CSII and MDI phases of the study.

Pickup [134]2006 UK Before and after study	Mean age 41.6 years (SD 11) n=30	Failed to achieve good control on MDI.	16 months	All subjects were already receiving MDI. Renewed attempts to improve control on MDI were made for a median of 5 months. Programme included frequent contact with a diabetes specialist nurse and dietitian. After switching to CSII, patients were seen at a hospital clinic for review at 2, 6, 11 and 16 months after the start of pump therapy and between times maintained regular telephone contact with the specialist nurse.
Radermecker [138]2005 [Abstract] Belgium Retrospective analysis of patient medical files	Mean age 43 years All ages n=95	Poor glycaemic control with HbA_{1c} > 8% (n=50), ongoing or programmed pregnancies (n=28), recurrent hypos (n=16), allergy to insulin (n=1).	Mean 5.1 years; Range < 5 years to > 10 years	NR
Reda 2007 [141] New Zealand Retrospective audit	Mean age 33 years (range 6.5 to 66.2) n=105 followed-up out of 125 starting	All patients had two or more of the following reasons: optimisation of metabolic control (n=25); prevention of severe hypos (n=63); increase flexibility of lifestyle (n=70); recurrent DKA (n=9); poor overnight glycaemic control (n=66).	Mean 3 years	Prior to CSII, all patients had been on MDI therapy. Pump users given intensive instructions in carbohydrate assessment, provision of correction factors and support in insulin self-adjustment.
Rodrigues 2005 [135] UK Retrospective before and after study	Mean age 33 years (range 10 to 62) n=40	Recurrent severe hypos (n=14); own choice (n=15); recurrent DKA (n=5), erratic lifestyle (n=2), gastroparesis (n=1), pregnancy (n=1), poor control (n=1).	Median 20.5 months CSII (range 1 to 192 months)	Reviewed prior to starting CSII by liaison psychiatrist and on-going support was available. In addition to re-education in diabetes care provided during the institution of CSII, this group was not only encouraged to use the 24 hr advice line available to them, but was contacted by the team if expected communication did not happen.
Ronsin 2005 [171] France Retrospective review of medical files	Mean age 35 years (range 15 to 67) n=70	HbA_{1c} >8%: n=39 (56%); Recurrent hypos: n=12 (17%); planned pregnancy /during pregnancy: n= 12 (17%); planned implantation: n=3 (4%); lipodystrophy: n= 2 (3%); patient's decision: n=2 (3%)	Maximum of 2 years	At least 40% had diabetes related medical problems.

Rudolph 2002 [98] USA Retrospective review of medical records	Mean age 36 years (SD 10.4) n=107	NR	Mean 36.1 (SD 25.5 months). Median 26.2 months.	Review of medical records. Patients were included in the analysis if they had used an insulin pump before 31 December 1999 and had more than two follow-up visits for collection of clinical data. CSII is initiated only in patients who are willing and able to measure blood glucose levels a minimum of 4 times daily, who understand carbohydrate counting, and who comprehend how to alter insulin dose on the basis of food intake and anticipated exercise. Patients also required to attend a class on insulin pump therapy.
Siegel-Czarkowski 2004 [158] [Letter] USA Retrospective before and after by chart review	Older adults (aged > 50 years). n=34	NR	1 year	Patients were 'carefully selected '. Those unwilling or unable to master the technological and other features of CSII were not included.
Sucunza 2005 [172] [Abstract] Spain Before and after study	Adults (mean age 35 years (range 19 to 73). n=172	NR	2 years	Patients were consecutively started on CSII and visited individually to evaluate their pump management skills.

NR= not reported

Table 8: Observational studies on CSII - Children/adolescent age groups

First Author Year Country Study type	Age group Sample size	Reasons for starting on pump	Duration of follow-up	Notes – including selection criteria and training (where reported)
Alemzadeh 2004[144] USA Matched before and after study	Mean age 14.7 years (range 10.1 to 17.8) n=40	To achieve optimal glycaemic control, to reduce hypoglycemic events, and to provide a more flexible lifestyle by allowing variable mealtime insulin dosing.	1 year	Before initiation of CSII, patients underwent an extensive diabetes care skills and psychosocial screening to minimize non-adherence on insulin pump therapy.
Ahern 2002 [161] USA Before and after study	Mean age 10.3 years (range 1.5 to 18) Pre-school (1-6 yrs): n=26 School age (7-11 yrs): n=76 Adolescents (12-28 yrs): n=59 Total n=161	Offered CSII if motivated, measuring BG ≥4 times/day or if repeated hypos.	Mean 32 months (range 19-57)	Frequent telephone contacts over the 1st 2-3 days. Training in pump and DM, nurse on call 24 hr/day.
Conrad 2002 [152] USA Before and after study	Mean age 11 years Pre-pubertal n=23 Pubertal n=42 Total n =65	Patient preference, recurrent hypos, unawareness of hypos, erratic swings in BG, strong dawn phenomenon, aspects of quality if life including desire for increased flexibility with meals and activity.	6 months	Participants had to show adequate skills. All children wore an insulin pump infusion set before initiation of CSII and some also wore a "dummy pump", education and support
Garcia-Garcia 2007 [162] Spain Controlled trial	Mean age 11.6 years n=8	Interest in improving control, indication for a change in therapy, HbA_{1c} >7.5% (>8% in prepubertal children) or frequent episodes of hypoglycaemia.	2 years	T1DM diagnosed before age 14 yrs, at least 2 yrs duration and follow-up, daily insulin requirement more than 0.75 U/kg, previous intensive treatment with more than four glycaemic analyses a day, good parental supervision and good relationship with the team (endocrinologist and nurse). Medical and nurse assistance and treatment goals were the same in CSII and MDI patients.

Hanas 2006 [145] Sweden Cross-sectional and longitudinal studies using data collected retrospectively from medical records	Age range 7 to 21 years n=27	High HbA_{1c} (67%); acceptable HbA_{1c} but too much work with multiple injections (11%), pain from insulin or needle (7%), unstable BG but acceptable HbA_{1c} (7%), high BG during the night or morning (4%), wanted to try pump (4%).	23 followed-up for 5 years on CSII	After the initial period of adjustment during the time after pump start, pump patients were not seen more often than injection patients.
Juliusson 2006 [166] Norway Before and after study	Mean age 14.4 years (SD 1.5) (range 9.7 to 17.1) n=31	The main indication for initiating CSII was HbA_{1c} above the target range of 7-8%.	15 months	To initiate pump therapy, patients were admitted to the clinic on Wednesdays and discharged on Mondays. Parents were given a demonstration pump with saline. Paediatric diabetologists and specialist nurses gave practical and theoretical information.
Kordonouri 2006 [146] Germany Matched pair analysis comparing CSII vs MDI	Mean age 6.7 years n=59	Patient preference or erratic BG (hypos, dawn phenomenon)	1-year. Data from 59 reported at 1-year	59/85 patients on CSII were eligible [not clear why others were excluded] Training: NR
Liberatore 2004 [167] Canada Before and after by revieing medical charts	Mean 12.9 years (range 2 to 17 years) n=73	No restrictions on children offered CSII	At least 6 months (range 6 to 30 months)	Using insulin pump for more than 6 months. Intensive education about pump and management of DM plus close contact with children and families and more clinic visits.
Mack-Fogg 2005 [168] USA Before and after retrospective chart review	Mean age 9.1 years (SD 2.9) Subgroups: 1) n=9, started CSII at between 2 and 4 yrs old 2) n=29, started between 5 and 9 years 3) n=32, started between 10 and 12 years Total n=70	Patients and families who were testing blood glucoses at least four times daily, who were interested in achieving tighter control, and/or who had experienced several episodes of severe hypoglycaemia while attempting to maintain good glycemic control.	Mean 336 (SD 58.5) days	Began CSII at age 12 or younger and using CSII for at least 6 months. Parents and the diabetes team worked to educate the adults who were responsible for 5-9 yrs olds while they were away from home. Training in general: NR

McMahon 2005 [147] Australia Before and after study	Mean age 12.5 years (SD 3.8) (range 3.9-19.6 years) n=105	5% were started on pump therapy because of recurrent severe hypoglycaemia, 5% because of poor control despite compliance with therapy and the remaining 90% at the request of the patient or caregiver.	Mean 1.4 (SD 0.9) years. Range 0.2 to 4.0 years.	Patients had to be motivated and able to test blood glucose levels at least 4 times per day. Insulin pump therapy started as an inpatient with a 24 h admission. Patients and families received intensive education and glucose monitoring, and followed up by daily telephone calls for one week. Clinic appointments were made 2-weekly for 4 weeks, than 3-monthly.
Mednick 2004 [173] USA Survey	Mean age 13.6 years (range 10 to 18 years) and parents n=22	Children were transitioning to insulin pump therapy. Reasons not reported. Patients had good metabolic control prior to pump start (mean HbA_{1c} 7.94).	Using CSII for mean 10.43 ± 5.05 months (range 3 to 22 months	Purpose of study was to describe satisfaction and subsequent QoL with the transition to insulin pump therapy among children and their parents. Training: NR
Plotnick 2003 [153] USA Before and after study	Mean age 12 years (range 4 - 18 years) (29% were < 10 years old n=95	Several reasons, including better control, less blood glucose variability, fewer injections, and improvement in lifestyle flexibility.	Median 15 months	Patients were highly selected. All patients and families needed to demonstrate a desire and ability for intensive management. Risks of pump use and risk prevention discussed: site infections, hyperglycaemia, ketosis and DKA Hypoglycaemia awareness, prevention and treatment reviewed. Problem solving strategies discussed: mechanical problems. 24-48 hour admission to initiate. After pump start, all patients had daily phone contact with the diabetes nurse educator for 3-7 days and then fax or phone contact 1-2 times per week for next 1-2 months.
Raile 2002 [154] Germany Prospective longitudinal non-randomised case control study	Mean age 13.6 years n=12	Dawn phenomenon, repeated hypos especially at night, patient request for more flexibility.	1 year	Adolescents interested in CSII and fulfilling inclusion criteria were admitted to a special diabetes education program for CSII. Prerequisites for CSII were: documented recording of BG tests and adequate technical skills.
Saha 2002 Finland [148] Case series	Mean age 8.7 years (range 0.2-16 years) n=16	Marked instability in BG resulting in numerous hypos, poor control and patient request since perceived as more convenient	Mean 2 years (range 0.4 to 4.2 years)	Started CSII between 1992 and 1997. Training: NR
Schiaffini 2005 [163] Italy Retrospective data collection comparing CSII with glargine	Mean age 12.7 years (SD 1.8) n=20	Suboptimal glycaemic control (HbA_{1c} > 8.0%), wide glycaemic oscillations with fasting hyperglycaemia, frequent hypoglycaemic episodes.	1 year	T1DM diagnosed at least 2 years. >10 years old. Support (for CSII and MDI groups) - dietary education, regular self-monitoring of blood glucose (at least 4–5 tests per day), medical and psychological care and frequent telephone consultations with the medical staff were encouraged in order to adjust the insulin dose appropriately.

Simmons 2006 [174] [Abstract] USA Matched non-randomised controlled study	Age range 6 to 19 years n=51 (aged 6 to 12) n=87 (aged 13 to 19) Total n=138	NR	Mean 1.7 years for 6-12 age group.	Subjects treated with CSII for ≥ 6 months 18% of patients 6-12 yrs (163/895) and 28% of patients 3-19 yrs (284/1025) cared for by the Barbara Davis Center were treated with CSII.
Sulli 2003 [155] Italy Prospective longitudinal trial	Mean age 13.5 years (range 2 to 25 years) n=41	Unstable DM control; high HbA_{1c}; recurrent hypos; early onset of microangiopathic complications; dawn phenomena; difficulty matching injections to meals.	6 months	CSII suggested for 41/350 children with DM. All patients had undergone intensive MDI insulin therapy for at least 1 year, with 4 insulin injections per day. Patients and other family members underwent training regime. Only those cases which the patients (or parents) had shown that they had mastered the technique and had the necessary skills and knowledge for CSII therapy.
Sullivan-Bolyai 2004 [175] USA Qualitative description	21 parents of 16 children aged < 12 years (mean age 7 years)	NR	On CSII for mean 16 ±11 months (range 3 to 36 months)	All patients <12 years invited to participate. Training: NR
Toni 2004 [176] [Letter] Italy Case series	Mean age 14.4 years (range 9 to 17.8) n=34	NR	2 years	Continued CSII for at least 1 year. Training: NR
Ugrasbul 2006 [177] [Abstract] USA Case series	Aged 4 to 21 years n=131	NR	Not clear	All patients starting CSII 2003-2004. Training: NR
Wallach 2005 [178] [Abstract] USA Case series	Mean age 12.4 years (range 2.8 to 21) n=73	NR	Mean 2.3 years	Consecutive patients. Training: NR
Willi 2003 USA Before and after study	Mean age 11.2 years (SD 0.3) (range 5-16) n=51	Selection was not guided by any strict criteria but encompassed several features believed to be important to success. Most patients had expressed an interest, and all agreed to a trial of CSII.	1 year	Duration of diabetes >1.5 years or a pattern of increasing insulin requirements was present in all cases. Patients and their families needed to demonstrate an ability to understand the concepts of insulin pump mechanics. The CSII training program included individual education sessions in carbohydrate counting, insulin pump mechanics, and site insertion, culminating in a 3-day outpatient pump trial using normal saline.

Wood 2006 [150] USA Cohort study	Mean age 14 years (range 3.7 to 21.7) n=161	Patients and families, in collaboration with diabetes team, elected to begin pump therapy. Self-selected pump model.	3.8 years	All youth who began pump therapy during 4 yrs 1998-2001. Patients and families completed clinic's standard pump assessment and education program.

Table 9: Observational studies on CSII - Young children (age ≤7 years)

First Author Year Country Study type	Age group Sample size	Reasons for starting on pump	Duration of follow-up	Notes – including selection criteria and training (where reported)
Alemzadeh 2006 [179] [Abstract] USA Before and after study	Mean age 3.9 years n=14	NR	1 year	NR
Berhe 2006 [160] USA Before and after study/retrospective chart review	Mean age 4.6 years (range 2 to 6) n=33	Started on CSII at discretion of attending paediatrician. No specific inclusion or exclusion criteria to start pump therapy.	1 year	Excluded: >6 yrs old at initiation of pump, still in honeymoon phase, on MDI Parents given intensive education support including initial weekly contact, additional clinic visits.
Litton 2002 [159] USA Before and after study	Mean age 34 months (range 20 to 58 months) n=9	On insulin for > 6 months; recurrent hypos or DKA, elevated HbA_{1c}; erratic fluctuations in BG.	Mean 1 year	After diagnosis of T1DM, families received extensive diabetes education and training, 24 hour phone access to staff. Patients on CSII: it was required that they would receive constant supervision by parents or caretakers throughout the day, parental understanding of management and pump, child had to be able to tolerate equipment.
Shehadeh 2004 [169] Israel/ Slovenia Before and after study	Mean age 3.8 years (range 1.3 to 5.7) n=15	CSII suggested for young children with DM ≥ 6 months	1 year	Parental education and training, 24-hour phone line support.
Weinzimer 2004 [151] USA Retrospective before and after study	Mean 4.5 years (range 1.4 to 6.9) n=65	Repeated episodes of hypoglycaemia. Initiated on pump therapy at request of parents and only with the approval of health care team. Preinitiation requirements for pump therapy included frequent monitoring of glucose levels, adequate adult supervision, ability to comprehend and implement pump treatment.	Mean 30 months	All children initiated on pump before 7th birthday and for whom at least 3 months of prepump and 3 months of postpump data were available. Families underwent education sessions. Telephone support provided.

2.8.6 Continuation rates

Continuation rates can be regarded as evidence of patient satisfaction. Less than half of the studies (22/48) reported continuation rates. Continuation rates at one to five years ranged from 74% to 100%. Continuation rates of 100% were reported in two studies: in adults/mixed age groups [139,158] and five studies in adolescents and children.[149,151,154,159,160]

A variety of reasons for discontinuing CSII were reported in 12 studies (table 10). Reasons for discontinuing included: end of pregnancy, lack of tolerance to carry the pump, perception of goals not reached, infection at insulin injection site and hypoglycaemic episodes[136]; not able to cope with the technical aspects of using an insulin pump and not convinced of the advantages [140]; cost and inconvenience [141]; site problems, sweating, costs and other illness [135]; patient's decision (most commonly due to reluctance to wear the system), end of pregnancy, cutaneous problem and poor compliance [171]; dislike or difficulty with needle insertion, insurance difficulties, trouble keeping the infusion site clean, tape not adhering, and general dislike of the pump [98]; wish to return to injections, and worsening control due to omitting bolus insulin [161]; extra work involved with changing infusion sets and dislike of something being attached to body [145]; psychiatric and dermatological conditions[147]; inconvenience in carrying the pump [166]; pump limited normal physical activity, recurrent DKA [148]; DKA due to insulin omission, diabetes burnout, minor problems with infusion site, body image concerns and concerns about weight gain.[150]

Table 10: Continuation rates for CSII and reason for discontinuing (where reported): Adults/mixed age groups

Study	Percentage continuing on pump	Reasons for discontinuing	Duration of follow-up
Bruttomesso 2006 [136] Italy	79%	571 (21%) had discontinued CSII. 187 (33% of those discontinuing) discontinued at end of pregnancy; other reasons included lack of tolerance to carry pump, perception of goals not reached, infection at insulin injection site, hypos, or moving (no % given)	Mean 3.9 years (adults) and 2.4 years (children)
D' Annunzio 2005 [139]	100%	Not applicable	18 months
Linkeschova 2002 [140]. Germany.	97%	One patient had had a combined kidney–pancreas transplant; one did not feel able to cope with the technical aspects of using an insulin pump; one with SH on MDI stopped after 3 months of CSII as not convinced of the advantages.	Mean 1.8 ± 1.2 years
Reda 2007 [141] New Zealand	Not reported	20 lost to follow up for various reasons (moved to care of other physicians, moved house, discontinued CSII due to cost or inconvenience).	Mean 3 years
Rodrigues 2005 [135] UK	87.5%	15 had classic contraindications to CSII (including psychiatric disorders) 5 patients (12.5%) discontinued CSII (2 site problems, 1 sweating, 1 due to costs, 1 other illness)- all these patients were self-funded	Median 20.5 months (range 1 to 192 months)
Ronsin 2005 [171] France	74% Including all patients who remained on some form of pump	At least 40% had diabetes related medical problems. 25 patients (36%) discontinued CSII (7 changed to implantable pump treatment; 10 patient's decision (most commonly due to reluctance to wear system); 4 end of pregnancy; 3 cutaneous problem; 1 poor compliance)	Maximum of 2 years
Rudolph 2002 [98]. USA	94.6%	Variety of reasons for discontinuing pump - usually multiple reasons; including, dislike or difficulty with needle insertion (n=3), insurance difficulties (n=2), trouble keeping the infusion site clean (n=2), tape not adhering (n=2) and general dislike of the pump (n=2).	Mean 36.1 ± 25.5 months
Siegel-Czarkowski 2004. [158] USA	100%	Not applicable	1 year

NR = not reported

Table 11: Continuation rates for CSII and reasons for discontinuing (where reported): Children/adolescent age groups

Study	Percentage continuing on pump	Reasons for discontinuing	Duration of follow-up
Ahern 2002 [161] USA	98%	3 stopped CSII (2 discontinued due to wish to return to injections and one failed to take bolus dose and control worsened)	At least 1 year (range 19 to 57 months)
Hanas 2006 [145] Sweden	92%	2 discontinued (one after 3 years since no longer motivated for extra work involved with changing infusion sets, one at 2 years since did not like something being attached to her body). Incomplete reporting of 5-year data	5 years
Juliusson 2006 [166] Norway	86%	Main reason given for withdrawing from CSII was inconvenience in carrying the pump.	15 months
McMahon 2005 [147] Australia	95%	Reasons for discontinuing. 2 patients had psychiatric conditions and one had a dermatological condition. Two discontinued at the patient or parent's request.	Mean 1.4 ± 0.9 years (range 0.2 to 4.0 years).
Raile 2002 [154] Germany	100%	Not applicable	1 year
Saha 2002 [148] Finland	75%	4 patients discontinued (2 since pump limiting normal physical activity, 1 pump needed for another child, 1 recurrent DKA)	Mean 2 years (range 0.4 to 4.2 years)
Toni 2004 [176] [Letter] Italy	88%	3 dropped out in year 1, one dropped out year 2	2 years
Wallach 2005 [178][Abstract] USA	92%	6 patients, all > 12 years, discontinued (none because of complications of therapy or weight gain)	Mean 2.3 years
Willi 2003. US	100%	Not applicable	1 year
Wood 2006 [150] USA	82%	Reasons for discontinuing: major problems (n=8, DKA, insulin omission); diabetes burnout (n=8); minor problems (n=6, infusion site problems), body image concerns (n=4) ; concerns about weight gain (n=3)	3.8 years

Table 12: Continuation rates for CSII and reasons for discontinuing (where reported): Young children (aged ≤7 years)

Study	Percentage continuing on pump	Reasons for discontinuing	Duration of follow-up
Berhe 2006 [160] USA	100%	Not applicable	1 year
Litton 2002 [159] USA	100%	Not applicable	Mean 1 year
Shehadeh 2004 [169] Israel/ Slovenia	93%	Not reported	1 year
Weinzimer 2004 [151] USA	'None returned to MDI because of family choice or practitioner discretion'	Not applicable	Up to 4 years

2.8.7 Glycaemic control as reflected in glycated haemoglobin

Forty-six studies reported comparable before and after data on HbA_{1c} levels (Table 13). Levels of statistical significance are reported where they were available (some papers did not report whether the change was significant or not).

All of the 18 studies in the adults/mixed age groups showed a significant decrease in HbA_{1c} levels (ranging from 0.2% to 1.4%) after participants started on pumps.

Few studies reported proportions reaching targets. Targets varied. Pickup and colleagues[134] reported that 37% of CSII subjects and 13% of MDI ones achieved HbA1c <7%; for a target of <85, the proportions were 73% and 30%. Radermecker and colleagues [138] noted that of 95 patients on CSII, only five reached HbA1c of 7% or less; most (66) were in the range 7.1 to 8.5%. In the Reda study,[141] only 9 of 105 reached the ADA target (7.0% or less) before CSII, but only 18 afterwards. Rodrigues[135] reported 40% reaching <75 and 785 <8% on CSII

There were 23 studies in the children/adolescents age group. Three of the studies showed an increase after using pumps. In Kordonouri 2006 (n=59) [146] and Garcia-Garcia 2007 (n=8) [162] the increases of 0.01% and 0.08% were neither clinically or statistically significant. The statistical significance level was not reported in Raile 2002 (n=12)[154] where the increase was 0.6%. The remaining 20 studies showed an overall decrease, ranging from 0.2% to 1.2%. In 13 of these studies, the overall decrease was statistically significant. However, in Mack-Fogg 2005[168], the decrease was only significant in the 10-12 year age groups, and not significant in the younger children. Willi 2003 [149] also reported the sub-groups by age, and found a significance decrease in the 5-9 and 13-17 year group, but no change in the 10-12 year group.

In four studies the decrease was not significant [145,148,152,178] and three studies [166,174,177] did not report the significance level of the decrease. Only one study reported proportions reaching targets. Simmons and colleagues [174] reported that 75% of 6-12 year olds reached the ADA target of 8% or less (for that age group). Only 15% of adolescents (13-19) reached their age range target of <7.5%.

There were five studies in young children and all showed decreases, which ranged from 0.2 to 1.6%. Four showed a statistically significant decrease and one (Alemzadeh 2006 n=14)[179] showed a non-significant decrease. Only one study reported on targets met – Berhe [160] reported that 76% of patients had HbA1c levels<8.5% after CSII compared to 35% before.

In summary, only three of 46 studies showed an increase in HbA_{1c}. These studies were all in children/adolescents, and the increases were insignificant in two, and 0.6% in the third (no significance level reported. Most studies showed decreases in HbA_{1c} varying from 0.2 to 1.6%.

Table 13: HbA_{1c} before/after CSII

Study	Pre-CSII HbA_{1c} % (± SD%)	HbA_{1c} After CSII (% ± SD) (longest follow-up with HbA_{1c} values)	Difference HbA_{1c} % (Before minus After) [+ve=decrease= Improvement]	Study duration
Adults/ mixed age group				
Cersosimo 2002 [164]	8.0 ± 1.2	7.1% ± 1.1	0.9 (p<0.05)	2 years
D'Annunzio 2005 [139]	Median 9.8	Median 8.6	1.2 (p=0.014)	18 months
Fahlen 2005 [156]	7.64 ± 1.5	NR	0.59 ± 1.19 (p<0.001)	Median 15 months
Garg 2004 [170]	7.7 ± 0.1	7.5 ± 0.1	0.2 (p<0.001)	At least 6 months
Hunger-Dathe 2003 [165]	relative HbA_{1c} (absolute HbA_{1c}/healthy mean): 1.58±0.34	relative HbA_{1c} (absolute HbA_{1c}/healthy mean): 1.449±0.32	0.45 (p<0.0001)	1 year
Jankovec 2005 [143]	9.43 ± 1.98	8.31 ± 1.76	1.1 (p<.001)	1 to 2 years
Lepore 2004 [157]	9.0 ± 1.3	8.0 ± 1.0 (Mean of 4 measures over 1 year)	1.0 (p<0.001)	1 year
Linkeschova 2002 [140]	7.7 ± 1.1	7.2 ± 1.0	0.5 (p< 0.001)	Mean 1.8 years
Nimri 2006 [142]	Entire cohort: 8.4 ± 1.3 Sub-groups: Prepubertal: 8.6 ± 1.2 Adolescent: 8.6 ± 1.3 Young adult: 8.1 ± 1.4	Entire cohort: 7.8 ± 1.3 Sub-groups: Prepubertal: 8.2 ± 0.7 • Adolescent: 8.3 ± 1.4 • Young adult: 7.3 ± 1.0	Entire cohort: 0.51 (p <0.001) Sub-groups: Prepubertal: 0.48 (p <0.05) Adolescent: 0.26 (p<0.05) Young adult: 0.76 (p <0.001)	Mean 2.4 years.
Norgaard 2003 [137]	8.5 ± 1.1	8.0 ± 1.2	0.5 (p<0.05)	Mean 13 years
Pickup 2005 [133]	8.8	7.4	1.4 (p<0.001)	6 months
Pickup 2006 [134]	8.5 ± 1.4	7.3 ± 0.9	1.2 (p<0.001)	16 months
Radermecker 2005 [138]	8.6 ± 1.3	8.4 ± 1.0	0.2 (p<0.001)	Mean 5.1 years
Reda 2007 [141]	All ages: 8.9 ± 1.3 Adults only: 8.8 ± 1.4	All ages: 7.9 ±0.95 Adults only: 7.9 ±0.79	All ages: 1.0 (p<0.001). Adults only: 0.9 (p<0.001	6 months
Rodrigues 2005 [135]	9.6 ± 2.7	8.3 ± 1.2	1.3 (p=0.011)	Median 20 months
Rudolph 2002 [98]	7.6 ± 1.5	7.1 ± 1.1	0.66 (p<0.0001)	Mean 36.1 months.
Siegel-Czarkowski 2004 [158]	7.64 ± 0.19	7.01 ± 0.10	0.6 (p<0.01)	1 year
Sucunza 2005	8.3 ± 1.3	7.7 ± 1.5	0.6 (p<0.005)	Mean 26 months
Children/adolescents				

Ahern 2002 [161]	Preschool: 7.1± 1.0 School age: 7.9% ± 1.0 Adolescents: 8.1% ± 1.5	Preschool: 6.5±0.7 School age: 7.3% (SD 1.1), p< 0.02 Adolescents : 7.4% (± 1.2) p<0.02	Preschool: 0.6 (p≤0.02) School age: 0.6 (p≤ 0.02) Adolescents: 0.7 (p≤0.02)	1 year
Alemzadeh 2004 [144]	8.4 ± 1.0	7.8 ± 0.8	0.6 (p<0.002)	1 year
Conrad 2002 [152]	All children: 8.4%±0.9 Pre-pubertal: 8.3%±0.7 Pubertal: 8.5%±0.9	No significant change in either prepubertal or pubertal patients. Data only presented graphically	NS	3-6 months
Garcia-Garcia 2007 [162]	7.62 ±0.62	7.70 ±0.64	- 0.08	2 years
Hanas 2006 [145]	8.9%±1.0	Graph of 5-year data appears to show little difference between baseline and final HbAIc (no values reported at 5 – years, approx 8.7% from graph)	0.2 (NS)	5 years
Juliusson 2006 [166]	10.4 ± 1.8	9.6 ± 1	0.8	15 months
Kordonouri 2006 [146]	8.17±1.03	8.27%±1.01	-0.01 (NS)	1 year
Liberatore 2004 [167]	8.3% ± 1.0	7.5% ± 1.1	0.8 (p<0.00003)	at least 6 months
Mack-Fogg 2005 [168]	Overall: 7.8 ± 0.8 2-4 yr group : 8.1 5-9 yr group : 7.7 10-12 yr group: 7.7	Overall: 7.3 ± 0.7 2-4 yr group: 7.6 5-9 yr group: 7.2 10-12 yr group: 7.3	Overall: 0.5 (p<0.001) 2-4 yr group: 0.5 (NS) 5-9 yr group: 0.5 (p<0.05) 10-12 yr group: 0.4 (p<0.05)	Mean 336 days
McMahon 2005 [147]	Overall: 8.3 (SEM ± 0.1) <12 yr: 8.3 ± 0.2 >12 yr: 8.4 ± 0.1	Overall: 7.8 (SEM ± 0.1) <12 yr: 7.5 ± 0.1 >12 yr: 7.9 ±0.1	Overall: 0.5 (p<0.0001) <12 yr: 0.8 (p<0.001) > 12 yr: 0.5 (p<0.001)	Mean 1.4 years,
Mednick 2004 [173]	7.94	7.41	0.53 (p=0.03)	3 to 22 months
Plotnick 2003 [153]	8.1	7.7	0.4 (p<0.001) after adjusting for duration of DM and age	Median 15 months
Schiaffini 2005 [163]	8.5 ± 1.8	7.6 ± 1.2	0.9 (p<0.05)	12 months

Simmons 2006 [174]	6-12 yr: 8.3 ± 0.9 13-19 yr: 8.7 ± 1.1	6-12 yr: 7.6 ± 0.9 13-19 yr: 8.4 ± 1.2	6-12 yr: 0.7 13-19 yr: 0.3	
Reda 2007 [141]	9.1 ± 1.0	7.9 ± 1.0	1.2 (p<0.005)	1 year
Raile 2002 [154]	7.4 ± 0.82	8.0 ± 0.7	- 0.6	1 year
Saha 2002 [148]	9.1 ± 2.4	8.7 ± 1.6,	0.4 (NS)	Mean 2 years
Sulli 2003 [155]	9.5 ± 1.7	8.8 ± 1.5	0.7 (p<0.05)	6 months
Toni 2004 [176]	8.35 ± 1.08	7.81 ± 0.95	0.5 (p=0.002)	1 year
Ugrasbul 2006 [177]	8.5	8.2	0.3	NR (started on CSII 2003/2004)
Wallach 2005 [178]	8.19 ± 1.05	7.48 ± 0.91	0.7 (p=0.126) NS	2 years
Willi 2003 [149]	All group: 8.4 ± 0.2 5-9 yr: 8.4 10-12 yr: 8.37 13-17 yr: 8.3 (Estimated from graphs)	All group: 7.9 ± 0.1 5-9 yr: 7.72 10-12 yr: 8.37 13-17 yr: 7.63	All group: 0.5 (p<0.01) 5-9 yr: 0.7 (p<0.01) 10-12 yr: 0 (NS) 13-17 yr: 0.7 (p<0.05)	12 months
Wood 2006 [150]	8.4 ± 1.4	8.1 ± 1.3	0.3 (p<0.01)	12 months
Young children				
Alemzadeh 2006 [179]	8.0 ± 0.50	7.8 ± 0.40	0.2 (NS)	1 year
Berhe 2006 [160]	8.7 ± 0.6	8.0 ± 0.5	0.7 (p<0.001)	1 year
Litton 2002 [159]	9.5 ± 0.4	7.9 ± 0.3	1.6 (p<0.001)	1 year
Shehadeh 2004 [169]	8.82 ± 0.98	8.18 ± 0.90	0.6 (p<0.05)	1 year
Weinzimer 2004 [151]	7.4 ±1.0	7.1±0.8	0.3 (p=0.006 for all postpump compared to prepump values)	Up to 4 years (analysed for >162 patient years of follow-up)

NR = not reported.

2.8.8 Hypoglycaemic episodes

The main interest was in severe hypoglycaemic episodes. Data are included from the 26 studies reporting comparable data on the rate of severe hypoglycaemic (SH) episodes before and after CSII was initiated (Table 14). Rates were reported in different units, so rate ratios were calculated to enable comparison between studies.

Ten studies were in adults/mixed age groups. Two [133,134] did not report any hypoglycaemia before or after pumps use. Of the eight remaining studies, all reported a significant decrease after going on

pumps. The rate ratios ranged from 0.07 to 0.4. One of these [142] reported no hypoglycaemic episodes in the prepubertal group either before or after pump use.

There were 11 studies in children/adolescents. One study [162] had no SH before or after going on pumps. Of the remaining 10 studies, the overall rate ratios varied from 0.12 to 0.80.

In four studies [144,150,155,161] the overall decrease was reported as statistically significant. However in Ahern 2002[161] (n=161) the decreases were not significant when broken down into three age groups (possibly due to smaller sample sizes).

Three studies [146,147,166] did not report the significance level of the decrease, but showed substantial reductions (rate ratios of 0.12, 0.30 and 0.35 respectively). In the remaining three studies in children/adolescents the overall decrease was not significant. However in one of the studies [168] the reduction was significant in the 10-12 year age group, but not in the 2-4 and 5-9 age groups.

There were five studies in young children, and the rate ratios ranged from 0 to 0.81. In three studies [151,159,160] this was significant, and the in the other two it was not significant.

In summary, of the 26 studies examined, 15 showed a statistically significant decrease in SH episodes after going on pumps, five showed a non-significant decrease, and three showed a decrease but the significance level was not reported. The remaining three studies did not report any SH episodes before or after going on pumps.

Table 14: Severe hypoglycaemic episodes per patient per year (unless otherwise stated)

Study	Before CSII	During CSII	Difference [+ve=reduction]	Rate Ratio
Adults/mixed age groups				
Hunger-Dathe 2003 [165]	0.46 ± 1.5	0.12 ± 0.51	0.34 (p<0.001)	0.26*
Lepore 2004 [157]	0.42 ± 0.49	0.17 ± 0.37	0.25 (p<0.05)	0.40*
Linkeschova 2002 [140]	1.23 (any external help) 0.70 (treated with i.v. glucose or glucagon injection)	0.29 0.06	0.94 (p<0.005) 0.64 (p<0.001)	0.24* 0.09*
Nimri 2006 [142]	Prepubertal: 0 Adolescent: 36.5 Young adult: 58.1 (per 100/patient years)	Prepubertal: 0 Adolescent:11.1 Young adult: 23.3	Prepubertal: 0 Adolescent: 25.4 (p=0.002) Young adult: 34.8 (p=0.02)	 0.30* 0.40*
Pickup 2005 [133]	0	0	0	0
Pickup 2006 [134]	0	0	0	0
Siegel-Czarkowski 2004 [158]	7/34	1/34	6/34 (p<0.05)	0.14*
Reda 2007 [141]	0.75	0.05	0.70 (p<0.001)	0.07*
Rodrigues 2005 [135]	0.92 ± 1.49	0.15 ± 0.38	0.77 (p=0.009)	0.16*
Rudolph 2002 [98]	73.2 (per 100/patient years)	19.1	54.1 (p<0.0003)	0.26*
Childen/adolescents				
Ahern 2002 [161]	All: 0.35 Pre-school: 0.42 School age: 0.33 Adolescents: 0.33	All: 0.24 Pre-school: 0.19 School age: 0.22 Adolescents: 0.27	All: 0.11 (p<0.05) Pre-school: 0.23 (NS) School age: 0.11 (NS) Adolescents: 0.06 (NS)	0.69* 0.45 0.67 0.82
Alemzadeh 2004 [144]	20.6 (per 100 patient years)	8.2	12.4 (p<0.05)	0.40*
Garcia-Garcia 2007 [162]	0	0	0	0
Juliusson 2006 [166]	43.8 (events per 100 patient years)	5.2	38.6	0.12
Kordonouri 2006 [146]	19.2 (SE ± 7.3) (per 100 patients per year)	5.8 (SE ± 3.3)	13.4	0.30
Mack-Fogg 2005 [168]	0.46	0.22	Overall: 0.24 (NS) 2-4 yr: 0.27 (NS) 5-9 yr: 0.16 (NS) 10-12 yr: 0.30 (P<0.02)	0.48
McMahon 2005 [147]	Total 32.9 <12 yr: 25.9 >12 yr: 37.5 (per 100 patient years)	Total: 11.4 <12 yr: 8.3 >12 yr: 13.5	Total: 21.5 <12 yr: 17.6[§] >12 yr: 24.0[§]	0.35 0.32 0.36
Plotnick 2003 [153]	14.3 (per 1,000 person-months)	6.6	7.7 (NS)	0.46
Schiaffini 2005 [163]	0.25 ± 0.4	0.2 ± 0.3	0.05 (NS)	0.80
Sulli 2003 (Hypos defined as <3.3mmol/l.) [155]	6.50 ± 5.50 /patient/month	3.50 ± 3.00	3.00 (p=0.04)	0.54*

Wood 2006. [150] Sub-group of children/adolescents who remained on pump after 3 years (n=132)	0.23	0.074	0.16 (p=0.001)	0.32*
Young children				
Alemzadeh 2006 [179]	0.225	0.174	0.05 (NS)	0.77
Berhe 2006 [160]	0.178	0	0.178 (p<0.001)	0*
Litton 2002 [159]	0.52 ± 0.10 /month	0.09 ± 0.02 /month	0.43 (p<0.05)	0.17*
Shehadeh 2004 [169]	0.36	0.29	0.07 (NS)	0.81
Weinzimer 2004 [151]	0.78	0.37	0.41 (p=0.02)	0.47*

* P<0.05; NS not statistically significant;

2.8.9 Diabetic ketoacidosis (DKA)

As reported in the last assessment report, it is likely that one of the reasons for the low use of CSII in the UK was fear of DKA. People with T1DM on CSII have no insulin store in the body, and if the pump fails, they will rapidly develop metabolic problems.

There were 15 studies that had comparable before and after data on DKA rates. These are summarised in Table 15.

Table 15: Rates of DKA before/after CSII

Study	Rate per annum before CSII (unless otherwise stated)	Rate per annum after CSII (unless otherwise stated)	Difference (Before-After) [+ve=reduction]
Adults/ mixed age groups			
Hunger-Dathe 2003 [165]	0.08 ± 0.4 (Severe)	0.05 ± 0.6	0.03 (p=0.003)
Linkeschova 2002 [140]	0.05	0.01	0.04
Nimri 2006[142]	Prepubertal: 0 Adolescent: 0.19 ± 0.74 Young adult: 0.12 ± 0.43	Prepubertal: 0.22 ± 0.52 Adolescent: 0.17 ± 0.46 Young adult: 0.09 ± 0.29	-0.22 (NS) 0.02 (NS) 0.03 (NS)
Reda 2007[141]	0.2	0.05	0.15
Rodrigues 2005[135]	1.83 ± 4.84	0.27 ± 1.12	1.56 (p=0.036)
Children/adolescents			
Ahern 2002[161]	1 episode in 161 patients over 1 year	2 episodes in 161 patients over 1 year	-1/161
Garcia-Garcia 2007[162]	0.10 ± 0.22	0.20 ± 0.27	-0.10 (NS)
Juliusson 2006[166]	15.5 (/100 patient years)	12.9(/100 patient years)	2.60 (NS)
Kordonouri 2006[146]	0. 9	0.096 (SE ± 0.041)	0.80 (p=0.024)
Mack-Fogg 2005[168]	0 episodes	2 episodes	-2 (NS)
McMahon 2005[147]	0	0	0
Plotnick 2003[153]	0.80 (95% CI: 0.11-5.65) (rate per 1,000 person months)	0.55 (95% CI: 0.08-3.91) (rate per 1,000 person months)	0.25 (NS)
Young children			
Berhe 2006[160]	0 (Severe)	0	0
Litton 2002[159]	0.06 (SE ± 0.03) (/month) (Severe)	0.06 (SE ± 0.03) (/ month)	0 (NS)
Weinzimer 2004[151]	0 (Severe)	0.04	-0.04

NR not reported; NS not statistically significant;

Five studies were in adults/mixed age groups. One study (Nimri 2006)[142] showed a non-significant increase in prepubertal children and a non-significant decrease in the adolescent and young adult age groups. Two studies (Hunger-Dathe 2003[165] and Rodrigues 2005)[135] showed a statistically significant decrease. The patients in the study by Rodrigues and colleages (2005)[135] had a higher DKA rate than most other studies, but they included some having particular problems, including with DKA. Two studies (Linkeshova 2002[140] and Reda 2007[141]) did not report the significance level of the reduction.

There were seven studies in children/adolescents. McMahon 2005[147] showed no change. Mack-Fogg (2005)[168] and Garcia-Garcia (2007)[162] showed a non-significant increase. Ahern (2002)[161] showed an increase (of one episode in 161 patients over one year) but the significance level not reported. Kordonouri (2006)[146] showed a significant decrease, and Juliusson 2006 [166]and Plotnick 2003[153] showed a non-significant decrease.

There were three studies in young children. Weinzeimer 2004 (n=65)[151] showed an increase (from 0 to 0.04 per annum) but the significance level was not reported. Berhe 2006 (n=33)[160] and Litton 2002 (n=9)[159] showed no change, but as these studies were small they may have been underpowered to detect a statistically significant difference.

In summary, none of the 15 studies reported a statistically significant increase in DKA rates after going on pumps. Three reported a significant reduction and three studies reported an increase; in one this was not significant and the other two did not report significance levels.

However, a conference abstract by Hanas and colleagues [180] gives worrying data from Sweden, where pump use is common in children. In 1999, 7.5% of children and adolescents used pumps, and this figure rose to 11.2% in 2000. The DKA rate in CSII users was double the overall rate - 3.5 per 100 patient years versus 1.7, but the true risk ratio will be higher, since the CSII DKA cases will presumably be included in the total for all patients. Hanas and colleagues note that most DKA occurred soon after CSII initiation, and that, along with the marked rise in CSII use, might perhaps suggest problems with adequate training. Full details will no doubt be published in due course.

2.8.10 Weight change

There were 30 studies in total reporting comparable before and after data on BMI or weight change (Table 16). However, some of the studies that involved adolescents and young children did not take account of changes in the child's development when considering weight change.[144,154,155,160,167,176,177]

Table 16: BMI/Weight change before/after CSII

Study	BMI/ weight at baseline	BMI/ weight on CSII	Difference [+ve = increase -ve = decrease in BMI/weight]
Adults/ mixed age groups			
Cersosimo 2002[164]	BMI ~25	Weight ~71 kg	(NS)
D'Annunzio 2005[139]	BMI median: 22.8	BMI median: 23.5	Change in BMI: +0.70 (p=0.02)
Garg 2004 [170]	Weight 76.2 kg	Weight 77.3 kg	+1.10 kg (p<0.001)
Lepore 2004 [157]	BMI 23.5	BMI 23.9	Change in BMI: -0.4 (NS)
Linkeschova 2002[140]	NR	Body weight under CSII therapy assessed by questionnaire was unchanged in 53% of the patients, increased in 22%, and decreased in 25% of the patients.	
Nimri 2006[142]	BMI SDS: Entire cohort: NR Prepubertal: 0.64 ±0.8 Adolescent: 0.31 ±0.6 Young adult: 0.35 ±0.7	BMI SDS: Entire cohort: NR Prepubertal: 0.68 ±0.81 Adolescent: 0.3 ±0.7 Young adult: 0.28 ±0.68	Change in BMI SDS: Entire cohort: -0.05 ± 0.01 (p=0.06) NS Prepubertal: +0.04 (NS) Adolescent: -0.01 (NS) Young adult: -0.08 ± 0.37 (p=0.016)
Pickup 2005[133]	Weight 71.4 ± 14.7 kg	Weight 70.0 ± 8.8 kg	-1.4 kg (NS)
Pickup 2006[134]	BMI 25.6 ± 3.9	BMI 25.9 ± 4.3	Change in BMI: -0.30
Rodrigues 2005 [135]	BMI 21.2	BMI 22.1	Change in BMI: +0.9 (NS)
Siegel-Czarkowski 2004[158]	BMI 23.7	Reports no significant change at 1 year (BMI not reported)	Change in BMI: (NS)
Children/ adolescents			
Ahern 2002[161]	BMI z-score: Pre-school: 1.18 ± 0.73 School age: 0.94 ± 0.75 Adolescents: 0.74 ± 1.41	BMI z-score: Pre-school: 1.18 ± 0.78 School age: 0.95 ± 0.84 Adolescents: 0.58 ± 1.83	Change in BMI z-score: 0 +0.01 -0.16
Alemzadeh 2004[144]	BMI 21.6 ± 3.2	BMI 23.0 ± 3.0	Change in BMI: +1.4 (p<0.05)
Garcia-Garcia 2007 [162]	BMI SDS: 0.42	BMI SDS: 0.33	Change in BMI SDS: -0.09
Hanas 2006[145]	BMI SDS: 0.65 ± 1.2	BMI SDS: 0.81 ± 1.2	Change in BMI SDS: +0.16 (NS)
Juliusson 2006[166]	BMI SDS: Boys: 0.43 ± 0.79 Girls: 1.13 ± 1.34	BMI SDS: Boys: 0.68 ± 0.79 and Girls: 1.40 ± 1.31	Change in BMI SDS: Boys: +0.25 (p=0.14) Girls: +0.27 (p=0.01)
Kordonouri 2006[146]	BMI SDS: <12 yr: 0.30	BMI SDS: < 12 yr: 0.28	Change in BMI SDS: -0.02 (NS) -0.03 (NS)

	>12 yr: 0.43	> 12 yr: 0.40	
Liberatore 2004 [167]	BMI 22.0	BMI 23.5	Change in BMI: +1.5 (p=0.00003)
Mack-Fogg 2005[168]	BMI z-score: NR	BMI z-score: NR	Change in BMI z-score: Overall: +0.13 (p<0.5) 2-4 yr: +0.19 (NS) 5-9 yr: +0.21 (p<0.008) 10-12 yr: +0.03 (NS)
McMahon 2005[147]	BMI z-score: 0.81 ± 0.08	BMI z-score: 0.75 ± 0.08	Change in BMI z-score: -0.06 (NS)
Raile 2002[154]	BMI 21.3	BMI 22.0	Change in BMI: +0.7 (NS)
Saha 2002[148]	Mean relative weight: 104.1%	Mean relative weight: 107.0%	Change in mean relative weight: +2.9% (NS)
Schiaffini 2005[163]	BMI SDS: 1.21 ± 1.2	BMI SDS: 1.24 ± 1.2	Change in BMI SDS: +0.03
Sulli 2003[155]	BMI 21.8	BMI 22.32	Change in BMI: +0.52 (NS)
Toni 2004[176]	BMI 20.7 ± 2.5	BMI 21.2 ± 2.4	Change in BMI: +0.5 (NS)
Ugrasbul 2006[177]	NR	NR	Change in BMI: +0.51 (p=0.019)
Willi 2003[149]	Weight SDS: 0.60 SEM ± 0.13	Weight SDS: 0.61 SEM ± 0.11	Change in Weight SDS: +0.01 (NS)
Wood 2006[150]	BMI z-score: 0.79	BMI z-score: 0.77	Change in BMI z-score: -0.02 (NS)
Young Children			
Berhe 2006 [160]	BMI 18.2	BMI 18.4	Change in BMI: +0.2 (NS)
Litton 2002 [159]	Weight z-score: 0.05	Weight z-score: 0.03	Change in Weight z-score: -0.02 (NS)
Weinzimer 2004 [151]	BMI z-score: 0.9	BMI z-score: 0.7	Change in BMI z-score: -0.2 (p=0.002)

NR not reported; NS not statistically significant;

Seventeen studies reported a non-significant change in weight. Nimri 2006 [142] reported a non-significant change overall, but a significant decrease in the sub-group of young adults (but not in younger age groups).

Linkeshova 2002[140] reported mixed results; i.e. unchanged in 53% of patients, an increase in 22% and decreased in 25%. Juliusson 2006 [166] reported a non-significant increase in boys, but a significant increase in girls.

Six studies reported a significant overall increase in BMI.[139,144,167,168,170,177] However, in Mack-Fogg 2005[168] the increase was not significant in age groups 2-4 years and 10-12 year (but was highly significant in 5-9 year olds). Also it should be noted that in Alemzadeh 2004[144] (mean age 14.7 years n=40) Liberatore 2004[167] (mean age 12.9 years n=73) and Ugrasbul 2006[177] (age range 4 to 21 years

n=131) they reported BMI change – and did not report BMI z-scores – so did not take account of the child's development.

The study by Weinzeimer 2004[151] in young children showed a significant decrease in BMI z scores. Significance levels were not reported in the four remaining studies. Pickup 2006[134] and Garcia-Garcia 2007[162] showed a decrease, Schiaffini 2005[163] showed an increase and Ahern 2002[161] showed mixed results in different sub-groups; i.e. no change in pre-schoolers, an increase in school age children, and a decrease in adolescents.

In summary, 17 of the 30 studies showed no significant weight change. Six showed a significant increase (but with the caveat that for three of these studies in children/adolescents the change did not measure z scores on BMI or weight, hence did take account of the child's development), and one showed a significant decrease. The remaining studies either did not report significance or showed mixed results.

2.8.11 Insulin dose

There were 21 studies that reported comparable before and after data on insulin dose. These are summarised in Table 17.

Of the eight studies in adults, five showed a significant decrease and one [156] showed a decrease, but the significance level was not reported. One study [170] showed a significant increase and the other [164] showed a non-significant increase.

There were 11 studies in children/adolescents. Four [150,163,167,176] showed a significant decrease, three showed a decrease but the significance level was not reported [144,154,155] and two [146,149] showed a non-significant decrease. Ahern 2002[161] showed non-significant change in all sub-groups (preschool age group increase and older age groups a decrease). Conrad 2002[152] showed an almost negligible decrease in the prepubertal age group and a significant decrease in the pubertal age group.

There were two studies in young children. One [159] showed a non-significant increase and the other [160] a non-significant decrease.

In summary, of the 21 studies examined, only five showed an increase in the insulin dose on pumps. This increase was only significant in two studies (Garg 2004[170]- in adults and Conrad 2002[152] - in the

pubertal sub-group). The reduction in insulin dose will provide some savings to modestly offset the cost of the pump.

Table 17: Insulin dose before/after CSII

Study	Insulin dose before CSII (U/kg/day – unless otherwise indicated)	Insulin dose on CSII (U/kg/day)	Difference (Before – after) [+ve = decrease -ve = increase]
Adults/ mixed age groups			
Cersosimo 2002[164]	0.50	~ 0.55	~ -0.05 (NS)
D'Annunzio 2005[139]	Median 0.92	Median 0.90	0.02 (p=0.049)
Fahlen 2005[156]	0.63 ± 0.27	0.57± 0.25	0.06
Garg 2004[170]	43.2 U/day	44.5 U/day	-1.3 (p<0.001)
Lepore 2004 [157]	48 ± 11.7 U/day	35.9 ± 8.5 U/day	12.1 (p<0.001)
Pickup 2005[133]	47.1 ± 16.4 U/day	34.1 ± 10.5 U/day.	13.0 (p<0.001)
Pickup 2006[134]	46.1 ± 16.7 U/day	35.7 ± 12.1 U/day	10.4 (p<0.001)
Rodrigues 2005[135]	47.6 U/day	37.4 U/day	10.2 (p=0.008)
Children/ adolescents			
Ahern 2002[161]	Pre-school: 0.7 School age: 1.0 Adolescents: 1.3	Pre-school: 0.8 School age: 0.9 Adolescents: 0.9	-0.1 (NS) 0.1 (NS) 0.4 (NS)
Alemzadeh 2004[144]	0.97 ± 0.2	0.91 ± 0.2	0.06
Conrad 2002 [152]	Pre-pubertal: 0.7 ± 0.2 Pubertal: 1.1 ± 0.3	Pre-pubertal: ~ 0.7 (est. from graph) Pubertal: ~0.91 (est. from graph)	Pre-pubertal: ~ 0 (NS) Pubertal:~ 0.1 (p<0.01)
Kordonouri 2006[146]	0.96	0.93	0.03 (NS)
Liberatore 2004[167]	1.10 ± 0.31	0.87 ± 0.17	0.23 (p=0.00001)
Raile 2002[154]	1.02 ± 0.27	0.79 ± 0.11	0.23
Schiaffini 2005[163]	0.93 ± 0.2	0.74 ± 0.15	0.19 (p<0.01)
Sulli 2003[155]	1.03 ± 0.30	0.75 ± 0.21	0.28
Toni 2004[176]	58.2 ± 15.3 IU	44.4 ± 11) IU	13.8 (p < 0.001)
Willi 2003[149]	0.90 ± 0.03	0.61 ± 0.11	0.29 (NS)
Wood 2006[150]	1.0 ± 0.3	0.8 ± 0.2	0.2 (p<0.01)
Young children			
Berhe 2006 [160]	0.74 ± 0.3	0.68 ± 0.25	0.06 (NS)
Litton 2002 [159]	0.61 ± 0.02	0.71 ± 0.07	-0.1 (NS)

NR not reported; NS not statistically significant

2.8.12 Quality of life

Nine studies evaluated aspects of quality of life associated with CSII use from the perspective of health care professionals, parents or children.[135,135,136,140,148,169,173,175,179]

Studies used varying methods to collect data including questionnaires, specified scales, scales developed for the study and interviews. Sample sizes were generally small; only one study evaluated more than 35 patients and this larger study assessed the views of health professionals and not patients/parents.[136]

Adults/ mixed age groups

Bruttomesso and colleagues (2006) sought the views of health professionals about CSII by sending a questionnaire to Diabetic Care Centres with patients on CSII (n=145 centres caring for 514 patients on CSII, age range four to 85 years).[136] Patients on CSII represented about 5% of patients with diabetes in centres using the pumps. The carers felt that the greatest benefits of CSII were better metabolic control and greater flexibility with mealtimes and physical activity; less important benefits included better control of dawn phenomenon and the reductions in insulin dose and hypoglycaemic episodes. Less than half of the physicians felt that CSII had improved patient comfort. Carers felt that the main inconvenience was cost. Other inconveniences included the burden of constantly carrying an external device, the need for special education and the need of special and continuous care in wearing the pump. Only paediatricians felt that weight gain was a problem. No details were given about the questionnaire.

Rodrigues and colleagues asked patients to compare CSII with their previous treatment.[135] All of the patients reported that they preferred CSII to previous treatment in overall terms and in terms of flexibility, convenience. All patients, including the four who discontinued CSII, would recommend CSII to others.

Linkeschova and colleagues assessed quality of life with a validated, diabetes-specific questionnaire. All quality of life parameters were significantly improved during CSII compared with ICT in the 50 patients who had completed a quality of life questionnaire under ICT immediately prior to starting CSII therapy.[140]

Children/adolescents

In the study by Mednick and colleagues (2004), parents and children (n=22 children aged 10 to 18 years on CSII for between 3 and 22 months) completed the Insulin Pump Therapy Satisfaction Questionnaire (IPTSQ) that was developed specifically for this study, and children completed the

Diabetes Quality of Life for Youths (DQOL-Y) questionnaire.[173] Scores on the DQOL-Y were compared with those from children who had participated in the original DQOL-Y. In the IPTSQ, children and parents reported greatest satisfaction with flexibility in relation to meal schedules (parents 73% and children 81%), sleep schedules (parents only) and food variety (children only). About one third (36%) of parents reported that the child was better able to manage diabetes on his/her own. Just under half of parents and children reported that the child had better control of the diabetes (parents 46% and children 43%). Rates of reporting an overall improved lifestyle were relatively low (parents 9% and children 5%). The main reported challenges were difficulties related to calculating insulin dose (parents 42% and children 41%) and difficulty inserting or changing pump cannulas (parents 38% and children 55%). Children reported that the main benefits of CSII were increased flexibility and convenience (76%) and the avoidance of painful insulin injections (33%). Just under half of the parents (45%) and about one fifth (19%) of children would recommend the pump to others. About one third of parents (35%) reported that the change to CSII did not go as well as anticipated. (One of our clinical experts told us that parents sometimes came back after the first six weeks saying that it had been harder work than they expected.) Children in the study reported lower satisfaction and less worry than the standardised sample on the DQOL-Y scale ($p \leq 0.001$ for both). This may be due to small sample size, differences in mean ages of the samples or the fact that the standardization sample included children on all types of insulin regimens. There was no significant difference between the groups for diabetes impact.

In a qualitative study involving 21 parents of 16 children (aged < 12 years), Sullivan-Bolyai and colleagues (2004) identified themes from interview audiotapes and field notes.[175] Parents reported learning about the pump from nurses, physicians, friends and websites. They perceived that the pump would improve diabetic control. Worries included the catheter falling out/ malfunctioning and the child being bullied. Parents reported that it took them between 10 days and three months to feel comfortable with CSII and from six weeks to nine months to feel confident. They had to alter their routines and learn to sleep through the night without checking the child's blood glucose. They felt that older children became more involved in the management of the diabetes. On the day-to-day management of diabetes, they felt that their children had better blood glucose control and reported increased flexibility of mealtimes. Using CSII, they worried less about overall care, said that their sleep had returned to normal, that they had more free time, that children were in a better mood with increased concentration and increased participation in social life, and were more flexible about mealtimes.

Juliusson and colleagues (2006) used generic (CHQ-CF87) and diabetes-specific QoL (DQOL) instruments, and reported significant improvements in some areas of CHQ-CF87.[166] There was a

higher score on the family activity scale (p=0.041) and change in health score (p=0.042). However, diabetes specific QoL was not significantly improved. The patient satisfaction data also showed a higher degree of general satisfaction, faith in disease self-management, and motivation to treatment.

In the study by McMahon and colleagues (2005), 43 of the first 51 children completed the Diabetes Quality of Life Instrument (DQOL) and Self-Efficacy for Diabetes Scale (SED) questionnaires before treatment and 6 months later.[147] The score for impact of diabetes on the patients fell indicating decreased impact ($p<0.05$). Scores of individuals' self-efficacy with diabetes increased significantly ($p<0.05$). There was no significant change in worries about diabetes. Satisfaction with life did not change.

Young children

Alemzadeh and colleagues (USA 2006) used the Pre-school Quality of Life (TAPQoL) to assess quality of life in young children (n=14) and reported no significant change in TAPQoL subscales from before to after CSII (baseline to one year).[179]

Saha and colleagues (Finland, 2002) stated that all parents of children under two (n=4 children) reported that CSII was easier to manage than conventional treatment.[148]

Shehadeh and colleagues (Israel and Slovenia, 2004) compared parents views about the quality of life before and after four months of CSII use in their in young children (n=15) using a modified version of the Diabetes Treatment Satisfaction Questionnaire (DTSQ, scores from 0 to a maximum of 36 for high satisfaction).[169] Parents reported that quality of life significantly improved after CSII was started (DTSQ: 30.67 versus 19.8, $p<0.001$). Both worry and impact subscales of the modified DTSQ (which measures treatment satisfaction not quality of life) were significantly improved on CSII ($p<0.001$ for both). Fourteen of the fifteen families preferred CSII to the previous multiple daily injections (MDI) and refused to return to MDI.

Of the three studies that asked if patients/parents would recommend CSII to others, two studies reported that almost all would recommend CSII to others.[135,169] Just under half of the parents (45%) and about one fifth (19%) of children would recommend the pump to others in the third study reporting this outcome.[173]

One study, available in abstract only at present, has looked at the dermatological complications of CSII. Conwell and colleagues from Toronto examined the skin of 50 consecutive patients and noted that most had skin lesions – scars, subcutaneous nodules, and erythema in over half.[181] But very few

patients would consider stopping CSII because of these lesions, which suggests that the benefits outweigh the disutility of the skin lesions.

2.8.13 Summary of findings of observational studies

There are far more observational studies available now than there were at the last review. In general, they report;

- *Much greater improvements in HbA_{1c} than reported in the RCTs.*
- *Considerable reductions in severe hypoglycaemia. This may reflect selection for CSII of people having particular problems with hypoglycaemia, but that would make the results more applicable to the patients who would get CSII in routine care.*
- *The majority of studies show no increase in DKA, and if anything it is decreased. The recent abstract from Sweden is concerning, but may reflect a period of very rapid expansion in CSII use.*
- *Some gain in weight, but usually minor.*
- *A reduction in daily insulin dose, which will provide some savings to offset the cost of CSII.*
- *Gains in quality of life, with comments on items such as flexibility of meal choices and timings and other aspects of lifestyle, and diabetes being easier to manage in children. In these studies, patients prefer pumps.*

2.9 Other evidence

2.9.1 Use of CSII at night-time only

Kanc and colleagues (1998) carried out a small trial to see if good control during the night, with avoidance of hypoglycaemia, would restore hypoglycaemic awareness in patients with T1DM who had lost it[70]. Fourteen patients took part in a cross-over study. In one arm, they continued their meal-time short-acting insulin and bedtime NPH. In the CSII arm, they continued their short-acting injections but switched to CSII at bedtime. Those who had been experiencing the dawn phenomenon used two or more basal rates during the night.

No differences in HbA_{1c} were seen between the two arms, but hypoglycaemia was about a third less frequent ($p = 0.03$) and warning signs were improved. The authors believe that this was due at least partly to avoidance of nocturnal hypoglycaemia, though nocturnal testing was not frequent enough for them to be sure. Total daily insulin requirements were lower with CSII (48 units versus 56 units), with more being taken as short-acting at meal-times.

Kaufman and colleagues (2000) carried out a similar study in children aged 7 -10 years, with two arms in a cross-over trial.[182] In one arm, children continued with three injections of lispro and NPH. In the CSII arm the pump was used to provide basal insulin and the breakfast and dinner lispro cover. The duration of the trial was short, four weeks on each arm. During the CSII period, blood glucose control was better (as reflected in fructosamine levels and five daily measurements, including at 3am. Fear of hypoglycaemia was halved. The authors report that there was less hypoglycaemia but do not provide data. Insulin dosage was reduced from a mean of 0.9u/kg/day to 0.7units. Quality of life was reported to be better on CSII but no data are given.

2.9.2 Use of different basal rates.

One of the differences between an analogue-based MDI and CSII, is that once glargine or detemir is injected, the basal rate is fixed for the day, and cannot be changed if, for example, unexpected exercise occurs. Nor can the user have different basal rates in, for example, morning and afternoon. However, pump users can programme different basal rates for different times of day, and for different days. We asked INPUT for data on how many different basal rates were used by members, and the results are shown in table 18.

Table 18: Number of basal rates used.

Number of basal rates used	Percentage of members
Just 1	9%
2	14%
3	19%
4	22%
5	16%
6	10%
7	4%
8	4%
9	2%
10 or more	1%

It would be interesting to look at HbA_{1c} and hypo frequency by number of basal rates used, but that is beyond the scope of this review.

The number of basals used raises an important issue about expertise in CSII use. Some of the trials are quite short – 16 to 24 weeks. Nearly all will recruit novice users (Maran and colleagues 2005[107] being an exception). How long does it take a pump user to get the full benefit from a pump? Are the trials too short for users to get full benefit? Those randomised to CSII will be testing their blood glucose, and aware of hypo frequency, but they will get at most one or sometimes two HbA_{1c} results during the trial. So they will not have time to adjust their regimens, repeat the HbA_{1c} three months later, and adjust again. Nor perhaps would they have enough time to try out different basal rates for different combinations of diet and activity.

It would be interesting to have data on HbA_{1c} and hypo frequency in pump users at three-monthly intervals for several years.

2.9.3 Who benefits most from CSII?

Previous meta-analyses reported that CSII gave HbA1c levels lower, on average, by 0.5% compared to MDI, a clinically significant but not dramatic improvement. The trials in these meta-analyses used mainly SA soluble, rather than SA analogues.[16,48] Switching to the latter gives another 0.2% improvement.[10]. A later meta-analysis of only studies using analogue insulins as the short-acting form, which at the time had only three trials, noted that the benefit of CSII relative to MDI was greater in those with high baseline HbA_{1c}.[183]

Pickup and colleagues explored ability to benefit further.[133] Firstly, they studied the patients to whom NICE guidelines most applied – those who could not achieve good control without disabling hypoglycaemia. (They noted that previous trials often excluded patients who were having problems with hypoglycaemia.) In a before and after study in patients having problems with hypoglycaemia on MDI, they first tried a more intensive period of MDI for five months, and then, if control had not been achieved, started CSII. The improvement in HbA1c was 1.4%.

In an extension of this study with a larger group of patients, Pickup and colleagues (2006) showed that the strongest predictors of improvement in HbA_{1c} were a high baseline level on MDI and variability of blood glucose.[134] They noted that one of the main reasons for failing to achieve good control was hypoglycaemia, and that hypoglycaemia was associated with large swings in blood glucose, and hypothesised that subjects with wide variability in blood glucose levels would find it most difficult to achieve control on MDI because of high rates of hypoglycaemia.

[redacted]

The pooled hypoglycaemia rate on MDI was [redacted]
There was a [redacted] on CSII. HbA_{1c} was reduced [redacted]
The before and after studies reported a [redacted]

2.9.4 Data from the Insulin Pump Clinical Database

A group of centres with considerable pumps experience and hence with larger numbers of pump users than most clinics, have pooled their data in a project sponsored by Roche but run independently by the Paediatric Epidemiology Group in Leeds. The usefulness of this data set is that it reflects, firstly, results in routine care outwith trials, and secondly, it gives results from centres of pumps expertise. The data currently available to us do not included details of what regimens patients were on before CSII, but we assume MDI. (*data requested)*. Current centres include Harrogate, Bournemouth, Leeds (paediatrics) and Middlesbrough.

[redacted]

19

[redacted]

2.9.5 Short-term studies

Hirsch and colleagues (2005) carried out a cross-over study comparing analogue MDI (aspart and glargine) with CSII.[184] It was excluded from our main analysis because of the short-duration – five weeks on each arm, and too short to use HbA_{1c} as a measure of glycaemic control. Fructosamine improved, and nocturnal hypoglycaemia was about 25% less frequent with CSII ($p = 0.0024$). Insulin dose was slightly lower on CSII.

One problem with short-term studies has been mentioned above. How long does it take users to achieve the maximum benefits of CSII, including the use of multiple basal rates when required? In their study in young children (where parents controlled the pump programming), Wilson and colleagues noted that pump users started with an average of 2.9 basal rates per day, but by the end of a year were using 4.8 different basal rates.[121]

There are also several very short studies of CSII in insulin-resistant T2DM, used to treat insulin resistance, but we have excluded these.

2.9.6. Quality of life.

Barnard and colleagues (2007) [185] recently reviewed studies reporting quality of life aspects on CSII. This group has received support from Roche, one of the pump manufacturers, for pump-related research, and a conference abstract version of the review carries the Roche logo, but the review is a high quality and properly critical one, and was carried out for a PhD thesis (Barnard, personal communication, June 26th 2007), not funded by Roche, and seems free of bias. Most of the 17 studies in their review are included in this review or the 2002 assessment report. Barnard and colleagues (2007) [185]pay particular attention to the quality of life instruments used, and note that some are not validated. They comment on problems with the design of the studies, such as the lack of control groups, and in particular the confounding role of structured education, which should be given to all before commencing CSII, but which may not be given to comparator groups if there are any. In before and after studies, it is difficult to say how much of the benefit is due to the education rather than to the CSII. They also note the small numbers in many of the studies. They conclude that there is currently no consistent quality of life gains from CSII in the current evidence base, but accept that this may be more a problem with lack of evidence than evidence of no benefit;

"*if a minimum standard were assumed to be a randomised controlled trial, which controls for increased education and contact time, uses appropriate sensitive measures, and recruits large numbers of participants to each group, there are no current published studies which meet these criteria."*

Barnard and colleagues recommend further research;
".. a large-scale multi-centre patient preference controlled trial is required to focus specifically on quality of life issues surrounding insulin pump therapy….It is important to be clear about what quality of life means, i..e increased independence, greater freedom, greater flexibility, easier management of diabetes, better control, etc"

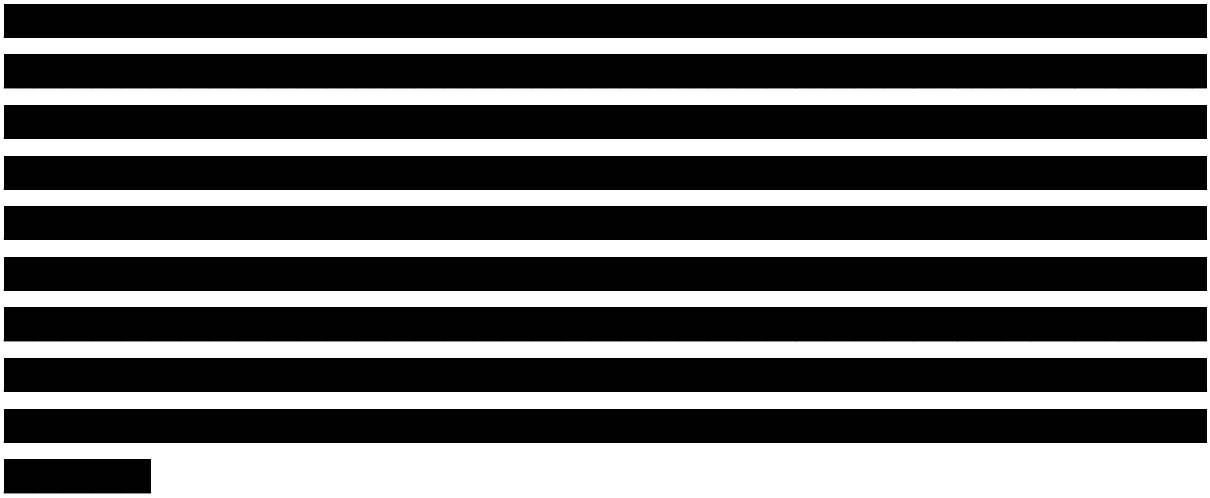
A key point in quality of life aspects of CSII is that some of the reported benefits are in health-related quality of life, but many are not. Some are in aspects such as social life (not having to worry abut what time meals arrive on social occasions), greater ease of travel, flexibility of lifestyle, and enhanced ability to enjoy physical activities. Once the basal insulin in MDI is in, it is there for the day and night. The pump infusion can be adjusted at any moment.

Having identified a shortage of evidence, Barnard and Skinner carried out two studies. The first was a qualitative study based on interviews with 80 pump users. [186]The study was funded by Roche Diagnostics; the patients were identified by Roche; and the interviews were carried our by Roche staff, trained by the investigators. The potential for bias seems considerable, but we think it provides

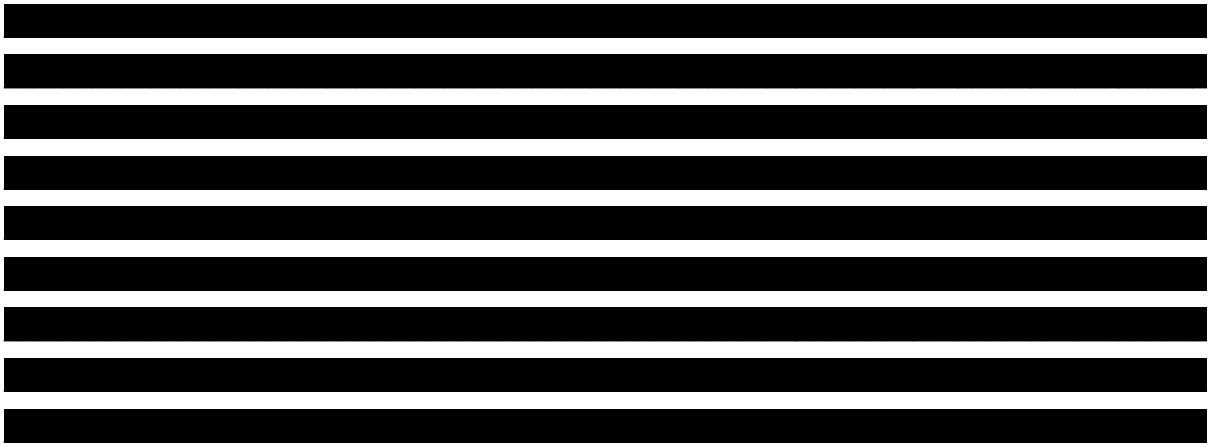
reliable data, for two reasons. Firstly, the disadvantages of CSII are dealt with as well as the benefits, and the authors report that 60% of the patients reported downsides to CSII. Secondly, many of the comments match those obtained from pump users in the previous assessment report (a source of evidence not mentioned by Barnard and Skinner in their systematic review).

The main disadvantages of CSII include visibility of the pump (though the latest versions may be smaller), problems with breakdowns (21% of respondents), and lack of appropriate advice from health care professionals. Three of the 80 noted cost was a problem, presumably because they were paying that themselves: some primary care trusts are very restrictive in funding. But the positives outweighed the negatives, as one would expect in a group of confirmed users. The authors summarise the results thus;

"Participants overwhelmingly reported experiencing benefits and improvements in their quality of life associated with insulin pump use."



This reflects a problem in research involving pump users. They tend to be enthusiastic and highly motivated individuals who are happy to take part in research, which may make it difficult to find a comparison group with the same characteristics.



[redacted]

[redacted]Again, these match the comments received from a far smaller number of users for the last assessment report.

2.9.7. New systematic reviews

Weissberg-Benchell and colleagues published a meta-analysis in 2003 but it included studies only up to 2001, and therefore does not add to the findings of the last assessment report.[187]

Retnakaran and colleagues (2004) carried out a meta-analysis of trials which used rapid-acting analogues in both MDI and CSII, and therefore included only three trials, two of which were included in the last assessment report.[183] The third is De Vries (2002), included above. All three trials used NPH as basal insulin. [114]

Siebenhofer and colleagues (2004) included studies comparing SA analogue and SA soluble, for both CSII and injection regimens.[188] They included eight trials in CSII, most of which had been included in the last assessment report and in the journal paper by Colquitt and colleagues.[10,48] Three trials were not included in the assessment report, two being definite exclusions because of short duration of follow up. One trial in the assessment report analysis was not included by Siebenhofer.

A high quality report from AETMIS drew heavily on the last assessment report but added trials published up to 2004.[17] These are included in this report.

2.9.8 Indications for CSII in different age groups: children and adolescents

The German working group for insulin pump treatment in paediatric patients[189] has identified seven indications for CSII, in a cohort of 1567 children and adolescents;

- Dawn phenomenon (27.4%)
- Reduction of hypoglycaemia (20%)
- Flexibility (22.4%)
- Improvement of hyperglycaemia (18.1%)
- Motivation (10.4%)
- Failure of injection therapy (1.6%), by which they meant CSII was used as a “last resort”

- Pregnancy (0.1%)

But the proportions varied widely amongst the four age subgroups. In the under 5s, the main reason (42%) was reduction of severe hypoglycaemia, followed by flexibility (22%). In the 5-9 year age group, hypoglycaemia was again the top indication (32%0 followed closely by the dawn phenomenon (28%). In the 10-14s, dawn phenomenon was the commonest reason (32%), followed by flexibility (22%) and hypo (17%) and hyper (18%) glycaemia. In the 15-20 year range, there was an even spread – flexibility 26%, dawn phenomenon 22%, hyperglycaemia 21%, motivation 18%.

One important finding of this study was that initial reductions in HbA1c were not always sustained. Amongst those who started CSII because of hyperglycaemia, HbA1c fell from an initial mean of 8.85 to 8.5% at 12 months, but then rose back up to 8.85 at 36 months. However, this represents success, since in children HbA1c usually rises with age. [41]. Those who started CSII because of hypoglycaemia had a lower starting HbA1c of 7.6%, maintained that at 12 months (7.5%), after which it rose to 7.9% at two years and 8.1% at three years.

2.9.9. Summary of clinical effectiveness

Since the last review, the number of observational studies has increased considerably, and there have been more trials of CSII against NPH-based MDI. We now have some trials in people with T2DM. Unfortunately, there is a relative scarcity of trials with analogue-based MDI, and some of those are very small.

The one study of CSII versus analogue MDI in adolescents/children shows a reduction of 1% in HbA_{1c}.

The recent RCTs of CSII versus NPH-based MDI do not add much to the previous review, which found a reduction in HbA_{1c} of 0.6%, a similar figure to that reported by Pickup and colleagues in their 2002 meta-analysis.[16]

The observational studies have variable results but show larger drops in HbA_{1c}.

(AiC) The Insulin Pump Database also shows [redacted]

Quality of life appears better on CSII, and most patients prefer it.

Most studies show a reduction in hypoglycaemia with CSII, and a reduction in insulin dose required.

Chapter 3: The industry submission.

The joint submission by the pump manufacturers, under the auspices of the Association of British Healthcare Industries, started by making two points about usage;

- that there was considerable variation of provision in England, with some PCTs being more restrictive than others, and probably more restrictive than NICE intended
- that UK usage was much less than in comparable countries

3.1 Clinical effectiveness

The main source of clinical effectiveness data was the unpublished Pickup meta-analysis (2007), [redacted]. An account of this analysis has been given previously (chapter 2).

The submission also comments that quality of life is better on CSII and that "many studies fail to capture the real-life benefits, such as convenience, reduced worry, and greater freedom, reported by patients receiving insulin pump therapy", a statement with which we agree, based on review of the literature and previous submissions by pump users or families.

The cost-effectiveness analysis in the industry submission uses three possible scenarios in terms of HbA_{1c} benefit in T1DM, discussed below. No modelling is done in T2DM. Nor is there any modelling of hypoglycaemia-only benefit, for example in those with HbA_{1c} under 7.5% (taking the NICE guidelines target as good control) whose HbA_{1c} does not improve on CSII but who have less trouble with hypoglycaemia. This group was identified through the patient perspectives section of the previous assessment report. The base case analysis was of a cohort 38 years of age and a duration of diabetes of 10 years. Baseline HbA_{1c} was taken to be 9.4% for MDI, with a standard deviation of 2.1%.

Immediate benefits included a reduction in severe hypoglycaemia events, as derived from the Pickup (2007) analysis and outlined below, but it should be noted that while the CORE model used for the modelling within the industry submission permits a death rate to be associated with severe hypoglycaemic events, the modelling within the industry submission appears to have conservatively assumed that no such deaths would occur. The BDA Cohort Study reported that of 22 of 949 (2.3%) deaths in the cohort (T1DM diagnosed under age 30) were due to hypoglycaemia.[26,190] Edge and colleagues (1999) reported that in patients aged under 20 at death, and with diabetes on the death certificate, 8% of deaths (7 out of 83) related to diabetes were due to hypoglycaemia, but hypoglycaemia was also suspected in another four patients found “dead in bed”.[191] This term refers to

people found dead in an undisturbed bed, having been in apparently good health the day before, and some are known to have had problems with hypoglycaemia.[192] Tunbridge (1981) looking at deaths of diabetics under age 50, concluded that 3-4% were due to hypoglycaemia.[193]

The industry submission cites a paper by Cryer [23] which estimates that 2-4% of deaths in T1DM are due to hypoglycaemia, which fits with the afore-mentioned studies.

Other points;

- as regards current management, the submission (page 13) states that "In T1DM, therapy is mainly through intensive insulin treatment as optimised MDI or CSII" but that may be unduly optimistic. Most children in the Scottish audit of under 15 year olds were still on conventional insulin regimens in 2002-4.[41]
- in cost comparisons, the cost of MDI is based in glargine, but given the high proportion still on NPH-based MDI, that could be seen as possibly misleading, and as reducing the marginal cost of CSII. However the use of MDI based on long-acting analogues is justified because current NICE guidance expects a trial of analogue MDI before CSII.

The clinical effectiveness section contains three sections;

- the Pickup and Sutton meta-analysis, already described
- quality of life data from the studies by Barnard and colleagues, already described
- a literature review, though it is more of an annotated bibliography than a systematic review. Most of the studies listed are in chapter 2 of this report.

The review of cost-effectiveness studies reports the results of the Scuffham and Carr 2003[194] and Roze and colleagues 2005[195] papers, and the abstract of the paper by Conget and colleagues (2006)[196] (the full paper was not translated). Our more complete review is in chapter 4.

3.2 Cost Effectiveness

The cost-effectiveness analysis used the CORE model, which we consider to be a highly developed and well-tested model, and one of the foremost of its kind, though there are only a few models of T1DM. Palmer and colleagues (2004a) outlined the broad structure of the CORE model for both T1DM and T2DM patients[197].

The CORE model can be briefly summarised as being an internet based model which is based upon 15 sub-models which simulate the main complications of diabetes. Each sub-model is a markov model

which employs monte carlo simulation which incorporates the time, the state, the time in state and transition probabilities which are typically diabetes type dependent as derived from published sources.

A common problem with standard markov modelling is the requirement that distinct mutually exclusive memory-less disease states have to be specified. This approach would overlook the interactions between the different complications of diabetes unless a prohibitively large number of disease states were defined. CORE modelling uses tracker variables to allow interactions between the different sub-models, with the progression of one or more complications influences the transition probabilities in other sub-models where a relationship has been established. For instance, the risk of a first myocardial infarction is linked to whether gross proteinuria, microalbumina or end stage renal disease has developed, a relative risk being specified for each of these.

The 15 sub-models of CORE are: Myocardial infarction; Angina; Congestive heart failure; Stroke; Peripheral vascular disease; Neuropathy; Foot ulcer, with possible amputation; Retinopathy; Macular Oedema; Cataract; Nephropathy; Hypoglycaemia; Ketoacidosis; Lactic Acidosis; and, General mortality. Note that a specific mortality is associated with the Myocardial infarction; Congestive heart failure; Stroke; Foot ulcer, with possible amputation; Nephropathy; Hypoglycaemia; Ketoacidosis and Lactic Acidosis sub-models. For Hypoglycaemia the specific mortality is specified by the user.

The population characteristics of source references for the 15 complications of diabetes sub-models within the overall CORE model are briefly summarised in appendix 5. It can be noted in passing that not all sub-models are differentiated by diabetic type. Myocardial infarction, angina, stroke, peripheral vascular disease and foot ulcers leading to amputation are modelled have the same model inputs for T1DM patients as for T2DM patients. The average age within the references contributing to the modelling is also often quite high, and while some references relate their effects to age groups, the age range within these studies may still give rise to some concerns around using the CORE model among younger age groups. In particular it does not appear suitable for modelling effects of CSII started in childhood.

The baseline population characteristics within CORE can be specified in terms of age, sex, duration of diabetes, racial characteristics, glycemic control, blood pressure, the body mass index, lipid levels, smoking and baseline rates of complications. Treatments can be specified as modifying glycemic control, hypoglycaemic event rates, severe hypoglycaemic event rates, blood pressure, the body mass index and lipid levels. Typically only glycaemic control and hypoglycaemic event rates are specified.

Palmer and colleagues (2004b) undertook a validation exercise of the CORE model using published data for the incidence of the complications associated with both T1DM and T2DM.[198] This exercise

appears to show reasonably good validation for the incidence of the complications examined. However, it should be noted that for T1DM the only complications for which validation data was available were the microvascular complications of diabetes. While these showed reasonably good correspondence within the validation exercise, macrovascular complications among those with T1DM such as CHF and MI were not explored within the validation exercise.

The results of Palmer and colleagues for the validation for overall survival rates within those with T1DM used data from the US Joslin Clinic Study.[199,200] Within this CORE appeared to overestimate the death rate among those with T1DM, this overestimation worsening with the time horizon employed. While correspondence was reasonably good at the ten year point with CORE estimating 94.8% survival in contrast to 96.8% within the Joslin Clinic Study, by the 25 year point the correspondence has worsened to CORE estimating 68.8% survival as against 81.0% within the Joslin Clinic Study. The source of this is not readily apparent, but given the validation results for the microvascular complications of diabetes, in comparison to the Joslin Clinic Study there may be a tendency for the CORE model to overestimate the incidence of macrovascular complications with an associated higher death rate. Data from EDIC suggests a link between HbA_{1c} control and macrovascular complications, but to the best knowledge of the authors the predictions of CORE have not been validated against this.

Within CORE modelling any improvement in baseline HbA_{1c} as a result of a novel treatment is typically assumed to be sustained. There is the possibility that while an improvement may be observed over a period of time, this relative improvement in HbA_{1c} may be eroded in the medium to long term. While CORE does permit some adjustment of this assumption through the use of a long term adjustment factor, it does not appear to permit the evolution of the gain in HbA_{1c} to be specified in detail. Given this, the longer term adjustment to the relative improvement in HbA_{1c} appears to be little used and the absolute gain over baseline HbA_{1c} is typically assumed to be maintained.

Within the CORE model deaths from hypoglycaemia can occur. However, while this can again be allowed for within the CORE model, given a lack of data this is typically not included, and has not been included within the industry modelling using CORE. Not including mortality is a conservative assumptions, and will to a degree under-estimate the QALY gain and over-estimate the cost per QALY, especially as deaths from hypoglycaemia may occur in young people, hence leading to large number of life years being lost..

Diabetes models are (if their developers submit them) tested in the Mount Hood Challenge. In the most recent of these, one test for the models was their ability to predict the outcomes of the DCCT trial.[201] The CORE model gave estimates very close to what was observed for renal disease,

retinopathy and peripheral neuropathy in the intensive group, and was also close for neuropathy and renal disease in the conventional group. It did somewhat under-estimate retinopathy in the conventional group. But overall, getting good results in a voluntary challenge reinforces our confidence that CORE is a good model, and given the paucity of models of patients with type 1 diabetes it is appropriate for the industry submission to have used it.

3.2.1 Modelling inputs

The cost effectiveness results presented within the industry submission were reviewed in tandem with additional data supplied through the web based CORE model implementation. As is clear from the summary of CORE above, from the summary the population characteristics within the clinical sources used for the CORE model as outlined in appendix 5, and from communication from the CORE modelling team, it is doubtful whether the CORE model would be applicable to the paediatric or adolescent population of patients with T1DM. The submission was been prudent in this regard, and modelled a cohort of baseline age of 38 years and an average duration of diabetes of 10 years.

The background prevalences for most of the vascular complications arising from diabetes were taken from the DCCT 1994 paper regarding the effect of intensive on the development and progression of long term complications in adolescents.[202] Baseline values for aspects such as cholesterol levels and blood pressure were drawn from two references.[66,203] As these references did not provide all background prevalences necessary for the CORE model, the background prevalences for angina, background diabetic retinopathy, proliferative retinopathy, macular oedema, cataract, foot ulcer and amputation were apparently set to zero. To the degree that background prevalences were underestimates within the modelling, this may have tended to slightly overstate the benefit of the anticipated improvement in HbA_{1c} arising from adoption of CSII. But give the baseline age of the cohort simulated it cannot be stated whether this would have necessarily been to the benefit of CSII.

The key clinical effectiveness inputs to the industry submission were drawn from the meta-analysis of Pickup and Sutton (2007) which analysed the effect of CSII relative to MDI within a population with T1DM with problems with severe hypoglycaemia episodes and a rate of severe episode of more than 10 per 100 patient years. Clinical effectiveness estimates were as below:

Table 20:Clinical effectiveness estimates

Simulation: Baseline HbA_{1c} 9.4% (SD ±2.1%)	**Mean change from baseline**	
	CSII	**MDI**
(A) Trial based analysis		
HbA_{1c} (%)	[redacted]	[redacted]
Severe hypoglycaemia (events/100 patient years)	[redacted]	[redacted]
(B) UK relevant analysis		
HbA_{1c} (%)	-1.29 (SD ±2.98%)	0 (SD 0)
Severe hypoglycaemia (events/100 patient years)	[redacted]	[redacted]
(C) Conservative UK analysis		
HbA_{1c} (%)	[redacted]	[redacted]
Severe hypoglycaemia (events/100 patient years)	[redacted]	[redacted]

The trial based analysis related to the meta-analysis of Pickup and colleagues (2007), which related the average baseline HbA_{1c} to the change that would be anticipated from the use of CSII. The average baseline HbA_{1c} within this was [redacted] and the reduction was [redacted]_The baseline HbA_{1c} may seem unduly optimistic, which means that patients have less to gain in terms of complications avoided. However, those who stand to gain from CSII include patients with good or even normal HbA_{1c}, but having problems with severe hypoglycaemia. It is therefore worth including this group.

[redacted] Given the relationship identified within Pickup (2007), this was mapped to given an average UK relevant improvement from CSII of -1.29%. This might be thought to be inappropriate because the HbA_{1c} level in all patients might be higher than in those being considered for CSII, who should already be on MDI. [redacted]

[redacted] Note that these changes were all applied to a baseline HbA_{1c} of [redacted]. As a consequence, MDI patients for the trial based analysis and the conservative UK analysis will have tended to have too high a baseline HbA_{1c} which may have tended to bias these analyses to a degree towards CSII.

The data underlying the trial based analysis, as summarised above and presented within table 20 of the economic appendix to the manufacturer submission, were not submitted electronically. Based upon the additional data submitted electronically, uncertainty appears to have only entered the model with respect to the baseline HbA_{1c} and the effect of CSII upon this.

The baseline level of HbA_{1c} as applied to the MDI cohort had a mean of [redacted] but this appears to have been subject to a standard deviation of [redacted]. As a consequence the range of HbA_{1c} levels within the MDI cohort was somewhat greater than might have appeared to be the case within the submission.

Similarly, it appears that at least for the UK relevant analysis and the conservative UK analysis, the impact of CSII upon HbA_{1c} also involved a large range having a standard deviation of ±2.98%. This uncertainty as to effectiveness does not appear to have been linked to patients' baseline levels of HbA_{1c} as would be implied by the logic applied within the submission to subsets within the Pickup (2007) meta analysis. This would tend to have increased the effect of CSII in patients with the worst control. Given this, some patients will have been simulated to have worse control under CSII than under MDI, but other CSII patients will be simulated to have very tight control of HbA_{1c} indeed.

While the submission is not explicit upon this point, the simulation inputs as uploaded by the CORE team to the CORE website implementation appear to indicate that distributions were placed upon both the baseline HbA_{1c} and reduction in this associated with CSII. Unfortunately, the current implementation of CORE does not permit a link between baseline HbA_{1c} and the effect of CSII upon this to be specified in the probabilistic sense: i.e. to specify a positive covariance between these variables. Given this, it may have been more appropriate to have modelled a representative patient than to have placed uncorrelated distributions upon these two variables where a clear covariance structure appears to be implied by the meta analysis of Pickup and colleagues (2007).

The direct costs of CSII and MDI treatment were drawn from industry sources and the British National Formulary (BNF), as outlined in appendix 6 and annualised within table 23 of the economic appendix to the industry submission. It is not immediately clear what dose or patient weight has been assumed, but a point to note is that the industry submission anticipated a 25% reduction in the need for insulin resulting in a cost saving from CSII of £177 per patient per year, reportedly drawing the dose assumption from the previous HTA and the cost from BNF. But the other costs of CSII more than offset this, with the annualised cost of CSII being £2,770 as against £1,224: an additional net cost of around £1,550 from the use of CSII.

The cost of a severe hypoglycaemia event was taken to be £413, this being stated as having been drawn from the NICE inhaled insulin HTA[204] which in turn cites the NHS reference costs as the source. However, it should be borne in mind that this is likely to relate to a very severe hypoglycaemia event, the average length of stay within hospital for this reference cost being slightly in excess of 2 days. As outlined within the NICE glargine HTA,[72] only a minority of patients are likely to be admitted to hospital following a severe hypoglycaemia event.

Given the centrality of the effect upon severe hypoglycaemia events within the submission an average cost of £413 may have been too high, and the £62 of the NICE glargine HTA may have been more appropriate or at a minimum appropriate as a sensitivity analysis. For instance, it appears that given an annual rate of 0.620 severe hypoglycaemia events under MDI as compared with 0.148 under CSII, the annual cost of treating these would be around £280 for MDI as compared with around £60 for CSII. This represents an annual saving of £220 from the use of CSII as against MDI. The parallel figures using the lower cost of £62 per severe hypoglycaemia event would appear to be £42 for MDI, £9 for CSII and a net annual saving of £33 per patient. Given the assumed 75% reduction in severe hypoglycaemia event from CSII and its centrality to the analysis, the assumed cost of £413 rather than £62 effectively reduces the additional annual cost of treatment with CSII by a little over 10%.

Costs of complications were mainly drawn from the Clarke and colleagues (2003) UKPDS65 paper[205], while utility values for were mainly drawn from the Clarke and colleagues (2002) UKPDS62 paper.[206] Note that UKPDS62 relates to patients with T2DM. There is no obvious reason to anticipate that the utility decrements arising from the complications associated with diabetes would be particularly different between patients with T1DM and T2DM. The appropriateness of the baseline utility value within UKPDS62 of 0.814 to patients with T1DM is a matter of conjecture, though an Australian study by Coffey et al (2002) found a somewhat lower baseline value of 0.672 for those with T1DM.[207]

Quality of life values were as below, the stated sources for these also being as below:

Table 21 Quality of life values

Complication	QoL	Source
Diabetes	0.814	Clarke (2002)[206]
Hemodialysis	0.490	Tengs (2000)[208]
Peritoneal dialysis	0.560	Tengs (2000)[208]
Kidney transplant	0.762	Tengs (2000)[208]
Background diabetic retinopathy	0.814	Clarke (2002)[206]
Proliferative diabetic retinopathy	0.814	AIHW (2003)[209]
Macular oedema	0.794	AIHW (2003)[209]
Severe vision loss / blindness	0.734	Brown (2004)[210]
Cataract	0.794	AIHW (2003)[209]
Neuropathy	0.624	AIHW (2003)[209]
Healed diabetic ulcer	0.814	Clarke (2002)[124]
Active ulcer	0.600	Carrington (1996)[211]
Amputation, year of event	-0.109	Clarke (2002)[124]
Amputation, years 2+ after event	0.680	Clarke (2002)[206]

Note that due to their short duration there are limited data on the quality of life impact arising from a severe hypoglycaemic event. Those studies that exist; e.g. Davis (2005),[212] Lundkvist (2005),[213] Tabaei 2004[214] (2004), Wikblad (1996)[215] are difficult to interpret due both to confounding variables and indeterminacy in terms of the duration of any quality of life impact from severe hypoglycaemic events. However, these papers do clearly show a significant effect upon quality of life from patients' most severe hypoglycaemic events. The impact may depend on where the episode happened. An event at home may have less impact than one at work, which may lead to time lost, and loss of confidence in both subject and employer.

The submission appears to have assumed that a quality of life detriment of -0.0121 is associated with each severe hypoglycaemic event. While this appears to have been an arbitrary assumption the value does not appear to be unreasonable. Perhaps as importantly and as demonstrated in the discusson and modelling of the subsequent chapter, given the average rate of severe hypoglycaemic events the results of the cost effectiveness modelling are relatively insensitive to the quality of life detriment associated with each severe hypoglycaemic event. Results are mainly driven by the effect upon glycaemic control.

3.2.2 Industry submission modelling results

Given the assumptions of the modelling and the 50 year time horizon, the aggregate results of the CORE modelling can be summarised as below:

Table 22: Aggregate results of the CORE modelling

Trial based analysis	**CSII**	**MDI**	**Difference**
Life expectancy	21.29	20.36	0.93
Life expectancy (discounted)	13.97	13.55	0.42
QALYs (discounted)	9.19	8.69	0.50
Treatment costs (discounted)	£40,074	£17,211	£22,863
Other costs (discounted)	£36,977	£42,682	-£5,705
Total costs (discounted)	£77,051	£59,893	£17,158
ICER : Cost per QALY	£34,330		
UK analysis	**CSII**	**MDI**	**Difference**
Life expectancy	22.34	20.36	1.99
Life expectancy (discounted)	14.44	13.55	0.89
QALYs (discounted)	9.64	8.69	0.95
Treatment costs (discounted)	£41,329	£17,211	£24,118
Other costs (discounted)	£34,550	£42,682	-£8,132
Total costs (discounted)	£75,879	£59,893	£15,986
ICER : Cost per QALY	£16,842		
Conservative UK analysis	**CSII**	**MDI**	**Difference**
Life expectancy	21.80	20.36	1.44
Life expectancy (discounted)	14.20	13.55	0.65
QALYs (discounted)	9.41	8.69	0.72
Treatment costs (discounted)	£40,683	£17,211	£23,472
Other costs (discounted)	£35,613	£42,682	-£7,069
Total costs (discounted)	£76,296	£59,893	£16,403
ICER : Cost per QALY	£22,897		

While an analysis based upon the entire Pickup (2007) meta analysis results sees a cost effectiveness of a little over £30,000 per QALY, increasing the average reduction in HbA_{1c} from CSII to 1.29% as would be implied by a baseline HbA_{1c} of 9.4% effectively doubles the anticipated patient gain from CSII while also slightly reducing the overall net cost given the reduced rates of complications requiring treatment.

The potential effect of the £413 cost per severe glycaemia event as opposed to £62 may have had some impact upon the total costs as already noted, possibly being equivalent to a little over a 10% reduction in the net direct treatment costs of CSII.

Note also that within the trial base analysis the cumulative effect of CSII upon macrovascular events over the 50 year time horizon was as leading to an absolute reduction in deaths from CHF of 0.7%, of deaths from MI of 0.6% and of deaths from stroke of 0.3% (table 28).

A full list of the results of the sensitivity analyses within the industry submission is presented in appendix 6, the main results of these being summarised below.

3.2.3 Time horizon

As usual with diabetes, improved control now reduces complications years into the future, and so discounting has a large effect. In a relatively newly-diagnosed patient, the costs of CSII will be incurred now and every year hereafter, but the savings from, for example, avoiding or postponing dialysis for end-stage renal failure, may not occur for 20-30 years. The industry submission includes various sensitivity analyses which alter the discount rates, which for the previous NICE discount rates of 1.5% for health effects and 6.0% for costs reduced the ICER for the trial based analysis from £34,330 per QALY to £18,997 per QALY (table 33). The results of this sensitivity analysis were not reported for the other scenarios deemed to be more relevant to the UK setting within the industry submission.

As noted within the cost effectiveness literature review, there may be some concerns around the possibility of CORE modelling tending to overestimate macrovascular events and in turn mortality within the population of those with T1DM. In parallel with the sensitivity analyses for discount rates, the results of sensitivity analyses on the time horizon appear only to be reported for the trials based analyses: time horizons of 15 years, 10 years and 5 years increasing the ICER from the base case value of £34,330 to £42,039, £47,921 and £63,795 per QALY respectively.

3.2.4 Hypoglycaemia

From the submission, it is not clear quite what the industry modelling includes in terms of the impact of reduction of hypos on quality of life, though the electronic modelling inputs uploaded to CORE website indicate a QoL loss from each severe hypoglycaemia event of 0.0121 and also a QoL loss from each non-severe hypoglycaemia event of 0.0052. As mentioned above, the cost of severe hypoglycaemic episodes is included at £413. The CORE model has a section for hypos, but tables 27 and 28 of the industry submission do not mention hypoglycaemia. Table 29 includes the cost of hypos. As already noted, it appears that the industry submission has conservatively assumed that severe hypoglycaemia events have no death rate associated with them.

3.2.5 Fear of hypoglycaemia

The submission does not appear to include allowance for benefits such as reduction in fear of hypoglycaemias, noted in the NICE appraisal of glargine.[49] In that technology appraisal (TA53) of long-acting insulin analogues (at that time only glargine), the NICE Appraisal Committee accepted that both hypoglycaemic episodes, and the fear of such episodes recurring, caused significant disutility. The relevant paragraph states;

"*The Committee accepted that episodes of hypoglycaemia are potentially detrimental to an individual's quality of life. This is partly the result of an individual's objective fear of symptomatic hypoglycaemic attacks as indicated in the economic models reviewed in the Assessment Report. In addition, as reported by the experts who attended the appraisal meeting, individuals' quality of life is affected by increased awareness and uncertainty of their daily blood glucose status and their recognition of the need to achieve a balance between the risk of hypoglycaemia and the benefits of longer-term glycaemic control. The Committee understood that improvement in this area of concern regarding the balance between hypoglycaemia and hyperglycaemia could have a significant effect on an individual's quality of life.*"

However, the guidance did not specify the amount of utility lost because of fear of hypos, and nor did the Assessment Report [72] because it was based on the industry submission from Aventis, which was classed as confidential. But clearly the utility gain from reducing the fear of hypos was enough to change a very large cost per QALY to an affordable one.

3.2.6 Other benefits not included.

The submission does not factor into the ICER calculations, aspects of quality of life, reduction in depression, less cognitive impairment in children, and non-health-related quality of life gains such as flexibility of lifestyle. Some of these omissions are understandable due to unavailability of data. In particular, it would be controversial to try to assess the impact of cognitive impairment on quality of life. If a child loses 10 points in IQ, that does not mean that quality of life is reduced. In other cases, such as flexibility of lifestyle, the measures used most often in quality of life studies in diabetes may not capture the effect . [216]

3.3 Summary

The strengths of the modelling include the use of the CORE model and the range of scenarios and sensitivity analyses.

The weaknesses are mainly due to data deficiencies (in the literature rather than the submission), which means that the effect of some benefits are not included. Modelling appears to be based only on the benefits of lowering HbA_{1c}, mediated through the reduction in long-term complications, and on short-term costs of a reduction in severe hypoglycaemia. It is possible that the net effect is that cost-effectiveness of CSII may be under-estimated, an unusual feature in industry submissions.

Chapter 4: Economics: CSII versus MDI

This chapter has four sections. The first examines the evidence on patient preference and quality of life. The second (4.2) reviews the existing literature on cost-effectiveness of CSII. The third (4.3) considers the costs of pumps. The fourth (4.4) provides our cost-effectiveness modelling.

4.1 Patient Preference and Quality of Life

The previous HTA identified and summarised one RCT of CSII versus MDI that also reported patient quality of life.[217] Tsui et al (2001). This randomly assigned 27 T1DM patients to either CSII or MDI, and reported DQoL scores at baseline and nine month follow up. Unfortunately, possibly due to the relatively small size of the trial none of the differences were significant.

Table 23: Quality of life on CSII and MDI TABLE 23

DQoL Dimension	CSII Score	MDI Score
Satisfaction	75.6	68.3
Impact	69.9	68.4
Diabetic worry	85.2	79.8
Social worry	89.6	94.0
Global health	68.2	67.3

The current review identified an additional 17 full papers that involved patient preference and quality of life for CSII, together with an additional four papers that were available only as abstracts. Among the 17 full papers, six were RCTs with results from an additional RCT being reported but without reference to the control arm. All but two of the RCTs were in T1DM. One controlled study was identified, with eight before and after studies being identified, all of which were in T1DM. An additional study surveying diabetic centres was identified, the vast majority of patients covered by this having T1DM.

Table 24 Patient preference and quality of life

Full Papers				
Type 1	Type	Sample	Country	Results
Weintrob (2003)[218]	Crossover RCT Paediatric	23	Israel	DQoLY NS 70% prefer CSII
Hoogma (2006)[219]	RCT	223	5 nation	DQoL CSII superior SF-12 CSII superior mental health
Devries (2002)[114]	RCT	79	Holland	11% randomised refuse to start CSII SF-36 CSII superior general health SF-36 CSII superior mental health
Dimeglio (2004)[115]	RCT Paediatric	20	US	CSII maintained in 19/20, only 1 family opts to switch back to MDI
Fox (2005)[116]	RCT Paediatric	26	US	Parental quality of life outcomes only significantly different among fathers
Hoogma (2004)[220]	Crossover	128	Dutch	DQoL NS WHO wellbeing NS
Garmo (2004)[221]	Before & After	27	Sweden	DTSQ before 20 average DTSA after 32 average

Sanfield (2002)[222]	Before & After	104	US	SF-36 general health, ability to perform physical activities, energy and physical pain better. CSII interfered with bathing and sexual activity
McMahon (2005)[147]	Before & After Paediatric	100	Australia	Impact of diabetes DQoL significant improvement
Juliusson (2006)[166]	Before & After	31	Norway	DQoL improved, but only significant for family activities subscale
Rodrigues (2005)[135]	Before & After	40	UK	DQoL NS SF-36 NS
Shehadeh (2004)[169]	Before & After Paediatric	15	Israel	DTSQ significantly improved DQoL significantly improved
Mednick (2004)[173]	Retrospective	22	US	Likert scale 1-5 values for satisfaction consistently with CSII above 3
Bruttomesso (2002)[223]	Retrospective	138	Italian	DQoL scores reported
Type 2	Type	Sample	Country	Results
Raskin (2003)[111]	RCT	132	US	CSII reported as superior to MDI in all subscales of poorly documented TOIS questionnaire, except pain.
Herman (2005)[110]	RCT Older patients	107	US	DQoL NS SF-36 NS

Note that in what follows, costs reported in foreign currencies have been converted to sterling using the relevant mid year exchange rate, or where this was not stated using the mid year exchange rate of the date of publication.

4.1.1 RCT studies: Type 1

Weintrob and colleagues (2003) performed a randomised crossover trial of CSII versus MDI among 23 Israeli children with T1DM aged nine to 14 years, with a crossover period of 3½ months after a two week run in period.[218] Quality of life aspects were measured with the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and for more general quality of life through the Diabetes Quality of Life Questionnaire for Youth (DQoLY). All children completed the two study arms. There were no significant differences between glycemic control between the two arms. However, there was a significant difference in DTSQ scores, which averaged 21.4 at baseline, 21.9 at the end of the MDI arm and 30.6 at the end of the CSII arm. No statistically significant differences were recorded within the DQoLY subscales, with the end of MDI arms and the end of CSII arm displaying similar central estimates for all DQoLY subscales. At the end of the trial patients were asked which regime they preferred: 70% preferred CSII on grounds of greater mealtime flexibility, avoidance of the pain of injections and better glycemic control or profiling. Of those preferring MDI, concern as to glycaemic control, overeating and weight gain were cited, coupled with the desire to keep diabetes a secret and shame at wearing the pump were also cited, as was the required frequency of self monitoring.

Hoogma and colleagues (2006) reported the results of a five nation randomised controlled cross over trial of CSII against MDI among 272 patients with T1DM of whom 223 completed the trial. Patient selection and patient characteristics were not presented in the paper.[219] While not explicitly stated, it appears that patients were randomised to starting an intensified regime of either CSII or MDI, with a run in period of two months. Trial duration thereafter was six months. HbA_{1c} results were similar after run in across both arms, with the mean difference at end of trial being in favour of CSII. Non inferiority of CSII in terms of HbA_{1c} was demonstrated, with subsequent analysis indicating statistically significant superiority. Similarly, the rate of respondent-defined severe hypoglycaemia events at 0.2 per years for CSII as compared with 0.5 for MDI was also statistically significantly different.

Against this background, patients completed the DQoL and SF-12 questionnaires at baseline and at end of treatment. The overall DQoL score at end of treatment was significantly higher for CSII, the individual subscales of satisfaction, impact and diabetes related worry also being statistically significantly better, though the social/vocational worry subscale did not reach significance. Within the SF-12 questionnaire, no significant differences in physical health were recorded, but the composite mental health subscale for CSII was statistically superior to that of MDI. The authors concluded by noting that once patients had experienced CSII they were more likely to recommend it than recommend the MDI regimen.

Hans DeVries and colleagues (2002) reported the results of a cross over trial of 79 Dutch patients with T1DM with an average age of 37 years.[114] Unfortunately, due to drop-outs at cross-over the trial was analysed as a parallel trial using only the first half of the cross-over phase. The authors noted that 11% of patients at randomisation or at cross over refused to start CSII. The trial found statistically significant differences in the general health and mental health subscales of SF-36, with CSII recording improvements of 5.9 and 5.2 on these subscales respectively, as against falls of 1.2 and 0.6 for MDI. Scores for the other subscales were not reported. Overall treatment satisfaction was assessed using the Diabetes Treatment Satisfaction Questionnaire. No statistically significant difference was recorded, with CSII scoring an increase of 1.3 and MDI scoring an increase of 0.2.

In an RCT of CSII versus MDI in US children of less than five years of age with T1DM, Dimeglio and colleagues (2004) reported that CSII was generally well tolerated with 19 out of the 20 families opting to continue with CSII after six months, rather than switch to MDI.[115] The preferences of those in the MDI arm with regards switching of therapy at the six month point were not reported.

Fox and colleagues (2005) performed a six month RCT of CSII versus MDI among 26 US children with T1DM, average age of a little under four years.[116] The children were randomly assigned to

continue receiving MDI, or to switch to CSII. Given the age of participants, aspects of parental rather than patient quality of life were measured, coupled with parental perceptions of patient quality of life. While both mothers and fathers reported more psychological distress in the MDI group as compared to the CSII group, when baseline differences were controlled for these differences were not statistically significant. Mothers in the MDI arm reported significantly greater stress at baseline, but this difference was no longer significant at six months follow-up. However, fathers reported significantly more positive quality of life changes in the CSII group over the six months. The authors noted that at the end of follow up all MDI patients started CSII therapy, while all CSII patients continued on CSII therapy.

4.1.2 RCT studies: Type 2 Diabetes

Raskin and colleagues (2003) undertook a randomised parallel trial over 24 months of CSII versus MDI among 132 US CSII naïve patients with T2DM, aged 35+ years.[111] Patient satisfaction was measured through administering components of a poorly documented PHASE V Technologies Outcome Informations System Questionnaire. Overall satisfaction with treatment as measured over the 10 subscales administered was scored as an increase from 59 to 79 in the CSII group as compared with an increased from 64 to 70 among the MDI group, which was described as being statistically significant. It is unclear whether baseline for the CSII group was prior to the initiation of CSII therapy or shortly thereafter. CSII was also statistically significantly superior to MDI in all subscales other than pain, where no statistically significant difference was noted.

Herman and colleagues (2005) in a 12 month RCT of CSII versus MDI among 107 older patients with T2DM, average age 66 years, evaluated patient satisfaction and quality of life through both the Diabetes Quality of Life Clinical Trial Questionnaire and the SF-36 questionnaire.[110] Over the period of the trial both arms reported similar increases in satisfaction with their treatment, DQoL scores for CSII increasing from 52 to 81 and for MDI increasing from 50 to 78. Likewise, changes in the composite SF-36 physical and mental health sub scales were similar between both arms: the physical score for CSII rising from 40.5 to 41.1 as compared to a rise from 40.6 to 41.0 for MDI, while the mental health score fell slightly for CSII from 51.0 to 50.0 as compared with a slightly greater fall for MDI from 53.0 to 50.5. None of these changes were statistically significant.

4.1.3 Case Controlled Study: Type 1 Diabetes

Hoogma and colleagues (2004) presented the results of a cross sectional study among 128 Dutch patients with T1DM with an average age of 42 years, 49 of whom received CSII and 79 of whom received MDI.[220] The design of the study intentionally recruited twice as many MDI patients as CSII patients. The selection criteria for CSII patients participating in the study was not stated, though MDI

patients were reportedly randomly selected from the same outpatient clinics. Quality of life aspects were evaluated through three questionnaires: DQoL, the Diabetic Treatment Satisfaction Questionnaire and the WHO Wellbeing Questionnaire.

Self measurement of blood glucose was once daily in 81% of CSII patients as against 63% in MDI patients. The majority of the remaining CSII patients, 10%, measured blood glucose one or two times a week, as compared with 19% for the MDI arm. Full daily blood glucose profiling showed a similar profile, with more frequent profiling being performed within the CSII arm. No differences were uncovered regarding the outcomes of DQoL, and the treatment satisfaction again showed no differences between the groups, even with regards to hypo and hyper glycaemia. With regards to the general wellbeing questionnaire, again no statistically significant differences were noted save for the Energy subscale where the MDI arm showed somewhat better results with a score of 8.7 as against 7.5 for CSII. As with much of the patient preference and quality of life literature, these results are difficult to interpret as patient characteristics and the reasons for receiving CSII are not well documented.

4.1.4 Before and After Studies: Type 1 Diabetes

Garmo and colleagues (2004) report the results of a study of 27 Swedish adults with T1DM, average age 41 years, changing from MDI at baseline to CSII with follow up at six months.[221] It appears that the change to CSII was medically driven rather than part of a research programme per se, which may make results more applicable to the sort of patients who would start CSII in routine care. Satisfaction with treatment was measured using the Treatment Satisfaction Questionnaire (DTSQ), possible values ranging from 0 to 36. Prior to the change to CSII the median DTSQ score was 20 with a range of 4 to 32, while at six month follow up after changing to CSII the median DTSQ score was 32 with a range of 17 to 36. However, these results are subject to a number of criticisms, the most significant of which is the before-after non-randomised nature of the study coupled with patients being in some sense self selecting due to their previous MDI therapy being presumably unacceptable for either clinical or personal reasons. Respondents were presumably failing on MDI, this also being reflected in a self reported fall in the frequency of unacceptable hypoglycaemia events.

Bruttomesso and colleagues (2002) retrospectively review quality of life using the DQoL questionnaire among 138 type 1 Italian diabetics who had were receiving CSII, and had been on average for 7.4 years.[223] Ninety-eight of the patients surveyed completed at least one aspects of the DQoL questionnaire, all 98 completing the satisfaction subscale, average score 72.5, and the impact of diabetes subscale, average score 71.3. 95 completed the diabetes worry subscale, average score 80.2, but only 51 completed the social worry subscale, average score 67.8. The overall average DQoL score across patients and subscales was 73.0.

Sanfield and colleagues (2002) reported the results of a before and after study of 104 US patients with T1DM prior to the initiation of CSII therapy.[222] Patient characteristics were not reported. Prior to initiating CSII, patients underwent up to three outpatient sessions to assess suitability, a large degree of which appears to have been education around self selection for suitability for CSII. One of the criteria within this was financial, in terms of patients having adequate financial resources to cover the initial and ongoing costs of CSII. Thirty-five per-cent of the 104 patients did not proceed through all three outpatient sessions to receive CSII. The reasons for this are not outlined, but given the financial criterion the relevance of this to the UK setting is questionable.

Patients proceeding to CSII completed SF-36 and three additional trial specific quality of life questionnaires. The great majority, 97%, of patients initiating CSII and remaining in the area remained on CSII after over 2½ years. Few details are provided as to the quality of life measures, but the paper notes that statistically significant improvements occurred over time in the SF-36 parameters of general health, ability to perform activities, energy and physical pain. Within the trial specific quality of life questionnaires, patients are reported as stating that eating, working, sleeping, bathing and sexual activity were the most important aspects of life. CSII was found to interfere with bathing and sexual activity, though many patients removed pumps during these activities.

McMahon and colleagues (2005) prospectively followed 100 Australian children and adolescents with T1DM starting CSII therapy.[147] Those selected for CSII therapy had demonstrated some or all of severe hypoglycaemia, poor glycemic control and erratic lifestyle with regards sport, food or routine, though commencement was typically at parental request. Quality of life was measured prior to starting CSII and after six months of CSII among the first 51 patients being switched to CSII through a modified DQoL questionnaire and the Self-Efficacy for Diabetes Scale (SED), with respondents being of more than 10 years of age. Within the DQoL results, the impact of diabetes score fell on average from 55.4 to 50.2 which was significant at the 5% level. Worries about diabetes and satisfaction with life scores showed no significant change over the six months. The SED scale improved from 159 to 174, which was described as being statistically significant. But in common with the Fox and colleagues study[116], these results require care in their interpretation given the before-after nature of the study, coupled with patients in some sense having been failing on their previous therapy.

Juliusson and colleagues (2006) performed another before-after study of the adoption of CSII upon patient quality of life, this being among 31 children with T1DM of average age 14 years and who were poorly regulated on MDI with an average HbA_{1c} of 10.4%. [166] Quality of life was measured with the DQoL questionnaire and generic CHQ-CF87 questionnaire prior to starting CSII and twice

during 15 months of follow up. Average differences in subscales of the CHQ-CF87 while uniformly showing improvements only reached statistical significance for the Family Activities subscale. Similarly, while an improvement was recorded across the dimensions of the DQoL, none of these reached statistical significance. The authors concluded that respondents might have had moderate improvements in diabetes specific quality of life scores, and were unlikely to have had appreciable deteriorations in them.

Rodrigues and colleagues (2005) reported the results of a before and after study of 40 UK patients with T1DM, average age 33 years, the study aiming to identify if current guidelines would correctly identify patients who would benefit from CSII.[135] Twenty-five of the 40 patients were initiated on CSII for reasons other than severe hypoglycaemia events, while 15 patients reportedly had contraindications to CSII. The median follow up was 20 months. Quality of life was measured though the DQoL, with the SF-36 and the Hypoglycemia Fear Survey (HFS) also being administered. Only 33 questionnaires were returned, including four responses from patients who had discontinued with CSII. These four responses from those who had discontinued with CSII were excluded from the analysis. No significant differences were observed within any of the DQoL subscales. The only significant difference within the SF-36 reported was not between baseline and follow up, but between those with and without contraindications to CSII. Those with contraindications had a significantly lower score on the mental health subscale of 47.5 as compared to those without who scored 69.9. Having excluded those discontinuing CSII from the analysis, all respondents as expected preferred CSII to their previous treatment.

Mednick and colleagues (2004) surveyed 22 US children with T1DM, average age 14 years, and their parents after having transferred to CSII and remaining on CSII.[173] Data was collected between three and 22 months after CSII was initiated. Telephone interviews were conducted using the Insulin Pump Therapy Satisfaction Questionnaire (IPTSQ), which had been specifically designed for the survey by the authors composed of 10 items ranked on a Likert scale coupled with three open ended questions as to life changes from pump use, the most challenging aspects of the pump and advice to prospective users to maximise their benefits from pump use. Satisfaction ratings were derived for parents and children. None were dissatisfied, and the average response on the 5 point Likert scale was consistently above 3 and typically above 4.

Shehadeh and colleagues (2004) briefly reported the results of a before after study of CSII among 15 Israeli children with T1DM aged one to six years.[169] Treatment satisfaction and quality of life were measured through DTSQ and DQoL for parents at baseline and at four months. Both the overall DTSQ scores and the DQoL scores showed a statistically significant improvement at four months as compared to baseline.

With all the above before and after studies, many patients will have commenced CSII due to failure on their previous regime. As a consequence, these results may be of limited relevance to the consideration of whether those moving onto intensive insulin therapy would be best starting on CSII or starting on MDI. However, the results appear to be more useful than if the results had been representative of the total T1DM population for the situation where CSII is used in patients who are in some way failing on current therapy, as with the current NICE guidance. There is the additional difficulty that participation in the study may have affected results over the time period of the study.

4.1.5 Diabetic Clinic Survey: Type 1 Diabetes

Bruttomesso and colleagues (2006) reported the results of a survey of Italian diabetic centres, with 145 centres out of 179 centres responding.[136] These covered a total of 2,702 CSII patients, of whom the average age was 39 and among whom 97% were patients with T1DM who had previously received MDI to CSII. The main reason for starting CSII was given as poor metabolic control, though quality of life, flexibility, reducing the number of hypoglycaemia events and correcting the dawn phenomenon were also cited. Reasons for not starting CSII were the inability to cope with the pump technology, lack of compliance, psychiatric problems and unwillingness to check blood glucose frequently. Notably 571 patients abandoned CSII, though quite what the relevant baseline or denominator figure for this was not clear from the paper. 187 of these stopped at the end of pregnancy. Intolerance of the pump was also cited as a reason for discontinuing, coupled with disappointment as to the goals attained, infection at the infusion site and hypoglycaemia.

4.1.6 Abstracts

Barnard and Skinner (2006) briefly reported the results of a qualitative telephone survey of 80 insulin pump users.[224] The country, patient characteristics and method of respondent selection were not specified. Respondents were asked about the benefits of insulin pump use, and quality of life effects, any downsides to insulin pump use and whether they wished to raise any other issues. A number of positive themes emerged from the survey, with 56% reporting greater control, 41% reporting greater flexibility, 35% reporting increased freedom, 9% reporting greater convenience and 6% reporting greater independence. However, 59% also reported downsides, with 31% reporting difficulties with concealment, 21% reporting technical issues when things go wrong, 6% reporting site reactions and pain and 4% reporting cost. The authors noted that these negative factors may explain why a number of patients only remain on pump therapy for a short period of time. Given this there may have been a degree of sample selection bias, with any results relating more to the quality of life of those finding insulin pumps of benefit in the longer term.

Reid and Lawson (2002) reported the results of a Canadian cross sectional survey of 74 children with T1DM, 28 of whom had been using CSII for more than four months and among whom the average duration of CSII usage was 16 months.[225] The average age of those using CSII was 14 years. Patients were matched for sex, age and duration of diabetes, with a linear regression model comparing values from the Diabetes Quality of Life Questionnaire for Youth. Treatment satisfaction was significantly higher in the CSII group with a score of 33.8 as against 27.5 in the MDI group. However, despite metabolic control also being significantly better in the CSII group with 7.7% as against 8.9% for the MDI group, no significant differences were observed in the DQoLY dimensions of satisfaction, impact or worry. The authors concluded that DQoLY may not be the most appropriate measure of quality of life in this group.

Galatzer and colleagues (2002) compared the treatment satisfaction among 208 CSII and MDI people with T1DM of average age of 20 years, though ages ranged from 10 years to 50 years though the use of the DQoL questionnaire.[226] Patient selection and other characteristics were not reported. The overall treatment satisfaction score was significantly different at 30.7 among CSII patients as compared with 22.7 among MDI patients. 86% of CSII patients were reported as recommending CSII to other patients as compared to only 19% of MDI patients.

Schweitzer and colleagues (2006) reported the results of a postal questionnaire sent to 36,450 CSII patients, from whom a 38% response rate was achieved.[227] The abstract restricted itself to the results of the 729 responses received from patients with T2DM, these having an average age of 56 years, an average duration of diabetes of 17 years and an average duration of CSII of 3.4 years. Most, 76%, reported selecting CSII due to poor glycaemic control on other therapies, with 44% also citing uncontrolled blood glucose fluctuations. A minority, 34% mentioned a high insulin requirement when using injections as a reason. The majority of patients initiated therapy as an inpatients, 44%,(which would be unusual in the UK) at a specialist diabetologist's office, 46%, or as a hospital outpatient, 5%. Only 3% initiated therapy at a general practitioner's. The authors concluded that patients were highly satisfied with CSII therapy, though the means of assessing this and associated results were not presented.

4.2 Cost Effectiveness Studies

The previous HTA report did not identify any studies of the cost effectiveness of CSII versus MDI. The current HTA has identified three full papers and eight abstracts relating to the modelling of cost effectiveness of CSII versus MDI. The preponderance of abstracts within the literature survey appears to be due to the recent availability of the CORE markov model for simulating the effectiveness of CSII versus MDI among people with T1DM. This has generated a large literature,

which is currently making its way into print. It appears likely that all but one of the cost effectiveness papers and abstracts fall into this category, though not all are explicit about their use of CORE or another markov model.

Table 25 Cost effectiveness literature

Full papers					
Mixed	Country	Model	Horizon	Perspective	Results
Scuffham (2003)[194]	UK	Own Markov	Lifetime	Health service	£11,461/QALY
Type 1	Country	Model	Horizon	Perspective	Results
Roze (2005)[195]	UK	CORE	60 years	Health service	£26,297/QALY
Conget Donlo (2006)[196]	Spain	CORE	Lifetime	Health Service	€29,957/QALY
Abstracts					
Type 1	Country	Model	Horizon	Perspective	Results
Castell (2005)[228]	Spain	CORE	Lifetime	Health Service	€30.453/QALY
Zakrzewska (2004)[229]	UK	CORE	Lifetime	Health Service	£32,753/QALY
Zakrzewska (2005)[230]	Switzerland	CORE	Lifetime	Social	CHF22,444/QALY
Roze (2002)[231]	France	CORE	50 year	Health Service	€1,348/Life Year
Goodall (2006)[232]	Sweden Norway	CORE(?)	Lifetime	Social	SEK58,830/QALY NOK24,837/QALY
Nicklasson (2006)[233]	Sweden	CORE	Lifetime	Social	SEK227,066/QALY
Roze (2002)[234]	US(?)	CORE(??) Paediatric	Lifetime	Health Insurance	US$115,082/Life Year

Scuffham and Carr (2003) developed their own relatively simple markov model to compare CSII with MDI among patients with T1DM.[194] This did not differentiate between T1DM and T2DM. The perspective was as recommended in NICE guidance, the time horizon was eight years as this is the anticipated pump longevity, and discount rates of 6.0% for costs and 1.5% for benefits were applied in the base case.

The markov model was implemented through monthly cycles and had two principal health states: well and dead. Within this, patients who were well could experience a hypoglycaemia events, which could also result in a need of inpatient treatment, and could also experience ketoacidosis. Baseline risk and death rates associated with these were taken from the literature; for hypoglycaemia events the baseline annual risk was taken to be 40% with a 0.5% death rate, while for ketoacidosis the baseline risk was taken to be 2.7% with a 10% death rate, which seems unusually high. Risk reductions associated with CSII upon these baseline risks were 43% for hypoglycaemia events, and apparently also a 2.5% risk reduction for ketoacidosis events. CSII also resulted in a 14% reduction in insulin use, though it is unclear whether this was restricted to basal insulin use alone.

Quality of life values were mainly drawn from the Boland and colleagues (1999) study among adolescents with T1DM. MDI was taken to result in a 5.3% utility loss, and as a consequence the utility of those in the well health state receiving CSII was taken to be 1.000 while the utility of those

well but receiving MDI was taken to be 0.947.[96] Similarly, both hypoglycaemic events and ketoacidosis events were taken to result in two days at zero utility, and so involve a disutility of 0.067. Distributions were placed upon all variables to enable probabilistic modelling.

While the annual direct costs of treatment were not stated, it appears that the annual cost of CSII appears to have been around £1,380 as compared with £468 for MDI. The overall cost of treatment over the eight years was estimated as £9,514 as compared with £4,052 for MDI: a net increase of £5,462. The QALYs accrued over the eight years were an average of 7.32 for CSII as compared with 6.85 for MDI: a net increase of 0.48 QALYs, implying a cost effectiveness of £11,461 per QALY.

A number of concerns arise with the study, not least the application of a 5.3% utility loss from MDI as against CSII and the estimates of the direct costs of treatment. The model was of relatively simple structure, and made no distinction between T1DM and T2DM or outlined any other patient characteristic which might be of interest, such as age. This is underlined by the reduction in event rates being direct, rather than modelled through the mechanism of any changes to baseline HbA_{1c} that CSII might result in: the more common modelling approach within models of therapies for both T1DM and T2DM. Note also that though the paper was a worthwhile attempt to model the short term impact is CSII relative to MDI, the longer term complications of diabetes are excluded. Despite this, the cost effectiveness estimate for CSII was considerably better than those papers which report models involving the long term complications as reviewed below. It is difficult to have confidence in its results.

Most of the remaining papers modelling CSII versus MDI among people with T1DM relied upon the CORE model as reviewed within the previous chapter, though one paper available only as an abstract undertook an RCT of CSII against MDI which also measured treatment costs. Most of the remaining papers list Palmer, Roze and Zakrzewska as authors even if not as principal authors, underlining the reliance of the area upon the CORE model. This is understandable. There are few T1DM models around, and the CORE model is one of the most used, being available to use (at cost) over the Web, with many papers based on it published in peer reviewed journals.

Roze, Valentine, Zakrzewska and Palmer (2005) presented the results of a cost effectiveness modelling exercise of CSII versus MDI implemented using the CORE model.[195] The perspective of the analysis was as recommended in the NICE methods guidance, with a 60 year time horizon, the use of 2003 costs, but unfortunately the use of 3.0% discount rates for both costs and benefits.

For MDI patients, the average HbA_{1c} was taken to be 8.68% coupled with an average BMI of 23.61kg/m^2. Clinical effectiveness estimates for CSII were drawn from the 2003 meta analysis of

Weissberg-Benchell, resulting in a relatively large improvement from baseline of 1.2% in HbA_{1c} but also a weight gain of 1.03kg/m^2. Note that Roze and colleagues[195] also assumed given a lack of evidence to the contrary that event rates of hypoglycaemia and ketoacidosis were the same for both treatment groups for the base case, with these rates being taken from DCCT data. These assumptions were varied in the sensitivity analyses. The rates of pre-existing complications of diabetes within the modelled cohort was not stated within the paper, though the average age at baseline was 26 years and the average duration of diabetes 12 years.

Costs of the treatment of the complications of diabetes were drawn from the literature, and were presented within the paper. Quality of life values were similarly drawn from the literature, though the values used were not presented in the paper. The direct costs of therapy were estimated to be £1,482 for MDI and £2,641 for CSII. The higher costs of pump and consumables of CSII of £1,449 as against £149 for MDI were partially offset by a lower cost of insulin of £281 for CSII as against £422 for MDI.

Base case results of the modelling suggested that CSII would by the end of the 60 year time horizon result in absolute reductions in the cumulative incidence of; amputation of around 1.7% (value taken from graph and reported relative percentage reduction); severe visual loss of around 4.9% (value taken from graph and reported relative percentage reduction); myocardial infarction of 2.6%; and, of end stage renal disease of 1.1%. Similar reductions were observed in the other complications of the model. These helped contribute to an estimated life expectancy of 17.44 years for CSII as against 16.73 years for MDI; an improvement of 0.71 years. Adjusting for quality of life, this increased the anticipated gain to 0.76 QALYs; i.e. the general effect of diabetes tending to reduce quality of life was more than offset by the gain in the avoidance of reduced complications.

Treatment costs were the largest cost component for the CSII arm, being £47,077 as against £25,266 for MDI; an increase of £21,811. These were partially offset by lower costs of complications of £31,267 as against £33,458 for the MDI arm; a net saving of £2,191 from complications. For reasons that are not immediately apparent Roze and colleagues[195] report these as resulting overall average lifetime costs of £80,511 for CSII as compared with £61,104 for MDI: a net additional overall cost for CSII of £19,407. Note that the direct treatment costs, and costs of complications cited in the paper would appear to suggest an overall cost for CSII of £78,344 and for MDI of £58,724, to give a net costs of CSII of £19,620. Given the anticipated average gain of 0.76 QALYs this translated into a central cost effectiveness estimate of £25,648 per QALY, and a likelihood of 74% that cost effectiveness would lie below £30,000 per QALY. Using the NICE recommended 3.5% discount rates increased the anticipated cost effectiveness ratio slightly to £26,297 per QALY.

Results were sensitive to the improvement in HbA_{1c} assumed. Application of the 0.51% improvement identified in the 2002 meta analysis of Pickup and colleagues increased the cost effectiveness ratio to £61,564 per QALY.[16] Changing the effect of CSII upon BMI from a weight gain of 1.03kg/m^2 had only a very marginal effect, improving cost effectiveness to £25,391 per QALY. The base case assumed CSII had no effect upon the rate of hypoglycaemia events. If CSII resulted in 50% fewer hypoglycaemia events relative to MDI the cost effectiveness improved to £20,104 per QALY, while a 75% reduction improved it still further to £18,047 per QALY. If CSII resulted in a doubling of ketoacidosis events, this worsened its cost effectiveness to £28,297 per QALY.

Conget Donlo and colleagues (2006) also used the CORE model to evaluate the cost effectiveness of CSII against MDI among people with T1DM.[196] The perspective for cost was that of the Spanish healthcare system, though was otherwise as for the NICE reference case. A lifetime horizon was applied, with all costs being at in euros at 2005 prices and a discount rate of 3.0% was applied to both costs and benefits.

Clinical effectiveness was the same as in Roze and colleagues,[195] CSII resulting in a baseline improvement of 1.2% in HbA_{1c} but also a weight gain of 1.03kg/m^2 as compared with MDI. Similarly, it was also assumed that event rates of hypoglycaemia and ketoacidosis were the same for both treatment groups. Patient characteristics were drawn from Spanish registry data relating to CSII treated patients, the average age being 36 years. The rates of pre-existing complications of diabetes within the modelled cohort were also drawn from the Spanish registry data, with an average duration of diabetes of 15 years.

Costs of the treatment of the complications of diabetes were drawn from the literature as it related to Spain, and were presented within the paper. Aside from myocardial infarction in the first year which was of somewhat higher cost than that used in Roze and colleagues, the unit costs of complications were typically of similar of lower cost than those used in Roze and colleagues. Quality of life values for the complications of diabetes were mainly drawn from the 2002 Clarke and colleagues paper,[206] which reported the results of an EQ-5D exercise conducted among UK PDS patients, and were presented within the paper.

The direct costs of therapy were estimated to be €2,087 [£1,410] for MDI and €3,773 [£2,549] for CSII. The assumed lifespan of pumps of eight years was as in Roze and colleagues, and the direct costs of treatment were consequently similar.

Conget Donlo and colleagues found that CSII would result in reductions in the cumulative incidence of; severe visual loss of 2%; myocardial infarction of 1%; and, of end stage renal disease of 7%.[196]

These reductions in the cumulative incidences of these complications are somewhat less than those reported in Roze and colleagues[195], with the exception of end stage renal disease. While the baseline average age assumed by Conget Donlo and colleagues was somewhat higher than that in Roze and colleagues, the smaller differential in rates of major complications over the period of the modelling may be mainly due to differences in the initial rates of complications that were assumed within the cohort. For instance, Conget Donlo and colleagues assumed that 32% had retinopathy at baseline.

In spite of these possible differences at baseline, the results of Conget Donlo and colleagues in terms of life expectancy were surprisingly similar to those of Roze and colleagues, with an estimated life expectancy of 16.83 years for CSII as against 15.94 years for MDI; an improvement of 0.89 years. Adjusting for quality of life, this reduced the anticipated gain to 0.85 QALYs. Again in contrast to Roze and colleagues, the gain in the avoidance complications was not sufficient to offset the general effect of diabetes tending to reduce quality of life.

The average cost per CSII patients was estimated as €105,439 [£71,242] as opposed to €79,916 [£53,997] for MDI, an average increase of €25,523 [£17,245]. Given the base case estimate of a 0.85 QALY gain this translated into a cost effectiveness estimate of €29,957 [£20,234] per QALY.

Conget Donlo and colleagues performed similar sensitivity analyses to Roze and colleagues also finding the effect upon HbA_{1c} to be the key variable. Adopting the 0.51% improvement identified in Pickup and colleagues (2002) increased the cost effectiveness ratio to €103,584 [£69,989] per QALY. Assuming that CSII resulted in a 66% reduction in hypoglycaemia events improved the cost effectiveness ratio to €25,680 [£17,351] per QALY.

The following papers in this section were available only as abstracts.

Castell and colleagues (2005)[228] in common with the paper of Conget Donlo and colleagues[196] reported above also ran the CORE model for patients with T1DM within the Spanish setting. Note that Roze and Zakrzewska were also listed as authors. The perspective was as in the NICE guidance, with a lifetime horizon and a 3.0% discount rate for both costs and benefits. Costs were in 2004 prices. No details were supplied as to baseline patient characteristics, or the assumed efficacy of CSII versus MDI in terms of glycaemic control.

The summary of their results stated that life expectancy in the CSII group was 0.859 years longer, which when quality of life was factored in resulted in a 0.836 QALY gain from CSII over MDI. Overall lifetime costs were €25,463 [£16,975] higher for CSII, resulting in a cost effectiveness estimate of €30,453 [£20,302] per QALY. These results are very similar to those of the Conget Donlo

paper, suggesting that Castell and colleagues made similar assumptions though the slightly lower gain from CSII in terms of life expectancy and QALYs could be due to patient baseline characteristics such as a higher baseline age and slightly greater baseline prevalence of the complications of diabetes.

Zakrzewska and colleagues (2004)[229] again use the CORE model to simulate the cost effectiveness of CSII against MDI among patients with T1DM. This was modelled from the perspective of the UK NHS, with the base year for costs being 2003 and a 3.5% discount rate being applied to both costs and benefits. Patient characteristics were an average age of 26 years, an average duration of diabetes of 12 years and an average HbA_{1c} of 8.68%. Unfortunately, the abstract did not itemise the assumed effectiveness of CSII relative to MDI though life expectancy result suggest a similar effectiveness to their 2004 paper published in full: a 1.2% in HbA_{1c} but also a weight gain of 1.03kg/m^2.
Patient outcomes in terms of life expectancy were marginally different compared to their paper published in full and summarised above, with an average life expectancy of 17.37 years for CSII as compared with 16.66 for MDI: a gain of 0.72 years as compared with 0.71 years in their fully published paper. This 0.72 life years gain translated to a 0.59 QALY gain. Note in passing that adjusting for quality of life in their paper published in full, caused the anticipated increase in life expectancy to change from 0.71 life years to 0.76 QALYs. CSII was estimated as costing £81,115 as against £57,015, a net increase of £19,413 which resulted in a central estimate for the cost effectiveness of CSII of £32,753 per QALY.

Zakrezewska and colleagues (2005)[230] reported cost effectiveness results of CSII versus MDI in patients with T1DM within the Swiss setting using the CORE model. It appears that a full societal perspective was adopted for costs rather than concentrating upon health care costs, though the abstract was not explicit about this. A lifetime horizon was adopted, with both costs and benefits being discounted at 3.0%. Costs appear to have been in 2004 prices, though again this was not explicitly stated within the abstract. Baseline patient characteristics were not stated. The clinical effectiveness of CSII against MDI in terms of glycaemic control was also not stated.

Overall survival for CSII was estimated as 17.15 years as against 16.27 years for MDI: a net gain of 0.87. The use of CSII was estimated to also yield relative reductions in severe vision loss, end stage renal disease and peripheral vascular disease were 16%, 18% and 16% respectively, though the absolute values of these were not given. The average overall cost per patient of CSII was estimated as CHF516,745 [£224,672] as against CHF497,117 [£216,138]: a net increase of CHF19,628 [£8,534]. The net cost of complications were stated as being CHF10,327 [£4,490] lower in the CSII group, which suggest that treatment costs were CHF29,955 [£13,024] higher for CSII as compared with MDI. Overall cost effectiveness of CSII relative to MDI was estimated to be CHF22,444 [£9,758] per life year gained.

Roze and colleagues (2002)[231] used the CORE model again to model the cost effectiveness of CSII against MDI among patients with T1DM within the French setting. The perspective was that of the French healthcare system for costs so only including the direct health care costs, with a 50 year time horizon and a discount rate of 5.0% being applied to costs. The base year for costs was not stated, nor was the discount rate for benefits. Patient characteristics were not itemized, but were reported as being similar to the DCCT primary intervention cohort. CSII was modelled as resulting in 1% better control of HbA_{1c}, reducing hypoglycaemia events by 50% but increasing the rate of ketoacidosis from 1.39 per 100 patient years to 3.09 per 100 patient years as compared with MDI.

The increase in life expectancy was broadly in line with that of other CORE modelling at 1.00 years, but the additional overall cost per patient was muted at only €1,348 [£807]. While the cost discount rate of 5.0% will have tended to reduce the cost impact over 50 years in comparison with the more usual 3.0% discount rate within the literature, the reason for the lifetime net cost of CSII being so much lower within this study are not apparent. Given the anticipated increase in survival, the cost effectiveness was similarly estimated as €1,348 [£807] per life year gained.

Goodall and colleagues (2006)[232] reported using a previously validated computer simulation model to simulate the effects of CSII versus MDI within the Norwegian and Swedish settings. It is unclear whether the model used was CORE, though the authorship would suggest so. A societal perspective was adopted for costs though the base year was not stated, with modelling adopting a lifetime horizon and discounting costs and benefits at 3.0%. The average age of patients was 26 years, with an average duration of diabetes of 12 years and a baseline HbA_{1c} of 8.68% as in Roze and colleagues.[195]

Baseline characteristics may have differed between the modelled populations, as the life expectancy gains from CSII differed: 0.95 years in the Norwegian setting as against 1.03 in the Swedish setting. Adjusting these figures for quality of life had relatively little effect, resulting in gains of 0.98 and 1.03 QALYs respectively. The Norwegian modelling resulted in average lifetime costs being NOK3,505,368 [£299,604] for CSII as against NOK3,480,974 [£297,519] for MDI: a small net increase of NOK24,394 [£2,085] due in part to the inclusion of indirect costs estimated through the human capital approach. This resulted in an overall cost effectiveness estimate within the Norwegian modelling for CSII against MDI of NOK24,837 [£2,123] per QALY. Within the Swedish setting CSII was estimated as having an overall lifetime cost of SEK3,026,056 [£223,325] as against SEK2,965,366 [£218,846] for MDI: again a relatively modest increase of SEK60,690 [£4,479] due to the inclusion of indirect costs. This resulted in an overall cost effectiveness estimate within the Swedish modelling for CSII against MDI of SEK 58,830 [£4,432] per QALY.

Another study of CSII versus MDI among patients with T1DM implemented using the CORE model and based in Sweden was reported in Nicklasson and colleagues (2006).[233] A societal perspective was adopted, though results were also reported that included only direct treatment costs. A lifetime perspective was adopted, with the base year for costs being 2005, and a 3.0% discount rate being applied to both costs and benefits. Baseline patient characteristics were an average age of 27, a somewhat shorter duration of diabetes compared to other studies of only six years and an average HbA_{1c} of 8.875%. The authors also referenced the meta analysis of Weissberg-Benchell [187] and resultant improvement of 1.2% in HbA_{1c} from the use of CSII, though no mention was made of the weight gain of 1.03kg/m^2.

CSII resulted in an average life expectancy of 17.55 years as compared with 16.71 for MDI: an increase of 0.84 years. Taking quality of life into account had little impact upon this, resulting in a QALY gain of 0.85 from CSII. The direct treatment costs, which appear to exclude the costs of complications, were modelled as being SEK348,582 [£25,821] higher for CSII. Including the costs of complications and anticipated productivity gains reduced this net lifetime cost of CSII relative to MDI to SEK193,078 [£14,302], and so a cost effectiveness estimate from the societal perspective of SEK227,066 [£16,820] per QALY.

The 0.51% improvement in HbA_{1c} from the Pickup and colleagues (2002) meta analysis[16] was also referenced for use in a sensitivity analysis, which resulted in a considerably lower survival gain of 0.37 years from CSII, with the quality adjusted gain falling to 0.51 QALYs.

The differential impact upon survival and quality adjusted survival from the adoption of the 0.51% improvement in HbA_{1c} as compared to the base case 1.2% is worth noting. The reduced relative effectiveness of CSII in terms of glycemic control should result in a more similar complications profile for CSII and MDI. It appears that the move from 1.2% impact upon HbA_{1c} to only 0.51% causes the CORE model to reduce the impact upon complications which may be fatal such as MI to a greater extent than it tends to reduce the impact upon complications which are non fatal such as visual loss.

Roze & Palmer (2002)[234] used a markov model which was stated as being focussed upon nephropathy in order to estimate the cost effectiveness of CSII among newly diagnosed patients with T1DM of age 14. CSII appears to have been taken as improving glycemic control to 7.5%, as compared with 8.3% HbA_{1c} for MDI. A health insurance perspective was taken for costs, with results being presented for a discount rate of 3.0% for both costs and benefits. Unfortunately the country was not specified and while the authors were Swiss-based the source of clinical evidence was the Adolescent Benefit from

Control of Diabetes (ABC) study.[96] This study appears to have been conducted in the United States, and it seems reasonable to assume that the modelling also relates to the United States.

Through the reduction of renal disease the undiscounted life expectancy was anticipated to be 0.81 years greater with CSII. Costs were not reported separately, but the discounted cost was estimated as $115,082 per discounted life year of additional survival. Given the concentration upon nephropathy and the authorship, the model used may have been an early form of the CORE model. However, it may also have been an entirely separate model given the focus upon adolescents within both the modelling and the clinical effectiveness data.

Given the preponderance of CORE based modelling, the above cost effectiveness papers may be better viewed as a range of sensitivity analyses performed on the CORE model rather than as a range of independent cost effectiveness studies tending to confirm the cost effectiveness of CSII over MDI. Given this, a number of themes clearly emerge relating to the CORE modelling and its results:

- Patient characteristics were most commonly patients with T1DM of 26 years of age, 12 years diabetes duration and an HbA_{1c} of 8-9%
- The effectiveness of CSII was an improvement of 1.2% in HbA_{1c} in the base case
- The anticipated average survival was 16-17 year to give an anticipated lifespan for the modelled T1DM patients of 42-43 years on average.
- The anticipated survival gain from CSII was around 0.8-0.9 years
- The anticipated QALY gain from CSII was also around 0.8-0.9 QALYs
- Most modelling found CSII to be cost effective
- If CSII halved hypoglycaemia events its cost effectiveness was much improved
- If CSII only resulted in a 0.5% improvement in HbA_{1c} its cost effectiveness was very much worsened

4.3 Costs of CSII versus MDI

In the light of the initial CSII HTA and NICE guidance, Feltbower and colleagues (2006)[235] analyzed the Yorkshire Register of Diabetes in Children and Young Adults. This indicated an annual incidence of T1DM under 15 years of age of 19 per 100,000 person years. The cost per patient receiving CSII was estimated as requiring an initial set up cost of £4,000 in the first year: £2,000 for the pump itself, £1,000 maintenance, £1,000 training and other costs. Annual ongoing costs were estimated as £1,800: £1,200 for consumables and £600 for insulin and ongoing maintenance. No real detail was provided as to these unit cost estimates. The average annual cost for a single PCT within the then North and East Yorkshire SHA and West Yorkshire SHA was estimated as being between £739 and £1,322 for a take up of 1%, rising to between £3,696 and 6,608 for a take up of 5%. As a consequence, the authors

concluded that the overall financial burden for a PCT of providing CSII to children with T1DM would be modest for individual PCTs.

The Canadian AETMIS review article[17] identified the following average costs in 2004 prices for CSII:

Table 26: AETMIS Review Average costs for CSII

Pump		CA$6063	£2,526
Annual Consumables			
Cartridge		CA$281	£117
Infusion Set		CA$2016	£840
Batteries		CA$87	£36
Total (Consumables)		CA$2384	£993
Initial Training and Set-Up			
Medical specialist prescription time: 1hr	1*CA$96	CA$96	£40
Meeting with nurse: 2hrs	2*CA$26	CA£52	£22
Meeting with dietician: 2hrs	2*CA$24	CA$48	£20
either Adults: 2*6hr nurse training	12*CA$26	CA$312	£130
or Children (inc. parents): 20hr nurse training	20*CA$26	CA$520	£217
Support and Follow-Up			
20*30min care team (Dr., nurse, dietician)	20*CA$48+13+12	CA$1460	£608
20*30 min calls to nurse	20*CA$13	CA$260	£108
Total (Adult)		CA$2,228	£928
Total (Child)		CA$2.436	£1,015

The review also identified some additional costs from CSII relative to MDI arising from 50% more lancets and test strips being necessary for blood glucose monitoring, these being costed at an additional CA$840 [£350], coupled with an additional CA$58 [£24] for transparent adhesive dressings. In contrast, CSII was estimated as requiring only one antiseptic swab every four days, in contrast to the four daily antiseptic swabs recommended for MDI (though whether necessary or used is a different matter), which increased the relative cost of MDI by CA$549 [£228]. Overall, these additional costs increased the annual cost of CSII relative to MDI by CA$349 [£145]

Nuboer & Bruining (2006)[236] present the results of a broad and at times qualitative review of the issues likely to affect the cost effectiveness of CSII versus MDI. This includes a review of a German study which evaluated the cost of CSII among 6,437 children and adolescents with T1DM of up to 20 years of age: average age 12 years. This covered more than 25% of the overall T1DM German population in this age range in 2000. The overall average total annual cost of CSII was €2,611 [£1,740], with blood glucose self monitoring, hospitalisation and insulin accounting for 37%, 26% and 21% of the overall costs. Ambulatory care and injection equipment accounted for 9% and 7% of cost respectively. Paralleling this, an American study was quoted as finding an average cost among adolescents of $2,342 [£1,463] in the early 1990s, while a Finnish study in 1993 found an average cost of €2,200 [£1,580]. Updating these prices to 2005 values the authors concluded that the average cost for CSII among children and adolescents was around €3,000 [£2,027]. The paper also formed its own estimate of the extra costs of CSII as compared to MDI among adolescents as being between €1,355 [£915] and €2,968 [£2,005]. The main source of variability in these cost estimates was the cost of the infusion sets which varied from €6 [£4] to €16 [£11].

Mbowe and colleagues (2004)[237] estimated the costs to a Belgian university hospital of the provision of CSII to 94 patients with T1DM, six of whom were paediatric. This adopted an activity based costing method of more than 40 micro-activities which included items such as outpatient visits, the initial provision of CSII, any initial hospitalisation coupled with any subsequent hospitalisations, and administration and maintenance. The average cost per patient to the hospital was estimated as €3,045 [£2,030] per year, though this appears not to include the cost of insulin. The largest cost element at 22% was the provision of self monitoring strips.

4.3.1 The Ulahannan study

The industry submission was also accompanied by a recently published study by Ulahannan and colleagues[238] which reported the costs associated with CSII, and made the case that there could be short-term savings from adopting CSII. It will probably be widely quoted in support of CSII use, when pump clinics negotiate with primary care trusts over funding.

The study was carried out in Gloucester. The aim of Ulahannan and colleagues[238] was to collect data on NHS resource use by 34 patients starting CSII between June 200 and June 2005. The resource use included;

- Diabetic Clinical visits
- Appointments at other OP clinics
- Hospital admissions, whether related to diabetes or not
- Primary care contacts, at GP surgery, home visits, out of hours calls, and telephone contacts.

The aim was to collect such data for up to five years before and after, though for most patients it would be for much less. The exception was the subset of 17 patients for whom primary care data were collected, where the aim was to collect data for two years before and after. They also collected data on HbA_{1c}. The average length of follow-up for hospital data was 31 months prior to CSII and 34 afterwards. The before and after HbA_{1c} showed an average drop of 1.2% being reported.

The impact of CSII upon hospital resource use was reported as;

- Consultant OP visits fell from 2.4 to 1.3 a year; these were costs at £88 each
- Nurse appointments were little change, from 5.3 a year to 4.8 a year.
- Hospital admissions were reported to have fallen, but few details are given. The median number of admissions per month in both periods was nil, so most patients were not admitted before or after. Means were not given, and would have been more useful. Those who were admitted before were assumed to have been so because of severe hypoglycaemia, and costed accordingly, but this could not be confirmed, because the authors received only a crude breakdown of reason for admissions into diabetes or other cause. The average length of stay

for diabetes admissions in the hospital was 10.7 days. The length of stay for a hypo episode would be much shorter. The costs were given as £757 for a hypo admission, and £1932.50 for other diabetes admissions.

- Primary care contacts were reported to have fallen by about half, from 11 to six appointments a year.

There are several problems with this study, with there being various data deficits (i.e. some data were not available to the authors), and some inconsistencies in the paper.

- The reduction in OP appointments would not release any real savings in that the consultant would not be paid less but would do other things: an opportunity cost gain but not a financial saving. The figure used to estimate cost savings is 1.44 fewer diabetes consultant appointments a year, which does not tally with the figure of 1.1 provided from hospital records in the previous table.
- Secondly, the lack of data on hospital admission costs makes any cost calculation unsafe. Table 3 of the paper suggests that 0.132 admissions per patient per year would be saved, but this is not compatible with the range of admissions per year given in the previous table, of 0 -1.2.
- Thirdly, any reduction in admissions would not release real savings unless beds were closed and staff made redundant, which would not happen given the very small number of admission involved. Again, while this may yield an opportunity cost gain there are unlikely to be any associated financial savings.
- Similarly, if there is a reduction in primary care contacts, no funds would be released. The practices would be very slightly less busy.

While the study provides some evidence for asserting that CSII may provide some gains in terms of opportunity costs and the freeing of resources to undertake other activities, the assertion that CSII will be accompanied by short-term savings in hospital and primary care cannot be supported by this study. A more detailed study is required.

4.3.2 Cost Abstracts

Bolli and colleagues (2004)[108] undertook a six month multi centre RCT of CSII versus MDI among 57 type 1 diabetics. Both arms of the trial showed similar improvements in glycemic control, blood pressure and glycemic events with any differences in outcomes being non-significant. While treatment costs were not reported, the authors did report that CSII treatment costs were 400% those of MDI. The authors concluded that a glargine based MDI regime was more cost effective than CSII plus glargine in an unselected type 1 diabetic population.

4.4 Cost Effectiveness Modelling

4.4.1 Clinical effectiveness

The key clinical elements within the modelling relate to the differences between the HbA_{1c} level and the rate of severe hypoglycaemia episodes between MDI and CSII . The base case uses the CORE model to assess the cost effectiveness of CSII in a population of average age 40 years with type 1 diabetes within whom it seems well suited. While the CORE model is not suited to modelling adolescent and paediatric use, the effect of a younger cohort will be explored through an adoption of an average age of 30 years.

The base case effect on the baseline HbA_{1c} level assumes a baseline level of [redacted] HbA_{1c} on MDI, reduced by [redacted] by CSII. (based on the results from the Insulin Pumps Clinical Database) Three sensitivity analyses are undertaken with regards the effect of CSII upon glycemic control.

- The first uses the results from the meta-analysis by Pickup and colleagues, of a reduction of [redacted]
- The second uses the results of a yet to be published analysis that show a reduction of [redacted] from a baseline of [redacted], but no reduction in the rate of severe hypoglycaemic events
- The third assumes that some pump users who have a high rate of severe hypoglycaemia events will gain no reduction in HbA_{1c} levels because they start with good control hence a baseline of 7.5%, but achieve a reduction in their rate of severe hypoglycaemia events.

A general population of those with type 1 diabetes can be characterised as having a rate of severe hypoglycaemia events of 18.7 per 100 patient years as within the NICE appraisal of the cost effectiveness of glargine. The costing within this report has assumed the use of glargine or other long-acting analogue, which the assessment group for the glargine appraisal estimated could reduce the severe hypoglycaemia rate to as little as 8.8 per 100 patient years. However, the FAD noted that this might be an overestimate and as a consequence a baseline rate for the general population with type 1 diabetes of 18.7 per 100 patient years will be assumed. The effect of CSII upon this rate will be explored as a 50% reduction and a 75% reduction in severe hypoglycaemic events, with no effect upon severe hypoglycaemic events also being explored as a sensitivity analysis.

It seems likely that the main focus for NICE for the application of CSII will be on patients with more severe problems with hypoglycaemia. In common with the industry submission, this will be explored through the assumption of a rate of [redacted] patient years as in the Pickup analysis, with reductions of 50% and 75% within this group. Simulations will also explore the possible effects of alternative cost scenarios as outlined within the costs section above. As noted within the literature review, the CORE model may have a tendency to overstate overall mortality within type 1 diabetes over longer time horizons, which may be due to a possible overestimation of macrovascular complications and their associated mortality. As a consequence, this will also be explored through 50, 30 and 10 year time horizons coupled with a reporting of the evolution of the estimated macrovascular events and survival over this period. While the 10 year time horizon is too short for an accurate evaluation of the cost effectiveness of CSII relative to MDI, it permits the evolution of cost effectiveness to be explored and highlight timing of the anticipated main gains.

The group of patients who start with good control as reflected in HbA1c, but achieved at the cost of more problems with severe hypoglycaemia, will get little or no reduction in HbA_{1c} levels, The effect of CSII upon HbA_{1c} levels will be set to nothing for this group. However, the baseline rate of severe hypoglycaemia events will be increased to 134 per 100 patient years as in Boland and colleagues (1999), with the effect of CSII being explored through reductions of 50% and 75%, the 50% reduction corresponding closely to the reduction to 76 per 100 patient years from CSII as reported by Boland.

4.4.2 Treatment costs

More detail on costs is given in appendix 7.

Capital costs

The NHS Supply Chain is currently engaged in a tendering exercise to establish a national price structure for pumps and consumables. The range of pump prices currently available within the UK is £2,375 to £2,750, with a usual warranty period of 4 years though the Roche Accu-Check Spirit carries a six year warranty.

After the warranty period, it was previously the case that an extension of the guarantee could be obtained through additional servicing. As outlined in the previous HTA report this could cost up to £500 in order for the guarantee to extend by an additional two years. This reduced the annualised cost per year of pumps under guarantee, though it was reported that this servicing was not always undertaken with pumps being disposed of when out of guarantee.

However, given the rate of change within the sector and the continuing evolution of pump types, it is reported by INPUT that extended servicing is no longer available. Pumps may be discontinued immediately after the warranty period expired with a new pump being purchased. Opinion from INPUT indicates that pump users are likely to want the most up to date pump and will wish to discontinue with pumps outside their warranty period. However, there is no necessary bar to using pumps outside their warranty period and a lifespan of an additional two years is used for sensitivity analysis.

Given this, the pumps purchase costs and their annualised values are as outlined below:

Table 27 Current costs of pumps and annualised costs.

	Deltec Combo	Accu Check	Animas IR1200	Medtronic
Purchase Price	£2,750	£2,375	£2,600	£2,750
Warranty (years)	4	6	4	4
Annualised (warranty)	£723	£431	£684	£723
Annualised (warranty+2)	£499	£334	£471	£499

With regards to the additional training that may be required for the use of CSII, this can be estimated as a one off cost of around £240 (based on the cost of a DAFNE course in Aberdeen) which would annualise to an approximate figure of £15 on the assumption that this is a one off cost for those transferring to pumps.

In contrast, the only capital items for MDI are the two pen devices necessary, which at a cost of around £22 each and a possible lifespan of 3 years would give an annualised capital cost of £15.

Consumables and total costs

The consumables for CSII of infusion sets and reservoirs as outlined within the manufacturer submission and by INPUT (see appendix 8) have an annual cost of between £1,090 and £1,361 with an average of around £1,220. However, these are pump specific. Other costs relate to the required insulin dose and the frequency of blood glucose monitoring. The meta analysis by Pickup and colleagues (2001) noted a reduced daily requirement for insulin of $0.6IUkg^{-1}$ for CSII as compared to $0.7IUkg^{-1}$ for MDI.

The previous review noted that CSII had a daily requirement of 4 or more blood glucose tests per day compared with 3 or more for MDI, though concluded that on average this would not result in any real additional cost for CSII. Given this, the base case for this review will assume a common rate for both CSII and MDI.

Given an assumed patient weight of 80kg this translates into the following costs for CSII:

Table 28 Annual costs of CSII.

	Deltec Combo	Accu Check	Animas IR1200	Medtronic
Infusion sets, reservoirs	£1,362	£1,214	£1,087	£1,374
Insulin	£312	£312	£312	£312
Lancets	£36	£36	£36	£36
Test strips	£329	£329	£329	£329
Glucometer	£10	£10	£10	£10
Consumables	**£2,048**	**£1,900**	**£1,773**	**£2,060**
Total (warranty)	**£2,771**	**£2,331**	**£2,457**	**£2,783**
Total (warranty+2)	£2,547	£2,234	£2,245	£2,559

Note that the above assumes that infusion sets are changed every three days as recommended. Additional data supplied by INPUT as to the frequency of infusion set changes among its members shows some variability in this as shown below. This averages a change every 3.3 days, which if generally applicable would tend to reduce the total annual cost of CSII by around £100 to £130. However, the recommended change every 3 days has been retained in the base case analysis.

Table 29 Frequency of Infusion Set Changes (from a survey by INPUT)

Frequency of Change	Percentage
Every 2 days	9%
Every 3 days	49%
Twice weekly	26%
Every 4 days	10%
Every 5 days	4%
Every 6 days	1%
Weekly	1%

In contrast, MDI is associated with the insulin costs of £466, a cost of needles of £32 and the same costs for lancets, test strips and glucometer of £374 to give a total annualised cost including the £15 annualised cost of pens, of £890. Averaging the CSII costs above suggests an annualised cost of CSII of £2,590, which implies a net marginal cost over MDI of £1,700 for the base case.

Costs of complications

Clarke and colleagues (2002)[206] provide costs for a number of the complications of diabetes among the patients with type 2 diabetes in the UK PDS cohort. These are broken down into the year in which the event occurred and subsequent years. Unfortunately, due to data problems the non-inpatient costs

could not be determined for the individual complications but were rather grouped by whether the complications were macrovascular or microvascular.

Updating the costs for inflation using the Unit Costs of Health and Social Care of the Personal Social Services Research Unit (2006)[239] implies the following costs in 2006 prices:

Table 30 Costs of complications

	Inpatient		Non-Inpatient		Total	
	Year 1	Year 2+	Year 1	Year 2+	Year 1	Year 2+
Fatal MI	£1,474	£0	£403	£0	£1,877	£0
Non-fatal MI	£5,207	£594	£403	£330	£5,610	£924
MI average	£3,863	£594	£403	£330	£4,266	£924
Fatal Stroke	£4,328	£0	£403	£0	£4,731	£0
Non-fatal stroke	£3,028	£319	£403	£330	£3,431	£649
Stroke average	£3,210	£319	£403	£330	£3,613	£649
Angina	£2,506	£631	£403	£330	£2,909	£961
CHF	£2,842	£807	£403	£330	£3,245	£1,137
Blindness in one eye	£1,116	£360	£349	£261	£1,465	£621
Amputation	£10,823	£384	£349	£261	£11,172	£645
Cataract Extraction	£1,987	£134	£349	£261	£2,336	£395

While these are from the same source as the industry submission, their values are typically slightly above those used in the industry submission. This difference appears to relate to the inclusions of non-inpatient costs coupled with some possible differences as to up-rating for inflation, the above applying the HSCS index. The base case uses the above values.

In common with the industry submission, the results of Ghatnekar and colleagues (2001)[240] are used for the costs of complications associated with uninfected ulcers, infected ulcers and gangrene, which in 2006 prices equate to event costs of £1,643, £1,684, and £2,700. Again, these are slightly higher than those of the industry submission, probably due to different inflation rates having been assumed. Similarly, the costs of haemodialysis and peritoneal dialysis can be taken from UKPDS 40[241] (as summarised in the industry submission) to give annual costs of £27,575 and £20,704 respectively. The other costs of treatment have been taken from the industry submission.

Cost sensitivities

As already noted, the duration of pump use is subject to some uncertainty given the changes to warranty status and extension. If pumps are used for two years beyond their warranty period this would suggest a reduction of around £100 and £200 in the cost of CSII.

Given the use of CSII in paediatric patients with type 1 diabetes, and the possibility of use in overweight patients with type 2 diabetes, we need to consider the extent to which patient weight could affect costs. However, the major cost components for CSII are the consumables and capital costs which do not vary with weight or diabetes type.

For a patient weight of 80kg CSII results in an annual insulin cost saving of £154. Reducing the patent weight to only 30kg reduces this cost saving to £58, so increasing the net cost of CSII by £96. In contrast, increasing the patient weight to 100kg increases the annual insulin cost saving to £192, so reducing the net cost of CSII by £38 though this does assume the same dosing per kilogram which may underestimate the annual saving in insulin costs.

The more pessimistic assumption of equal dosing under CSII and MDI of $0.6IUkg^{-1}$ reduces but does not eliminate the insulin cost savings from CSII, since MDI still require half the insulin used to be the slightly more expensive long acting analogues. Given this the equalisation of insulin dosing sees CSII result in a reduced saving of £87 in the insulin cost, hence an increase in the net cost of CSII of £67.

If CSII requires one additional daily blood glucose test, the additional cost to CSII would be £120, and it should be noted that the previous HTA review suggested that this might be required. Similarly, the AETMIS review anticipated additional costs being associated with increased monitoring frequency from CSII as compared with MDI.

In sensitivity testing of different costs, a high cost of CSII corresponding to equal insulin dosing and increase monitoring frequency will be explored: CSII £2,710, MDI £803 resulting in a high net cost of £1,907. A low net cost will also be explored, this arising from the base case assumptions but a longer pump lifespan to give: CSII £2,400 MDI £890 resulting in a low net cost of £1,510.

Another element subject to a degree of uncertainty is the ongoing costs of legal blindness to the NHS/PSS. These may be somewhat higher than the cost of blindness in one eye as identified by Clarke and colleagues.[205] Meads et al (2003)[242] estimated the average annual cost to the NHS/PSS of severe visual impairment arising in an elderly population from wet age-related macular degeneration to be £5,345. Given this, the sensitivity of results to a higher ongoing cost of legal blindness of £4,000 per year will be explored as an illustration, though as shown below this has minimal effect upon results.

Other model inputs and sensitivity analyses

Other baseline population characteristics, utilities and costs of complications will be as per the industry submission with the exception of the cost of a severe hypoglycaemia event which will in the base case be taken to be £65, reflecting the value used within the glargine appraisal, rather than the £413 assumed by industry. The higher cost used by industry assumes admission, whereas most patients are not admitted to hospital after a severe hypo. Sensitivity analyses with regards to the effect of CSII upon glycemic control, the effect upon rates of hypoglycaemic episodes, and the net treatment cost will be conducted for the base case populations with the baseline rate of severe hypoglycaemia events of [redacted] per 100 patient years.

The full list of simulations as outlined within appendix 9 were run in CORE. However, with regards to the reduction in severe hypoglycaemia events a reduction of one severe hypoglycaemia event would be anticipated to result in an annual saving in reduced downstream costs of complications of £65 while yielding an additional annual 0.0121 QALYs in the base case.

Following from this, if there were no other benefits from CSII over MDI other than a reduction in severe hypoglycaemia events then for a cost effectiveness willingness to pay of £20,000 per QALY, the QoL gain from an absolute annual reduction of one severe hypoglycaemia event could be monetised at a value of £242(£20,000 * 0.0121). Given the cost saving of £65 this implies that at a threshold of £20,000 per QALY the annual willingness to pay to avoid one severe hypoglycaemia event would be £307. The parallel figure for a threshold of £30,000 per QALY would be £428. More concretely, a 50% reduction in severe hypoglycaemia events from [redacted] as in many of the simulations could be monetised at £95 for the £20,000 per QALY threshold (£242 * [redacted] * 50%), and at £133 for the £30,000 per QALY threshold.

Had the cost per severe hypoglycaemia event been £413 as in the industry submission, the parallel figures for a reduction of one severe hypoglycaemia event would be monetised at £655 at the £20,000 per QALY threshold, and £776 at the £30,000 per QALY threshold. As a consequence a 50% reduction in severe hypoglycaemia events from [redacted] would be monetised at £203 for the £20,000 per QALY threshold, and to £241 for the £30,000 per QALY threshold.

It can be seen from the above that for a cost saving per severe hypoglycaemia event of only £65, the monetised value of a reduction from [redacted] severe hypoglycaemia events per year of between £95 and £133 arising from the adoption of CSII, while not insignificant, is not large compared with the anticipated increase in treatment costs of £1,700. The base case requires there to be additional downstream gain in terms of reductions in the micro and macrovascular complications of diabetes for CSII to be cost effective. The adoption of the industry cost per severe hypoglycaemia event of £413 somewhat increases the monetised value of the reduction in severe hypoglycaemia

events, so only requires a lesser effect upon the micro and macrovascular complications for CSII to be cost effective. This is one of the sources of the better cost effectiveness estimates for CSII within the industry submission as compared with the current modelling.

4.4.3 Results

Base case for type 1diabetes

The type 1 population has been characterised by the baseline rate of severe hypoglycaemia events being 18.7 per 100 patient years as in the glargine appraisal. Given this and the anticipated 0.9% improvement in HbA_{1c} the CORE model over a 50 year time horizon anticipates the following results:

Table 31 Cost effectiveness : general population

Type 1	CSII	MDI	Difference
Life expectancy	21.831	20.536	1.295
Life expectancy (discounted)	14.237	13.652	0.585
QALYs (discounted)	**9.571**	**8.97**	**0.601**
Treatment costs (discounted)	£38,129	£12,599	£25,530
Other costs (discounted)	£21,463	£24,316	-£2,853
Total costs (discounted)	**£59,592**	**£36,915**	**£22,677**
ICER : Cost per QALY	**£37,712**		

The above results assume a 50% reduction in severe hypoglycaemia events. Other simulations for this group use a 0% reduction and a 75% reduction in severe hypoglycaemia events, the results of which are presented in appendix 10. All these simulations show similar results given the relatively low baseline rate of severe hypoglycaemia events of 18.7 per 100 patient years.

Higher severe hypoglycaemia rates

For the base case population with a baseline HbA_{1c} of 8.8% and a severe hypoglycaemia event rate of 62 per 100 patient years, the anticipated impact from CSII of reduction in these to 7.9% and 31 per 100 patient years respectively is as outlined below:

Table 32 Cost effectiveness : Higher severe hypoglycaemia rates

50 year horizon	CSII	MDI	Difference
Life expectancy	21.808	20.563	1.245
Life expectancy (discounted)	14.224	13.665	0.559
QALYs (discounted)	**9.504**	**8.892**	**0.612**
Treatment costs (discounted)	£38,097	£12,611	£25,486
Other costs (discounted)	£21,662	£24,761	-£3,099

Total costs (discounted)	**£59,759**	**£37,372**	**£22,387**
ICER : Cost per QALY	**£36,587**		

Given the similarity in terms of clinical assumptions between what was labelled the conservative UK based analysis of the industry submission, and those of the base case above, the average life expectancies are similar at around 21.8 years for CSII as compared with 20.6 years for MDI. The base case analysis above anticipated a slightly smaller gain from CSII of 1.2 years as compared with 1.4 years within what was labelled the conservative UK based analysis of the industry submission. The anticipated discounted QALY gain is also a little lower in the base case at 0.61 QALYs, as compared with 0.72 QALYs in the conservative UK based analysis of the industry submission.

The small difference in cost per QALY between the two tables above, despite the difference in severe hypoglycaemia events is because the results of the CORE modelling are principally driven by the effect upon glycemic control rather than the rates of severe hypoglycaemia. However this assumes that the reduction in severe hypoglycaemia events does not also yield a quality of life gain from a reduction in the fear of severe hypoglycaemia events.

For the base case, while the savings from CSII within other costs provide around a 12% net cost offset to the net treatment costs, the additional total costs of £22,387 give an ICER in the base case for CSII over MDI of £36,587 per QALY.

For illustration, and to test the model, curtailing the time horizon to 10 years markedly increases the cost per QALY

Table 33 Time horizon sensitivity analysis:

30 year horizon	**CSII**	**MDI**	**Difference**
QALYs (discounted)	**9.299**	**8.721**	**0.578**
Treatment costs (discounted)	£36,967	£12,293	£24,674
Other costs (discounted)	£19,107	£22,565	-£3,458
Total costs (discounted)	**£56,074**	**£34,858**	**£21,216**
ICER : Cost per QALY	**£36,710**		
10 year horizon	**CSII**	**MDI**	**Difference**
QALYs (discounted)	**5.603**	**5.392**	**0.211**
Treatment costs (discounted)	£20,637	£7,059	£13,578
Other costs (discounted)	£5,062	£6,412	-£1,350
Total costs (discounted)	**£25,699**	**£13,471**	**£12,228**
ICER : Cost per QALY	**£58,013**		

The effect of a time horizon of 30 years is minimal, as would be anticipated given the expected average life expectancy of a little over 21 years: few live to this point and the effects of CSII are

mostly contained within this horizon. However, with a time horizon of 10 years the cost effectiveness has worsened to £58,013 per QALY. This is because there is almost no gain in anticipated average life expectancy, since almost all would live beyond the truncated time horizon whether receiving CSII or MDI. The long term timescale for the development of complications means that the great majority of the gains from CSII occur after the ten year point.

Curtailing the time horizon to 30 years causes relatively more of the complications of diabetes to be excluded from the CSII group than from the MDI group, since better glycemic control under CSII tends to postpone these. This gives rise to the anticipated increase in savings among other costs, and also accounts for the relatively muted effect that curtailing the time horizon has upon the net QALY gain. While the effect is not overly large, it can be illustrated by the cumulative incidences of three of the macrovascular complications which lead to both cost and quality of life impacts.

Table 34 Macrovascular complication rates

	10 year	30 year	50 year
CSII			
CHF	4.7%	22.3%	28.7%
Stroke	1.5%	8.1%	11.6%
MI	4.2%	21.2%	26.6%
MDI			
CHF	4.9%	22.6%	27.7%
Stroke	1.6%	7.9%	10.6%
MI	5.1%	23.8%	28.3%
Net			
CHF	-0.2%	-0.3%	1.0%
Stroke	-0.1%	0.2%	1.0%
MI	-0.9%	-2.6%	-1.7%

Within this subset of complications, while the cumulative incidence of stroke evolves differently its overall cumulative rate is relatively low as compared with CHF and MI events. For CHF and MI events the net effect of CSII upon these increases at the 30 year point, then falls back again at the 50 year point. In addition to the explanation given above, the greater increases in the cumulative incidences of CHF and MI among the CSII group as compared with the MDI group will also be due in part to the greater proportion of CSII patients remaining alive during this period.

Younger age group

The base case and the above high severe hypoglycaemic event rates population have assumed an average age of 40 as seems well suited to the CORE model. Reducing this to 30 years while retaining all other assumptions as within the high severe hypoglycaemic event rates population leads to the following.

Table 35 Younger cohort

	CSII	MDI	Difference
Life expectancy	25.146	23.498	1.648
Life expectancy (discounted)	15.528	14.854	0.674
QALYs (discounted)	**10.357**	**9.648**	**0.709**
Treatment costs (discounted)	£41,352	£13,631	£27,721
Other costs (discounted)	£23,558	£27,055	-£3,497
Total costs (discounted)	**£64,910**	**£40,686**	**£24,224**
ICER : Cost per QALY	**£34,136**		

While the baseline age of the cohort has been reduced by ten years, the average life expectancy as modelled by CORE increases by only a little under 5 years. As would be anticipated the net treatment costs increase, but these are offset to a slightly greater degree by increased net savings from downstream complications. While these complications are likely to be more prevalent within the modelling for both CSII and MDI, the net effect is likely to be greater given the greater additional life expectancy. Given these changes, the cost effectiveness of CSII improves slightly to £34,136 per QALY. While this still does not lead to a conclusion of cost effectiveness, it does represent an improvement of 7%.

Lesser effect upon glycemic control

The meta analysis of Pickup and Sutton (2007) suggested an overall reduction in HbA1c with CSII of [redacted] this also being modelled within the manufacturer submission as the trial based analysis. Undertaking a similar analysis with a baseline HbA_{1c} of 9.0% and a [redacted] improvement, and retaining the assumption of a 50% reduction in the rate of severe hypoglycaemia events gives the following.

Table 36 Cost effectiveness : Reduced effect upon glycemic control

	CSII	MDI	Difference
Life expectancy	21.399	20.563	0.836
Life expectancy (discounted)	14.044	13.665	0.379
QALYs (discounted)	**9.318**	**8.892**	**0.426**
Treatment costs (discounted)	£37,645	£12,611	£25,034
Other costs (discounted)	£22,673	£24,761	-£2,088
Total costs (discounted)	**£60,318**	**£37,372**	**£22,946**
ICER : Cost per QALY	**£53,788**		

As would be anticipated the net effects on life expectancy and quality of life from CSII are reduced, as are the savings. The effect upon the net discounted treatment costs is also a slight reduction, but as this arises due to the reduced impact upon net life expectancy it is not in itself desirable. The reduced

relative clinical effect has a major detrimental effect upon cost effectiveness, increasing the anticipated ICER to £53,788 per QALY.

Note that if the effect of CSII upon severe hypoglycaemia events is a 75% reduction, the cost effectiveness of CSII within the scenario improves slightly to £47,780 per QALY.

Greater effect upon glycemic control

As noted within the introduction to this section, a further analysis by Pickup and colleagues [133] indicates an improvement of 1.4% from the use of CSII on a baseline of 9.0% under MDI. However, within this analysis no effect upon severe hypoglycaemic events was recorded. This results in the following.

Table 37 Greater effect upon HbA1c

	CSII	MDI	Difference
Life expectancy	22.239	20.226	2.013
Life expectancy (discounted)	14.415	13.505	0.91
QALYs (discounted)	**9.633**	**8.747**	**0.886**
Treatment costs (discounted)	£38,574	£12,473	£26,101
Other costs (discounted)	£21,204	£25,416	-£4,212
Total costs (discounted)	**£59,778**	**£37,889**	**£21,889**
ICER : Cost per QALY	**£24,720**		

As would be anticipated, the anticipated life expectancy is worse for MDI given the poorer baseline glycemic control. Also, since CSII improves this control to 7.6%, near to good control, the anticipated lifespan under CSII is greater than in the base case and an average additional two years life expectancy under CSII are anticipated by the modelling. Net treatment costs increase slightly given this increased survival, but these are more than offset by increases net savings from reduced treatment of the complications of diabetes. The overall net cost is less than for the base case. This leads to CSII having a cost effectiveness ratio relative to MDI of £24,720 per QALY.

Greater and lesser effects upon severe hypoglycaemia events

As has already been noted, given the baseline annual rate of severe glycaemia events of 0.620 and the implied relatively limited annual impact of these upon both quality of life and cost, the effect of CSII upon these has only a relatively limited impact upon the anticipated cost effectiveness of CSII. If CSII has no effect upon severe hyperglycaemic events its cost effectiveness is anticipated to worsen from £36,587 to £41,062 per QALY, while a 75% reduction in severe hypoglycaemic events from CSII would improve its cost effectiveness to £33,361 per QALY.

Higher and lower treatment costs

The cost of CSII varies with both the device used and the assumptions made as to post-warranty longevity, and also with any insulin savings and monitoring differences between CSII and MDI. Given that the base case costs result in estimates of cost effectiveness for CSII which are outside normal cost effectiveness limits, the impact of a high annual net treatment cost for CSII of £1,907 as outlined within the section on costs above will be explored, but only with an increased effectiveness of a 75% reduction in the baseline rate of severe hypoglycaemia episodes. The lower net cost of £1,510 is explored for both the base case situation of a 50% reduction in severe hypoglycaemia events, and a greater reduction of 75%.

Using a higher net cost of CSII increases the base case discounted net treatment costs by £3,000 from £25,526 to £28,526. As nothing else changes, total costs show a parallel increase from £22,171 to £25,171 for the same 0.664 QALY gain, resulting in a cost effectiveness estimate for CSII of £37,874 per QALY.

Using a lower net cost of CSII reduces the net treatment costs from £25,486 to £22,691 and results in an improvement in the cost effectiveness estimate to £32,020 per QALY. With a larger gain of a 75% reduction in severe hypoglycaemic events, in addition to the 0.9% improvement in glycemic control, net treatment costs are reduced from £25,526 to £22,728 with the overall cost effectiveness ratio falling to £29,151 per QALY.

Costs of blindness

As outlined earlier, the costs of legal blindness used for the base case may be something of an underestimate. However, increasing these to £4,000 per annum has only a marginal effect upon results, very slightly improving the cost effectiveness of CSII to £36,429 per QALY.

Fear of severe hypoglycaemia events

A reduction in the rate of severe hypoglycaemic events can give quality of life gains in two ways. Firstly, the immediate disbenefits at the time of the hypoglycaemic episodes are avoided. Secondly, there is an additional gain from reduced fear of hypos - reduced worry, better mental health and improved ability to undertake usual social activities. The utility gain from this may be more likely to apply to those with more frequent severe hypoglycaemia .

For the base case population, if there is a sub-group that derives this benefit, given an anticipated longevity of a little over 21 years an annual 0.01 QoL increment arising from CSII for this reason would translate into approximately an additional discounted 0.15 QALY gain. Factoring this into the base case results would be sufficient to improve the incremental cost effectiveness ratio to approximately £29,300 per QALY. An annual increment of 0.03 would lead to an ICER of approximately £21,000 per QALY.

High severe hypoglycaemia rate but good HbA1c

As noted, some people with type 1 diabetes have good glycaemic control, but when using MDI achieve that level of control at the cost of a higher baseline rate of severe hypoglycaemia, say 134 per 100 patients years. Improvements of 50% and 75% in the rates of severe hypoglycaemia events through use of CSII can be simulated for this group, with there being no gain in glycaemic control, but these yield cost effectiveness estimates of £273,992 per QALY and £152,058 per QALY respectively, not allowing for any utility gain from reduced fear of hypos.

Only reducing severe hypoglycaemic events is not cost effective, unless we take into account that there are some patients whose fear of severe hypoglycaemia limits their ability to lead normal day to day lives. If CSII reduces the rate of severe hypoglycaemia events by 50%, without affecting HbA1c, the additional annual QoL increment from the reduced fear of severe hypoglycaemia has to be of the order of 0.05 to improve the cost effectiveness of CSII to around £28,600 per QALY. With a 75% reduction in severe hypoglycaemia events, for CSII to move towards cost effectiveness requires that the additional annual QoL increment from the reduced fear of severe hypoglycaemia events to be 0.04, resulting in a cost effectiveness of around £31,300 per QALY.

4.4.4 Conclusions

The possible benefits of CSII include;

- improved glycaemic control
- reduced frequency of hypoglycaemia
- a reduction in the chronic fear of severe hypoglycaemia
- a reduction in insulin dose giving modest savings
- improved non-health related quality of life arising from greater flexibility of lifestyle

If severe hypoglycaemia has a cost of only £65 per event, whether CSII has no effect on frequency of events, halves it or reduces it by 75% has little impact upon the estimated cost effectiveness of CSII.

This is because the main driver of cost-effectiveness in the CORE model is HbA1c. Severe hypoglycaemia has little effect because episodes are of short duration.

This is underlined by simulation among those with high rates of severe glycaemia events but good baseline HbA1c, in whom CSII has no effect upon glycemic control, but causes reductions of 50% and 75% in the rate of severe glycaemia events. Despite the larger absolute falls in severe glycaemia events within this group, the estimates of the cost effectiveness of CSII relative to MDI rise to six figure sums per QALY. This does not take chronic fear of hypoglycaemia into account.

For the base case estimate of a 0.9% reduction upon a baseline 8.8% HbA_{1c} the central estimate of the cost effectiveness of CSII relative to MDI is estimated as £36,587 per QALY. These figures are based upon an estimated reduction in severe hypoglycaemia events from [redacted] per 100 patient years to [redacted] per 100 patient years. If CSII reduces this rate to only 15.5 per 100 patient years the cost effectiveness of CSII for a 0.9% reduction to a baseline 8.8% HbA_{1c} is only slightly reduced to an estimate of £33,361 per QALY.

A lesser effect upon glycemic control of only a [redacted]% reduction upon a baseline 8.8% HbA_{1c} while retaining a 50% reduction in severe hypoglycaemic events leads to a cost effectiveness estimate for CSII of £53,788. A greater effect upon glycemic control of a 1.4% reduction upon a baseline 9.0% HbA_{1c} with no reduction in severe hypoglycaemic events leads to a cost effectiveness estimate for CSII of £24,720 per QALY.

There is uncertainty as to the net treatment cost of CSII, it being plausible for this to range from a central estimate of £1,700 up to a high of around £1,900 and down to a low of around £1,500. Despite this range, the estimate of the cost effectiveness of CSII relative to MDI remains slightly above the usual cost effectiveness thresholds.

However, if the net price of CSII is lower than assumed for the base case, the impact of a 75% reduction in severe hypoglycaemia events as opposed to a 50% reduction is just sufficient to tip the cost effectiveness of CSII from being slightly above £30,000 per QALY to being slightly below £30,000 per QALY.

One of the main uncertainties relates to the additional quality of life benefit from a reduction in the fear of severe hypoglycaemia. While this effect may apply only to a sub-group of patients, the quality of life gain from a reduced fear of severe hypoglycaemia would have to be only relatively minor to make CSII to be cost effective.

An annual gain of only 0.01 in quality of life from the reduced fear of severe hypoglycaemia would be sufficient to cause the cost effectiveness of CSII to be around the £30k per QALY, while an annual gain of around 0.03 in quality of life would cause the cost effectiveness of CSII to fall to around £20k per QALY. But note that this is within the base case population: those patients with type 1 diabetes who are poorly controlled on MDI and for whom CSII results in a 0.9% improvement in glycemic control and a halving in the rate of severe hypoglycaemia events.

Chapter 5 Patient perspectives

This chapter has three sections. Firstly, there is an account of some of the points made in the submission to NICE from pump users. Secondly, insulin pump use has been increasing in very young children, in whom achieving tight control can be particularly difficult. We have therefore interviewed some parents of young children on CSII, in order to find out what the practical problems and benefits are in that age group. Thirdly, we summarise some of the key points from the patients' perspectives chapter of the previous assessment report.

We can think of the benefits of CSII as lying on a spectrum of different ease of measurement, with improvements in HbA1c at the easy end to measure accurately, and "flexibility of lifestyle" at the more difficult end. The published research tends to focus on the easy end. This chapter is concerned more with the other end.

5.1 The submission from INPUT

INPUT is the organisation of insulin pump users. It is a patient led group which is independent of the manufacturers, and whose aims are;

"*to increase the awareness and understanding of insulin pump therapy, and to help, support and educate insulin pump users and their families in their use." (INPUT website www.input.me.uk, accessed May 2007)*

INPUT submitted evidence to NICE, in conjunction with Insulin Pumpers UK, a web-based discussion group (INPUT "Joint submission from INPUT and Insulin Pumpers UK" 2007 - to become available on NICE website). Some of it provides information on aspects such as control of HbA1c and reduction in frequency of hypoglycaemia, which has been reported in chapter 2. However it also provides evidence on other benefits of CSII, such as quality of life.

The submission consists of two sections – a formal submission, and a collection of commentaries by insulin pump users (including families). The formal section makes points which include;

- the previous NICE guidance[71] has been implemented to widely varying extents in different parts of the country, ranging from full support for CSII, to capping at an arbitrary level of 1-2% of the numbers with T1DM, to no support at all (particularly for children)
- this is partly because the guidance about who should receive CSII was open to differing interpretations

- in addition to tighter control of diabetes, CSII provides quality of life gains and flexibility of lifestyle – the freedom to eat only when hungry, the opportunity to sleep better without nocturnal hypoglycaemia or setting alarm clocks for blood tests, the chance to undertake sports and exercise, and greater self-confidence in education and careers. (Again, similar comments have been made after DAFNE courses, by people on MDI)
- that the opinion of individual diabetologists and paediatricians had a major effect on provision, and that there are "anti-pump" professionals
- the need for a cohesive service for all people with T1DM. The submission recognises that there are resource constraints on diabetes care
- that if a diabetes service supports basal/bolus (MDI) insulin regimens, it should be able to support a pump service, because MDI is just as demanding of specialised dietetic and nursing time as CSII is
- that with pumps, it is easier to control the boluses, but more importantly the basals, particularly during the night
- that an algorithm should be developed to identify which patients would be suitable for CSII
- the need for transitional arrangements between paediatric and adult clinics
- problems when patients move from an area with a pump service with funding to one without
- the usefulness of CSII in children who need very little insulin
- that in some patients, HbA1c does not change but blood glucose is kept within a much narrower range, avoiding extreme swings
- that for children and families, quality of life gains include being able to eat out, to go on excursions of uncertain duration such as school trips, to get up at different times, and to not to have to force children to eat when they don't want to
- that school routines are easier to manage on CSII, especially as some schools cannot cope with lunchtime injections, which prevents children moving to MDI. Children on pumps do not need to go to the medical room to inject, don't need to go to lunch first, but can wait and go with their peers, thus reducing social exclusion ([redacted]
- that exams are easier to cope with if blood glucose is more stable
- that children feel more in control on CSII

The submission is of course based on successful users of pumps, and INPUT accepts that not all children or adults will wish to use pumps.

The individual submissions added detail to some of the above;

- that mood often improved in children with better control
- that pre-pump, patients often had very wide swings in blood glucose levels – daily blood sugar ranges from 2 to 26. One patient reported a pre-pump range of 2 to 30mmol/l, reduced to 4.8 to 7.5 on CSII
- that very high levels such as the post-breakfast spike reduced academic ability during that period. One girl did well in most subjects but poorly in maths, which she did mid-morning. Once her blood glucose was stable on a pump and the spike was prevented, her maths improved.
- the usefulness of being able to set different basal rates for different times of day and night, and for different activity levels. (Though this can be done to some extent with twice daily detemir or NPH).
- the ease of travelling through time zones when on business or holiday
- going to Scout camp without mother
- return of hypo awareness
- reduced insulin doses, varying amongst patients. One adult uses 30-40% less insulin on CSII.
- no support from some diabetes clinics, making travel to a pump centre a nuisance. "After a three-year fight to get a pump and find a suitable hospital…"
- life more like normal youngsters…not feeling different.
- a recurring phrase – "being in control of the diabetes rather the other way round" (Again, echoes of comments by DAFNE graduates).
- some very large drops in HbA1c, such as "My HbA1cs were in the mid to high tens despite blood testing and injections up to 10 times a day….on pump therapy my HbA1cs dropped to around 6-7%".

Some patients and families were self-funding.

5.2 Changing from injections to pumps: A qualitative study of parents' accounts of young children with Type 1 Diabetes

5.2.1. Background

Many centres across the UK are experiencing a demand for insulin pumps from patients, as the awareness of the success of this form therapy has entered the public domain. This has become particularly so for with children and young people.[243]

This section examines particularly the accounts of the parents of young children with T1D in starting pump therapy and using this form of therapy in young children. We believe provision of CSII to young children may be one of the current growth areas and perhaps one of the most marked changes since the last assessment report.

Understanding patient-centred care for children and young people with TID, as outlined in the National Service Frameworks for both Children (DOH 2004)[244] and diabetes (Scottish Executive 2002),[245] requires an understanding of children's individual autonomy as well as the executive role of parents, and the important contribution they make to the successful management of diabetes. In this section, parents' accounts of switching to pumps from multiple daily injections (MDI) are divided into themed headings. Time did not allow a larger study.

5.2.2. Methods and Subjects

Details of methods and rationale are given in appendix 11. The main questions posed are given below:

1. Who decided that your child should try pumps and where did you get information from?
2. Can you describe how it was when you began using the pump?
3. Can you describe how you use it?
4. Describe the pros and cons of pumps and insulin injections.
5. What are your aims for using the pump?
6. If you could look 5 years into the future what would you like to know about using the pump?

The ages at onset of diabetes, at start of CSII, and at time of interview are shown in Table 38, along with funding arrangements and HbA1c changes.

Table 38: Demographic details of the children

Patient	1	2	3	4	5	6	7	8	9	10
Age of child (yr.)	7 yr	8 yr	5 yr	5 yr	5 yr	6 yr	8 yr	7 yr	6 yr	6 yr
Age at diagnosis (yr; mt & wk)	5 wk (after removal of pancreas)	2 yr	27 mt	18 mt	14 mt	4 yr	4 yr	18 mt	2 yr	17 mt
Age starting pump	7 yr	7 yr	2 ½ yr	4 yr	4 yr	5 yr	7 yr	6 yr	4 yr	4 yr
Type of pump*	S	A	S	M	A	M	A	M	M	M
Number of hospitals visited during seeking pump	3	2	1	3	2	USA	3	1	4	2
Paid for by PCT	✓ (Hospital & PCT)	✓	✓	✓	✓	USA (insurance) & PCT	✓	✓	✓	✓
Change in glycated haemoglobin (%) from injections to pump	8.5 to 7.6	8 (MDI) to 7	10 to 5.1-5.6	9.5 to 6.5	7.6 to 6.8-6.5	unknown to 7.6	8.1 to 6.8	10-11 to 7.2	8 to 7.1 - 7.2	8.8 -9 (MDI) to 7.1

*Type of pump: M= Medtronic; D=Disetronic; C= Cosmo; A= Accuheck; S= Sensor

5.2.3. Results

5.2.3.1. The parent's perspective

Parents were asked to describe the history of how they found out about the pump and how they began to use one. All but two said they found out about the pump from the 'Children with Diabetes' website, and that they, rather than the clinical team, had raised the idea of transferring their child from insulin injections to pump therapy. One parent knew of pumps because her husband had T1DM, although he was not on the pump himself, and another said her diabetologist had recommended it. All the parents identified poor glycaemic control and the associated risks of complications as main reasons for searching for an alternative therapy to multiple daily injections:

Parent: "*I first heard about them through the Children with Diabetes newsgroup (internet group). At the time there were only a few people on them* [pumps] *so I got in touch with Medtronic and everything she said just seemed so right. His HbA_{1c} wasn't that bad, 8.5, but we weren't satisfied with that. His control wasn't horrendous but it was the feeding, you had to force feed him and then you'd have to say you can't have anything to eat. It was just so horrible.*"

Implicit in the accounts was the feeling that parents should not question the health professionals authority:

Parent: *"It's funny all the literature talks about patients being experts, but I don't think we've got there yet. It's more lip service really and it's about knowing your place and not challenging the staff's authority, even though it's you that's living with your child."*

Parent: "*The consultant kept telling me 10 [blood control] was the best we could expect, but I knew it wasn't because I'd done the reading and I'd discussed in with parents on the 'Children with Diabetes' web.*"

These sentiments were echoed by another parent who said:

Parent: "*I read all there was and asked if I could change him from 2 injections a day to the pump because I had to force feed him, but the consultant was very against it."*

Two children were started on pumps as toddlers (see table 1); however all of the parents believed the pump should be accessible to very young children including babies. In fact, a number believed they had missed out by not being able to start using the pump until their children were older:

Parent*: "There's no doubt that it should be available for your child once their diagnosed and established on insulin. It's hell trying to feed a baby and child to fit in with the injections. If I had known how much easier the pump was I would have pushed for it earlier."*

5.2.3.2. The clinical team

All but two of the parents said they had had to ask their general practitioner to refer them from their regular hospital out-patients to another hospital where they could be in contact with a consultant that was comfortable with pump therapy for their child. All had to travel significant distances to see the new diabetes team, but all felt that the journey was worthwhile, if this meant their child would receive the pump:

Parent: "*I went to INPUT* [web based support group for insulin therapy]. *Then I went to my GP and asked for a referral to another hospital. We had to go about 50 miles away, it's a trek, but she* [the consultant] *was fantastic; she couldn't understand why he wasn't on a pump. She went through all the history with him and said yes, he could have one. That was a whole year after I started trying to get one. But then I asked about the Cosmo® pump because I'd heard it was good and she recommend I go to XX* [another hospital] *which is even further away."*

Parent: "*He* [consultant] *is anti any pumps; we didn't get the pump through him. I don't know, it's difficult to explain but he gave the impression that 'I'm the consultant, I know what I'm doing and you don't, you're only the parent.' And my attitude was that I wanted to do the best I could for my son and I would do whatever it took.*"

Parent: "*At our clinic we were told she was too young to go on the pump. It* [the pump] *wasn't good for them psychologically (5 years). Also, that she shouldn't have her blood checked at school because it would make her stick out, which was something I couldn't get my head around because I come from a science background and he was basically telling us that for six hours of her day we wouldn't know what as going on. So I had to go into the school and ask if they'd go against the diabetes nurse and*

check her bloods to make sure she was getting enough insulin. And I have to say they did what I asked. They were very good."

Parent: *"I'd done my homework so there wasn't anything they* [doctors] *could tell me really, only confirm what I already knew and heard. Which was if you're prepared to put the work in your child will have better control and quality of life and will be at less risk of complications. And it's true, his last HbA1c was 6.5" [8.5 on insulin injections].*

Almost all of these parents believed they needed to do 'their home work' because many of the consultants lacked the appropriate knowledge about diabetes, which all believed was dangerous for their child. As one parent told us:

"They seem to lack the appropriate interest to find out what is best for your child, to prevent complications."

Parent*: We do eight blood tests a day on the pump but we did that when he was on injections. Although his consultant said we only needed to do 2. He said that 'if you test him so may times you'll get different reading, like 8 one time, 15 another and 10 another, so why worry yourself. So it was a case of ignorance is bliss.' But I wanted not to have the 10s and 15s but to know about then if we did so we could do something about them. So we've always done a lot of blood tests anyway. It's just a shame, when we eventually found the doctor that put X on the pump; you just want to clone them so that other parents get the benefit too."*

Parent: "*We were having a nightmare with her blood control, but I was told* [clinicians] *that even though her levels were very high if I hadn't checked it I wouldn't have known so just leave it and they'll sort themselves out and again, but I couldn't get my head around it."*

Parent: *"I was doing all this reading, you know, the book by Hanas, and I was getting contrary advice from Dr A. And she* [daughter] *was getting headaches, her eyes were hurting and she was feeling shaky and I was told it wasn't possible and had nothing to do with diabetes. I contacted Diabetes UK and they told me about Dr B, so I traveled to see him, just to chat about how things were progressing. It was a bit of a distance, but his approach made sense….. And he* [Dr B] *was brilliant. The next day the diabetes nurse phoned us and said she'd written a letter for funding ….and she asked if X* [daughter] *or I would be interested in speaking to anyone else on the pump. But I don't think X would have cared. She was just so feed up with feeling ill on injections and her mood swings were just horrendous."*

Other parents also felt the choice was ultimately their own children's:

Parent: *"He's a different child on his pump. He says he doesn't want injections ever again."*

Parent: "*What upsets me is that when your child is first diagnosed you have total trust in the people your child sees. I run a local support group for parents with children with diabetes and its awful how*

many of them lose faith so quickly and they're being told that their child's symptoms can be nothing to do with diabetes. And then when I manage to get transferred to in our case Dr X who is so fantastic in his level of knowledge then backs you up in everything you thought was related to the diabetes, like the headaches. There's nothing worse than being the parent of a newly diagnosed child and being told the symptoms don't have anything to do with diabetes and so you think OK, does that mean they have something else awful.

Parent: *Its awful being told you don't know what's wrong with your child and that her diabetes symptoms are just because she's upset at being diagnosed. And when I quote things out of the Hanas's book they didn't even know about it which to me, rings alarm bells. .*

Parent: *I think if it hadn't been for my scientific background I probably wouldn't have pushed so hard [for pump]. When it comes to your own child you're at low ebb anyway, when they've been diagnosed with this condition that you're trying to get your head around, you've no guidance from the hospital team, which you think should know. It's very stressful. So if we hadn't moved to Dr B then I think I would have become extremely depressed. I think I would have found it very difficult to cope with the situation of no one knowing or acknowledging your anxieties. And of course X [daughter] was beginning to stand out at school because she has to put her hand up to have biscuits. So everyone, including the hospital was beginning to label her as manipulative.*

Parent: *"In the end I had to say I'm sorry I can't deal with this anymore and so I'll have to transfer to Dr B if they'll have us.*

Despite these parents beliefs in the effectiveness and safety of the pump for younger children, most did not wish to try and influence other parents. However, most believed it was important to let parents have access to the information and make the choice themselves:

Parent: "*I run a local support groups for parents with children with diabetes, so I hear a lot of horrendous stories. I don't talk about insulin pumps personally, but I try to set up meetings where people can be more involved, so they are in a position to ask questions and then they can go back to their consultants and say hang on this isn't clear and they know they can change if they need to. So now in our area, all the people from the different hospital are talking to each other and so they know if they're not getting the right care and that they're not stuck and can move to someone who is knowledgeable."*

Another parent with a similar experience felt her doctor wasn't sympathetic to her choice despite her child's improved control. This was important because parents who had to be referred to another consultant for their child to go on the pump had to return to their original out-patients clinic once pump therapy had been established:

"His control was much better, but our old doctor, the one that wouldn't put us on the pump, wasn't very pleased. All he said was, 'oh I see you've had a couple of hypos.'"

Interviewer: *"So you went back to the original team?"*

Parent: *"Yes we've had to, but the doctor* [referral to another hospital] *that put him on the pump said we could ring him at anytime. He's given us his work number, his home telephone and his mobile and his email at work and at home. And he's just said to ring him at anytime."*

Interviewer: *Once he went on the pump* [by being referred to another hospital] *you then had to go back to your original clinic. Did the staff there use it* [the pump] *as an opportunity to learn?"*

Parent: *"No, so that's why if there's a problem I write an email to 'Children with Diabetes', but if there's an emergency I go to A and E. I can't use my clinic because they don't know enough. I know more than them about pumps.*

All of the parents interviewed believed that if you wanted a pump for your child you would not only need to search the literature for yourself, but also be articulate and determined. These parents believed that certain parents wanting pump therapy for their child would be at a disadvantage; those who were less confident, those that were less well read and those who were less likely to question the decision of the doctor. Most parents believed they were more determined to *'seek-out'* the best treatments for their children, whereas they might be less likely to go to such efforts for themselves.

Parent: "*I think it makes a difference if you're articulate. I've spoken to a few parents at the hospital and they said they were interested but as soon as they mentioned it to the consultant it was 'no, pumps are dangerous, it won't work for your child, they're not suitable for children at all, children on pumps go into DKA and they die.' These views don't seem to change even when you bring information from INPUT* [support group for pump therapy]*."*

Parent: "*I think it's wrong that getting the pump should be such a fight. I think you have to be quite a determined person if you want your child to go on the pump, a bit evangelistic. If there's the slightest hesitation on your part you won't get a pump2.*

As this parent said:

"The doctor we see gets sponsored to raise funds himself so that he has personally paid for every child that wants a pump to go on one. It's incredible."

A large number of these felt that pushing for the pump labeled them as a troublesome parent by staff, rather than one wanting the best for their child:

Parent: "*I think if I hadn't pushed I wouldn't have got it, but then this makes you out to be a bit of a trouble maker rather than just wanting the best for your child. He was on multiple injections, and the school wasn't too keen so I was determined to get him on the pump before he started, but the*

consultant just said he could go back on two a day. Believe it or not he said: 'just make sure you run him high all the time so that he doesn't have a hypo at school and there won't be a problem.' I was just flabbergasted. I said: 'no there won't be a problem because by the time the complications kick in he'll be in the adult clinic.' His idea was to run things between 10 and 15 every day. The school was brilliant and they said I could go in every day to give the injections. They could see how worried I was."

Yet, not all staff felt this way. However, the likelihood was that if the consultant did not support pump therapy the other professionals in the team, such as the diabetes nurse specialists, would not have the option of going on a training course, and would not therefore be unable to advise or support families wanting the pump:

Parent: *"The nurses can be for it, ours is about 80% certain, but they're blocked by the consultants who are the gate keepers. So I can't ask her for advice because she's not trained which a shame because she can see the benefit of it. So I use the internet group if I have a problem."*

5.2.3.3. Education

A major concern for most parents was the lack of support they received from the school education system, and in particular the lack of knowledge most people had about diabetes:

Parent: "*There's a lot of ignorance about diabetes, especially type 1. Everyone thinks it's something you can prevent or that you bring it on yourself through lifestyle.

I since found out from the diabetes nurse and the school nurse that the head teachers was enquiring what the legal position was if they refused to take my son. They were told they couldn't refuse him entry but that they didn't have to do any of the treatment, but that if he was unconscious or having a fit they could call an ambulance, and that was it, there was nothing else they would do for him at four years old."

Only one parent had experienced teachers that were prepared to take responsibility of her child's diabetes.

Parent: *"The school he's at is brilliant. They have three teachers who know how to do blood test."*

Interviewer: *"Why is that?"*

Parent: "*Before he started I went in with the diabetes nurse and trained them. I've got a really good relationship with them. They check his blood in the morning before he goes out to play in the morning at lunch and in the afternoon again and any other time he needs it. The nursery nurse knew about diabetes so they were really supportive and that reassures my son and me."*

Another parent had to organize a teaching assistant to help give her bloods.

5.2.3.4. Employment

All but one of the mothers, and one father, were unemployed. A large number of these gave diabetes as the reason and most of these felt it would have been impossible to work because the schools were so unhelpful when their child was on insulin therapy. Multiple daily injections, even when parents were not working, was impossible in most junior and nursery schools, despite the evidence that MDI were preferable to twice daily injections:

Parent: "*I did work at first, but they* [the school] *were struggling to keep him conscious. That's when he was on multiple injections. It does affect you economically but it's worth it as far as I'm concerned."*

[redacted]

5.2.3.5. Getting used to the pump

Parents suggested that their eagerness to uses pumps meant they were prepared to tackle learning the technicalities of the pump, which most felt was more complicated than the injections, but after a while reassuringly became routine.

Parent: *"X* [child] *had a saline pump for about three weeks before so I was quite confident by the time I got it. But the first night I had to check it every hour and I was thinking when will this night end and then the next night I checked it two hourly and then three hourly. For the first 3 to 4 days X's readings were amazing, between 4 and 6 then we went from there and altered the setting. It was quite incredible the first meal I thought I don't need to get the injections out. I kept thinking am I doing it right, what if I do it wrong."*

Parent: *"The doctor* [consultant parents were referred to] *set up all the basal levels and he phoned us every day in the morning and evening so we felt very supported. It was also getting used to not panicking when it read 5 on the pump, which you would on injections, but thinking this is great. So that takes a while not to panic. This is fine. Probably about two to three months to understand the trends. And because her levels are so stable you could see reactions to specific food. Whereas before it was just like white noise, now you can pin point certain of the variables and you can adjust for those."*

5.2.3.6. The pros and cons of the pump

All of the parents spoke about the major benefit of the pump. A key point for all parents was that the pump prevented blood level swings as well as improving glycated hemoglobin:

Parent: "*When you go to the clinic they want to know about your HbA_{1c},, but even it it's good you're still having to cope with the daily blood level swings which are a constant battle. You feel so out of control"*

As important, was the improvement to both their child's and the family's quality of life. Good quality of life was important to ensure children led normal lives, even with diabetes; to prevent strain on couples' relationships as well as between siblings. Poor control while their child was on insulin injections had, two parents believed, caused marital problems.

Parent: *"The pros of the pump are quality of life. He can eat what he wants, he can lie in, and he can join in any sports activity he wants. Although it's water proof we always take it off for swimming. My daughter* [9years] *knows how to look after him if they go and stay with family. She knows how to change the cannula, count carbohydrates, but she'd never do his injections."*

Parent: *"I think the pumps are user-friendly. You can say to people now just press that and that, rather than saying 'now here's the needle', so it gives him as slightly more normal identify."*

A few of these commented on the challenges of having a pump, although none of these would consider going back on insulin injections:

Parent: *"It got blocked once."*

Most believed that as parents they had to be committed to transfer to pump therapy:

Parent: *"I think if you're not so motivated it might not be so easy because if something goes wrong you need to act on it."*

Parent: "*We were concerned that only fast acting insulin so you're very vigilant at night. Before the pump everyone had to fit in with X's meal times. Now we can do activities that over run and it doesn't matter."*

Parent: "*Her blood levels were always at the high end, so we knew there would probably be complications, but the main problem for us wanting to change* [to pump] *was she did not feel well, she didn't act well, she was up every night feeling shaky because her levels were high then feeling ill because her levels were plummeting, so we didn't have a clue what was going on. So she was doing everything right, she was eating well, exercising but she still isn't feeling well. So to me now, the insulin pump means she is a child that feels well. I means yes, I would still want her HbA_{1c} to come down. I means since she's been o the pump her levels are between 5, 6 and 7. But the overriding thing is that she feels well. And this is the first year ever, that she has not missed a day off school. I mean that's not to say she doesn't get ill, but because of the flexibility with the pump, when you first see the signs of illness you can act quickly and put up the basal levels. And you can get the illness under control quite quickly and she'll start to feel better. Whereas, before because you didn't have the flexibility she'd get ill for longer."*

Parent: *"It gives you the reassurance that you can sleep through the night and actually it was the first time she slept through the night. Before she needed to go to the toilet, blood levels swinging and waking her up."*

Parent: *"She's scared of having injections, but with the pump she only has to have one injection every three days.*"

Parent: *"The problem with glargine is that you give your child the dose, but if your child becomes ill you've not got the flexibility to change it. You're stuck with having this amount in. And you have to make her eat when she doesn't want to or visa versa. Also with glargine, what she needed in the day was not what she needed in the night so we had problems because after its shot into her you loose control. Whereas on the pump she can have a quiet day if she wants and I'm not having to say, no you've got to go on 10 minute bike ride or if she want to go absolutely mad, she can do so she can be more like a normal child."*

Parent: *"She [8 years] joined a drama club. If she'd been on injections I doubt very much I'd have allowed her to do that. So it's given here more breadth what she can do."*

Parent: *"My only concern that is that she's [8 years] going away on a school trip and if the cannula gets dislodged there's no one there that knows how to put it back, so I'm very tempted to offer to go along."*

5.2.3.7. Body image.

Most of the parents believed their children were not concerned about wearing the pump. Several felt it made them feel special, were proud of it, like the fashionable bags that came with them, felt that pumps were like other gadgets that children took for granted, such as mobile phones. One mother however, was concerned that her daughter might be psychologically affected by wearing the pump when she reached adolescence:

Parent: *"He doesn't mind wearing pump. He just gets on with it. There's not hiding it, but we were like that with the injections. There are other kids at school with impaired hearing so they have battery contraptions too, so it's not so abnormal.*"

Parent: *"He'd rather than the cannula in him than six injections a day. On the odd occasion when we've had to back to injections [pump broken] he's got in quite state 'I don't need those I've got my pump now!"*

Parent: *"Probably the worst thing [of the pump] is she gets marks left on her body. Despite the literature, they don't fade in two-three weeks, so I worry that she'll become more body conscious when she's older. But despite that she says she doesn't want to go back on the injections.*"

Another parent was conscious that wearing the pump meant her daughter was always aware of being diabetic:

Parent: *"X is aware that she's diabetic all the time because she wears it and so is her sister."*

Parent: *"She's very proud of it. Apparently in the first day she wore it, I was quite surprised, she asked the teacher if she could tell the whole school about it . But now she gets fed up with people asking. And she's going through a stage when she's feeling vulnerable because there's the realization that this isn't going to go away, so she's not keen on the attention."*

5.2.3.8. Expectation of long-term use of the pump.

All parents felt that the commitment associated with using the pump was worth it because it was easier to mange a blood glucose control.

Parent: "*To minimize long term damage. I'm hoping things will develop and eventually they'll be cure, but we can't hold our breath for that. But the pumps giving him a quality of life he didn't have before.*"

5.2.3.9. Foreseeable problems

Parent: "*None, nothing that I've heard about.*"

Parent: *"I don't know if having the pump as a constant remainder may have psychological effects in the long run."*

5.2.3.10. Looking at the future

Parent: *"I would hope that there might be like a closed loop system where it checks his blood automatically and delivers the insulin automatically. They are such 'little things' and they're having sometimes up to 9 or 10 blood tests a day and sometimes he says' Mummy I've just got not more blood in me anymore' ".*

Parent: "*Was it worth the commitment? The options available make it valuable but I'm anxious about the future and whether wearing the pump all the time creates psychological problems.*"

Parent: *"If I could look into the future I'd want doctors to understand that it's easier for kids to deal with requirements than restrictions. For example, having insulin involves somebody to figure out what's in the food before you eat it, you have to check your blood sugar, you have to press the button on the pump before you can do this, this and this. It's easier than saying you can't have a biscuit when your friends are having a biscuit because it not your set time. In a sense, the pump enables a 'can do' situation."*

5.2.3.11. Summary of perceived benefits by parents of pump therapy in children

- To control daily blood glucose fluctuations (high and low) and glycated haemoglobin, in line with national recommendations, to prevent long-term complications;
- To control problems of hypoglycaemia and the 'dawn phenomenon', which result in parents testing their children's blood throughout the night;
- Only having to have 'one injection' every 3 days rather than numerous and sometimes painful injections everyday;
- To improve child's flexibility of lifestyle by allowing greater flexibility in term of diet and social and physical activities;
- In relation to the above, to improve family's flexibility of lifestyle by allowing greater flexibility in term of diet and social and physical activities, reduce anxiety about child's health, especially during the night, and, as a consequence reduce tensions between family members;
- Pumps were more acceptable in schools. Multiple injections were not an option at most school because school staff lacked knowledge about diabetes and were not prepared to take responsibility for multiple injections, e.g. several parents needed to give up work so that they are available to give injections. Consequently, most relied on two daily injections before starting on the pump.
- To control mood swings in children particularly at school where they could be labeled 'moody', 'difficult', 'tired', 'lacking concentration', 'introverted;'
- Pump represents modern technology and fashionable gadget (particularly gender specific bags), which provide kudos among peers, while at the same time allowing them to feel normal (join in everything seem normal while at the same time marking out the normality of the child;
- Enhances child's status and individuality as an expert who is mature and 'capable' among peers and adults (e.g., teachers);
- Best system available to improve blood control and prevent complications until a cure is found, e.g. pancreatic transplant not acceptable in children;
- Appropriate for toddlers, not only children

5.2.3.12. Summary of perceived challenges of pump therapy by parents of young children

- Too expensive, both the pump and the disposables
- Parents need to be rather 'evangelistic' or have contact with 'evangelistic' clinicians to receive pump. Too few clinicians have expertise and are therefore unlikely to recommend or support parents initiatives, even when there is a chance it will improve blood control and prevent complications;

- May have to change clinical teams (2-3 times) and travel quite long distances to receive pump. Consequently parents rely heavily on parent network web sites for advice and support;
- Parents have to be committed in terms of regular blood tests and carbohydrate counting;
- Easier if adults are technologically minded
- Worry that child may have problems with body image when wearing pump during adolescence;
- Not enough support from patient bodies re: changing policy (particularly education) to better accommodate T1D and pump therapy for children

5.2.4. Discussion

This qualitative study examined the beliefs and attitudes of parents of young children who have been successfully started on pump therapy in the UK in the last five years. While accepting that this is a biased account from parents who have had considerable difficulties in starting their children off on this therapy, they nonetheless reflect some important aspects of the benefits and challenges of pump therapy.

Interestingly, none of the children concerned had treated themselves for any length of time with 'classical' intensive insulin injection therapy – MDI. This was because of several reasons – very young age, erratic eating and exercise patterns and a difficulty in interpreting multiple blood glucose results. However, perhaps the major factor was the reluctance of schools to take on children requiring MDI, forcing the parents to use 'conventional' twice daily injections of insulin. Schools frequently insisted on extra staff to supervise the intensive therapy. The parents, therefore, moved rapidly in the course of their young child's diabetes on to pump therapy, with few difficulties. This was reflected by the schools, who also seemed more at ease with pump therapy, accepting that the parents and the children themselves were the experts and no additional supervision was necessary.

Overall for this age group the benefits of the pump outweighed significantly the challenges and difficulties. Glycaemic excursions were dramatically reduced, with improvement in overall glycaemic control, less hypoglycaemia and no episodes of DKA. The children felt better. This was with fewer injections compared with MDI. The wearing of the pump did not produce significant difficulties and these young children appeared to cope well with the practical issues; pump technology; wearing of the pump; managing diabetes with the pump. The "quality of life" for both parents and children appeared to be markedly improved.

These were all committed parents who had to seek information about the availability and the practical issues of pump therapy. A significant amount of their information came from outwith the UK. Their local diabetes teams for the majority were not supportive of pump therapy and the parents appeared to

become evangelists in order to seek out pump therapy, often traveling some distance to receive sympathetic and expert advice. The majority felt this process had delayed the placing of their child on a pump and most believe that if appropriate children of all ages should be considered for pump therapy from diagnosis.

The parents expressed a strong view that considerable commitment was required to master pump therapy and accepted that not all parents would be prepared and/or able to give this commitment. However, a significant factor in allowing parents to consider pump therapy would be the valuation that a clinical team places on this form of therapy.

The parents were aware of the cost issues for the NHS. However, all had made a case to their funding committees in their local PCTs within the NHS. (Eight out of the ten had their pumps paid for totally by the NHS; two parents were paying towards the cost of the consumables.) Undoubtedly all felt that the benefits of pump therapy made it cost effective.

5.2.5. Acknowledgements

We are grateful for INPUT for recruiting the families and thank the parents who freely gave us their time, and intimate thoughts.

5.3 Summary of patient perspectives from last assessment report

We started the patient perspectives section of the last assessment report with some caveats, which bear repeating. (That section of the last assessment report was written by one of the authors of this one).

Caveats.

The patients' perspectives section is based largely on written statements from pump users, and several caveats are required. First, most comments have come from members of INPUT who have responded to a request for comments. They are likely to be a more motivated group than average and some are clearly highly organised individuals. This does not affect the validity of their comments, but may have implications for generalisability. Second, they are successful pump users and tend to be enthusiasts for the technology. That is less important because those who do not succeed will not incur the ongoing costs of pumps. Third, most have had to pay for the pumps and consumables themselves, which creates another selection bias. Fourth, because pumps are little used in the UK, it appears that most of those who have gone on to CSII have done so because they have had a lot of trouble with control of blood glucose or frequent hypoglycaemic episodes, that is, a severity bias. They may have more to gain than the average person with insulin-treated diabetes. Again, this does not affect the

validity of the findings, but will be relevant to discussions about the proportion of people with diabetes who should be considered for CSII.[10]

The respondents for the last assessment report mentioned the expected gains in HbA1c and hypoglycaemic episodes, but also emphasised flexibility of lifestyle and working patterns, having more energy, feeling in control, less visibility of diabetes (being able to take bolus insulin without anyone noticing), and better moods in children (an almost universal comment in submissions by parents, but not mentioned in the trials):[48]

"Her HbA1c levels dropped from 10.6 to 8.2, and her mood and personality changed – we got our little girl back again." (Parent 8)

One comment from several mothers was that they found it very difficult to work full-time with a young diabetic child;

"*I have found it hard to go back to work as I seem to be on call for him all the time. For example, I will drop him off at school at 9.30 and by 11am they can phone me because he has gone low, and I have to go back to the school" (Parent 3)*

There were many problems with schools, but the comments were consistent in saying that school life was easier on CSII and, because staff can not take responsibility for injections, children find it easier to look after themselves, have fewer hypos, do not need to eat at special times, can miss meals if necessary, and do not need to carry insulin syringes and vials.

Chapter 6 Implementation

If NICE recommends increased use of CSII, and if funds are available, factors to be considered include;

a) patient selection criteria. Ideally NICE should specify these in such a way that patient selection is uniform across the country. Selection criteria are discussed below
b) training of staff
c) education of patients
d) on-going support, including initial out-of-hours telephone advice
e) the speed of roll-out, taking note of the Swedish experience (para 2.8.13) after a time of rapid expansion.

6.1 Education of patients

Based on the previous NICE guidance, all adult patients starting CSII will presumably do so after failing to achieve satisfactory results on MDI. So they would come to CSII well experienced in home blood glucose testing and self-adjustment of insulin dosage. One option might be that all patients being considered for CSII should have had a trial on MDI and have attended a DAFNE or similar course. Khoo and colleagues (2007)[246] from Nottingham reviewed the first few years of their CSII service and noted that nearly all patients had attended a DAFNE or other structured education course. If so, the additional training needed for CSII would be modest. Similarly, they will be able to cope in the event of pump failure, by reverting to MDI.

Unpublished data from Aberdeen Royal Infirmary, where all patients starting pumps do the DAFNE course, show the cost per patient of a five-day full-time DAFNE course to be about £240 (McKillop-Smith personal communication January 2007). The last assessment report estimated that staff costs involved in switching a patient from MDI to CSII was about £148 at 2002 prices. Training costs for staff were estimated to be £2715 per centre, but those were criticised as over-estimating the time cost for physicians to learn about pumps. The assessment report assumed three days; critics said one was enough.

The DAFNE programme has set up training centres around the country and these are training staff from other centres. This may reduce the training required for clinics starting a CSII service.

However, children may come to CSII without having had a spell on MDI, due to problems with taking lunch-time insulin at school, and they and their families may require more staff support. All patients on CSII will need to have immediate access to syringes or pens, and insulin, in case of pump malfunction. If the pump infusion ceases, blood glucose levels quickly rise. Zisser (2007)[247] reported

that stopping CSII for 30 minutes led to a rise in blood glucose of about 0.5 mmol/l by the end of that period, and by almost 2 mmol/l three hours later, despite re-connection.

6.2 Barriers to implementation.

These are likely to include;

- staff time. Our impression from the literature and contacts with clinicians is that people going on to CSII need more support at first, but less later
- lack of experience with pumps amongst clinic staff
- in some centres, an apparent lack of willingness to move to tighter control by intensive insulin regimens
- competing priorities for diabetes services which are having to cope with rising numbers of patients, especially with T2DM. This is partly due to a steep rise in age-specific prevalence rates, couple with demographic change, but is also partly due to better survival
- financial constraints

Professor John Pickup, in his submission to NICE on CSII for this appraisal, noted that in Denmark the main barriers to implementing CSII were lack of resources, and ignorance of the benefits and safety of CSII. His view is that both are true in the UK too. He comments that;

"It is perhaps understandable that many areas of the UK do not have the resources to start a pumps service or have not yet put a team in place for delivering a pump service, but it is of considerable concern that, as experience from my clinic shows, patients are often referred to a specialist pump centre because their local consultant "does not believe in pumps", or "does not know anything about pumps" or thinks "pumps are dangerous".

Professor Pickup goes on to say that considerable education of health care professionals will be necessary, but envisages two forms of this: firstly training in pump use for those who will provide it, and secondly education on CSII for the wider medical community who will refer patients to pumps clinics.

This prompts the question of whether CSII should be provided at a limited number of centres, or whether all diabetic clinics should provide CSII? One view is that CSII is just another way of giving insulin and that all clinics should be able to provide it. However we note from the patient and family submissions that there is clearly resistance to CSII in some centres. In some cases, this may be due not to opposition to CSII itself, but to competing priorities, in that if more money is available, there are higher priorities than CSII. Diabetes UK reported recently that services were being reduced in

some areas because of lack of funds. (*Copy of survey requested from Diabetes UK)* A Diabetes UK news release[248] stated that;

"*Four years on (from the NICE guidance), and in some areas, people with diabetes are experiencing unacceptable delays in accessing services and in some cases no services to support people using this form of therapy are available at all."*

The alternative to CSII being provided in all clinics would be, perhaps only for an interim period, that there should be a limited number of pumps services, serving populations, of say 400,000, on the assumptions that;

- 0.3% of the population have T1DM
- 5% of people with T1DM will go on to CSII (this is a guess, not a prediction)
- About 60 people would then attend the pumps service
- 60 CSII users provides a reasonable number for a centre to develop and maintain expertise

However in less densely parts of the country, some services would need to cater for smaller numbers. In the 2003 guidance, NICE expected that CSII would be initiated only by "a trained specialist team that comprises a physician with a specialist interest in insulin pump therapy, a diabetes specialist nurse and a dietician" (TA 57, para 7.5.2)[71]

6.3 Selection criteria for CSII

Various sets of criteria for CSII have been produced, with inevitable overlap. The report of the Insulin Pumps Working Group[103] suggested the following.

Table 39: Criteria as suggested in IPWG report

- In adults, the criteria for initiating CSII are that the patient should:
- Be motivated to succeed
- Have realistic expectations
- Be willing to monitor blood glucose values at least four times a day
- Be willing to work with multi-disciplinary team
- Have tried a basal bolus regiment with long acting insulin analogue
- The patient should also fulfill at least one of the following criteria:
- Repeated episodes of hypoglycaemia
- Unawareness of hypoglycaemia
- High HbA_{1c} with hypoglycaemia despite high level of self-management.

- Adults will be expected to monitor blood glucose levels at least four times a day and to be competent at dosage adjustment and carbohydrate counting for meals, physical activity and other lifestyle issues. They should be able to self-manage hypo and hyperglycaemia, ketone testing, and understand that they should revert to subcutaneous injections when appropriate.

Pickup and Keen's (2001)[19] selection criteria are given in Table 41

Table 40: Pickup and Keen (2001) selection criteria

Selection criteria for a trial of CSII:

Type 1 diabetic patients who have failed to achieve good glycaemic control after a 3-month trial of intensive insulin injection therapy, including re-education in injection technique, dietary advice and blood glucose self-monitoring, because of:

- Frequent unpredictable hypoglycaemia or
- A marked dawn blood glucose increase.

Prerequisites for insulin pump therapy:

All patients should be:

- Willing to undertake CSII
- Motivated
- Compliant in diabetes management
- Able to perform CSII procedures
- Able to perform frequent blood glucose self- monitoring
- Meet clinical indications for CSII
- Free of major psychological and psychiatric problems

Since this list was published in 2001, an additional criterion has been added – "elevated HbA1c and unpredictable swings in blood glucose concentrations during best MDI". (Pickup, personal communication July 2007).

Professor Pickup (personal communication July 2007) now considers that the section on the dawn phenomenon should be revised, to focus on patients with a marked dawn phenomenon who experience disabling nocturnal hypoglycaemia when attempts are made to lower fasting blood glucose towards normal by intensifying MDI.

The Canadian review[17] commented that there was a general consensus on criteria for selecting the limited number of patients for whom CSII was indicated. Their criteria are in table 42 below, somewhat abbreviated.

Table 41: AETMIS 2005 selection criteria

- Inadequate glycemic control
- Severe hypoglycemic episodes (two or more a year), nocturnal hypoglycemia, or hypoglycaemia unawareness, causing incapacitating anxiety and affecting the quality of life
- Morning hyperglycemia (BG level of 8 or 9mmol/l)

And for children, the same plus:

- Extreme insulin sensitivity, i.e <20 units per day

In addition, the patient or family should have the following characteristics:

- Measures BG level at least four times a day
- Is motivated and serious when trying the pump
- Does not have false hopes or illusions regarding the pump
- Has the ability to learn to use the pump and to adjust his/her insulin doses
- Is able to communicate with the treatment team and exhibit good therapeutic compliance

The current NICE guidance is that CSII should be used in suitably committed and competent patients when MDI has failed, with failure defined as;

- HbA_{1c} greater than 7.5%, or 6.5% in the presence of microalbuminuria or adverse features of the metabolic syndrome
- Achieving those targets but at the cost of disabling hypoglycaemia

And the NICE guidance assumed that only 1-2% of people with T1DM would become pump users. However it could be argued that many people with T1DM could be fitted into the above guidance on the grounds of having higher HbA_{1c}. Microalbuminuria is common (about 10% of patients with T1DM), and most patients would not get down to an HbA_{1c} of 6.5% without hypoglycaemia. The average HbA_{1c} in the DCCT intensive arm was about 7%, and severe hypoglycaemia was very common with 62 episodes per 100 patient years. It should be noted that a minority of patients had frequent hypoglycaemia, but during the study, half of the intensive group had had severe hypoglycaemia. It should also be noted that in the DCCT, hypoglycaemic episodes were as common amongst those on CSII as those on MDI.

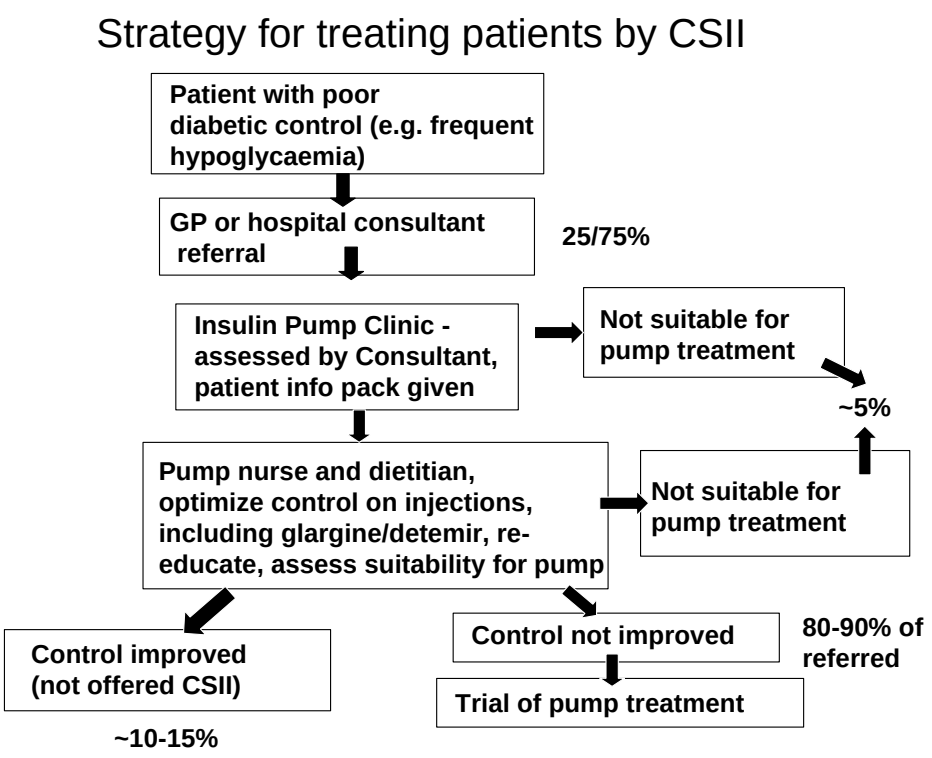
The only people on MDI who would not qualify would be those achieving the HbA_{1c} targets without severe hypoglycaemia. Based on the DCCT, some of these patients would, if transferred to CSII, still have severe hypoglycaemia, in which case it would be logical to transfer them back to MDI.

The IPWG base their selection criteria in effect on hypoglycaemia.

The resource implications of CSII should include the "run-in" period before it, when extra clinic visits will be needed, partly to select out people who are probably not suitable. Sanfield and colleagues (2002)[222] excluded about a third by having a trial period, and thereby ensured a high continuation rate amongst those who did start. The trial period involved three visits over a 20-month period, and a trial on a saline pump for several days.
It is likely that the more rigorous the selection criteria, the lower to discontinuation rate afterwards.

The protocol for the Guy's Hospital CSII service is shown in Figure 2

Figure 2



What the diabetes specialist nurse and dietitian do in the pre-pump assessment programme

- Try again to improve control on MDI (succeeds in about 10-15% of cases)
  - *Injection technique (e.g. sites), change insulin regimen if necessary, reteach BGSM and insulin adjustment, appropriate dietary advice including 'carb counting'*
- Discuss and demonstrate insulin pump therapy with patient
- Give patient time to discuss insulin pump therapy with friends and relatives at home
- Assess suitability of patient for insulin pump therapy

Why there is a need for a dietitian in insulin pump therapy?

- Some patients are obese on MDI
  - *Overeating because of hypoglycaemia, over-insulinized*
- Some patients have existing CVD or risk factors
  - *reduce saturated fats, cholesterol, low salt diets etc*
- Some patients can gain weight on pump as control improves ('I can eat anything now')
- Some patients need dietary advice about avoiding hypoglycemia
  - *E.g. alcohol moderation*
- 'Carbohydrate counting' integral part of all intensive insulin regimens, including pump therapy

Figure 2: Guy's Hospital CSII Protocol

The need for dietetic time is also noted.

6.4 Contracts

Some CSII centres, mindful of the extra cost to the NHS, ask patients to sign a "contract" which asks them to commit to achieving good control, in return for getting a pump. The implication is that if control does not improve, the pump may be taken away (though in practice, getting it back may not be so easy, but patient could be left to pay for the consumables).

This is regarded as controversial by some clinicians, who point out that contracts are not used for other forms of care where patient compliance affects outcomes. An example of one such contract is show in Appendix 9. It is also regarded as unacceptable by pump users (personal communications from INPUT members, August 2007).

One problem would be defining success. Many, perhaps most, patients on CSII do not achieve targets for HbA1c. However they may get a considerable improvement, or have fewer hypoglycaemic episodes, or just a feeling of greater well-being. How much benefit should the NHS expect for the extra £1,700 per annum?

Chapter 7 Discussion

7.1 Statement of principal findings

The main conclusions from this review are;

- CSII, used properly, is a safe and effective form of insulin administration
- In trials against traditional NPH-based MDI, it provides a modest but clinically useful reduction in HbA1c but a considerable reduction in hypoglycaemic episodes
- There are few trials against analogue MDI, which should now be the comparator in T1DM, and some are very small. Only two are published in full. One in children and adolescents show a good drop in HbA1c. The other in adults is a pilot which shows no advantage over MDI.
- In T2DM, the evidence so far shows no benefit of CSII over analogue-based MDI, but there is now evidence that CSII is better than NPH-based MDI in T2DM.
- The large number of observational studies tend to show greater benefits that in the trials, but are more susceptible to bias. Conversely, by recruiting patients who are having particular problems with, for example, hypoglycaemia, they may be a useful guide to results in routine care.
- The benefits of CSII include easily measurable results such as HbA1c and frequency of hypoglycaemia, but also other benefits such as greater flexibility of lifestyle, an easier way to move to intensified insulin treatment in school-children, reduction in fear of hypoglycaemia, and reduction in variability of blood glucose levels. CSII makes it easier to cope with unpredicted changes in activity or food intake. People with diabetes often report feeling more in control. Some of these benefits cannot easily be fitted into a simple cost per QALY calculation.
- CSII costs about £1,700 more per annum than MDI. The increased cost of CSII is only modestly offset by reduced insulin dose. The main part of the annual cost is from consumables such as tubing.
- Cost-effectiveness estimates vary according to assumptions used, but CSII does not appear cost-effective if based only on modest gains in reduced Hba1c and frequency of hypoglycaemia. It does appear cost-effective if larger gains in HbA1c, or the disutility of chronic fear of hypoglycaemia, are factored in.
- There is general consensus about which patients are most suitable for CSII, both in terms of clinical need, and in personal commitment and ability to use CSII.
- CSII is far from a complete solution in T1DM, and many users still fail to achieve the NICE target of HbA1c of 7.5% or less, though most do get improvements in HbA1c or severe hypoglycaemia or both.

7.2 Strengths and weakness in evidence

The evidence base has increased considerably since the last assessment report. We now have trials and other studies in children, and in people with T2DM. We have the unpublished meta-analysis by Pickup and colleagues which focuses on patients deemed by NICE to be most suitable for CSII.
We have the views of successful pump users from INPUT, which reminds us of the less quantifiable benefits of CSII, and from the studies by Barnard and colleagues on quality of life aspects.[185,186] We have also carried out a small survey of parents of very young children which has provided information on the benefits and costs in that group, and in passing, on differing attitudes to CSII amongst some paediatricians.
Weaknesses in evidence include;

- The shortage of trials against optimal MDI. We have an abundance of observational studies which have their uses, such as results in routine care, adverse effects, discontinuation rates, and long-term results. But they are prone to bias and RCTs are the gold standard for efficacy research.
- A lack of medium term data on NHS costs. It is likely that pump users need more support when starting but less later.
- The problems of fitting some benefits, especially non-health-related ones, into cost per QALY estimates.

We used MDI based on long and short-acting analogues as the key comparator, influenced by the NICE guidance on long-acting analogues.[49] We did not have time to do a full systematic review to update the evidence base on long-acting insulins. However in the course of the review and the peer review which followed, we noted that there are reservations about the advantages of long-acting analogues over older insulins such as NPH. The Canadian Agency for Drugs and Technologies in Health reviewed the case for glargine in both 2005 and 2006, and concluded (CEDAC recommendation October 2006)[249] that there was "*no convincing evidence that insulin glargine consistently led to a reduced HbA1c".* There was some evidence of reduced problems with hypoglycaemia, but the benefits did not justify the three-fold difference in cost. Doubt has also been case on the value of short-acting analogues over short-acting soluble insulin in both CSI and MDI, by Siebenhofer and colleagues[188] whose meta-analysis found only a small benefit in HbA1c of 0.19% in use in CSII. This is similar to the 0.26% in the meta-analysis derived from the previous assessment report for NICE,[10] the difference being due to slightly different inclusions and exclusions.

7.3 Research needs

A) It would be useful to have larger RCTs of CSII versus analogue MDI, looking at glycaemic control (HbA1c and variability), hypoglycaemia, quality of life, and costs. The costs should include not just

short-term costs of starting people on CSII, but medium-term ones, over say five years, looking at total use of NHS resources. When appropriate, quality of life should be estimated amongst families as well as patients, particularly in parents of young children.

B) There may also be a case, in people on MDI, of an RCT between CSII and DAFNE.

C) Selection of patients for CSII has been mentioned, and several centres reported that they had a work-up phase involving reinforced education and MDI, or structure education such as DAFNE. It would be interesting to record how many patients heading for CSII managed without it after such intensification. There may also be a case for such interventions to be offered to patients on CSII, to see how many could revert to MDI. Though anecdotal evidence suggests that once established on a pump, very few people wish to stop CSII.

D) There is a lack of data on how long it takes to get full value out of CSII. Patients tend to increase the number of basals as they gain experience. One implication is that short-term trials, of say 12-16 weeks on CSII, may not reveal the full benefits.

E) This might be relevant to pregnancy trials, in that perhaps they should start at least six months before conception. A recent Cochrane review by Farrar and colleagues (2007)[250] on CSII versus MDI commented that
"*There is a dearth of robust evidence to support the use of one form of insulin administration over another for pregnant women with diabetes.*"
The target group for further research on CSII in pregnancy need not include all pregnant women, but only those who meet the NICE criteria of not getting good control without severe hypoglycaemia. No RCT has yet been done in this group (Pickup, personal communication July 2007) and so the effectiveness and cost-effectiveness is not known. Trials in unselected groups of pregnant women might miss benefits in higher risk subgroups.

F) Linkage to continuous glucose monitoring systems could provide automated feedback and adjustment of infusion rate. Some pumps provide CGM systems.[251,252] Intra-peritoneal infusion would be more physiological than subcutaneous, since insulin normally goes into the liver via the portal vein. This could be done in two ways;

- From an external pump as used for CSII but with the catheter into the peritoneal cavity. This would create a risk of infection, at entry site, along the tunnel through the subcutaneous tissues, and peritonitis.

- From an implanted pump. Such pumps have been in use for over 20 years in countries such as France, the USA and Holland.[253,254] The EVADIAC group, which maintains a register of patients with implanted pumps suggests three main indications;[254]
    - poor glycaemic control despite intensive CSII with good patient education and close follow-up
    - good control achieved but with unacceptable hypoglycaemia
    - to improve quality of life

Continuous glucose monitoring systems are moving into clinical practice, and can be used in combination with insulin pumps. However most current use seems to be intermittent, with patients using CGMS for a few days to assess glycaemic control, rather than every day. A review by NHS Quality Improvement Scotland in 2005[255] noted a paucity of evidence on the cost-effectiveness of CGMS and recommended further trials. The cost of a continuous glucose monitor to go with a pump is about £750. The problems and potential of closed loop systems, sometimes referred to as "the artificial pancreas", are reviewed by Hovorka [256]

Several parents both in this assessment and the previous one have commented on problems at school. There is a need or a survey of school problems and policies, and consideration of solutions.

G) We are aware that CSII is used in children with other much less common forms of diabetes, such as cystic fibrosis related diabetes (not common in children with CF, but very common in the over 15s) and associated with treatment for acute leukaemia. No research has been published for such groups. Numbers may be too small for research to be worthwhile.

7.4 Current research

The National Research Register shows a number of studies as being currently underway on CSII in the UK;

- Two studies of the psychosocial impact of CSII, but with no controls.
- A quality of life study in adolescents, which starts with the hypothesis that quality of life will be better on CSII. The patients are not randomly assigned to CSII, MDI of twice daily insulins so there will be confounding variables which may make interpretation difficult.
- A multi-centre trial in East Anglia of CSII versus conventional bolus insulin treatment (it is not clear if this is MDI or twice daily mixtures) in pre-school, newly diagnosed children (ISRCTN77773974).
- Two register studies following up patients on pumps, one children under 16 in Yorkshire, the other type 1 patients over 12 in England (presumably part of the Insulin Pump Database already referred to in the clinical effectiveness section).

The Current Controlled Trials website (accessed 29th June 2007) shows additional trials;

- CSII versus analogue MDI in newly diagnosed adolescents, in Florida (NCT00357890)
- CSII with multiple basal infusion rates versus analogue MDI (was due to finish in 2005: CTN37153662)
- CSII plus continuous glucose monitoring (CGM) versus MDI (without CGM) in patients naïve to pump therapy in the USA (NCT00417989)
- CCSII versus continuous intra-peritoneal insulin infusion, in patients in whom CSII was unsuccessful (defined as frequent hypoglycaemia and/or HbA1c above 7%) (ISRCTN68954085)

Work is emerging on the use of home blood ketone monitoring in a large American study.[257] Only an abstract is available at present but it reports an observational study, which also notes that only 36% of pump users met HbA1c targets. Blood ketone monitoring was used by 24% of all patients (age range 0 to 22 years) of whom 63% were on CSII. However allocation to both CSII and ketone monitoring was not random, so we don't know if these patients would have done better anyway.

7.5 Conclusion

CSII is an effective way of administering insulin, but is little used in the UK. Many more people could benefit from it than currently do. However it does not overcome all the problems of exogenous insulin and is far from a complete answer. It is also more expensive than MDI, at a time when the needs for diabetic care are increasing but funds are tight. If use is expanded, there will be considerable educational needs for both patients and health care professionals. The education for patients should include structured education such as DAFNE, and that alone might suffice.

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Appendix 1: Summary of last assessment report

Description of the proposed service

This systematic review examines the clinical and cost-effectiveness of continuous subcutaneous insulin infusion (CSII) using insulin pumps compared with multiple daily injections (MDI) for diabetes.

Epidemiology and background

There are two main types of diabetes. Type 1 diabetes involves a process of destruction of the beta cells of the pancreas, leading to severe insulin deficiency, so that insulin treatment is required for survival. It represents about 10-15% of all diabetes in England and Wales. Type 2 diabetes is much more common, and is characterised by insulin resistance and relative insulin deficiency. Type 2 diabetes is linked to overweight and obesity, and to physical inactivity. The number of people with insulin-treated diabetes has increased due to the marked increase in incidence of Type 1 diabetes and also due to a greater number of people with Type 2 diabetes being treated with insulin to improve diabetic control. There has also been an increase in the prevalence of Type 2 diabetes, particularly among the Asian community. Poor control of diabetes, reflected in high blood glucose levels can in the short term result in diabetic ketoacidosis, a serious and potentially fatal condition, and in the long term increase the risk of complications such as diabetic retinopathy and nephropathy. However, studies have shown that good diabetic control is associated with a reduced risk of these complications.

If insulin levels are too high and blood glucose falls, hypoglycaemic episodes occur. The effects of a hypoglycaemic episode depend on how low the blood glucose level falls, varying from mild and rapidly corrected by food or sugary drinks, to severe where help is required. Severe hypoglycaemia can lead to unconsciousness, convulsions or death.

There are several problems with current treatment. In the non-diabetic state, the body needs a little insulin all the time (basal insulin) boosted by increased output after meals. This is difficult to achieve with conventional insulin injections, and in particular good control of blood glucose during the night is difficult. Intensive insulin regimens such as CSII aim to more closely resemble the output of a normal pancreas by providing basal insulin for fasting periods and additional short-acting supplements to cover meals.

Methods

A systematic review of the literature and an economic evaluation were undertaken.

Data sources

Electronic databases were searched, including the Cochrane Library, Medline, Embase, PubMed, Science Citation Index, Web of Science Proceedings, DARE and HTA databases, PsychINFO, CIHAHL, NHS Economic Evaluation Database, EconLIT, and Health Management Information Consortium database. References of all retrieved articles were checked for relevant studies, and experts were contacted for advice and peer review, and to identify additional published and unpublished references. Manufacturer submissions to the National Institute of Clinical Excellence (NICE) were reviewed.

Study selection

Studies were included if they fulfilled the following criteria:

- Interventions: CSII using insulin pumps compared with optimised MDI (at least 3 injections per day). Analogue compared with soluble insulin in CSII.
- Participants: people with insulin-treated diabetes (Type 1 or Type 2). Newly diagnosed patients were excluded.
- Outcomes: glycated haemoglobin, insulin dose, weight change, lipid levels, patient preference, quality of life, adverse effects.
- Design: Parallel randomised controlled trials (RCTs) and randomised and non-randomised crossover studies with a minimum duration of 10 weeks on each treatment.

Studies in non-English language or available only as abstracts were excluded from the main analysis.

For questions where no eligible studies were identified, information from selected observational studies was discussed (sections 3.2.5 to 3.2.7 and section 3.4).

Titles and summaries of studies being assessed for inclusion were checked by two reviewers. Full texts of selected studies were assessed for inclusion by one reviewer and checked by a second. Differences in opinion were resolved through discussion.

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer, with any disagreement resolved through discussion. The quality of included studies was assessed in accordance with CRD Report 4.

Data synthesis

Data on the clinical effectiveness of CSII for diabetes were synthesised through a narrative review with full tabulation of results of all eligible studies, with meta-analysis performed where appropriate.

Cost effectiveness analysis examined the marginal costs of CSII compared to MDI, and considered evidence on the marginal benefits such as improved control, adverse events and quality of life.

Number and quality of studies

Searching identified 20 studies comparing CSII with MDI. These included eight parallel RCTs, nine randomised crossover studies and three non-random crossover studies. Fourteen studies included adults with Type 1 diabetes, four studies included pregnant women, and two studies included adolescents. The quality of reporting and methodology of the studies, many of which dated from many years ago, was often poor by today's standards, with just two studies having adequate randomisation and none reporting adequate allocation concealment.

No RCTs or crossover studies were identified in children, overnight use of CSII, in patients with poorly controlled Type 2 diabetes, or on discontinuation rates, therefore selected observational studies were discussed in these sections.

Six studies (one parallel RCT and five random crossover studies) were identified comparing analogue with soluble insulin in CSII. Randomisation and allocation concealment were adequate in the parallel RCT but not reported in the crossover studies.

No economic evaluations comparing CSII with optimised MDI were found.

Summary of benefits

Adults with Type 1 diabetes: If all trials were included, a mean improvement in glycated haemoglobin of about 0.6% was found with CSII compared with MDI in both short term (-0.64, 95% CI -1.28, 0.01) and longer term (-0.61, 95% CI -1.29, 0.07) studies. This improvement was less if a study which used bovine ultralente in the control arm was excluded; the reduction is HbA1c is then only 0.5%. Short term studies show a reduction in insulin dose of about 12 units (-11.90, 95% CI -18.16, -5.63), with less difference in longer term studies. Body weight was similar during treatment with CSII and MDI. The two studies that reported data on cholesterol levels found no significant difference between the treatments. There was no consistency between the studies in patients preferring CSII or MDI, although many of the older studies used older, bulkier and less reliable pumps, and progress has also been made with discreet 'pen' injectors in MDI, therefore these findings are probably not relevant to the present devices. Hypoglycaemic episodes did not differ significantly between CSII and MDI in most trials, but some found fewer episodes with CSII and one study found more hypoglycaemia and hypoglycaemic coma with CSII. In some observational studies, much greater reductions in the number of severe hypoglycaemic episodes were seen with CSII, which may be because these studies tend to select patients having particular problems.

Pregnancy: Three studies found no difference in glycated haemoglobin between CSII and MDI. Less insulin per kilogram was required by patients with CSII in one study, but two other studies found no significant difference. Patient preference and quality of life were not reported.

Adolescents: One study found no significant difference between CSII and MDI, whilst the second study found lower glycated haemoglobin and insulin dose with CSII. Over half of the patients chose to continue treatment with CSII in the former study.

Children: No randomised trials were identified. Case series suggest that CSII has a place in treatment of children with diabetes, but this needs to be confirmed in randomised studies.

Overnight only in children: The combination of overnight CSII and daytime MDI may help in children, by reducing nocturnal hypos and the dawn phenomenon, but no randomised trials were identified, and further research is necessary.

Short term use in adults with poorly controlled Type 2 diabetes: It has been suggested that short-term CSII may help in patients with Type 2 diabetes on high doses of oral drugs and who are resistant to insulin. No good evidence was found.

Analogue vs soluble insulin: In CSII, analogue insulin was associated with lower glycated haemoglobin levels than soluble insulin and was preferred by patients. No difference in insulin dose or weight change was observed. Some studies found fewer hypoglycaemic episodes with analogue insulin, although this varied according to the definitions used.

Costs

The extra cost of CSII compared to MDI varies according to the make of pump and the estimated life of the device, from £1075 per annum using the cheapest pump and assuming an 8 year life of the pump, to £1423 per annum with the most expensive model and assuming a life of only 4 years. The largest component of cost is consumables such as infusion sets (tubing etc), with the capital cost of the pump secondary. There is a need for considerable initial education.

Costs per life year gained

There are definite benefits of CSII over MDI, including improved control of diabetes, not just as reflected in glycated haemoglobin and in a slightly reduced incidence of severe hypos, but also in

flexibility of lifestyle and hence quality of life. However, evidence on quality of life is reported in only one trial, and comes mainly from testimonies of pump users.

One would expect the improvement in HbA_{1c} to be reflected in reduced long-term complications, and for that to be accompanied by reduced costs to the NHS. However, we have not found a satisfactory method of converting the observed benefits into a cost per QALY.

The main problem with the current evidence is that it does not fully reflect the selection of patients for CSII. Most people on insulin therapy would not have much to gain from CSII, but those with particular problems such as recurrent severe hypoglycaemia would. Their benefits would include not only fewer hypoglycaemic episodes, but also a reduction in fear of hypos. However the utility effect of the reduction is fear of hypos has not been quantified. The cost-effectiveness of CSII is likely to be much better for certain subgroups.

Sensitivity analysis

The main costs are of consumables and pump. The price of pumps might come down with bulk purchase, but this is speculative. This would not have much impact on the cost per annum.

Conclusions

Control of diabetes consists of more than just control of blood glucose as reflected in glycated haemoglobin. Compared to optimised multiple injection insulin therapy, CSII results in a modest but worthwhile improvement in glycated haemoglobin, but its main value may be in reducing other problems such as hypoglycaemia and the dawn phenomenon, and in improving quality of life by allowing greater flexibility of lifestyle. They appear to be a useful advance for patients having particular problems, rather than a dramatic breakthrough in therapy, and would probably be used by only a small percentage of patients.

Implications of approval of an increased use of CSII

Many health authorities are not funding insulin pumps, and some of those which are have restricted the number. Many patients are funding their own pumps. According to clinical consensus, it is unlikely that CSII would be used by more than a small proportion of people with Type 1 diabetes, but the exact proportion is not known. We would not expect any use in true Type 2 diabetes in the foreseeable future. The cost to the NHS per year would be around £3.5 million in England and Wales if 1% of people with T1DM used CSII, £10.5 million for 3%, and £17.5 million for 5%. The educational needs of patients starting CSII are significant, and it would usually be diabetes specialist nurses who would provide this. However there are many other demands on their time.

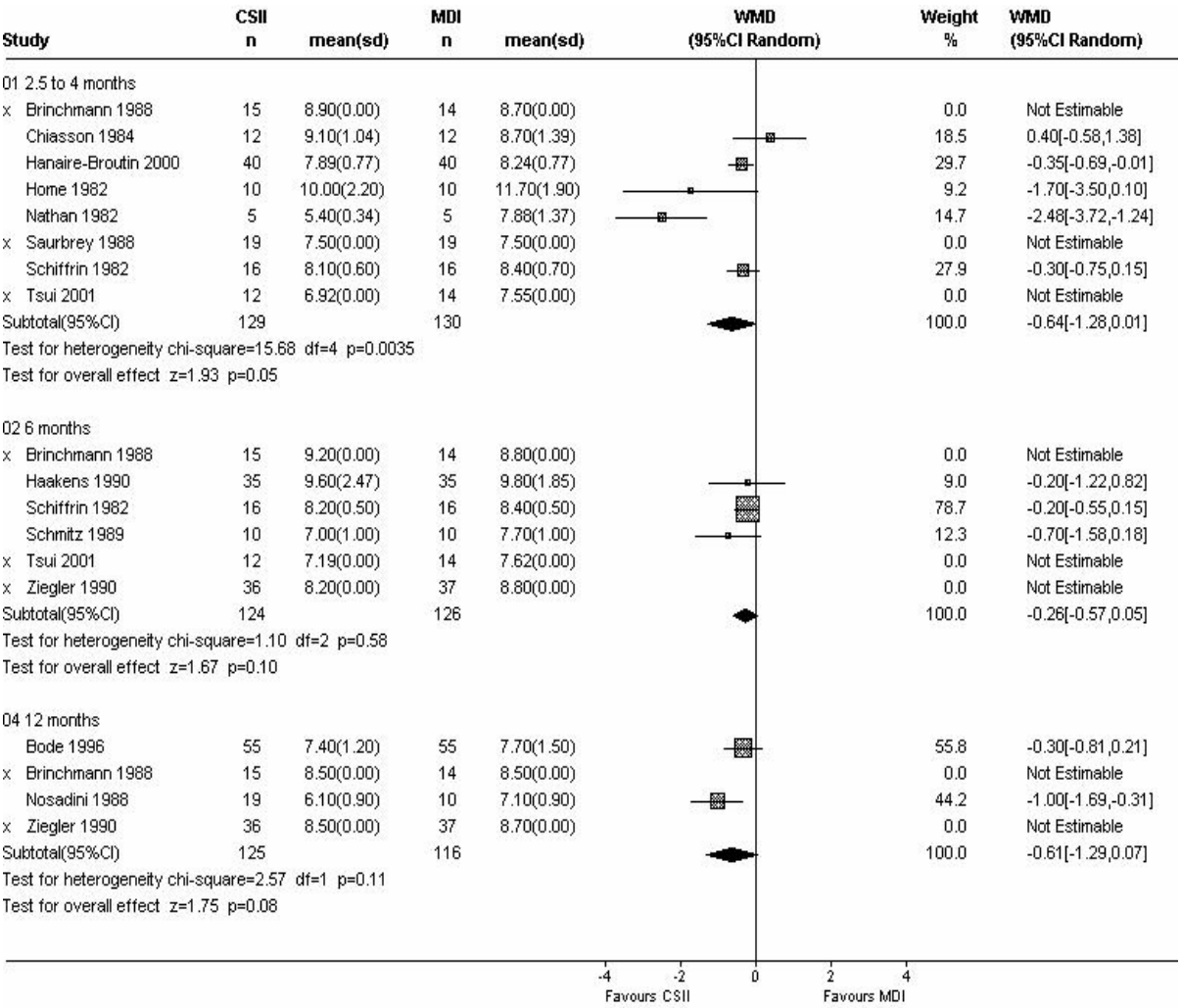
Need for further research

The trials to date have focused on easily measurable outcomes such as glycated haemoglobin. The main benefits may be in terms of flexibility of lifestyle and quality of life, and data on those would help with cost-effectiveness analysis. Some of the implications for patients such as the psychological impact of wearing a device for 24 hours every day have not been quantified.

Research is needed into the use of CSII in children of different ages.

Appendix 2: Selected meta-analyses from last TAR

Figure 3: Meta-analysis of the effect of CSII versus MDI on glycated haemoglobin in adults with Type 1 diabetes



Note: HbA_1 is reported by Brinchmann 1988, Chiasson 1984, Haakans 1990, Home 1982, Schiffrin 1982, and Ziegler 1990. HbA_{1c} is reported by Bode 1996, Hanaire-Broutin 2000, Nathan 1982, Nosadini 1988, Saubrey 1998, Schmitz 1989 and Tsui 2001.

Figure 4: Meta-analysis of the effects of CSII versus MDI on insulin dose (U/day) in adults with Type 1 diabetes

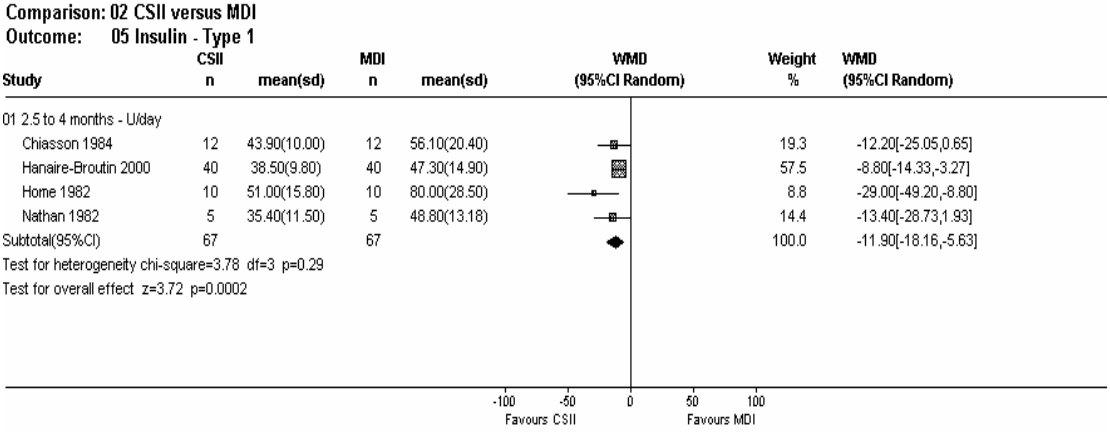
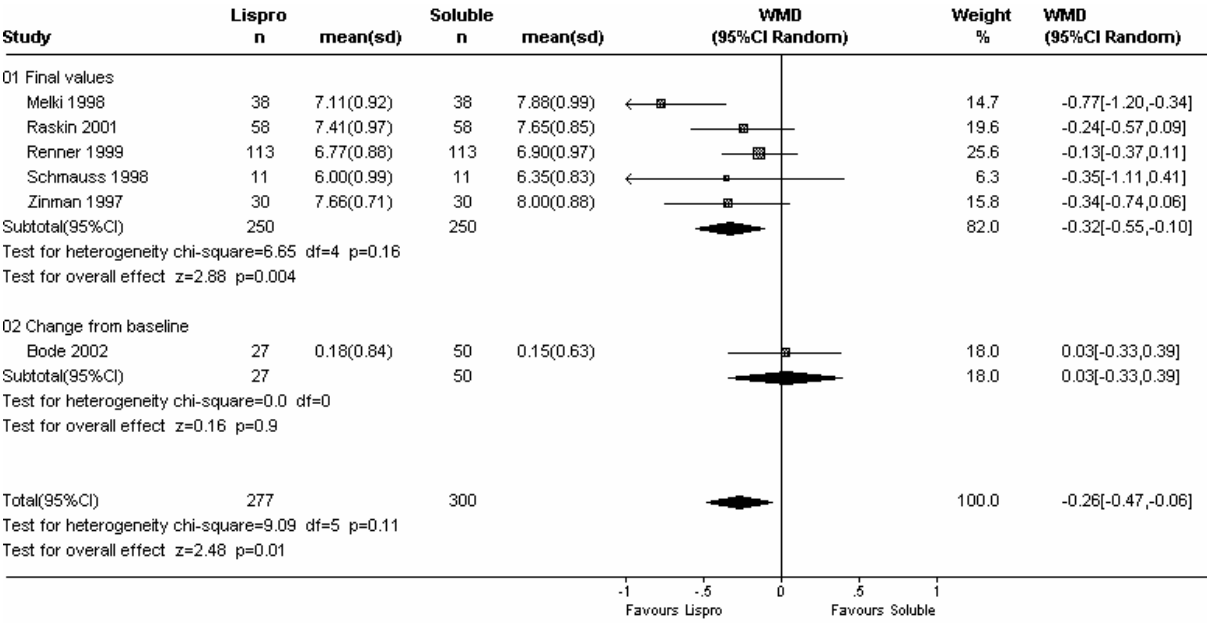


Figure 5: Meta-analysis of the effect of lispro versus soluble insulin on glycated haemoglobin in Type 1 diabetes



Note: Subgroup 1 'final values' includes studies reporting mean HbA_{1c} at crossover or end of study (3 months with treatment). Subgroup 2 'change from baseline' includes one study reporting mean change in baseline HbA_{1c} at end of study (4 months with treatment).

Appendix 3: Sources of information and search strategies used

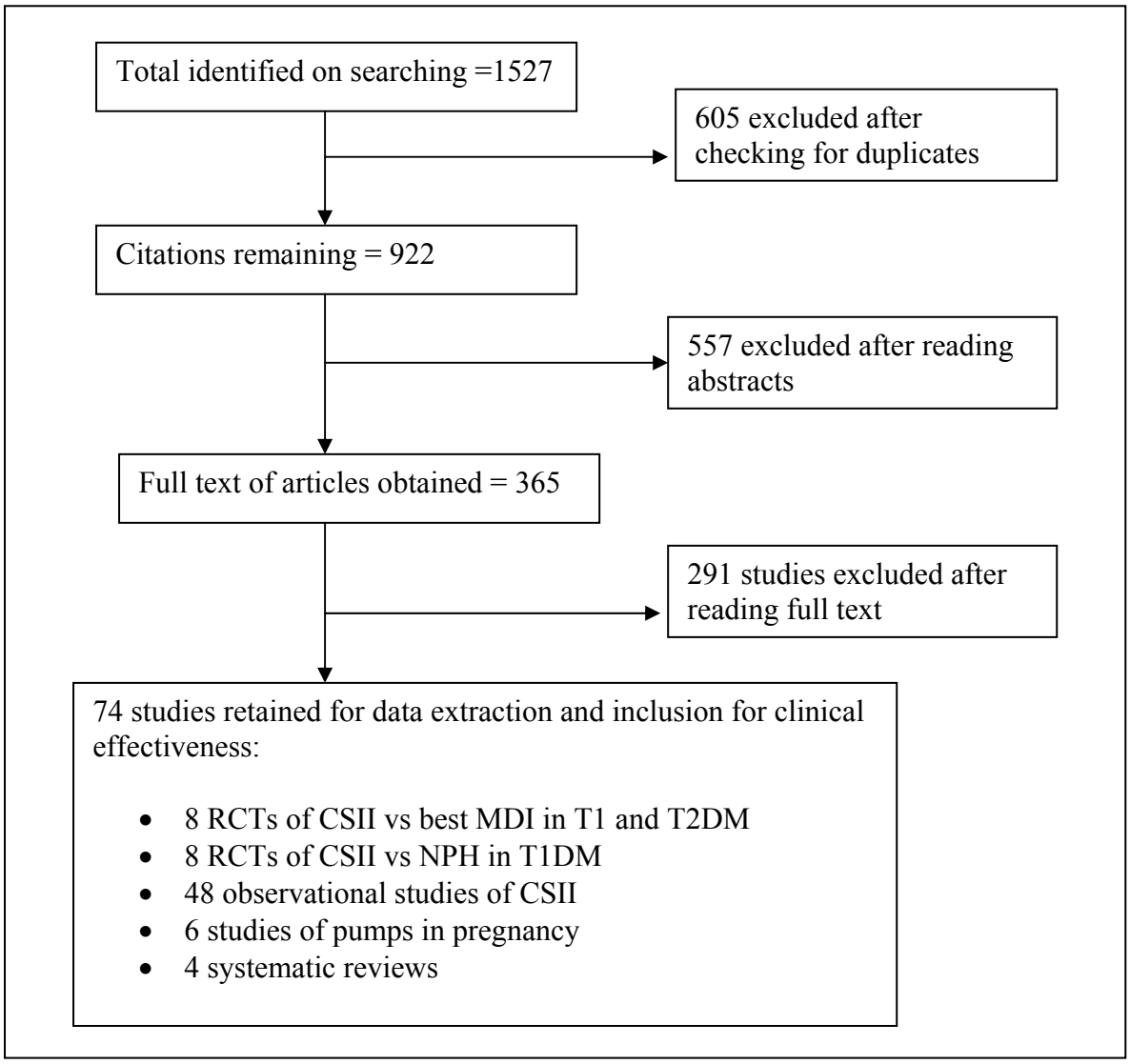
MEDLINE and Embase, 2002-June 2007
1. ((insulin adj3 pump$) or csii or (continuous adj3 insulin adj3 infusion) or (subcutaneous adj3 insulin adj3 infusion) or continuous subcutaneous insulin infusion$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2. limit 1 to yr="2002 - 2007"

Cochrane Library 2007 Issue 1 – all sections
(CSII):ti,ab,kw or (continuous subcutaneous insulin infusion):ti,ab,kw or (insulin pump*):ti,ab,kw

Science Citation Index (for meeting abstracts only) 2002-June 2007
TS=(CSII or (continuous subcutaneous insulin infusion) or (insulin pump*)) AND PY=(2002-2007)
DocType=Meeting Abstract; Language=All languages;

National Research Register, Current Controlled Trials and web site of ADA 2007 meeting abstracts
(CSII or (continuous subcutaneous insulin infusion) or (insulin pump*))

Figure 6: Flowchart of studies identified for clinical effectiveness



Appendix 4: Characteristics of included trials of CSII versus best MDI.

Type 1 diabetes

Doyle et al. 2004 (full publication)

Description and quality of study

This randomised controlled trial enrolled 32 adolescent participants with T1DM and compared CSII with MDI using parallel trial design. No power calculation was reported. Inclusion criteria were explicitly stated; T1DM, aged 8-21 years, otherwise healthy except for treated thyroid or coeliac disease, treated with insulin for at least 6 months, naive to CSII and glargine, willing to perform at least four blood glucose tests/day and screening HbA_{1c} level between 6.5 and 11%. No specific exclusion criteria were reported. Randomisation methods were described in detail with participants stratified according to sex and age. Treatment groups were similar at baseline, and baseline analysis was reported. Analysis was intention to treat using last observation carried forward method to account for missing values. Statistical analysis was comprehensively reported. Protocol violations were specified along with reasons for drop out; one participant in the MDI group was withdrawn after 8 weeks due to two episodes of dehydration and ketosis. The study was supported by a grant from Medtronic MiniMed.

Study quality = A

Participants

Doyle and colleagues recruited 32 participants with T1DM. In both the CSII and MDI groups mean age was between 12 and 13 years, 50-60% of participants were male, and mean diabetes duration of between 5 and 7 years. Total mean daily insulin dose prestudy was between 1 and 1.5 U/kg.

Intervention

Participants were randomised either to CSII or MDI for 16 weeks with the goal of achieving HbA_{1c} <7% and blood glucose levels of 70-120mg/dl before meals and 90-150mg/dl at bedtime. CSII intervention (Medtronic MiniMed 508 or Paradigm 511 pump with insulin aspart) consisted of an initial basal CSII dose 50% of previous total daily insulin dose. MDI intervention (glargine insulin) consisted of initial dose 80% of total previous daily insulin dose, administered in the morning and at bedtime together with aspart insulin at mealtimes (need to check whether this is correct). Both groups also participated in education sessions relevant to their treatment.

Results

1. Primary outcomes

HbA_{1c}

Doyle 2004 assessed glycaemic control by measurement of HbA_{1c} between baseline and 16 weeks. HbA_{1c} (%) was significantly lower following CSII treatment at 16 weeks compared both with baseline and MDI treatment (baseline CSII 8.2% ± 1.1 vs. MDI 8.1% ± 1.2; 16 weeks CSII 7.2% ± 1.0 vs. MDI 8.1% ± 1.2; $p<0.05$ between groups; $p<0.02$ CSII vs, baseline). Significantly more participants in the CSII treatment group met the HbA_{1c} goal of $\leq$7% at 16 weeks compared with the MDI group (CSII 8 vs. MDI 2 participants; $p<0.05$).

2. Secondary outcomes

Blood glucose levels

Blood glucose levels before breakfast were similar in the MDI and CSII groups (8.3 ± 5.3 vs. 8.2 ± 5.2 mmol/l). However, all other mean blood glucose levels were lower in the CSII than in the glargine group ($p<0.01$)

Insulin dose requirement

CSII treatment group required significantly less insulin per day after 16 weeks compared with MDI treatment group ($p<0.01$ CSII vs baseline; $p<0.01$ CSII vs MDI at 16 weeks; p=NS MDI vs. baseline).

Quality of life and treatment satisfaction

Health-related quality of life was assessed using the Diabetes Quality of Life-Youth (DQOL-Y) scale which is composed of 3 subscales: a Disease Impact Scale (23 items), a Disease-Related Worries Scale (11 items), and a Diabetes Life Satisfaction Scale (17 items). There was no significant difference between groups at baseline or 16 weeks. The authors noted that only half of each group successfully completed the DQOL-Y questionnaire and that this precluded any conclusions being drawn from this study regarding impact on quality of life.

3. Adverse Events

Participants received education on the management of hypoglycaemia and hyperglycaemia. There were no significant differences between CSII and MDI groups in the occurrence of severe hypoglycaemia. One patient on MDI was hospitalised for ketosis and dehydration and one patient on CSII had diabetic ketoacidosis.

In summary, Doyle and colleagues reported that "in contrast with those patients on MDI, CSII patients were able to significantly lower HbA_{1c} levels and one half were able to lower HbA_{1c} levels to

≤7%". However, the authors conceded that the difference in metabolic control may be attributable to the number of dose changes and frequency of telephone contacts beyond the first two weeks as these were not systematically collected. CSII patients also had longer initial education sessions.

Thomas et al. 2007 (full publication)

Description and quality of study

This randomised open parallel pilot trial recruited 21 participants with T1DM and compared three intervention groups over 24 weeks: CSII (lispro), MDI (lispro and glargine) and education and relaxation of glycaemic targets on existing therapy. Inclusion criteria were adults with T1DM characterised by altered hypoglycaemia awareness and severe debilitating hypoglycaemia. Patients were naïve to MDI analogue insulin therapy.. As this was a pilot study no power calculation were performed. The study was open label, so no blinding was possible. Details of statistical analysis, and withdrawals were given, and baseline characteristics (no statistical analysis) were provided. No details of the randomisation process were provided.

Study quality = B

Participants

The Thomas trial recruited 21 participants with T1DM. The mean age of the participants was 43 years, mean weight was 75.6 kg, mean duration of diabetes was 25 years, and mean HbA_{1c} between 8.5 and 8.6%.

Intervention

Participants were randomised into three treatment groups; CSII (lispro), MDI (lispro and glargine) and education and relaxation of glycaemic targets on existing therapy.

Results

1. Primary outcome

Glycaemic control – HbA_{1c}

Thomas 2007 assessed glycaemic control by measuring HbA_{1c}. Statistical analysis to assess differences within treatment groups at zero and 24 weeks was reported, but no statistical analysis on differences between groups was reported. However, HbA_{1c} declined significantly from baseline in the CSII and MDI treatment group, by 1.1% and 1.0% respectively, but only the latter difference was reported as statistically significant ($p<0.05$). There was no change in the education group.

2. Secondary outcomes

Mean daily blood glucose

There was no reported significant difference in mean daily blood glucose (mM) between treatment groups (CSII baseline 8.2 ± 2.5 mmol/l to 24 weeks 8.5 ± 1.5 mmol/l vs. MDI baseline 9.7 ± 1.9 mmol/l to 24 weeks 9.5 ± 0.9 mmol/l). Glucose excursions below 4mM were reduced by CSII.

Glycaemic excursions

There was no significant difference in glucose excursions between treatment groups.

Quality of life

Quality of life was assessed using DQOL and the Hypoglycaemia Fear Survey (which has a behaviour subscale of 15 items and a worry subscale of 18 items using a 0-to-4 Likert scale. A high score indicates a greater degree of worry or a greater hypoglycaemia driven behavioural change). There were no reported differences between groups.

In summary, the authors concluded that CSII reduced glucose excursions below 4mM and HbA_{1c} declined by 1, but there was no difference from the MDI group.

Maran et al. 2005 (abstract)

Description and quality of study

This randomised open crossover trial conducted in Italy recruited 10 participants with T1DM and compared CSII (lispro) with MDI (glargine) over four months. Inclusion criteria were C-peptide negative T1DM, previously on CSII therapy for at least six months. No power calculation was reported, no blinding, no details of randomisation, no statistical analysis, no details of protocol violations or withdrawal. Baseline characteristics (no statistical analysis) were provided.
Study quality = C

Participants

The Maran trial recruited 10 participants with T1DM. Mean age was 41 ±8 years, mean HbA_{1c} was 7.7 ± 0.7% and mean duration of T1DM was 19.5 ± 10 years.

Intervention

Following a one-month run-in period participants were randomised into two treatment groups; CSII with lispro and MDI using glargine with lispro.

Results

1. Primary outcome

Glycaemic control – HbA_{1c}

Maran et al., assessed glycaemic control by measuring HbA_{1c}. There was no significant difference between treatment groups from baseline to endpoint (CSII 7.2 ± 0.2 vs. MDI 7.2 ± 0.2; p = NS).

2. Secondary outcomes

Mean daily blood glucose

Mean daily blood glucose was assessed using 48 hours continuous glucose monitoring at the end of each study period. Compared with MDI, the CSII group had significantly lower mean glucose levels (CSII 8.2 ± 0.7 vs. 10.5 ± 0.8 mmol/l; p<0.03).

3. Adverse events

Hypoglycaemia reactions exposure (AUC <65 mg/dl)

There was no significant difference between groups (CSII 1.88 ± 1.4 vs MDI 2.63 ± 1.88 mg/dl).

Time spent in night time glucose range >65 mg/dl and <180 mg/dl

CSII participants spent significantly more time in the glucose range >65 mg/dl and <180mg/dl than MDI participants (CSII 298 ± 63 vs. MDI 194 ± 51 minutes; p<0.02)

In summary, the authors of this abstract concluded that "CSII with insulin lispro provided lower nocturnal variability and better glycaemic control than MDI with lispro and basal glargine without increasing the risk of hypoglycaemic episodes".

Bolli et al. 2004 (abstract)

Description and quality of study

This randomised open parallel trial recruited 57 participants with T1DM and compared CSII (lispro) with MDI (glargine). Inclusion criteria were T1DM, $HbA_{1c} \leq 9\%$ and naive to SCII and glargine. Participants were randomised into two treatment groups; CSII with lispro and MDI using glargine once-daily with mealtime lispro

Study quality = C

Participants

The Bolli trial recruited 57 participants with T1DM.

Intervention

Participants were randomised into two treatment groups; CSII with lispro and MDI using glargine once-daily with mealtime lispro

Results

1. Primary outcome

Glycaemic control – HbA_{1c}

Bolli et al., assessed glycaemic control by measuring HbA_{1c}. There was no significant difference between treatment groups from baseline to endpoint (CSII 7.7 ± 0.7 to 7.0 ± 0.8 vs. MDI 7.8 ± 0.6 to 7.2 ± 0.7). Baseline/centre adjusted difference -0.1 (95% CI -0.5, 0.3 p = NS).

2. Secondary outcomes

Mean daily blood glucose

There was no significant difference in mean daily blood glucose (mg/dl) between treatment groups from baseline to endpoint (CSII baseline 9.1 ± 2.3 mmol/l endpoint 8.1 ± 1.8 mmol/l vs. MDI baseline 8.9 ± 1.7 mmol/l endpoint 8 ± 1.1 mmol/l; difference 0.06 95% CI -0.77 to 0.83; p= NS)

Mean amplitude of glycaemic excursions (MAGE)

There was no significant difference in MAGE from baseline to endpoint between treatment groups (CSII baseline 144 ± 43 endpoint 115 ± 40 vs. MDI baseline 137 ± 31 endpoint 115 ± 38; p= NS)

Coefficient of variation of 8-point blood glucose profiles

There was no significant difference in coefficient of variation of 8-point blood glucose profiles from baseline to endpoint between treatment groups (CSII baseline 53 ± 10 endpoint 46 ± 8 vs. MDI baseline 52 ± 12 endpoint 47 ± 11; p= NS)

3. Adverse events

Confirmed hypoglycaemic events per patient

There was no significant difference in the incidence of blood glucose <72 mg/dl between treatment groups (CSII 41 (SE ± 8) vs. MDI 35 (SE ±7); p= NS)

In summary, the authors of this abstract concluded that both CSII and once-daily glargine-based MDI regimen improved blood glucose to a similar extent with no difference in HbA_{1c}, mean blood glucose, blood glucose excursions and frequency of hypoglycaemia. A glargine-based MDI regimen is less expensive and therefore more cost-effective when used in an unselected population of people with T1DM.

Type 2 diabetes

Herman et al. 2005 (full publication)

Description and quality of study

This randomised controlled trial enrolled 107 elderly participants with T2DM and compared CSII with MDI using parallel trial design at two centres. Power calculations estimated that 180 subjects would have the power to detect HbA_{1c} difference of 0.5% between groups; however, recruitment was halted when an observed difference of 0.2% at interim analysis was deemed unlikely to become significant upon further recruitment. Inclusion criteria were explicitly stated; T2DM for $\geq$1 year, $\geq$60 years, taking at least one injection of insulin per day for the past month (with or without oral antidiabetes medications), $HbA_{1c} \geq 7\%$. Exclusion criteria were;BMI >45 kg/m^2;severe impairment of cardiac, hepatic or renal function; the presence of any physical, psychological, or cognitive impairments that would interfere with adherence to an intensive insulin therapy program ; more than two episodes of severe hypoglycaemia in the past year or a history of hypoglycaemia unawareness. Block randomisation was used at each site. Treatment groups were similar at baseline although more men were randomised to CSII than MDI. The study was not blinded. Analysis was ITT. Statistical analysis was comprehensively reported. Protocol violations were only reported in terms of technical and mechanical problems relating to CSII and MDI delivery; however, follow-up and reasons for withdrawal were fully described. Ninety-eight (92%) participants completed the study; eight subjects withdrew (four from CSII and four from MDI), and one subject (CSII) died of cancer. The study was not supported by commercial sources.

Study quality = A

Participants

Herman and colleagues recruited 107 participants with T2DM. In both the CSII and MDI groups mean age was between 66 and 67 years. In the CSII group 72% of participants were male compared with 44% in the MDI group. Mean diabetes duration was between 15 and 17 years and mean HbA_{1c} between 8 and 8.5%. Participants had been on insulin for a mean number of 8 to 8.3 years in both CSII and MDI groups. Authors noted that more men were randomised to CSII than MDI.

Intervention

Participants were randomised either to CSII or MDI for 12 months with the goal of achieving HbA_{1c} <5.6% and blood glucose levels of 80-120mg/dl before meals and 100-150mg/dl at bedtime without incurring unacceptable hypoglycaemia. CSII intervention (Medtronic MiniMed 508) consisted of an initial basal CSII dose 50% of previous total daily insulin dose. MDI intervention (preprandial lispro insulin and basal glargine insulin) consisted of initial basal dose 50% of total previous daily insulin dose, and at bedtime together with lispro insulin at mealtimes.

Results

1. Primary outcomes

HbA_{1c}

Herman 2005 assessed glycaemic control by measurement of HbA_{1c} between baseline and 12 months. There was no significant difference between CSII and MDI treatment groups at study end (CSII 6.6 ± 0.8% vs. MDI 6.4 ± 0.8%; p = NS), although both groups had lower HbA_{1c} compared with baseline (change from baseline CSII -1.7 ± 1.0% vs. MDI -1.6 ± 1.2%).

2. Secondary outcomes

Insulin dose requirement

There was no significant difference between CSII and MDI in mean total insulin dose requirement, mean basal insulin dose, and mean daily bolus insulin dose.

Weight

The weight of participants in both groups increased from baseline (change from baseline CSII +2.1kg vs MDI +2.6kg; $p<0.01$ vs baseline); however, there was no significant difference between groups.

Quality of life

Health-related quality of life was assessed using the SF-36 and Diabetes Quality of Life Clinical Trial Questionnaire (DQOLCTQ) scale, a validated questionnaire which was used to measure trearment satisfaction, treatment flexibility, frequency and bother of symptoms, social stigma, diabetes satisfaction, diabetes impact, social worry and diabetes worry. Treatment satisfaction score, diabetes impact score and worry score all improved significantly ($p<0.05$ for all three measures) from baseline in both groups; however there was no significant difference between groups.

3. Adverse Events

Hypoglycaemic episodes were defined as minor (≤65 mg/dl during week before scheduled visits every 2 months, able to treat themselves), severe (<50mg/dl associated with confusion, loss of consciousness, or seizures that resolved with the administration of oral carbohydrates, glucagon or intravenous glucose by another person), or catastrophic (life-threatening injury to patient or another person, hospitalization and/or death). There was no significant difference in the occurrence of episodes of minor, severe or catastrophic hypoglycaemia between groups; however, the authors noted that the rates of minor and severe hypoglycaemia were higher than those in a previous study in people with T2DM. They concluded that "this may be due to the older age of the study population or lower levels of HbA_{1c} achieved in the study"

In summary, Herman and colleagues reported no significant difference in reduction in mean HbA_{1c} levels or occurrence of hypoglycaemic episodes between treatments in patients >60 years with T2DM. The number of technical and mechanical difficulties associated with pump therapy was higher than

reported in previous studies; the authors suggests that this may have been because of "better ascertainment" or (of relevance to whether pumps are suitable for certain populations) potentially because the older population in this study were "less technologically savvy".

Wainstein et al. 2005 (full publication)

Description and quality of study

This randomised controlled trial enrolled 40 obese participants with T2DM and compared CSII with MDI using crossover trial design at seven centres in Israel. For this review only the first treatment period of 18 weeks was assessed. Power calculations estimated that 39 subjects would have the power to detect HbA_{1c} difference of 0.85% between groups. Inclusion criteria were explicitly stated; uncontrolled T2DM (HbA_{1c} >8.5%), obese (BMI 30-45 kg/m^2), aged 30-70 years and treated for at least 3 months with diet, metformin (850mg 2-3 times daily) and high doses of insulin (above 1 unit/kg/day), divided into two or three daily injections. Exclusion criteria were; those with new-onset diabetes (< 6 months); T1DM, or diabetes secondary to pancreatitis or other disease; history of active ischaemic heart disease or CVA within the last 12 months; pre-proliferative or proliferative diabetic retinopathy; advanced nephropathy as evidenced by proteinuria or plasma creatinine >1.5 mg/dl; liver enzymes twice above the upper limit of the normal range HbA_{1c} >15% at screening. No details of randomisation were reported. Baseline characteristics were reported. The study was not blinded. Analysis was ITT. Statistical analysis was comprehensively reported. Protocol violations mentioned but no details provided. Reasons for withdrawal were reported; five subjects randomized to MDI dropped out (two were non-compliant, two for protocol violations and one diagnosed with cancer; three subjects randomized to CSII dropped out (one was unable to use pump, one had severe hypoglycaemia and one had hyperglycaemia).

No competing interests were reported.

Study quality = B

Participants

Baseline HbA_{1c} levels were similar in CSII and MDI groups (CSII 10.2 ± 1.4 vs.10.3 ± 1.2). Similarly, there was no significant difference in insulin dose (CSII 99.3 ± 24.5 U/day vs. MDI 113.4 ± 28.04 U/day) or weight (CSII 91.8 ± 17.4 kg vs. MDI 94.01 ± 12.4 kg) between groups at baseline. It should be noted that only obese (BMI 30-45 kg/m^2) participants were selected.

Intervention

Participants were randomised either to CSII (n=20) or MDI (n=20) for 18 weeks. Thereafter participants crossed over to the alternative treatment (however, for this study only the first 18 week parallel period is reported). CSII intervention regimen consisted of CSII using insulin lispro. MDI regimen consisted of four injections daily using regular insulin or Humulin R and NPH or Humulin N.

All participants continued with their prior treatment with diet and metformin and the goal for all treatments was to achieve HbA_{1c} <7%.

Results

1. Primary outcomes

HbA_{1c}

Wainstein 2005 assessed glycaemic control by measurement of HbA_{1c} between baseline and 18 weeks. At the end of this period HbA_{1c} levels had decreased significantly (CSII -2.2% vs MDI – 1.9%) in both groups (CSII from 10.2 ± 1.4 to 7.9 ± 1.0, p=0.01 vs. MDI from 10.3 ± 1.2 to 8.4 ± 1.3, p=0.01). There was no significant difference between treatments.

2. Secondary outcomes

Insulin dose requirement

At the end of 18 weeks insulin dose had decreased in the CSII group from baseline value of 99.3 ± 24.5 U/day to 87.2 ± 25.4U/day whilst dose had increased in the MDI group from 113.4 ± 28.04 to 118.7 ± 31.3. There was no significant difference between treatments.

Weight

The weight of participants in both groups remained stable throughout the study. No significant difference between treatments

3. Adverse events

Hypoglycaemic episodes were defined as minor (<3.3 mmol/l able to handle without assistance), major (<2.8 mmol/l, symptoms remitted after intake of IV glucose, IM glucagon or food intake and patient was unable to self treat).There was no significant difference in the occurrence of episodes of hypoglycaemia between groups.

In summary, Wainstein and colleagues 2005 showed that in obese insulin treated patients with uncontrolled T2DM, CSII and MDI both significantly reduced HbA_{1c} levels, but the decrease was not significantly different between treatments. Insulin dose, weight gain and adverse events were similar with both treatments.

Raskin et al. 2005 (full publication)

Description and quality of study

This randomised controlled trial enrolled 132 adult participants with T2DM and compared CSII with MDI using parallel trial design at 14 sites. Power calculations estimated that 102 subjects would have the power to detect HbA_{1c} difference of 0.4% between groups. Inclusion criteria were explicitly

stated; T2DM for ≥2 years, treatment for six months with at least one insulin dose per day (regular insulin, lispro insulin, NPH, premixed insulin, Lente or Ultralente, with or without an oral antidiabetic agent. Exclusion criteria were; subjects with impaired hepatic, renal or cardiac function or recurrent major hypoglycaemia; women of childbearing age if they were pregnant, breast-feeding or not practicing contraception. Randomisation method was described but no stratification. Treatment groups were similar at baseline. The study was not blinded. Data was not ITT (based on the 127/132 who received treatment (five people withdrew during 2 week training period); last observation carried forward analysis). Statistical analysis was reported. Protocol violations were not reported; however, follow-up and reasons for withdrawal were fully described. Of those on CSII 6 withdrew during treatment; one was non-compliant, five withdrew consent. Of those on MDI two were noncompliant, one withdrew consent and two experienced adverse events (maculopapular rash, osteomyelitis and skin ulceration). The study was supported by Novo Nordisk Pharmaceuticals.
Study quality = B

Participants

Raskin and colleagues recruited 132 participants with T2DM. In both the CSII and MDI groups mean age was between 55 and 56 years, 36% in the CSII group were male and 43% in the MDI group, mean BMI was 32.2 kg/m^2 in both groups, mean weight was between 96.4 and 96.9kg. Mean HbA_{1c} at baseline was between 8.0 and 8.2 (%). Mean duration of diabetes was between 11.9 and 13.8 years.

Intervention

Participants were randomised either to CSII or MDI for 24 weeks with the goal of achieving fasting (prebreakfast) blood glucose levels of 4.4-6.7mmol/l (80-120 mg/dl) without incurring unacceptable hypoglycaemia. CSII intervention (Medtronic MiniMed 507C) consisted of insulin aspart (100units/ml) with CSII bolus doses administered just before meals. MDI intervention (preprandial insulin aspart and basal NPH). Instructions on the use of CSII and MDI were received on two separate visits, and doses of insulin were adjusted during initial 8 weeks after randomisation.

Results

1. Primary outcomes

HbA_{1c}

Raskin 2003 assessed glycaemic control by measurement of HbA_{1c} between baseline and 24 weeks. There was no significant difference between CSII and MDI treatment groups at study end (CSII 7.6 ± 1.22% vs. MDI 7.5 ± 1.17%; p = NS), although both groups had lower HbA_{1c} compared with baseline (change from baseline CSII -0.62 ± 1.11% vs. MDI -0.46 ± 0.89%; $p<0.05$).

2. Secondary outcomes

Insulin dose requirement

There was no significant difference between CSII and MDI in mean total daily insulin dose requirement at 24 weeks (both treatment groups +0.1U/kg; p=NS).

Weight

The weight of participants in both groups increased slightly from baseline (CSII baseline 96.4 ± 17.0kg 24 weeks 98.1 ± 18.1kg; MDI baseline 96.9 ± 17.9 kg 24 weeks 97.6 ± 19.2kg); however, there was no significant difference between groups.

Quality of life and treatment satisfaction

Quality of life and treatment satisfaction was assessed using validated questionnaires that are components of the Phase V Technologies Outcomes Information System incorporating a diabetes treatment satisfaction components and quality of life scale. CSII had significantly greater improvement in overall treatment satisfaction compared with MDI (CSII baseline 59.4 ± 2.1 24 weeks 79.2 ± 1.8 vs. MDI baseline 63.6 ± 1.9 vs. 70.3 ± 2.3; p<0.001 between groups). Of the 59/66 (89%) of CSII-treated subjects who responded to a questionnaire on CSII use, 93% preferred the pump to their previous injectable insulin regimen.

3. Adverse Events

Hypoglycaemia

Hypoglycaemic episodes were defined as minor (blood glucose <2.8 mmol/l (50 mg/dl), symptoms of hypoglycaemia ie palpitations, tiredness, sweating, strong hunger, dizziness, tremor etc, and able to deal without assistance), major (blood glucose <2.8 mmol/l (50 mg/dl) associated with severe CNS dysfunction that required the assistance of another person or required administration of prenteral glucose or glucagon). There was no significant difference between groups in the number of subjects reporting hypoglycaemic episodes (CSII 54% vs. MDI 59%; p=NS) or in the mean rate of hypoglycaemic episodes per 30 days (CSII 0.8 ± 1.6 vs. MDI 1.2 ± 3.1; p = NS). Nocturnal hypoglycaemic episodes were reported in 16% of CSII subjects and 22% of MDI subjects.

In summary, Raskin and colleagues reported no significant difference in reduction in mean HbA_{1c} levels or occurrence of hypoglycaemic episodes between CSII and MDIs in patients with T2DM. CSII subjects had significant improvements in treatment satisfaction scores compared with MDI.

Berthe al. 2007 (full publication)

Description and quality of study

This two centre randomised cross-over trial set in France enrolled 17 patients with T2DM. Those eligible for inclusion were uncontrolled by two daily injections of regular plus NPH, and included

those receiving insulin for >6 months, aged 40 to 65 years, BMI ranging from 26 to 42 kg/m^2 and willing to use an insulin pump device. The exclusion criteria were: patients with renal failure, proliferative retinopathy, high triglyceride level, use of OAD or oral corticosteroid drugs, insulin does requirements >1.5 U/kg/day, and refusing pump device. The study was open-label and there were no drop-outs. The method of randomisation was not stated**.** All patients completed the study so ITT was not an issue.

The trial was supported by Ely Lilly France.

Study quality = B

Participants

The 17 participants were randomly assigned to either CSII or MDI for a 12 week period and thereafter switched to the other treatment for another 12 week period (hence the total study period was 24 weeks). Dietary counselling was also received at the beginning of each study period. Group 1 (n=7) received pump then MDI and Group 2 (n=10) received MDI then pump. The baseline characteristics of both groups were similar except that Group 2 patients were older by a mean of 8 years. Patients were hospitalized for 24 to 48 hours at the beginning MDI period for 5 days and at the beginning of the CSII period, in order to receive individual education sessions including pump training sessions. MDI training sessions, and instructions about hypoglycaemic and hyperglycaemic events. Patients also received dietary counselling (in accordance with ADA guidelines) at the beginning of each study period.

Intervention

The CSII used a Medtronic 508 pump deliverying insulin lispro. Patients started with 70% daily dose as basal and 30% as prandial bolus. The MDI arm used 3 daily injections of pre-mixed lispro-NPH insulin. All patients completed the study.

Results

1. Primary outcomes

HbA_{1c}

The HbA_{1c} decreased from 9.0 ± 1.6% to 8.6 ± 1.6% at the end of the MDI period and to 7.7 ± 0.8% at the end of the CSII period ($p<0.03$). (As this was a cross-over trial it was not clear how this overall change in HbA_{1c} was calculated for the two treatments). A carry over effect was tested by comparing the two groups of patients defined by the treatment order. No effect was observed.

2. Secondary outcomes

Quality of life and treatment satisfaction

Both groups reported that they were satisfied with their insulin regimens. There was a slight but not significant preference for MDI over CSII.

3. Adverse Events

Hypoglycaemia

There was no difference in hypoglycaemic episodes between the two groups.

In summary, Berthe and colleagues study showed that CSII with lispro gave improved glycaemic control over MDI with 3 daily injections of premixed lispro-NPH insulin, in patients with T2DM who have failed to respond to conventional insulin therapy. This was achieved with comparable patient satisfaction in both groups and no increase in hypoglycaemia.

Table 42: Study quality assessment

Study	Power calculation	Randomisation method	Allocation concealment	Assessors blinded	Groups similar at baseline	ITT	Protocol violations specified	Missing value treatment	Attrition	All patients accounted for
Type 1 diabetes										
Doyle 2004[105]	No	Stratified according to sex and age Random number table in block of four	Open	No	Yes	Yes	Specified. Two violations – would not affect results.	LOCF	31/32 (97%) completed study	Yes
Thomas 2007[106]	No	No details given	Open	No	Yes	Not stated	No	Not stated	Not stated	Not stated
Maran 2005[107]	No	No details given	Open	No	No comparison between groups	Not stated	No	Not stated	Not stated	Not stated
Bolli 2004[108]	No	No details given	Open	No	No baseline characteristics	Not stated	No	Not stated	Not stated	Not stated
Type 2 diabetes										
Herman 2005[110]	Yes	Block randomisation	Open	No	Yes (although more men in CSII)	Yes	Technical and mechanical delivery violations specified – may affect results	Not stated	98/107 (92%) completed study	Yes
Wainstein 2005[112]	Yes	No details given	Open	No	Yes	Two cohorts 1) ITT 2) completers	Two protocol violations resulting in dropout	LOCF in ITT analysis	32/40 (80%) completed 18 weeks	Yes

Raskin 2003[111]	Yes	Inadequate method and no stratification.	Open	No	Yes	No. Analysis based on 127/132 (96%) who received treatment	No	LOCF	127/132 (96%)	Yes
Berthe 2007[109]	No	Cross-over – no details given of method.	Open	No	Yes (although group 2 patients older by 7.8 years)	Not stated	No	Not stated	Not stated	Not stated

Table 43: Participant characteristics at baseline

Study	Number of participants	Inclusion criteria	Exclusion criteria	Mean age (years)	Mean HbA_{1c} (%)	Mean BMI (kg/m^2) [unless Weight (kg) is stated]
Type 1						
Doyle 2004[105]	32	T1DM Aged 8-21 years Otherwise healthy except for treated thyroid or celiac disease Treated with insulin for at least 6 months Naïve to CSII and glargine Willing to perform at least 4 blood glucose tests/day Screening HbA_{1c} level between 6.5 and 11%	Not explicitly stated	CSII 12.5 ± 3.2 MDI 13 ± 2.8	CSII 8.2 ± 1.1 MDI 8.1 ± 1.2	Not stated
Thomas 2007[106]	21	T1DM C-peptide negative Adults At least one episode of severe hypoglycaemia within the preceding 6 months Naïve to MDI insulin analogue therapy.	Not explicitly stated	CSII 40 ± 7 MDI 46 ± 9	CSII 8.5 ± 1.9 MDI 8.6 ± 1	CSII Weight =72.5 ± 8.6 MDI Weight 78.0 ± 15.2

Maran 2005[107]	10	C-peptide negative T1DM Previously on CSII therapy for at least 6 months	Not explicitly stated	All 41 ± 8	All 7.7 ± 0.7	Not stated
Bolli 2004[108]	57	T1DM $HbA_{1c} \leq 9\%$ Naiive to CSII and glargine	Not explicitly stated	Not stated	CSII 7.7 ± 0.7 MDI 7.8 ± 0.6	Not stated
Type 2						
Herman 2005[110]	107	≥60 years of age Clinical diagnosis of T2DM for at least 1 year Taking at least one injection of insulin per day for the past month (with or without oral antidiabetes medications) $HbA_{1c} \geq 7\%$	BMI >45 kg/m^2 Severe impairment of cardiac, hepatic or renal function The presence of any physical, psychological, or cognitive impairments that would interfere with adherence to an intensive insulin therapy program More than two episodes of severe hypoglycaemia in the past year or a history of hypoglycaemia unawareness	CSII 66.6 ± 5.9 MDI 66.2 ± 4.5	CSII 8.4 ± 1.1 MDI 8.1 ± 1.2	CSII 32.5 ± 5.8 MDI 31.8 ± 5.8
Wainstein 2005[112]	40	Uncontrolled T2DM (HbA_{1c} > 8.5%). obese (BMI 30–45 kg/m2) aged 30–70 years treated for at least 3 months with diet, metformin (850 mg 2–3 times daily) and high doses of insulin (above 1 unit/kg/day), divided into two or three daily injections.	those with new-onset diabetes (less than 6 months), T1DM, or diabetes secondary to pancreatitis or other disease. History of active ischaemic heart disease or CVA within the last 12 months pre-proliferative or proliferative diabetic retinopathy, advanced nephropathy as evidenced by proteinuria or	Not stated	CSII 10.2 ± 1.4 MDI 10.3 ± 1.2	Not stated

			plasma creatinine > 1.5 mg/dl, liver enzymes twice above the upper limit of the normal range HbA 1c > 15% at screening.			
Raskin 2003[111]	132	T2DM of 2 years' duration ≥ 35 years Treatment for 6 months with at least one insulin dose per day (regular insulin, lispro insulin, NPH, premixed insulin, Lente, or Ultralente), with or without an oral antidiabetic drug.	Subjects with impaired hepatic, renal, or cardiac function or recurrent major hypoglycaemia Women of childbearing age were excluded if they were regnant, breast-feeding, or not practicing contraception.	CSII 55.1 ± 10.2 MDI 56.0 ± 8.18	CSII 8.2 ± 1.4 MDI 8.0 ± 1.1	CSII 32.2 ± 4.2 MDI 32.2 ± 5.1
Berthe 2007[109]	17	T2DM Receiving insulin for >6 months Aged 40 to 65 years BMI ranging from 26 to 42 kg/m2 Uncontrolled by two daily injections of regular NPH (HbA_{1c} level of ≥ 6.5% on two determinations) Willing to use an insulin pump device	Patients with renal failure, proliferative retinopathy, high triglyceride level Use of OAD or oral corticosteroid drugs Insulin does requirements >1.5 U/kg/day Refusing pump device	Group 1 (Pump then MDI) 50.6 ± 6.4 Group 2 (MDI then pump) 58.4 ± 4.6	CSII 9.0 ± 1.6 MDI 9.0 ± 1.6	Group 1 (Pump then MDI) 34.6 ± 4.0 Group 2 (MDI then pump) 33.0 ± 4.9

Table 44: Quality of life and patient satisfaction

Study	Outcome measure(s)	Result
Type 1 diabetes		
Doyle 2004	DQOLY	Baseline to 16 weeks p = NS between CSII and MDI
Thomas 2007	DQOL Hypoglycaemia Fear Survey	P = NS between CSII and MDI P = NS between CSII and MDI
Type 2 diabetes		
Herman 2005	SF-36 DQOLCTQ	P = NS between CSII and MDI P = NS between CSII and MDI
Raskin 2003	Components of the PHASE V Technologies Outcomes Information System - included a diabetes treatment satisfaction module and a quality-of-life summary scale	CSII vs. MDI overall treatment satisfaction P<0.001
Berthe 2007	Satisfaction questionnaire [adapted from Raskin 2003]	P = NS between CSII and MDI

Table 45: Adverse events

Study	Mean blood glucose levels	Mild hypoglycaemia	Severe hypoglycaemia	Other	Hyperglycaemia	Diabetic ketoacidosis
Type 1 diabetes						
Doyle 2004[105]			P = NS between groups			CSII n = 1 MDI n = 1 (hospitalised for ketosis and dehydration)
Thomas 2007[106]	P = NS between treatment groups in mean daily blood glucose (mM)	P=NS trend toward reduced incidence in MDI and CSII groups.	P=NS trend toward reduced incidence in MDI and CSII groups.	P = NS between groups in glucose excursions (<2.4mM/<4mM/<7mM hr/24hr)		
Maran 2005[107]	CSII group had significantly lower mean glucose levels (CSII 147 ± 12 vs. 189 ± 14 mg/dl; p<0.03).			P = NS between groups in hypoglycaemia reactions exposure (AUC <65mg/dl) CSII spent significantly more time in glucose range >65mg/dl and <180mg/dl than MDI (CSII 298 ± 63 vs. MDI 194 ± 51 minutes; p<0.02)		
Bolli 2004[108]	CSII baseline 164 ± 41 endpoint 146 ± 32 vs. MDI baseline 160 ± 30 endpoint144 ± 20; difference 1 95% CI -14 to 15; p= NS			P = NS between groups in incidence of blood glucose <72 mg/dl between treatment groups (CSII 41 vs. MDI 35) P = NS between groups in mean amplitude of glycaemic excursions and 8-point blood glucose profiles.		
Type 2 diabetes						

Herman 2005[110]		P = NS between treatment groups	P = NS between groups	P = NS between groups in incidence of catastrophic hypoglycaemia		
Wainstein 2005[112]		P = NS between treatment groups	P = NS between treatment groups			
Raskin 2003[111]				P = NS between groups in the number of subjects reporting hypoglycaemia episodes or mean rate of hypoglycaemic episodes.	CSII 3(5%) reported 6 episodes MDI 11 (18%) reported 26 episodes	
Berthe 2007[109]	Duration (% of 24-h) time of glucose maintained within the target (60-180mg/dl) was significantly reduced P=0.0085 between groups	Rate and duration of hypoglycaemic excursions. P=NS between groups	Rate and duration of hypoglycaemic excursions. P=NS between groups		Rate of hyperglycaemic excursions over 24 hr. P=NS between groups Duration of hyperglycaemic excursions,%= P=0.012 between groups.	

Appendix 5: Structure of the CORE model

Palmer et al (2004) outline the broad structure of the CORE model for both type 1 and type 2 diabetics, providing references for the 15 complications of diabetes sub-models within the overall CORE model.

Note that where the study has analysed diabetics as a specific subgroup, where the sample size is stated without qualification this refers to the size of the diabetic subgroup. Similarly, if the study was specific to diabetics, either entirely or as a subgroup, but without identifying or sub-analysing diabetic types this is stated as "Yes". Where a specific type of diabetes is analysed separately this is stated; i.e. T1, T2 or T1&T2.

Submodel:		**MYOCARDIAL INFARCTION**					
Submodel differentiated between T1 and T2:		**NO**					
Submodel differentiated by patient age:		**YES**					
Submodel differentiated by patient duration of diabetes:		**YES if simulations based upon UKPDS risk engine**					
Variable	**Reference**	**Country**	**Diabetes**	**Dur**	**HbA_{1c}**	**N**	**Av. Age**
a) Probability 2nd MI	45: Herlitz 1996	Sweden	Yes	10yrs	n/a	96	72
b) MI immediate death rate	46: Sonke 1996	New Zealand	No	n/s	n/s	5,106	55
c) MI 12 month death rate	47: Almbrand 2000	Sweden	Yes	n/s	n/s	620	n/s
d) Effect of intensive insulin on (c)	48: Malmberg 1997	Sweden	Yes	n/s	n/s	620	n/s

Submodel:		**ANGINA**					
Submodel differentiated between T1 and T2:		**NO**					
Submodel differentiated by patient age:		**YES**					
Submodel differentiated by patient duration of diabetes:		**NO**					
Variable	**Reference**	**Country**	**Diabetes**	**Dur**	**HbA_{1c}**	**N**	**Av. Age**
a) Probability of developing angina	43: DeAgostina 2000	US	Yes	n/s	n/s	500	49
b) Cardiovascular risk multipliers	49: Mann 2001	Multi	Yes	n/s	n/s	3,573	66

Submodel:		**CONGESTIVE HEART FAILURE**					
Submodel differentiated between T1 and T2:		**YES**					
Submodel differentiated by patient age:		**YES**					
Submodel differentiated by patient duration of diabetes:		**NO**					
Variable	**Reference**	**Country**	**Diabetes**	**Dur**	**HbA_{1c}**	**N**	**Av. Age**
a) CHF risk profile	50: Kannel 1999	US	Yes	n/s	n/s	486*	62
b) Death following CHF event	51: Ho 1993	US	No	n/a	n/a	652	41**
c) HbA_{1c} risk adjustment	53: Stratton 2000	UK	T2	n/s	7.1%	3,642	53
d) CHF Risk adjustment: ACE etc.	54: HOPE 2000	Multi	T2***	11yr	n/a	2,577	65
		*All patients, as number of diabetics not stated ** at enrolment in Framingham ***T2 comprised more than 97% study population					

Submodel:		**STROKE**					
Submodel differentiated between T1 and T2:		**NO**					
Submodel differentiated by patient age:		**YES**					
Submodel differentiated by patient duration of diabetes:		**YES if simulations based upon UKPDS risk engine**					
Variable	**Reference**	**Country**	**Diabetes**	**Dur**	**HbA_{1c}**	**N**	**Av. Age**
a) T2 stroke probability	56: Kothari 2002	UK	T2	n/s	6.7%	4,549	52*
b) T2 risk adjustments	42: Valmadrid 2000	US	T2	15yr	9.3%	840	68
c) Probability recurrent stroke	57: Petty 1998	US	Yes`	n/s	n/s	1,111**	75
d) 12 month stroke death rate	58: Sprafka 1994	US	Yes	n/s	n/s	n/s	30-74
e) Risk adjustment: ACE etc	59: ADA 2002 60: Buring 1990	US Multi	Yes No	n/s n/a	n/s n/a	n/s 17,187	30+ n/s
		` But reference 58 appears to be used for adjusting stroke risk *Age at diagnosis **All patients, not restricted to diabetic subgroup					

Submodel:		**PERIPHERAL VASCULAR DISEASE**					
Submodel differentiated between T1 and T2:		**NO**					
Submodel differentiated by patient age:		**YES**					
Submodel differentiated by patient duration of diabetes:		**YES**					
Variable	**Reference**	**Country**	**Diabetes**	**Dur**	**HbA_{1c}**	**N**	**Av. Age**
a) PVD risk profile	61: Murabito 1997	US	Yes	n/s	n/s	381*	28-62
b) T2 risk adjustment for HbA_{1c}	62: Stratton 2001	UK	T2	n/s	7.0%	1,919	52
		*All patients, nor restricted to diabetic subgroup					

Submodel:		**NEUROPATHY**					
Submodel differentiated between T1 and T2:		**YES**					
Submodel differentiated by patient age:		**NO**					
Submodel differentiated by patient duration of diabetes:		**YES**					
Variable	**Reference**	**Country**	**Diabetes**	**Dur**	**HbA_{1c}**	**N**	**Av. Age**
a) T1 neuropathy prevalence	63:DCCT 1995	US & Canada	T1&T2	1-5yr	n/s	1,441	26
b) T2 neuropathy prevalence	18: Partanen 1995		T2				
c) T1 transition probabilities	63:DCCT 1995	As above					
d) T2 transition probabilities	18: Partanen 1995	As above					
e) T1 risk adjustment for HbA_{1c}	63:DCCT 1995	As above					
f) T2 risk adjustments	43: DeAgostina 2000 53: Stratton 2000 56: Kothari 2002 64: Adler 2000	US UK UK UK	Yes T2 T2 T2	n/s n/s n/s n/s	n/s 7.1% 6.7% 7.1%	500 3,642 4,459 3,642	49 53 52 53

Submodel:		**FOOT ULCER AND AMPUTATION**					
Submodel differentiated between T1 and T2:		**NO**					
Submodel differentiated by patient age:		**YES – Indirectly via PVD**					
Submodel differentiated by patient duration of diabetes:		**YES – Indirectly via Neuropathy and PVD**					
Variable	**Reference**	**Country**	**Diabetes**	**Dur**	**HbA_{1c}**	**N**	**Av. Age**
a) probability of developing: also linked to PVD and neuropathy	68: Tenvall 2001	Sweden	Yes	n/s	n/s	1,677	66

Submodel:		**RETINOPATHY**					
Submodel differentiated between T1 and T2:		**YES**					
Submodel differentiated by patient age:		**NO**					
Submodel differentiated by patient duration of diabetes:		**YES**					
Variable	**Reference**	**Country**	**Diabetes**	**Dur**	**HbA_{1c}**	**N**	**Av. Age**
a) T1 transition probabilities	69: DCCT 1995	US & Canada	Yes	2.6yr	8.8%	1,441	26
b) T1 risk adjustments	70: DCCT 1996	US & Canada	Yes	2.6yr	8.8%	1,441	26
	71: DCCT 1993	US & Canada	Yes	2.6yr	8.8%	1,441	26
	72: Malik 1998	UK	Yes	n/s		41	
c) T2 transition probabilities	73: Javitt 1994	US	T2	n/s	n/s	n/s	n/s
	74: Klein 1989	US	T1[?]	14yr	12.6%	1,210	29
d) transition to SVL	62: Stratton 2001	UK	T2	n/s	7.0%	1,919	52
e) ACE effect on BDR and PDR	75: Chaturvedi 1998	Multi	T1	9yr	7%	409	31
		[?] described as younger onset, prescribed insulin					

Submodel:		**MACULAR OEDEMA**					
Submodel differentiated between T1 and T2:		**YES**					
Submodel differentiated by patient age:		**NO**					
Submodel differentiated by patient duration of diabetes:		**YES**					
Variable	**Reference**	**Country**	**Diabetes**	**Dur**	**HbA_{1c}**	**N**	**Av. Age**
a) T1 onset and progression SVL	71: DCCT 1993	US & Canada	Yes	2.6yr	8.8%	1,441	26
b) T2 transition probabilities	73: Javitt 1994	US	T2	n/s	n/s	n/s	n/s
c) T1 onset risk adjustment HbA_{1c}	71: DCCT 1993	As above					
d) T1 onset risk adjustment SBP	64: Adler 2000	UK	T2	n/s	7.1%	3,642	53
e) T2 onset risk adjustment HbA_{1c}	62: Stratton 2001	UK	T2	n/s	7.0%	1,919	52
f) T2 onset risk adjustment SBP	64: Adler 2000	As above					

Submodel:		**CATARACT**					
Submodel differentiated between T1 and T2:		**YES**					
Submodel differentiated by patient age:		**NO**					
Submodel differentiated by patient duration of diabetes:		**NO**					
Variable	**Reference**	**Country**	**Diabetes**	**Dur**	**HbA_{1c}**	**N**	**Av. Age**
a) T1 incidence and subsequent	76: Janghorbani 2000	UK	T1&T2	7.6yr	~12%	3,606	49
b) T2 incidence	77: UKPDS33 1998	UK	T2	n/s	7.5%	3,862	54
c) T2 subsequent	76: Janghorbani 2000	As above					
d) T2 risk adjustment HbA_{1c}	53: Stratton 2000	UK	T2	n/s	7.1%	3,642	53

Submodel:		**NEPHROPATHY**					
Submodel differentiated between T1 and T2:		**YES**					
Submodel differentiated by patient age:		**NO**					
Submodel differentiated by patient duration of diabetes:		**YES**					
Variable	**Reference**	**Country**	**Diabetes**	**Dur**	**HbA_{1c}**	**N**	**Av. Age**
a) T1 transition probabilities	78: DCCT 1995	US & Canada					
b) T2 transition probabilities	79: Ritz 1996	Multi : meta	T2	n/s	n/s	n/s	n/s
	80: Wolfe 1999	US	Yes*	n/s	n/s	46,164	40-59**
	84: Ravid 1998	Israel	T2	n/s	~9%	574	49
	85: Ravid 1993	Israel	T2	6.7yr	n/s	108	44
c) death from ESRD	80: Wolfe 1999	As above					
d) T1 risk adjustments	71: DCCT 1993	US & Canada	Yes	2.6yr	8.8%	1,441	26
	79: Ritz 1996	As above					
	80: Wolfe 1999	As above					
	83: Kshirsagat 2000	Multi : meta	?	n/a	n/a	n/a	n/a
e) T2 risk adjustment HbA_{1c}	87: UKPDS34 1998	UK	T2	11yr	7.7%	753	53
f) T2 risk adjustment SBP	88: UKPDS 38 1998	UK	T2	2.7yr	6.9%	1,148	56
		* end stage renal patients awaiting transplantation **median ? patients with renal disease					

Submodel:		**HYPOGLYCAEMIA**					
Submodel differentiated between T1 and T2:		**YES**					
Submodel differentiated by patient age:		**NO**					
Submodel differentiated by patient duration of diabetes:		**NO**					
Variable	**Reference**	**Country**	**Diabetes**	**Dur**	**HbA_{1c}**	**N**	**Av. Age**
a) T1 probability: HbA_{1c} and age	89: DCCT 1997	US & Canada	Yes	2.6yr	8.8%	1,441	26
b) T2 probability	90: Stepka 1993 91: Ben Ami 1999	Poland Israel	T1 and T2 T1 and T2	n/s n/s	n/s n/s	20,798* 102	** 72
c) T2 risk adjustment medication	77: UKPDS33 1998	UK	T2	n/s	7.5%	3,862	54
d) ACE risk adjustment	92: Morris 1997 93: Herings 1995	UK Netherlands	Yes Yes	n/s n/s	n/s n/s	500 748	n/s 60-74^
e) probability death	70: DCCT 1993	US & Canada	Yes	2.6yr	8.8%	1,441	26
		*diabetic hospitalisations, of which 236 serious hypoglycaemia. **98/101 T2 patients admitted with hypoglycaemia were over 60 ^ range within which median fell					

Submodel:		**KETOACIDOSIS**					
Submodel differentiated between T1 and T2:		**ONLY APPLIES TO TYPE 1**					
Submodel differentiated by patient age:		**NO**					
Submodel differentiated by patient duration of diabetes:		**NO**					
Variable	**Reference**	**Country**	**Diabetes**	**Dur**	**HbA_{1c}**	**N**	**Av. Age**
a) event probability	71: DCCT 1993	US & Canada	Yes	2.6yr	8.8%	1,441	26
b) probability of death	94: MacIsaac 2002 95: Umpierrez 1996	Australia Review	Yes Yes	n/s n/a	n/s n/a	312 n/a	33-69¬ n/a
		¬33 average for DKA, 44 average for DKA-HHS and 69 average for HHS alone					

Submodel:		**LACTIC ACIDOSIS**					
Submodel differentiated between T1 and T2:		**ONLY APPLIES TO TYPE 2 (Treated with Metformin)**					
Submodel differentiated by patient age:		**NO**					
Submodel differentiated by patient duration of diabetes:		**NO**					
Variable	**Reference**	**Country**	**Diabetes**	**Dur**	**HbA_{1c}**	**N**	**Av. Age**
a) event probability	96: Campbell 1985	Review	Yes	n/a	n/a	n/a	n/a
b) probability of death	96: Campbell 1985	As above					

Submodel:		**NON-SPECIFIC MORTALITY**					
Submodel differentiated between T1 and T2:		**NO**					
Variable	**Reference**	**Country**	**Diabetes**	**Dur**	**HbA_{1c}**	**N**	**Av. Age**
a) non specific mortality US default	98: NVSR 2001	US	No	n/a	n/a	..	..

Appendix 6: Sensitivity analyses within the industry submission

	QALY Gain	Net Cost	ICER
Base case : Trial Based Analysis	**0.500**	**17,158**	**£34,330**
Glycemic control			
Upper 95% CI for change in HbA_{1c}	0.590	16,848	£28,540
Lower 95% CI for change in HbA_{1c}	0.411	17,283	£42,015
Probabilistic sensitivity analysis	0.559	16,031	£28,656
Time horizon			
5 years	0.085	5,421	£63,795
10 years	0.189	9,080	£47,921
15 years	0.275	11,570	£42,039
Pump Price			
plus 20%	0.500	18,817	£37,649
minus 20%	0.500	15,499	£31,010
Discounting			
0% costs and 0% benefits	0.903	28,058	£31,084
6% costs and 6% benefits	0.354	13,090	£36,927
6% costs and 1.5% benefits	0.689	13,090	£18,997
Severe hypoglycaemic events			
upper rate	0.526	16,632	£31,636
lower rate	0.478	17,761	£37,189

Appendix 7: Treatment Costs

Capital costs

NHS Supply Chain is currently engaging in a tendering exercise to establish a national price structure for pumps and consumables. Work to date indicates a range of pump prices from £1,900 to £2,600, with a usual warranty period of 4 years.

After the 4 year warranty period servicing is required, at an average cost of around £500, in order for the pump to remain under guarantee. This subsequent guarantee lasts for between 1 and 2 years. However, NHS Supply Chain reports that as pump technology changes over time, after the initial 4 year warranty period many PCTs will simply purchase another pump, with the older newly serviced pumps possibly being retained as "testers" for patients trying CSII. New pumps would be purchased for these patients if they were found to suit pump therapy.

Given this for an average pump cost of £2,300 as per the industry submission, if this lasts only 4 years the annualised cost of this given a discount rate of 3.5% is £605. Increasing pump longevity to six years through servicing would reduce this annualised capital cost including the costs of service to £505, while a maximum lifespan of eight years involving two services would imply an annualised cost of £455, though a lifespan of 8 years may be viewed as unlikely to occur in practise.

Similarly with regards the additional training that may be required for the use of CSII, this can be estimated as a one off cost of around £240 which would annualise to an approximate figure of £15.

This gives an annualised capital and training cost for CSII of £620, £520 and £470 for pump lifespans of 4, 6 and 8 years respectively. In contrast, the only capital items for MDI are the two pen devices necessary, which at a cost of around £22 each and a possible lifespan of 3 years would give an annualised capital cost of £15.

Consumable costs

Given the consumables for CSII of infusion sets and reservoirs and needles for MDI as outlined within the manufacturer submission, the other consumables relate to the required insulin dose and the frequency of blood glucose monitoring.

The meta analysis by Pickup et al noted a reduced daily requirement for insulin of $0.6 IU kg^{-1}$ for CSII as compared to $0.7 IU kg^{-1}$ for MDI. These doses will be used for the base case analysis.

In a similar vein, the previous review noted that CSII had a daily requirement of 4 or more blood glucose monitorings as compared with 3 or more for MDI, though concluded that on average this would not result in any real additional cost for CSII. Given this, the base case for this review will assume a common rate for both CSII and MDI.

Total annual cost
The above assumptions coupled with an assumed patent weight of 80kg results in the following overall annual costs for CSII and MDI

	CSII	MDI	Net
Insulin			
Humalog	£312.21		
Humalog Cartridge		£200.72	
Lantus Catridge		£265.72	
Total Insulin	**£312.21**	**£466.44**	**-£154.23**
Consumables			
Infusion sets	£1,058.87		
Insulin reservoir	£325.82		
Needles		£31.83	
Lancets	£35.59	£35.59	
Test strips	£328.50	£328.50	
Glocometer	£10.00	£10.00	
Total Consumables	**£1,758.78**	**£405.92**	**£1,352.86**
Capital Costs			
Pump - 4 year lifespan	£620.00	£15.00	**£605.00**
Pump - 6 year lifespan	£520.00	£15.00	**£505.00**
Pump - 8 year lifespan	£470.00	£15.00	**£455.00**
Total			
Pump - 4 year lifespan	£2,690.99	£887.36	**£1,803.63**
Pump - 6 year lifespan	£2,590.99	£887.36	**£1,703.63**
Pump - 8 year lifespan	£2,540.99	£887.36	**£1,653.63**

Given the possible role for CSII within paediatric patients with type 1 diabetes, coupled with an additional possibility of use in relatively overweight patients with type 2 diabetes, patient weight will affect relative costs. However, only insulin use and possibly dosing would vary with patient weight and type of diabetes and as can be seen above the major cost components for CSII are the consumables and capital costs which do not vary with weight or diabetes type.

As a consequence, maintaining the same dosing assumptions and assuming a pump lifespan of 6 years, a patient weight of £30kg increases the net cost of CSII over MDI from £1,703 to £1,800 as the net cost of insulin drops to around a saving of £58 for CSII. In contrast, increasing the patient weight to 100kg increases the insulin saving to around £193 so reducing the net cost of CSII over MDI from £1,703 to £1,665.

The more pessimistic assumptions of equal dosing under CSII and MDI of $0.6IUkg^{-1}$, a daily requirement of 4 blood glucose monitorings for CSII as compared with 3 for MDI, and both of these combined have a greater effect, resulting in the following for an 80kg patient:

	CSII	MDI	Net
Equal insulin dose			
Pump - 4 year lifespan	£2,690.98	£820.72	**£1,870.26**
Pump - 6 year lifespan	£2,590.98	£820.72	**£1,770.26**
Pump - 8 year lifespan	£2,540.98	£820.72	**£1,720.26**
Higher CSII monitoring			
Pump - 4 year lifespan	£2,812.34	£887.36	**£1,924.99**
Pump - 6 year lifespan	£2,712.34	£887.36	**£1,824.99**
Pump - 8 year lifespan	£2,662.34	£887.36	**£1,774.99**
Equal insulin dose and higher CSII monitoring			
Pump - 4 year lifespan	£2,812.34	£820.72	**£1,991.62**
Pump - 6 year lifespan	£2,712.34	£820.72	**£1,891.62**
Pump - 8 year lifespan	£2,662.34	£820.72	**£1,841.62**

Appendix 8: Information supplied by INPUT on the range and costs of pumps currently available within the UK.

Smiths Deltec Cozmo	**Units**	**Price**	**1st year cost**
Pump Price model 1700 and 1701	1	£2,750.00	£2,750.00
Cartridge, Insulin, Unfilled box 25	25	£62.50	£312.50
Comfort, Single all sizes 10 sets	10	£86.00	£1,049.20
Comfort, Combo 5 sets & 5 extra cannula	5	£70.00	
Warranty	4 years		
Roche Accu-Chek Spirit	**Units**	**Price**	**1st year cost**
Pump Price	1	£2,375.00	£2,375.00
Accu-Chek Spirit Cartridges-25 Pieces	25	£45.55	£227.75
Flexlink Accu-Chek Flexilink I 8/30 10 Cannula	10	£80.85	£986.37
Warranty	6 years		
Animas IR1200	**Units**	**Price**	**1st year cost**
Pump Price	1	£2,600.00	£2,600.00
IR1200 Cartridge Stamped ETO Sterile 10ct pack 10	10	£23.50	£282.00
Infusion Set,Comfort 17mm, 23, 10ct Pack 10	10	£66.00	£805.20
Warranty	4 years		
Medtronic Paradigm	**Units**	**Price**	**1st year cost**
Pump Price 522/722 Realtime with CGM	1	£3,200.00	£3,200.00
Pump Price 522/722 Realtime without CGM	1	£2,750.00	£2,750.00
Continuous Glucose Monitor for Realtime Pump	1	£750.00	£750.00
Paradigm Reservoir 3ml pack of 10	10	£26.00	£312.00
Paradigm Quick set 110cm 9mm pack 10	10	£87.03	£1,061.75
Warranty	4 years		

World Wide use of insulin is stated as being 44 IU per day. Unlike with the previous HTA, INPUT also reports that servicing to extend the warranty period of pumps is no longer available.

Appendix 9: Cost-effectiveness simulations – assumptions used.

Simulation	HbA1c	Hypo rate	Hypo effect	Price	Horizon
Type 1					
Sim01	0.9% less		0% less	Mid	50 year
CSII	7.9%	0.187		£2,590	
MDI	8.8%	0.187		£890	
Sim02	0.9% less		50% less	Mid	50 year
CSII	7.9%	0.094		£2,590	
MDI	8.8%	0.187		£890	
Sim03	0.9% less		75% less	Mid	50 year
CSII	7.9%	0.047		£2,590	
MDI	8.8%	0.187		£890	
Higher hypoglycaemic event rate : Time Horizon					
Sim04	0.9% less		50% less	Mid	50 year
CSII	7.9%	0.310		£2,590	
MDI	8.8%	0.620		£890	
Sim05	0.9% less		50% less	Mid	30 year
CSII	7.9%	0.310		£2,590	
MDI	8.8%	0.620		£890	
Sim06	0.9% less		50% less	Mid	10 year
CSII	7.9%	0.310		£2,590	
MDI	8.8%	0.620		£890	
Higher hypoglycaemic event rate : Lesser effect upon HbA1c					
Sim07	0.6% less		50% less	Mid	50 year
CSII	8.2%	0.310		£2,590	
MDI	8.8%	0.620		£890	
Sim08	0.6% less		75% less	Mid	50 year
CSII	8.2%	0.155		£2,590	
MDI	8.8%	0.620		£890	
Higher hypoglycaemic event rate : Effect upon severe hypoglycaemia					
Sim09	0.9% less		0% less	Mid	50 year
CSII	7.9%	0.620		£2,590	
MDI	8.8%	0.620		£890	
Sim10	0.9% less		75% less	Mid	50 year
CSII	7.9%	0.155		£2,590	
MDI	8.8%	0.620		£890	
Higher hypoglycaemic event rate : Price					
Sim11	0.9% less		75% less	High	50 year
CSII	7.9%	0.155		£2,710	
MDI	8.8%	0.620		£803	
Sim12	0.9% less		50% less	Low	50 year
CSII	7.9%	0.310		£2,400	
MDI	8.8%	0.620		£890	
Sim13	0.9% less		75% less	Low	50 year
CSII	7.9%	0.155		£2,400	
MDI	8.8%	0.620		£890	
Higher hypoglycaemic event rate : Higher costs of blindness of £4,000 per year					
Sim14	0.9% less		50% less	Mid	50 year
CSII	7.9%	0.310		£2,590	
MDI	8.8%	0.620		£890	
Sim15	0.9% less		75% less	Mid	50 year
CSII	7.9%	0.155		£2,590	
MDI	8.8%	0.620		£890	

High hypoglycaemia group					
Sim16	0.0% less		50% less	Mid	50 year
CSII	7.5%	0.670		£2,590	
MDI	7.5%	1.340		£890	
Sim17	0.0% less		75% less	Mid	50 year
CSII	7.5%	0.335		£2,590	
MDI	7.5%	1.340		£890	
Higher hypoglycaemic event rate : Younger age cohort : average 30 years					
Sim18	0.0% less		50% less	Mid	50 year
CSII	7.5%	0.670		£2,590	
MDI	7.5%	1.340		£890	
Grater effect upon HbA1c					
Sim19	1.4% less		0% less	Mid	50 year
CSII	7.6%	0.620		£2,590	
MDI	9.0%	0.620		£890	

Appendix 10: Results of cost effectiveness simulations

General Population

Sim01 General Population : No hypo effect	CSII	MDI	Difference
Life expectancy	21.848	20.536	1.312
Life expectancy (discounted)	14.244	13.652	0.592
QALYs (discounted)	**9.547**	**8.97**	**0.577**
Treatment costs (discounted)	£38,145	£12,599	£25,546
Other costs (discounted)	£21,637	£24,316	-£2,679
Total costs (discounted)	**£59,782**	**£36,915**	**£22,867**
ICER : Cost per QALY	**£39,586**		

Sim02 General Population : 50% hypo effect	CSII	MDI	Difference
Life expectancy	21.831	20.536	1.295
Life expectancy (discounted)	14.237	13.652	0.585
QALYs (discounted)	**9.571**	**8.97**	**0.601**
Treatment costs (discounted)	£38,129	£12,599	£25,530
Other costs (discounted)	£21,463	£24,316	-£2,853
Total costs (discounted)	**£59,592**	**£36,915**	**£22,677**
ICER : Cost per QALY	**£37,712**		

Sim03 General Population : 75% hypo effect	CSII	MDI	Difference
Life expectancy	21.855	20.536	1.319
Life expectancy (discounted)	14.246	13.652	0.594
QALYs (discounted)	**9.591**	**8.97**	**0.621**
Treatment costs (discounted)	£38,150	£12,599	£25,551
Other costs (discounted)	£21,365	£24,316	-£2,951
Total costs (discounted)	**£59,515**	**£36,915**	**£22,600**
ICER : Cost per QALY	**£36,373**		

Base Case

Sim04 Base Case : 50 year horizon	CSII	MDI	Difference
Life expectancy	21.808	20.563	1.245
Life expectancy (discounted)	14.224	13.665	0.559
QALYs (discounted)	**9.504**	**8.892**	**0.612**
Treatment costs (discounted)	£38,097	£12,611	£25,486
Other costs (discounted)	£21,662	£24,761	-£3,099
Total costs (discounted)	**£59,759**	**£37,372**	**£22,387**
ICER : Cost per QALY	**£36,587**		

Sim05 Base Case : 30 year horizon	CSII	MDI	Difference
Life expectancy	20.579	19.6	0.979
Life expectancy (discounted)	13.86	13.367	0.493
QALYs (discounted)	**9.299**	**8.721**	**0.578**
Treatment costs (discounted)	£36,967	£12,293	£24,674
Other costs (discounted)	£19,107	£22,565	-£3,458
Total costs (discounted)	**£56,074**	**£34,858**	**£21,216**
ICER : Cost per QALY	**£36,710**		

Sim06 Base Case : 10 year horizon	CSII	MDI	Difference
Life expectancy	9.416	9.35	0.066
Life expectancy (discounted)	7.863	7.813	0.05
QALYs (discounted)	**5.603**	**5.392**	**0.211**
Treatment costs (discounted)	£20,637	£7,059	£13,578
Other costs (discounted)	£5,062	£6,412	-£1,350
Total costs (discounted)	**£25,699**	**£13,471**	**£12,228**
ICER : Cost per QALY	**£58,013**		

Lesser HbA1c effect

Sim07 0.6% HbA1c & 50% hypo effect	CSII	MDI	Difference
Life expectancy	21.399	20.563	0.836
Life expectancy (discounted)	14.044	13.665	0.379
QALYs (discounted)	**9.318**	**8.892**	**0.426**
Treatment costs (discounted)	£37,645	£12,611	£25,034
Other costs (discounted)	£22,673	£24,761	-£2,088
Total costs (discounted)	**£60,318**	**£37,372**	**£22,946**
ICER : Cost per QALY	**£53,788**		

Sim08 0.6% HbA1c & 75% hypo effect	CSII	MDI	Difference
Life expectancy	21.403	20.563	0.84
Life expectancy (discounted)	14.048	13.665	0.383
QALYs (discounted)	**9.366**	**8.892**	**0.474**
Treatment costs (discounted)	£37,656	£12,611	£25,045
Other costs (discounted)	£22,366	£24,761	-£2,395
Total costs (discounted)	**£60,022**	**£37,372**	**£22,650**
ICER : Cost per QALY	**£47,780**		

Effect upon Severe Hypoglycaemia events

Sim09 No hypo effect	CSII	MDI	Difference
Life expectancy	21.831	20.563	1.268
Life expectancy (discounted)	14.235	13.665	0.57
QALYs (discounted)	**9.445**	**8.892**	**0.553**
Treatment costs (discounted)	£38,122	£12,611	£25,511
Other costs (discounted)	£21,974	£24,761	-£2,787
Total costs (discounted)	**£60,096**	**£37,372**	**£22,724**
ICER : Cost per QALY	**£41,062**		

Sim10 75% hypo effect	CSII	MDI	Difference
Life expectancy	21.842	20.563	1.279
Life expectancy (discounted)	14.241	13.665	0.576
QALYs (discounted)	**9.556**	**8.892**	**0.664**
Treatment costs (discounted)	£38,137	£12,611	£25,526
Other costs (discounted)	£21,406	£24,761	-£3,355
Total costs (discounted)	**£59,543**	**£37,372**	**£22,171**
ICER : Cost per QALY	**£33,361**		

PRICE

Sim11 High price & 75% hypo effect	CSII	MDI	Difference
Life expectancy	21.842	20.563	1.279
Life expectancy (discounted)	14.241	13.665	0.576
QALYs (discounted)	**9.556**	**8.892**	**0.664**
Treatment costs (discounted)	£39,904	£11,378	£28,526
Other costs (discounted)	£21,406	£24,761	-£3,355
Total costs (discounted)	**£61,310**	**£36,139**	**£25,171**
ICER : Cost per QALY	**£37,874**		

Sim12 Low price & 50% hypo effect	CSII	MDI	Difference
Life expectancy	21.808	20.563	1.245
Life expectancy (discounted)	14.224	13.665	0.559
QALYs (discounted)	**9.504**	**8.892**	**0.612**
Treatment costs (discounted)	£35,302	£12,611	£22,691
Other costs (discounted)	£21,662	£24,761	-£3,099
Total costs (discounted)	**£56,964**	**£37,372**	**£19,592**
ICER : Cost per QALY	**£32,020**		

Sim13 Low price & 75% hypo effect	CSII	MDI	Difference
Life expectancy	21.842	20.563	1.279
Life expectancy (discounted)	14.241	13.665	0.576
QALYs (discounted)	**9.556**	**8.892**	**0.664**
Treatment costs (discounted)	£35,339	£12,611	£22,728
Other costs (discounted)	£21,406	£24,761	-£3,355
Total costs (discounted)	**£56,745**	**£37,372**	**£19,373**
ICER : Cost per QALY	**£29,151**		

Cost of blindness

Sim14 Higher Cost of Blindness 50% Hypo	CSII	MDI	Difference
Life expectancy	21.808	20.563	1.245
Life expectancy (discounted)	14.224	13.665	0.559
QALYs (discounted)	**9.504**	**8.892**	**0.612**
Treatment costs (discounted)	£38,097	£12,611	£25,486
Other costs (discounted)	£21,993	£25,189	-£3,196
Total costs (discounted)	**£60,090**	**£37,800**	**£22,290**
ICER : Cost per QALY	**£36,429**		

Sim15 Higher Cost of Blindness 75% Hypo	CSII	MDI	Difference
Life expectancy	21.842	20.563	1.279
Life expectancy (discounted)	14.241	13.665	0.576
QALYs (discounted)	**9.556**	**8.892**	**0.664**
Treatment costs (discounted)	£38,137	£12,611	£25,526
Other costs (discounted)	£21,735	£25,189	-£3,454
Total costs (discounted)	**£59,872**	**£37,800**	**£22,072**
ICER : Cost per QALY	**£33,213**		

High Glycemia Event Group

Sim16 High Glycaemia Event 50% less	CSII	MDI	Difference
Life expectancy	22.425	22.394	0.031
Life expectancy (discounted)	14.497	14.481	0.016
QALYs (discounted)	**9.702**	**9.61**	**0.092**
Treatment costs (discounted)	£38,778	£13,312	£25,466
Other costs (discounted)	£20,908	£21,270	-£362
Total costs (discounted)	**£59,686**	**£34,582**	**£25,104**
ICER : Cost per QALY	**£273,992**		

Sim17 High Glycaemia Event 75% less	CSII	MDI	Difference
Life expectancy	22.425	22.394	0.031
Life expectancy (discounted)	14.499	14.481	0.018
QALYs (discounted)	**9.772**	**9.61**	**0.162**
Treatment costs (discounted)	£38,783	£13,312	£25,471
Other costs (discounted)	£20,494	£21,270	-£776
Total costs (discounted)	**£59,277**	**£34,582**	**£24,695**
ICER : Cost per QALY	**£152,058**		

Sim18 Younger cohort	CSII	MDI	Difference
Life expectancy	25.146	23.498	1.648
Life expectancy (discounted)	15.528	14.854	0.674
QALYs (discounted)	**10.357**	**9.648**	**0.709**
Treatment costs (discounted)	£41,352	£13,631	£27,721
Other costs (discounted)	£23,558	£27,055	-£3,497
Total costs (discounted)	**£64,910**	**£40,686**	**£24,224**
ICER : Cost per QALY	**£34,136**		

Sim19 Greater effect upon HbA1c	CSII	MDI	Difference
Life expectancy	22.239	20.226	2.013
Life expectancy (discounted)	14.415	13.505	0.91

QALYs (discounted)	**9.633**	**8.747**	**0.886**
Treatment costs (discounted)	£38,574	£12,473	£26,101
Other costs (discounted)	£21,204	£25,416	-£4,212
Total costs (discounted)	**£59,778**	**£37,889**	**£21,889**
ICER : Cost per QALY	**£24,720**		

Appendix 11: Patient Perspectives Methodology

The aim of social research is to represent 'reality' as far as possible, with the understanding also, that representation is always from some point of view that emphasizes some aspects of reality over others. To choose a method is to choose a point of view and there can be "multiple, non-contradictory and valid descriptions and explanations of the same phenomenon" (Hammersley 1992:51). [258] This research is, therefore, an interpretive undertaking, where data are constructed jointly by the researcher and the researched in the social context within which the research is embedded. From this perspective, all interview data are jointly created in the social interaction between interviewer and interviewee (Seale 1999). Interview data are never a description of the facts of the topic at hand, but rather an account whose form and content are shaped by the context of the interview. For instance, in this study, a particular issue is that participants were advocates of pump use for young children and the researcher (AG) was wanting to hear their story.

Volunteer families were members of a patient led support group for insulin pumps - Insulin Pump Therapy (INPUT) 8. While we accept that this study, therefore, uses advocates of this treatment, our aim was to identify the reasons why they not only chose a pump for their children but how they secured and managed this form of therapy. Parents with young children (> 9 years age) on pumps were invited to be interviewed by a qualitative researcher. Semi-structured interviews were undertaken over the phone with the 10 parents from England, UK, using interview prompts. The demography of the children and details of logistics of care are given in section 5.2.2. Table 27.

Telephone interviews lasted between 1 hour and 1hour and 45 minutes, and were audio-taped, transcribed and anonymised. Initial topic guides were developed based on the literature and evolved throughout the study according to early analysis. Initial topic guides were developed based on the literature and, in accordance with the generative nature of qualitative research, evolved throughout the study according to early analysis. Validity was ensured by repeated reading of whole transcripts to keep the analysis comprehensive; by the use of a form of constant comparison using an active search for counter examples to emerging analysis, and by modification of the topic guide in response to early analysis. Reliability was ensured through regular meetings between the main analyst and one other researcher to discuss all analytical notes written, shared analysis of a sample of transcripts, and disagreements being resolved by discussion and re-analysis (Seale 1999, Silverman 1993). When no new themes emerged during analysis of interviews with parents it was considered that saturation had been achieved.

Our aim was to elucidate the deeper meanings that inform the participants' conversations and behaviour and thus, to allow for their subjective experiences to inform the analysis and explanation.[259,260] (Geertz 1973, Rosaldo 1993). While we are grateful to the generosity of the participants in the field, the following account rest on our interpretation of the data.

Appendix 12: Insulin Pump Patient Contract

The contract below is used by the Diabetes Clinic of Aberdeen Royal Infirmary.

……..

Although insulin pump therapy can be successful, this form of treatment is time-consuming and expensive. It is also important to make sure that people on pumps continue to benefit from their use in the long-term. The benefits seen with a pump are:

- Less risk of severe hypoglycaemia
- Return of early warning hypoglycaemia symptoms
- Improved glucose control – lower HbA_{1c} level
- Better quality of life

The reduction in HbA_{1c} level should be at least 0.5% less than your current average level.

In order to benefit from the pump, it is extremely important that you are confident in:

- Using the technical features of the pump including temporary basal rates
- Altering the amount of insulin given depending on the carbohydrate content of meals, exercise etc
- Appropriate blood glucose monitoring

We are extremely happy to provide the education necessary to make the most of insulin pump therapy and would like to formally invite you to participate. We anticipate that you will see the benefits after 3 months and these will be sustained at least for a further 6 and 12 months. We hope to measure the benefit by checking your HbA_{1c} levels at these times. We will also check your awareness of hypoglycaemia and use a questionnaire to assess quality of life.

If, however, the pump does not prove to be successful, it would make sense to look at alternatives including the use of multiple daily insulin injections with modern insulin.

I, the undersigned, recognise that it is important that there should be demonstrable improvement in my diabetes control by continuing to use insulin pump therapy. One way of demonstrating this would be to examine my HbA_{1c} levels in 3, 6 and 12 months time to make sure that they are either $\leq$8.5% or have fallen at least 0.5% below the current level. Alternative measurements of the success of insulin pump therapy may include a return of hypoglycaemia warning symptoms, less frequent severe hypoglycaemic episodes or a better quality of life.

I understand that continued funding for the pump (including consumables) is dependent on my active participation in on-going education provided by Aberdeen Diabetes Centre and by demonstrating measurable improvements in my diabetes control. I also undertake to monitor my blood sugars at least 4 times a day and have been informed of the dangers of omitting to do this (risk of DKA).

Signed:

Patient Dated:

Name of Patient:
Signed:

NHS Signatory Dated:
Name of NHS Signatory: