Health Technology Assessment 2004; Vol. 8: No. 43

Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes

JL Colquitt, C Green, MK Sidhu, D Hartwell and N Waugh

October 2004

Health Technology Assessment
NHS R&D HTA Programme

How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes

JL Colquitt,* C Green, MK Sidhu, D Hartwell and N Waugh

Southampton Health Technology Assessments Centre, Southampton, UK

* Corresponding author

Declared competing interests of authors: none

Published October 2004

This report should be referenced as follows:

Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N. Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes. *Health Technol Assess* 2004;**8**(43).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE.

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, consumer groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a limited time period.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 01/53/01. The authors have been wholly responsible for all data collection, analysis and interpretation and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

T

Abstract

Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes

JL Colquitt,* C Green, MK Sidhu, D Hartwell and N Waugh

Southampton Health Technology Assessments Centre, Southampton, UK

* Corresponding author

Objectives: To assess the clinical and cost-effectiveness of continuous subcutaneous insulin infusion (CSII) compared with multiple daily injections (MDI) in the delivery of intensive insulin therapy for the treatment of diabetes mellitus.

Data sources: Electronic databases, references of retrieved articles and manufacturer submissions. Experts in the field were consulted.

Review methods: For the systematic review of clinical and cost-effectiveness, studies were assessed for inclusion according to predefined criteria by two reviewers. Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer. Data on clinical effectiveness were synthesised through a narrative review with full tabulation of all eligible studies, with meta-analysis performed where appropriate.

Results: Twenty studies comparing CSII with MDI were identified. Quality was generally poor. In adults with Type 1 diabetes, glycated haemoglobin improved by 0.61% (95% CI –1.29 to 0.07) in longer term studies, although this improvement was smaller when a study using bovine ultralente was excluded. A reduction in insulin dose with CSII of about 12 units per day (–11.90, 95% CI –18.16 to 5.63) was found in short-term studies, with smaller differences in longer term studies. Body weight and cholesterol levels were similar between treatments. Hypoglycaemic events did not differ significantly between CSII and MDI in most trials, but some found fewer events with CSII and one found more hypoglycaemia and hypoglycaemic coma with CSII. There was no consistency between the studies in patient preference, but progress has been made both with insulin pumps and injector pens since the publication of many of the older studies. No difference in glycated haemoglobin between CSII and MDI was found in pregnancy; one study found less insulin was required by patients with CSII, but two other studies found no significant difference. One study of adolescents found lower glycated haemoglobin and insulin dose with CSII whereas a second study found no significant difference. In CSII analogue insulin was associated with lower glycated haemoglobin levels than soluble insulin. No economic evaluations comparing CSII with MDI were identified. The estimated additional cost of CSII compared to MDI varies from £1091 per annum to £1680 per annum, according to the make of the insulin pump and the estimated life of the device. These estimates include the costs for the insulin pump, the consumables associated with delivery of CSII, and an allowance for the initial education required when patients switch from MDI to CSII. The largest component of the annual cost for CSII is the cost of consumable items (e.g. infusion sets).

Conclusions: When compared with optimised MDI, CSII results in a modest but worthwhile improvement in glycated haemoglobin in adults with Type 1 diabetes. It has not been possible to establish the longer term benefits of such a difference in glycated haemoglobin, although there is an expectation that it would be reflected in a reduction in long-term complications. More immediate primary benefits from CSII may be associated with an impact on the incidence of hypoglycaemic events and the dawn phenomenon, and greater flexibility of lifestyle. However, there is limited evidence on this, and information presented to offer context on quality-of-life is based on testimonies from those patients who have had a positive experience of CSII. The estimated cost to the NHS per year for CSII would be around £3.5 million in England and Wales if 1% of people with Type 1 diabetes used CSII, £10.5 million for 3%, and £17.5 million for 5%. Further research should focus on wider benefits of CSII, such as flexibility of lifestyle and quality of life, and on the psychological impact of wearing a device for 24 hours every day. Research into the use of CSII in children of different ages is also needed.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Types of diabetes The classifications of diabetes have changed in recent years, with the old terminology of insulin-dependent and non-insulin dependent being replaced by Type 1 and Type 2. This was because many patients with non-insulin-dependent diabetes are now treated with insulin. The new classification is based on the aetiology and pathology of diabetes, rather than on treatment.

Type 1 diabetes Type 1 diabetes indicates that there has been a process of destruction of the beta cells of the pancreas, leading to insulin deficiency. Eventually, insulin is required for survival in order to prevent the development of ketoacidosis and death. There is usually a process of autoimmunity with autoantibodies, but these are not seen in all patients. The cause is unknown.

Type 2 diabetes Type 2 diabetes is more common, and is characterised by insulin resistance and insulin deficiency. The deficiency may be relative to insulin needs, rather than absolute, and there may be higher than normal production of insulin at some stages. Type 2 diabetes is linked to overweight and obesity and to physical inactivity.

List of abbreviations

BDR	background diabetic retinopathy
BMI	body mass index
CI	confidence interval
CRD	Centre for Reviews and Dissemination
CSII	continuous subcutaneous insulin infusion, delivered with the aid of an insulin pump
CT	conventional therapy. In Type 1 diabetes, conventional therapy in the UK usually means that patients take twice daily injections of mixtures of short-acting and intermediate or long-acting insulin.
DC	day case
DCCT	Diabetes Control and Complications Trial
DKA	diabetic ketoacidosis, a life-threatening metabolic disturbance related to shortage of insulin. It is often brought on by other illnesses such as infections, which increase the body's insulin needs
DQOL	diabetes quality of life
DSN	diabetes specialist nurse
DTSQ	Diabetes Treatment Satisfaction Questionnaire
ELIP	elective inpatient cost
FBR	fixed basal rate
FCE	finished clinical episode, i.e. a hospital admission to one unit
HbA_{1c}	glycated haemoglobin A_{1c}
HFS	Hypoglycaemia Fear Survey

continued

List of abbreviations *continued*

HOR	higher overnight rate
HRG	health-related resource group
hypo	hypoglycaemic event
IDDM	insulin-dependent diabetes mellitus
INPUT	voluntary organisation promoting Insulin Pump Therapy
ITT	intention-to-treat
MDI	multiple daily injections
NELIP	non-elective inpatient cost
NICE	National Institute for Clinical Excellence
p = ns	not statistically significant
OR	odds ratio
PDR	proliferative diabetic retinopathy
PUMP	Pump Management for Professionals
QALY	quality-adjusted life-year
QoL	quality of life
QWB	quality of well-being scale
RCT	randomised controlled trial
SCL-90R	Symptom Checklist-90R
SD	standard deviation
SF-36	Short Form with 36 Items
SG	standard gamble
TTO	time trade-off
UKPDS	United Kingdom Prospective Diabetes Study
VAS	visual analogue scale
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
WMD	weighted mean difference

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

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 owing to the marked increase in the incidence of Type 1 diabetes and also 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 resemble more closely 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, PsycINFO, 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 for 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 three 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.

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 the Centre for Reviews and Dissemination (CRD) Report 4 quality assessment scale.

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 with 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, were 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, on 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% confidence interval (CI) –1.28 to 0.01] and longer term (–0.61, 95% CI –1.29 to 0.07) studies. This improvement was smaller if a study which used bovine ultralente in the control arm was excluded; the reduction in glycated haemoglobin A_{1c} (HbA_{1c}) is then only 0.5%. Short-term studies show a reduction in insulin dose of about 12 units (–11.90, 95% CI –18.16 to –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, whereas 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 CSII
The combination of overnight CSII and daytime MDI may help in children, by reducing nocturnal hypoglycaemic episodes 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 versus 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 additional cost of CSII compared with MDI varies according to the make of pump and the estimated life of the device, from £1091 per annum using the cheapest pump and assuming an 8-year life of the pump to £1680 per annum with the most expensive model and assuming a life of only 4 years. These estimates include costs for consumables and the initial education required when patients switch from MDI to CSII. The largest component of cost is the consumable items, such as infusion sets (tubing, etc.), with the capital cost of the pump secondary. Initial education for those switching to CSII is very important, and we estimated an additional cost per patient switching from MDI to CSII to be in the region of £150.

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 hypoglycaemic events, 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 quality-adjusted life-year.

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 them. However, the utility effect of the reduction in fear of hypoglycaemic episodes 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 pumps. 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 with 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. Pumps 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 that 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 Type 1 diabetes 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.

There appears to be no wholly satisfactory economic model for diabetes, which would allow improvements in diabetes control to be converted into a cost per quality-adjusted life-year. Research is also needed into the use of CSII in children of different ages.

Chapter 1

Aim of the review

The main aim of this review is to assess the clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion (CSII) using insulin pumps, compared to intensive treatment with multiple daily injections (MDI). The benefits could be improved control of blood glucose levels as reflected in glycated haemoglobin A_{1c} (HbA_{1c}), or a similar level of control but with other advantages such as fewer problems with hypoglycaemic episodes (hypos), or greater flexibility of lifestyle and hence better quality of life (QoL).

Both CSII and MDI are forms of intensive insulin treatment. The benefit of intensive treatment, for those whose diabetes is inadequately controlled on conventional insulin therapy, is not in doubt following trials such as The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS). Conventional insulin therapy (CT) is assumed to be twice daily injections usually of a mixture of short-acting and long-acting insulins. This report assumes that Type 1 patients would normally try twice-daily mixtures, and would then be treated with MDI before trying CSII, that is, patients would not go directly from conventional to CSII. However, increasingly, patients may start on MDI from diagnosis. Type 2 patients would usually start with a once-daily injection of a long-acting insulin (ultralente or a long-acting analogue such as glargine) or twice-daily NPH, and if not well-controlled would progress next to CT, before going on, if necessary, to MDI and then CSII. This report therefore excludes the use of CSII in newly diagnosed patients.

Intensive treatment with MDI is taken to mean treatment with a combination of short-acting insulins (soluble or analogue) to cover meals, with long-acting insulin (intermediate, ultralente or very long-acting analogues such as glargine) to provide basal insulin. In practice, MDI will mean a minimum of three injections a day, but may involve more than that. It will also involve blood glucose testing. There will be varying levels of intensity within MDI, and so the comparator for CSII is *optimised* MDI.

It should be noted that treatment of Type 1 diabetes involves more than just injection of insulin:

"Modern insulin therapy is a package of insulin administration according to basal and bolus principles, frequent blood glucose self monitoring, insulin adjustment according to blood glucose results and meal size, exercise, plus intake of a healthy diet, and full diabetes education."
(Pickup J, Guy's, King's and St Thomas' School of Medicine, London: personal communication, 2002)

Subsidiary questions

A number of subsidiary questions are also addressed. Where eligible RCTs and crossover studies are lacking, evidence from selected observational studies will be sought.

1. Does CSII have advantages over MDI in women with Type 1 diabetes pre-conceptually and during pregnancy?
2. What is the role of CSII in adolescents and children?
3. What is the role of overnight-only CSII (injections taken as usual during the day)?
4. What is the value of short periods of CSII in patients with Type 2 diabetes who are very resistant to oral drugs such as the sulphonylureas?
5. In CSII, do analogue insulins have advantages over older short-acting (soluble) insulins?
6. How many patients continue to use CSII (discontinuation rates)?

Implantable pumps are not covered by the review.

Insulin pumps are used for insulin therapy in some patients in hospital, for example those having surgery. Such very short-term use is not relevant to this review.

Chapter 2
Background

Introduction

The number of people with insulin-treated diabetes has increased over recent decades for two reasons. Firstly, there has been a marked increase in the incidence of Type 1 diabetes mellitus [formerly called insulin-dependent diabetes mellitus (IDDM)].[1–7] In some parts of the UK, the incidence of Type 1 diabetes has trebled over the last 30 years.[1,5] Rates in the UK are high in international terms,[8] although more so in Scotland. Second, more people with Type 2 diabetes (formerly non-insulin-dependent diabetes mellitus) are being treated with insulin in order to achieve better control of blood glucose levels. This trend started before, but was probably accelerated by the results of, the UKPDS.[9] There has also been an increase in the prevalence of Type 2 diabetes,[10,11] particularly among those from ethnic communities.[12] A recent study by the Office for National Statistics shows a rise in prevalence from 1994 to 1998.[13]

The need for insulin arises for different reasons in the two main types of diabetes. Insulin is produced by the islet cells of the pancreas. In Type 1 diabetes, there is a true insulin deficiency because the islet cells are destroyed as the result of an autoimmune process, for cause or causes unknown. In Type 2 diabetes, it is more common to have a normal or increased insulin production initially, with insulin resistance being a feature. However, over the years the pancreas may fail, leading to insulin deficiency. Insulin production rates will have fallen in patients to about 50% by the time of diabetes diagnosis in the UK, as was shown in one of the UKPDS papers.[14] It is probable that this progressive worsening would be much less, or might not occur, if patients adhered to lifestyle measures such as weight loss and exercise.

There are some patients who do not fit neatly into the two groups, because at diagnosis they appear to have Type 2 diabetes, but then progress to insulin treatment over the course of a few years; they may have slow onset Type 1 diabetes.[15,16]

The approximate prevalences of insulin-treated diabetes in different age groups are shown in *Table 1*.

Control of high blood glucose levels

If insulin levels are too low, blood glucose levels are too high and there are other accompanying metabolic abnormalities. In the long run, poor control of blood glucose increases the risk of complications such as eye disease (diabetic retinopathy), which can potentially lead to loss of vision. Diabetic retinopathy is the single most common cause of blindness in people in the working years of life in the UK and other industrial countries, and kidney disease (diabetic nephropathy) is now the leading cause of renal failure, leading to the need for dialysis and transplantation. Amputation rates are high in diabetes owing to the combination of peripheral vascular disease and neuropathy, and the care of those with severe peripheral vascular disease leading to amputation is one of the most expensive complications of diabetes.[15] In the short term, poor diabetic control in Type 1 diabetes can result in the metabolic derangement known as diabetic ketoacidosis, which is a serious and occasionally fatal condition, often referred to as 'diabetic coma', because it can lead to reduced consciousness and coma. Heart disease is more common amongst people with diabetes, but is less clearly linked with blood glucose control.

Both randomised trials and large cohort studies have shown that good control of blood glucose levels by treatment is associated with reduced risk of complications such as retinopathy and renal disease (older studies are in the meta-analysis by Wang and colleagues,[18] DCCT[19] and Reichard and colleagues[20]). For example, in the DCCT study, there was a marked drop in the prevalence of serious eye disease at 9 years, from 32% in the conventional treatment group to 9% in the intensive group.[21] In this study, the intensive group maintained an average HbA_{1c} level of 7.2%, about 2% below those treated conventionally (but note that the conventional group was better controlled than the US average). There has therefore been great emphasis on better ('tighter') control of blood glucose.

A meta-analysis by Egger and colleagues[22] examined the risk of ketoacidosis during intensified treatment compared with conventional treatment. For trials where patients could choose between

TABLE 1 *Prevalence of insulin treated diabetes per 1000 patients, by age, sex and year: 1994–98 in England and Wales*

	0–4	5–15	16–24	25–34	35–44	45–54	55–64	65–74	75–84	85+	Crude rate (all ages)	Age-standardised rate (all ages)
Males 1994												
Rate/1000	0.2	1.1	3.1	4.7	5.4	5.6	7.8	9.2	8.3	4.4	4.8	4.6
LCL	0.1	0.9	2.7	4.3	4.9	5	7	8.3	7.1	2.7	4.6	4.4
UCL	0.5	1.4	3.6	5.2	5.9	6.1	8.6	10.1	9.6	6.7	4.9	4.8
No. of cases	*7*	*86*	*171*	*388*	*393*	*375*	*390*	*372*	*163*	*20*	*2365*	*2365*
Males 1995												
Rate/1000	0.2	1.4	3	4.5	5.5	5.8	8.3	9.7	9.4	5.9	5	4.8
LCL	0.1	1.2	2.6	4.1	5	5.3	7.5	8.7	8.1	4	4.8	4.6
UCL	0.5	1.7	3.5	5	6	6.4	9	10.6	10.7	8.5	5.2	4.9
No. of cases	*7*	*112*	*169*	*380*	*421*	*420*	*437*	*406*	*200*	*29*	*2581*	*2581*
Males 1996												
Rate/1000	0.2	1.5	3.2	4.6	5.7	6.2	8.9	10	9.9	5.8	5.2	5
LCL	0.1	1.2	2.7	4.2	5.2	5.7	8.1	9.1	8.6	3.9	5	4.8
UCL	0.4	1.8	3.7	5.1	6.2	6.8	9.7	11	11.2	8.2	5.4	5.2
No. of cases	*7*	*125*	*184*	*401*	*463*	*481*	*495*	*439*	*227*	*30*	*2852*	*2852*
Males 1997												
Rate/1000	0.3	1.6	3.3	4.7	5.8	6.9	9.5	11.4	10.2	6.9	5.6	5.3
LCL	0.1	1.3	2.8	4.3	5.3	6.3	8.7	10.4	8.9	4.9	5.4	5.1
UCL	0.6	1.9	3.7	5.2	6.3	7.4	10.2	12.3	11.4	9.4	5.8	5.5
No. of cases	*10*	*139*	*196*	*418*	*495*	*554*	*556*	*515*	*246*	*38*	*3167*	*3167*
Males 1998												
Rate/1000	0.2	1.7	3.5	4.6	6.2	7.2	10	13.3	10.9	6.8	6	5.7
LCL	0	1.4	3	4.1	5.7	6.6	9.3	12.3	9.7	4.9	5.8	5.5
UCL	0.4	1.9	3.9	5	6.7	7.7	10.8	14.3	12.2	9.2	6.2	5.8
No. of cases	*5*	*151*	*219*	*413*	*565*	*609*	*634*	*627*	*282*	*41*	*3546*	*3546*
Females 1994												
Rate/1000	0.1	1.7	3.2	3.4	4.4	4.5	7.7	8.3	8	4.7	4.4	4.1
LCL	0	1.4	2.7	3	3.9	3.9	7	7.5	7	3.6	4.2	3.9
UCL	0.3	2	3.6	3.8	4.9	5	8.5	9.1	9	6.1	4.6	4.3
No. of cases	*3*	*117*	*160*	*270*	*309*	*289*	*383*	*396*	*253*	*59*	*2239*	*2239*
Females 1995												
Rate/1000	0.4	1.6	3.5	3.7	4.6	4.6	7.9	9.2	8.4	4.9	4.7	4.3
LCL	0.2	1.3	3	3.3	4.1	4.1	7.2	8.3	7.5	3.8	4.5	4.1
UCL	0.6	1.9	4	4.1	5	5.1	8.7	10	9.4	6.2	4.9	4.5
No. of cases	*11*	*120*	*178*	*305*	*340*	*323*	*415*	*450*	*289*	*65*	*2496*	*2496*
Females 1996												
Rate/1000	0.3	1.7	3.3	3.8	4.8	5.1	8	9.5	8.8	4.5	4.8	4.5
LCL	0.1	1.4	2.8	3.4	4.3	4.6	7.2	8.6	7.8	3.5	4.7	4.3
UCL	0.6	2	3.8	4.2	5.3	5.6	8.7	10.3	9.8	5.8	5	4.6
No. of cases	*9*	*133*	*174*	*323*	*376*	*381*	*436*	*476*	*320*	*64*	*2692*	*2692*
Females 1997												
Rate/1000	0.4	1.8	3.4	3.9	5	5.3	8.8	10.8	9.5	5.2	5.2	4.8
LCL	0.2	1.5	2.9	3.5	4.5	4.8	8	9.9	8.5	4.1	5	4.6
UCL	0.6	2.1	3.9	4.3	5.5	5.8	9.6	11.7	10.5	6.6	5.4	4.9
No. of cases	*11*	*147*	*189*	*340*	*410*	*412*	*508*	*558*	*362*	*78*	*3015*	*3015*
Females 1998												
Rate/1000	0.3	1.9	3.2	4.3	5.2	5.7	9.4	12.1	9.4	5.9	5.5	5.1
LCL	0.1	1.6	2.8	3.8	4.7	5.2	8.6	11.1	8.4	4.7	5.3	4.9
UCL	0.5	2.2	3.7	4.7	5.6	6.2	10.1	13	10.3	7.2	5.7	5.2
No. of cases	*8*	*165*	*193*	*380*	*452*	*473*	*582*	*644*	*372*	*93*	*3362*	*3362*

LCL, lower confidence limit; UCL, upper confidence limit.
Source: Office for National Statistics.[17]

multiple injections or pump treatment, there was some evidence of an increased risk of ketoacidosis with intensified treatment, although this did not reach statistical significance [odds ratio (OR) 1.28, 95% confidence interval (CI) 0.90 to 1.83, $p = 0.17$]. For trials that randomised patients to pumps, there was a substantial increase in the risk of ketoacidosis (OR 7.20, 95% CI 2.95 to 17.58, $p < 0.0001$). However, in the latter meta-analysis the most recent study was conducted in 1992, therefore these results may no longer apply to newer pumps.

Hypoglycaemia

However, insulin treatment may lead to blood glucose levels falling below normal, potentially robbing the brain of its essential glucose supply. This is called hypoglycaemia. Hypoglycaemic episodes are usually known as 'hypos'. The consequences vary depending on how low the blood glucose level falls. Mild hypoglycaemic events may cause only a feeling of hunger and sweating, and can be rapidly corrected by food or sugary drinks. However, they may reduce the amount and quality of sleep when they occur during the night (nocturnal hypoglycaemic events). More serious or sustained falls in glucose level may mean that the diabetic person needs help in order to recover, and severe hypoglycaemic events can lead to behavioural disturbances, unconsciousness, convulsions or death. In young children with frequent or severe hypoglycaemic events, there may be some impairment of intellectual function.[23]

People with Type 1 diabetes, especially younger ones, may be more afraid of hypoglycaemic events than of long-term complications. As one of our expert advisers commented;

"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 very profound effect so that the patient will do everything they can to avoid a recurrence. Many patients have a greater fear of hypos than they have 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." (Tieszen K, Hope Hospital, Salford: personal communication)

Egger and colleagues[22] reported that the incidence of severe hypoglycaemia ranged from 0 to 33 per 100 person-years amongst conventionally treated patients and from 0 to 66 in intensively treated patients, in a meta-analysis of 14 randomised controlled trials (RCTs) comparing conventional with intensive insulin regimens. The risk of severe hypoglycaemia was three times as high in the intensive arms of the trials. However, because of the relative sizes of the trials, the result was dominated by the DCCT study,[24] which provided 459 of the 531 hypoglycaemic events in the intensive group and 255 of the 315 in the conventional group, in the meta-analysis. Taking out DCCT would leave only 72 and 60 hypoglycaemic events in the intensive and conventional groups, respectively. The risk of severe hypoglycaemia in the intensively treated group fell after the first 2 years of the DCCT feasibility study, suggesting a learning experience in the trialists, but there was no reduction over time in the annual rate of hypoglycaemic events in patients recruited to the main study, suggesting that hypoglycaemia will always be a risk in intensive therapy. Over an average follow-up of 6.5 years, 65% of patients in the intensive and 35% of those in the conventional group had at least one severe hypoglycaemic event.

In a representative group of people with IDDM, Muhlhauser and colleagues[25] found that 10% of conventionally treated patients and 9% of CSII treated patients had at least one severe hypoglycaemic event per year. The intensively treated group successfully improved their control of blood glucose as reflected in HbA_1 without an increased risk of severe hypoglycaemia. There is good evidence that although all patients with Type 1 diabetes are at some risk, the risk of severe hypoglycaemia tends to be concentrated in a relatively small subset of individuals. Rewers and colleagues[26] found that 79% of severe hypoglycaemic events occurred in the 14% of children who had recurrent hypoglycaemic events. Thus, the strongest risk indicator for severe hypoglycaemia is a history of an episode in the past and this led the DCCT to modify their recruitment protocol after the first year to exclude such patients. Loss of the warning symptoms of a hypoglycaemic events (see below) and deliberate or uniformed misuse of insulin also contribute to risk.

Insulin treatment

Insulin is ineffective if given by mouth, because it would be digested. Therefore, at present, it has to be given by injection. Inhaled forms are being

TABLE 2 *Insulin preparations*

Duration of action	Type	Time to onset
Rapid-acting	Analogues	15 minutes
Short-acting	Soluble human	15–60 minutes
Intermediate	NPH and human and porcine ultralentes	2–4 hours
Long	Long-acting analogues	

developed but bioactivity is low (10–20%) and variable, and there have been problems with accurate delivery.

There are many forms of insulin on the market, but they fall into a number of groupings by duration of action (*Table 2*).

There are several problems with current treatment. First, the body needs a little insulin all the time ('basal insulin', which accounts for about half of the total insulin production) with brief peaks of increased levels for an hour or two after meals. The basal insulin need is around 0.5–1.0 units/hour in adults. After meals blood levels normally increase 5–10-fold in the first 30 minutes, dropping back to basal after about 2 hours.[27] It is difficult to achieve this normal profile of insulin release with injected insulin. The rapid-acting analogues are closest. Soluble insulin injections start to act about 30 minutes after injection, rise to a peak of action over the next hour and fall 4–6 hours later, although they can cause hypoglycaemia up to 8 hours after injection, particularly in the early part of the night. The newer analogue insulins such as lispro and aspart start much more promptly but are shorter lived in effect and still do not replicate the normal non-diabetic state. If larger doses of short-acting insulins are given to control hyperglycaemia, which occurs 1–2 hours after meals, hypoglycaemic events may result at 2–4 hours or even up to 8 hours later, particularly during the night.

Figure 1 illustrates some of the problems. In each, the dotted lines show the insulin requirements after meals, when in non-diabetic people there is a steep but short-lived rise in insulin production. The dark solid lines show the timing of action of soluble insulin and the light solid lines that of long-acting insulin. The diagrams show that soluble insulin has a longer but lower peak of action; it does not mimic normal pancreatic function at all well, being

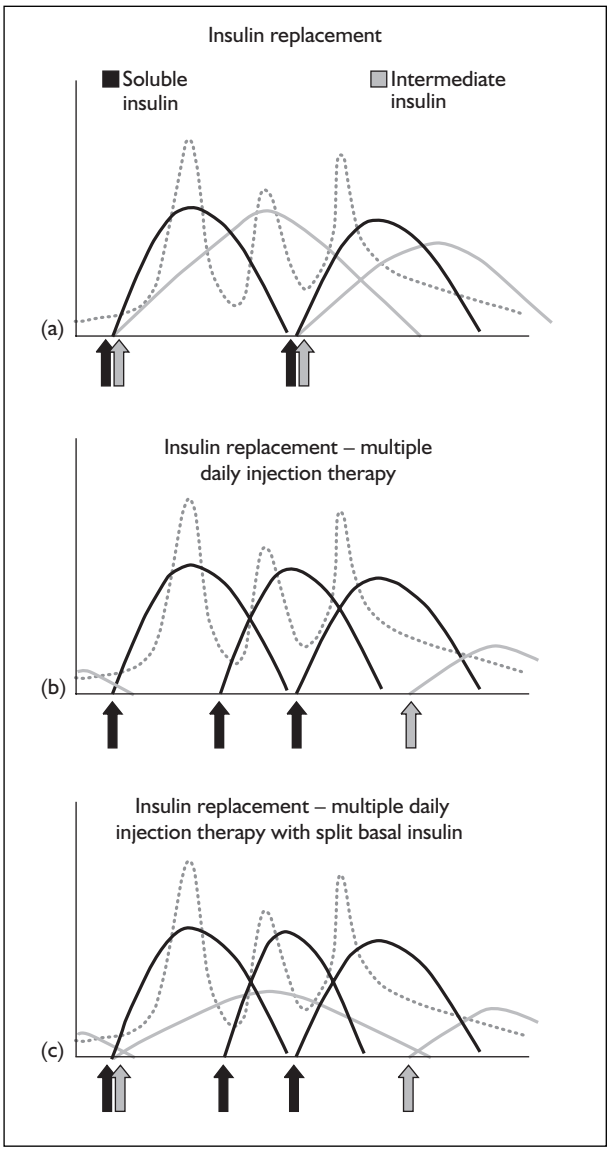

FIGURE 1 *Insulin profiles*

insufficient in the hour or so after the meal, but then liable to have too much effect 3–4 hours after the meal. Giving two injections a day of a mixture of short-acting and longer acting insulin fails to control peaks of blood glucose (not shown, but represented by the dotted lines of insulin needs) but will provide too much insulin for much of the day (*Figure 1a*). Moving to MDI (several injections of short-acting insulin during the day with one long-acting at night) still does not provide satisfactory cover (*Figure 1b*), nor does a yet more complicated regimen of three injections of short-acting and two of long-acting (*Figure 1c*). However, the MDI regimens do approximate more closely to insulin needs. Using more rapid acting analogue insulins (not shown, but shorter peaks than soluble) is an improvement but still does not replicate normal pancreatic insulin production.

Second, absorption rates from the injection sites vary from day to day. Absorption is affected by injection site and depth, adiposity, exercise, temperature, skin blood flow and insulin preparation.[28] Absorption varies in the same individual by about 25%.[28] This can lead to unpredictable hypoglycaemic episodes, usually associated with longer acting insulins.

Third, there is a problem with overnight control, when a low basal level is needed, but with a rise in the morning to counteract the rise in blood glucose which then occurs (before wakening). Isophane and lente insulins cannot maintain normal blood glucose levels overnight without increasing the risk of hypoglycaemic events. Nocturnal hypoglycaemic events may not be severe, but can be troublesome and disruptive of sleep. If the dose is reduced to avoid hypoglycaemia, it is likely that glucose levels will be high by morning. The rise in blood glucose levels towards the end of the night and the loss of control which then occurs with long-acting insulin injections given the night before are sometimes referred to as the 'dawn phenomenon'.

Fourth, patients may not comply with advice, and it is known that some patients do not take all their prescribed insulin.[29] This may be partly because of the limitations placed on lifestyle by the diet and insulin regimens still used in most places. The limitations are imposed by the need to have meals at regular intervals. There may be other options such as the intensive educational programme Dose Adjustment for Normal Eating (DAFNE), which will be covered by another National Institute for Clinical Excellence (NICE) review.

The net effect of the limitations in conventional insulin therapy is that diabetes is not well controlled in the majority of patients. In a recent audit, only a minority of young people with diabetes achieved good control.[30]

A recent review[31] concluded that:

"A substantial advance in diabetes care would allow individuals to have euglycaemia (normal blood glucose) without risk of severe hypoglycaemia, and with much less effort than is currently devoted to intensive therapy."

Continuous subcutaneous insulin infusion

The first studies of CSII delivered via insulin pumps came from Guy's Hospital, London, in 1978[32] and Yale in 1979.[33] 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 (crystalline or rapidly absorbed analogues) insulin is used.

There have been several reviews of CSII. Thorp,[34] writing after a relatively short period of CSII experience in 1986, noted that: "Efforts to improve insulin administration have resulted in the development of a myriad of electromechanical pump devices." He noted that technical problems were common. He also commented that 30% of patients in one of the studies discontinued use of the pump, and that: "All of those discontinuing use of the pump identified the physician as the key person involved in the decision to try this form of treatment, rather than themselves."

Davies and Baum in 1988[35] considered the evidence on CSII use in children, and noted a lack of enthusiasm amongst British paediatricians, but commented that the recent advent of injection devices such as pens might be part of the answer, since those were being seen as an alternative way of administering intensive insulin regimens.

Over the past decade, much effort has gone into improvement of both pump and insulin technology and there have been several recent reviews. Lenhard and Reeves[36] carried out a review, using MEDLINE only. 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, reduced to three in number from the 'myriad' described by Thorp, were smaller, more reliable and easier to use. They estimated that about 8% of all adults in North America with Type 1 diabetes 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.

The annual position statement from the American Diabetes Association for 2002[37] was cautious, and said that: "an insulin pump may provide greater lifestyle flexibility, particularly with regard to meal schedules and travel but may be too demanding for some individuals." The statement did not make any recommendation on the relative merits

of CSII and MDI, but said that: "pump therapy is as safe as multiple-injection therapy when recommended procedures are followed."

Pickup and Keen,[38] who were the originators of CSII, reviewed the history of and evidence base for CSII.[39] They note the considerable world-wide use of pumps (over 200,000 patients) and the disproportionately low UK use. They conclude 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 propose a set of clinical guidelines for identifying which patients should be considered for CSII, and conclude that the proportion of patients who would be suitable is relatively small. They observe that individual patient choice and preference is not possible unless the CSII option is available for a comparative trial, a condition rarely met in the UK. In a complementary study, Pickup and colleagues[40] 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 events; none appeared to report effect on QoL. The CSII group needed 14% less insulin.

Three health technology assessment reports have examined CSII. The Catalan Agency for Health Technology Assessment and Research (CAHTA)[41] concluded that CSII was no more effective than MDI, but appears to have based this only on the DCCT study. However, in the DCCT study patients were not randomised to pumps or MDI; it was left to individual centres to decide, and it would be unsafe to draw any comparison of the relative merits of CSII and MDI.

The report from the Spanish Health Technology Assessment Agency [Agencia de Evaluacion de Tecnologies Sanitarias (AETS)] came to similar conclusions.[42] The US Agency for Health Care Policy and Research (AHCPR, 1990)[43] report is superseded by new evidence.

It is always interesting to know what treatments clinicians with diabetes choose for themselves. A survey[44] by the American Association of Diabetes Educators (AADE) and the American Diabetes Association (ADA) asked members if they had diabetes and, if so, how they were treated. About 6.4% of members had diabetes, of whom 72% had Type 1. The survey found that 96% of those with Type 1 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 and, anecdotally, a number of diabetic specialist physicians are known to have been on CSII for about 20 years.

Modern pumps

Modern pumps are small and lightweight compared with the early ones (*Figures 2* and *3*). 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,[38] and may have alarms for empty cartridges, low batteries,

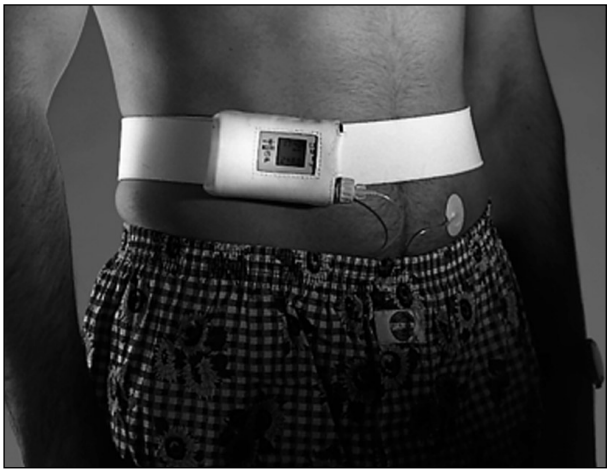

FIGURE 2 *Disetronic H-TRON*

FIGURE 3 *Medtronic MiniMed 508*

occlusion of tubing and faulty electronics, giving rise to less fear of undetected malfunction, which was a problem with some of the older pumps. There were isolated reports of pumps delivering too much insulin (pump 'run-away', reported with the Graseby MS36[45]) or being susceptible to electrical forces.[46] Mobile phones were thought to be capable of upsetting pump function and this appeared to be true with at least one older pump (the Microjet Quark) and one older phone, but only when the phone was transmitting at maximum power (8 W) and placed in direct contact with the pump.[47] No such problem was reported with the MiniMed pump regardless of model of phone and direct contact. Modern phones have much lower maximum power, of 1–2 W,[47] and modern pumps have mechanisms to protect against over-delivery.[48]

Why are pumps little used in the UK?

Despite the invention of the technique in the UK, pumps are used much less there than in other countries such as the USA, Germany, France and Italy (*Table 3*, *Figure 4*). The reasons for this probably include conservatism and cost concerns, but there have also been concerns about early reports of episodes of diabetic ketoacidosis (DKA) on CSII. A series of papers in the mid-1980s reported adverse events. Mecklenburg and colleagues in 1984[49] found that diabetic control improved considerably on pump therapy but that 42% of 161 patients experienced one or more adverse events, the most serious being ketoacidosis (38 episodes in 26 patients; once in every 78 patient months on CSII), which was commoner after CSII than before, and commoner than in a comparison group on conventional insulin injections. The comparison group was not obtained by randomisation but some measures were taken to make it reasonably well matched, except for pregnancies, with the pump group. Patients suffering DKA fell into three groups. The largest number had no DKA in the 5–25 months before starting pump therapy. The two other groups consisted of those who had DKA both before and after (pumps made little difference) and those who had DKA before but not after. Most

TABLE 3 *Estimated pump use*

Country	Numbers	Funding
USA	140,000	Fully funded by Medicare and private insurance
Germany	33,000	Fully reimbursed by insurance after 3-month trial
France	9,500	Fully funded
Italy	5,700	Limited funding in 8 of 25 regions
The Netherlands	4,700	Fully reimbursed by insurance after 1-month trial
Sweden	4,200	Fully funded
Israel	1,900	Fully funded
Japan	1,500	No reliable information
Czech Republic	1,350	Fully funded
Switzerland	1,300	Rental scheme
UK	1,200	Random funding; no cohesive policy
Norway	1,000	Fully funded
Austria	1,000	Fully funded by various schemes
Finland	750	70% of cost refunded
Belgium	750	Diabetic patients receive income support for 70% of cost
Australia	500	Private insurance for pumps only
Spain	350	No funding
Denmark	350	Selective funding by hospital budgets
Poland	250	No funding, special cases only
China	250	Funded by hospital budgets
Irish Republic	100	Fully funded
Slovenia	50	Full funding for children
Hungary	20	No reliable information
Greece	20	No reliable information
Northern Ireland	20	Health Boards looking at uniform policy and criteria
Latvia	20	No reliable information
Russia	10	No reliable information
Korea	20,000	No reliable information (pumps produced locally)

Source: INPUT, May 2002, reproduced with permission.

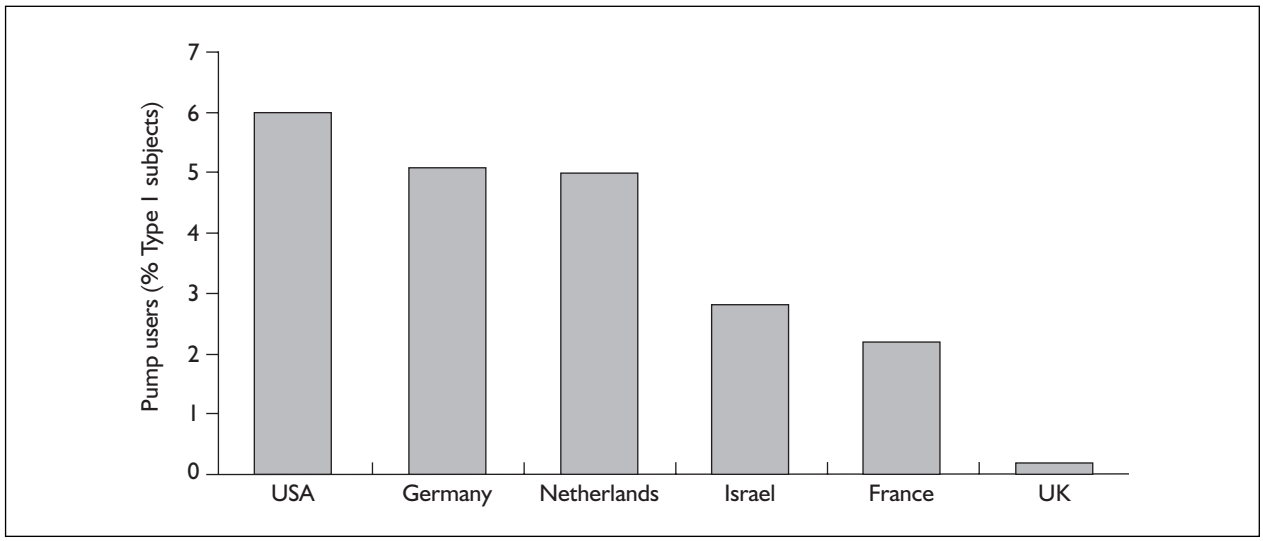

FIGURE 4 *CSII use in different countries. Source: Pickup J, Guy's, King's and St Thomas' School of Medicine, London: personal communication, 2002.*

(128 of 161) patients did not have DKA on pump therapy. The main cause of DKA was intercurrent illness; in half the episodes, patients had not been checking urine for ketones, which would have alerted them to the need to increase insulin dosage; in half the episodes they had not followed instructions about pump settings. Most of the episodes of DKA happened in the first 5 months of CSII. Hence the failure may be partly attributable to lack of education, or perhaps too much reliance on pumps, rather than CSII itself, although the authors reported pump malfunction, usually tubing problems, of some kind in 79% of patients. The commonest adverse event was injection site infection (once every 27 patient months)

Also in 1984, Teutsch and colleagues[50] reported that there had been 35 deaths amongst the estimated 3500 pumps users in the USA at that time, a rate no different from that expected amongst non-CSII users. Two deaths appeared to be directly attributable to pump therapy, one being due to pump malfunction and the other to bacterial endocarditis secondary to an infected injection site.

In the UK, Knight and colleagues[51] in Sheffield reported 13 episodes of DKA in 150 patient years of CSII. Nine of these occurred in the first year of CSII. There were no instances of mechanical failure of the pump itself, but one episode followed disconnection of the cannula and another when the patient did not realise that there was no insulin left. As in the Mecklenburg study, many occurrences of DKA followed other illnesses.

Knight and colleagues concluded that: "At present, the potential problem of severe hyperkalaemia associated with ketoacidosis during treatment with a pump creates doubt about the feasibility of CSII … ."

Also in 1984, the Kroc group reported an increased risk of DKA in CSII compared with conventional therapy, but this time from a randomised study.[52] However, the duration was only 8 months; eight patients had DKA.

Another adverse report came from Steel and West,[53] in the form of a case history of a pregnant diabetic woman whose baby died *in utero*. This was related to incorrect use of the pump.

In 1986, the Sheffield group[54] compared patients on CSII who had had DKA with those on CSII who had not. The main differences found were length of full-time education and psychological measures such as locus of control. Those who suffered DKA had left education 3 years earlier on average and were less likely to feel that they could take control of their diabetes. The authors therefore concluded that it may be possible to select out patients unsuitable for CSII or to provide better education and training.

In the DCCT, by contrast, there was no evidence of increased DKA risk in pump users and this has been the experience of groups with extensive experience of the use of CSII in the UK,[55] Germany[56] and the USA.[57]

There have been two reports of CSII injection sites becoming infected with unusual organisms such as *Mycobacterium fortuitum*[58,59] and one set of authors wondered if the risk of infection with organisms found in soil and water might be increased because users could bathe and swim with some devices.[59]

The earlier reports nevertheless seem to have given rise to a widespread belief in the UK that CSII is unsafe. For example, one hospital replying to a patient enquiry about funding a pump, said that: "Problems which arose from use of earlier CSII systems include reports of death due to diabetic ketoacidosis following accidental disconnection of the pump and abscess formation at the site."

One of the submissions received from patients for this review said that doctors had old-fashioned opinions about pumps: "Many consultants I have spoken to have preconceived views on the pump. Because pumps were unreliable a few years ago they don't seem to realise that technology moves on. Look at mobile phones 10 years ago. Look at them now."

There could be several reasons why the UK has had a much lower use of pumps than other countries:

- Experience with early, less reliable technology and the 'learning curve'
- 'Migration' of organised CSII research and development for want of resources in the UK (suggested by Keen H, Guy's Hospital: personal communication, 2002).
- The fear of ketoacidosis.
- Non-prescribability of pumps and adnexae (perhaps partly based on the fear that large numbers of patients with Type 1 diabetes would be referred for CSII).
- Cost concerns and competition for funding from other desirable developments. There may be some clinics where there is support in principle for pump use, but where their priority is lower than other items.
- Manpower resources, especially diabetes specialist nurses (DSNs).

There is considerable interest in pumps amongst patients and a growing interest from health professionals, and two new groups have been formed in the UK. The first is a users' group, INPUT (Insulin Pump Therapy), which is: "… a patient led support group for diabetics using insulin pumps, run by pump users and their families, an information centre for people seeking facts about insulin pumps, their use and how to obtain and fund them."

The main aim of INPUT is to "increase the awareness and understanding of pump therapy and to have it funded by the Department of Health" (INPUT, October 2001, www.webshowcase.net/input).

The other group is an educational initiative for professionals in diabetes care, Pump Management for Professionals (PUMP),[60] which organises training courses for medical and nursing staff.

Subsidiary questions

Children, including overnight use

Good control is difficult in children, and only a minority achieve it.[30] Case series carried out in the 1980s showed mixed results.[61–64] A review in 1986 summarised the finding of the early studies, and noted conflicting results.[65]

Children at different ages need to be considered separately, perhaps grouped as follows;

- infants and toddlers under constant supervision by parents
- young children attending nurseries or school, away from parents for part of the day
- older children who might be able to manage pumps at school without supervision
- children old enough to look after themselves.

There has been debate about ages at which children can manage their own pumps. It will vary amongst children according to their abilities.

One option that has been used, probably infrequently, is for children to have CSII only overnight,[66,67] when they are under parental supervision. Overnight-only CSII has also been used in adults.[68,69]

Pregnancy

CSII has been suggested as a way of normalising diabetic control in women with Type 1 diabetes during pregnancy,[70] or preconceptionally in order to reduce the increased malformation rate seen in poorly controlled diabetes.[71] Various small early studies either had no control group[72] or involved non-randomised comparisons.[73,74]

In a 2000 review, Gabbe[70] noted that CSII could be particularly useful in pregnancy because the bolus from pumps can be modified to fit with the slower absorption of nutrients associated with the delayed gastric emptying seen in pregnancy.

However, he also noted that there is relative insulin resistance in the third trimester of pregnancy, and that any interruption to insulin supply could lead to an increased risk of DKA. He recommended blood glucose testing at 2–3 a.m. in order to check on insulin delivery.

In Auckland,[75] CSII has been used for improving control in women with Type 2 diabetes and gestational diabetes, particularly those who required large (over 100 units per injection) doses of insulin. These women were mainly Maori or South Sea Islanders. Insulin dosage and weight gain were greater on CSII but the comparison was not based on an RCT and numbers were small.

The key question for this review is whether CSII has any advantages over MDI when used preconceptually (for reducing malformations) or during pregnancy (for improving outcomes for the baby).

Insulin-resistant Type 2 diabetes

A few studies have suggested that short periods of CSII may be useful in patients with true Type 2 diabetes who are poorly controlled on oral drugs. The rationale seems to be that improved control will reduce insulin resistance.

Analogue insulins in CSII

There are theoretical advantages of short-acting analogues in CSII because of the more rapid effect when used for bolus doses. The bolus could be given when patients sit down to eat, rather than 30 minutes before as with soluble, which may be useful when the time of a meal is uncertain.

One implication is that in comparisons of MDI with CSII, it is necessary to make sure that both forms of intensive treatment use the same type of insulin. To compare CSII using analogues with MDI using soluble would introduce a confounding factor.

Chapter 3

Clinical effectiveness

Methods

The *a priori* methods used for systematically reviewing evidence of clinical effectiveness were described in the research protocol (Appendix 1), which was sent for expert comments to members of the advisory panel for the review. Although many helpful comments were received relating to the general content of the research protocol, there were none that identified specific problems with the methods of review. Some changes, additions or points of clarification were made to the methods discussed in the original protocol, and these are outlined below.

- The evidence from the eligible RCTs and crossover studies was supplemented with information from selected non-randomised and observational studies, to provide information on areas where no evidence eligible for inclusion was identified. A sensitive search for observational studies was undertaken. These were filtered by an information scientist and studies for inclusion were then selected by an experienced reviewer, looking specifically for studies that could help answer questions 2, 3, 4 and 6 on p. 1. An assessment of quality was not undertaken for these selected studies.
- Importantly it should be noted that the sections 'Quantity and quality of research' (p. 14), 'Results in adults with Type 1 diabetes' (p. 16), 'Pregnancy' (p. 32), 'Adolescents' (p. 36) and 'Analogue versus soluble insulin in CSII' (p. 38) are based on a systematic review of the evidence from eligible RCTs and crossover studies, while information from selected observational studies is discussed in the sections 'CSII in children' (p. 37), 'Overnight-only CSII in adults' (p. 37), 'Short-term CSII in poorly controlled adults with Type 2 diabetes' (p. 37) and 'Discontinuation rates' (p. 42).

The methods outlined in the protocol are summarised below.

Sources of information, search terms and a flow chart outlining the identification of studies are described in Appendix 2. It was decided to run a very sensitive search in order to capture not only RCTs for efficacy, but also a wide range of evidence, including:

- QoL studies
- safety and side-effect studies, including a selection of individual case reports that might illustrate problems with pumps
- 'real-life' case series, especially those that gave data on discontinuation rates
- a selection of reviews, old and new, partly to look for reasons why the enthusiasm for pumps waxed and waned in the last period of pump activity in the 1980s
- cost studies
- studies on different types of insulin, such as analogue versus soluble
- studies using CSII for short periods to improve insulin sensitivity in Type 2 diabetes
- studies using CSII only for part of the day, usually at night.

Background papers on the effect of improved control on long-term complications, mainly from the DCCT, Oslo, Stockholm and UKPDS studies, were also obtained. The search was carried out by a skilled information scientist. Abstracts (or just titles in the minority of studies where no abstract was available) were checked by two people. Of the 3760 studies retrieved, 106 were selected for further scrutiny. Some of these were recent reviews, to give a check on completeness of ascertainment of RCTs and other studies. Others were exchanges of correspondence on controversial areas. A search of the electronic *BMJ* was carried out to capture correspondence following the 2001 editorial,[38] and the references cited were checked. The Cochrane Library was searched for RCTs, reviews and protocols and the Cochrane Metabolic and Endocrine Group was consulted regarding any ongoing activity. Experts in the field, including some of the pioneers of pump use, were consulted as part of the advisory panel. An unpublished meta-analysis and historical review were thus obtained. Manufacturers' submissions to NICE were reviewed as a check on completeness of retrieval of published trials.

The full text of relevant studies was examined and inclusion criteria were applied independently by two reviewers. An Access database was designed for data extraction, which was carried out by one reviewer and checked by a second reviewer. The

quality of eligible RCTs and crossover studies was assessed in accordance with chapter II.5 of CRD Report 4 (2nd Edition) (Appendix 3). Quality criteria were applied by one reviewer and checked by a second reviewer. At each stage, any differences in opinion were resolved through discussion or consultation with a third reviewer.

Inclusion criteria

Studies comparing CSII using insulin pumps with optimised MDI (at least three injections per day) were included in the review. Comparisons of analogue and soluble insulin in CSII were also included. Comparisons of conventional therapy, implantable pumps and hospital inpatient pumps were excluded.

The review includes people with insulin-treated diabetes (Type 1 or Type 2), including adults, children, adolescents and pregnant women. Newly diagnosed patients were excluded.

Parallel RCTs and randomised and non-randomised crossover studies were included in the review. Studies with a duration of less than 10 weeks on each treatment were excluded.

Studies were included if they reported one or more of the following as primary outcomes: glycated haemoglobin, insulin dose, weight change, lipid levels, patient preference, QoL or adverse effects.

Studies in non-English language or available only as abstracts were excluded from the main analysis.

Studies excluded from the review are listed in Appendix 4 and a list of recent studies reported only as abstracts is given in Appendix 5.

Data synthesis

Data were synthesised through a narrative review with tabulation of all eligible studies. Data on glycated haemoglobin and insulin dose were combined where appropriate in a meta-analysis summarising the weighted mean difference (WMD) using the random-effects model. In assessing glycated haemoglobin, HbA_1 and HbA_{1c} were considered sufficiently similar on clinical grounds to be combined within the meta-analysis, focusing on changes rather than absolute values. Further stratification by assay type was not undertaken owing to the lack of additional clarity provided by the small number of studies reporting at each length of follow-up. A sensitivity analysis was performed excluding non-randomised crossover studies.

CSII versus MDI

Quantity and quality of research

Twenty studies comparing CSII and MDI met the inclusion criteria for the review and are shown in Tables 4–15 and Appendices 6–13. 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. One study was reported in three publications.[76–78] Only two of the studies comparing CSII and MDI used analogue insulins for both groups.[79,80]

No RCTs or crossover studies were identified in children [see the section 'CSII in children' (p. 37)], CSII overnight only in adults [see the section 'Overnight-only CSII in adults' (p. 37)] or in poorly controlled adults with Type 2 diabetes [see the section 'Short-term CSII in poorly controlled adults with Type 2 diabetes' (p. 37)]. Selected observational studies were discussed in these sections, and no assessment of quality was undertaken.

Adults with Type 1 diabetes

The quality of reporting and methodology of the included studies was generally poor by today's standards (*Table 4*). Of the 14 studies including adults with Type 1 diabetes, the method of randomisation was adequate in just two, by Brinchmann-Hansen and colleagues[76] and Tsui and colleagues,[79] both of which were parallel RCTs. The three non-randomised crossover studies were assessed as having an inadequate method of randomisation[81–83] and the method was not reported in the remaining studies. Allocation concealment was inadequate in four studies[79,81–83] and unknown in 10 studies; therefore, they may be subject to selection bias. Moreover, the similarity of groups at baseline was reported by just four studies.[76,79,84,85] Eligibility criteria for entry into the study were reported in eight studies[76,79–81,83,84,86,87] but were not reported in six.[82,85,88–91] Point estimates and measure of variability were presented for the primary outcome measure in most studies, but this was only partially reported in three studies where the data were presented in figures only and had to be extrapolated.[76,84,90] Data were analysed according to intention-to-treat (ITT) principles in four studies[79,84–86] and withdrawals were adequately

TABLE 4 *Quality assessment of studies comparing CSII versus MDI*

Study	Random	Allocation concealment	Group similarity	Eligibility	Point estimates	ITT	Withdrawals
Type 1 diabetes							
Bak, 1987[87]	Unknown	Unknown	Unknown	Adequate	Adequate	Inadequate	Adequate
Bode, 1996[81]	Inadequate	Inadequate	Unknown	Adequate	Adequate	Inadequate	Unknown
Brinchmann-Hansen, 1988[76]	Adequate	Unknown	Reported	Adequate	Partial	Inadequate	Adequate
Chiasson, 1984[82]	Inadequate	Inadequate	Unknown	Unknown	Adequate	Inadequate	Unknown
Haakens, 1990[83]	Inadequate	Inadequate	Unknown	Adequate	Adequate	Inadequate	Adequate
Hanaire-Broutin, 2000[80]	Unknown	Unknown	Unknown	Adequate	Adequate	Inadequate	Adequate
Home, 1982[88]	Unknown	Unknown	Unknown	Unknown	Adequate	Inadequate	Inadequate
Nathan, 1982[89]	Unknown	Unknown	Unknown	Unknown	Adequate	Inadequate	Unknown
Nosadini, 1988[85]	Unknown	Unknown	Reported	Unknown	Adequate	Adequate	Adequate
Saurbrey, 1988[90]	Unknown	Unknown	Unknown	Unknown	Partial	Inadequate	Adequate
Schiffrin, 1982[91]	Unknown	Unknown	Unknown	Unknown	Adequate	Inadequate	Partial
Schmitz, 1989[86]	Unknown	Unknown	Unknown	Adequate	Adequate	Adequate	Adequate
Tsui, 2001[79]	Adequate	Inadequate	Reported	Adequate	Adequate	Adequate	Partial
Ziegler, 1990[84]	Unknown	Unknown	Reported	Adequate	Partial	Adequate	Partial
Pregnancy							
Burkart, 1988[95]	Unknown	Unknown	Unknown	Adequate	Partial	Inadequate	Unknown
Carta, 1986[94]	Unknown	Unknown	Reported	Unknown	Partial	Inadequate	Unknown
Coustan, 1986[93]	Partial	Inadequate	Reported	Unknown	Adequate	Inadequate	Unknown
Nosari, 1993[92]	Partial	Inadequate	Unknown	Unknown	Adequate	Inadequate	Unknown
Adolescents							
Schiffrin, 1984[97]	Unknown	Unknown	Unknown	Unknown	Partial	Inadequate	Partial
Tamborlane, 1989[96]	Unknown	Unknown	Unknown	Adequate	Adequate	Inadequate	Unknown

See Appendix 3 for description of coding.

reported in seven studies.[76,80,83,85–87,90] Three studies[79,84,91] partially reported loss to follow-up (numbers but not reasons, or vice versa) and in one study[88] the numbers were not specified for either group. Three studies did not report loss to follow-up.[81,82,89]

Pregnancy

Two of the four parallel RCTs comparing CSII and MDI in pregnancy were thought to have randomisation that was partially adequate,[92,93] but allocation concealment was inadequate (*Table 4*). The method of randomisation was not stated in the studies by Carta and colleagues[94] and Burkart and colleagues,[95] and therefore concealment of allocation was unknown. The similarity of groups at baseline was reported by just two of the studies.[93,94] Eligibility criteria for entry into the study were not clearly stated in three studies.[92–94] Point estimates and measure of variability were presented for the primary outcome measure in two studies;[92,93] however, this was only partially reported in the study by Carta and colleagues,[94] where the data were presented in figures only and had to be extrapolated, and by Burkart and colleagues,[95] where mean blood glucose or glycated haemoglobin was not reported. ITT analysis was not used in the studies and, although it may be assumed that no loss to follow-up occurred, this was not clearly stated in any of the studies.

Adolescents

The two studies comparing CSII and MDI[96] or CSII, MDI and CSII during the night plus MDI during the day[97] in adolescents were of poor methodological quality (*Table 4*). The crossover studies were said to be randomised, but the method of randomisation was not specified and allocation concealment was unclear.[96,97] The similarity of groups at baseline was not reported by either study. Eligibility criteria were not reported in the study by Schiffrin and colleagues[97] and point estimates and measure of variability were only partially reported in that study as the data were presented in figures and had to be extrapolated.[97] ITT analysis was not used in either study and, although Schiffrin and colleagues reported the numbers withdrawn from each group, the reasons for withdrawal were not given[97] and Tamborlane and colleagues did not report loss to follow-up.[96]

Results in adults with Type 1 diabetes

Four randomised parallel,[76,79,84,85] seven randomised crossover[80,86–91] and three non-randomised crossover[81–83] studies compared CSII and MDI in adults with Type 1 diabetes, and are shown in *Tables 4–10* and Appendices 6 and 10. Two of the 14 trials (one randomised crossover[80] and one randomised parallel[79]) compared CSII and MDI using the analogue insulin lispro, whereas the remaining studies compared CSII and MDI using regular insulin. Not all studies used the HbA_{1c} that is standard today, but it is the difference rather than the absolute values that matters. Six of the studies report HbA_1,[76,82–84,88,91] seven report HbA_{1c}[79–81,85,86,89,90] and one reports blood glucose only.[87] Data are discussed in this review according to the reported length of follow-up. One caveat is that many of these studies are fairly old and used obsolete technologies.

Glycated haemoglobin and blood glucose

Eight studies reported glycated haemoglobin at 10 weeks to 4 months of follow-up (*Table 5*).[76,78–80,82,88–91] A mean reduction in glycated haemoglobin from baseline of between 0.5% and 5.1% was found for CSII treatment, and between –1.0% to 4.8% for MDI treatment. Much of this variation may be explained by differences in baseline glycated haemoglobin between studies, which ranges from 7.7% for the CSII group in the parallel RCT by Tsui and colleagues[79] to 13.2% in the random crossover study by Schiffrin and colleagues.[91] At 10 weeks to 4 months follow-up, five studies found that glycated haemoglobin was lower with CSII than MDI, reporting a mean reduction of between 0.3% and 2.48%.[79,80,88,89,91] This difference was statistically significant in just two of the studies (0.35%, $p < 0.0001$;[80] 1.7%, $p = 0.026$[88]), two other studies reported a non-significant reduction[79,91] and one study[89] did not report statistical significance. Saurbrey and colleagues found no difference in glycated haemoglobin between CSII and MDI at 10 weeks of follow-up,[90] and two trials reported slightly higher glycated haemoglobin with CSII compared with MDI [8.9% versus 8.7%, p not reported;[76,78] 9.1% versus 8.7%, p = not statistically significant (ns)[82]]. Five of the eight studies provided data

TABLE 5 *Glycated haemoglobin in adults with Type 1 diabetes*

Study	Mean glycated haemoglobin (SD)		Difference (MDI – CSII)
	CSII	**MDI**	
Bak, 1987[87] Random crossover *N*: 20; end of study: 16 Baseline BG not reported	Glycated haemoglobin not reported *Blood glucose*: Month 6: 7.7 mmol/l (0.7)	 *Blood glucose*: Month 6: 7.9 mmol/l (0.7), p = ns	 0.2 mmol/l
Bode, 1996[81] Non-random crossover *N*: 55. HbA_{1c} data collected Baseline not reported	Month 12: 7.4% (1.2) Month 24: 7.7% (1.7) Month 36: 7.4% (1.7) Month 48: 7.4% (1.2)	7.7% (1.5), p = ns Not reported Not reported Not reported	0.3%
Brinchmann-Hansen, 1988[76,78] Parallel RCT CSII *n*: 15; MDI *n*: 15 HbA_1 data collected Baseline CSII: 10.1% (1.55) Baseline MDI: 9.4% (1.55)	Month 3: 8.9% Month 6: 9.2% Month 12: 8.5% Month 24: 8.7% (1.16) Month 41: 9.1%	8.7% 8.8% 8.5% 9.1% (1.55) 9.4%	–0.2% –0.4% 0% 0.4% 0.3%
Chiasson, 1984[82] Non-random crossover *N*: 12 HbA_1 data collected Baseline: 11.9% (2.08)	Month 3: 9.1% (1.04)	8.7% (1.39), p = ns	–0.4%
Haakens, 1990[83] Non-random crossover *N*: 52; end of study: 35 HbA_1 data collected Baseline: 10.4% (1.85)	Month 6: 9.6% (2.47)	9.8% (1.85), p = ns	0.2%

continued

TABLE 5 *Glycated haemoglobin in adults with Type 1 diabetes (cont'd)*

Study	Mean glycated haemoglobin (SD)		Difference (MDI – CSII)
	CSII	**MDI**	
Hanaire-Broutin, 2000[80] Random crossover *N*: 41; end of study: 40 HbA_{1c} data collected Baseline: 8.39% (0.87)	Month 4: 7.89% (0.77)	8.24% (0.77), p<0.001	0.35%
Home, 1982[88] Random crossover *N*: 11; end of study: 10 HbA_1 data collected Baseline: 10.7% (1.9)	Month 2.5: 10% (2.2)	11.7% (1.9), $p = 0.026$	1.70%
Nathan, 1982[89] Random crossover *N*: 5 HbA_{1c} data collected Baseline: 9.03% (1.43)	Month 3: 5.4% (0.34)	7.88% (1.37), *p* not reported	2.48%
Nosadini, 1988[85] Parallel RCT CSII fixed *n*: 19; MDI *n*: 15 CSII variable *n*: 10 HbA_{1c} data collected Baseline not reported	*CSII fixed night basal rate:* Month 12: 6.3% (0.7) *CSII with variable night basal rate:* Month 12: 6.1% (0.9), $p < 0.01$ (vs MDI)	*MDI:* 7.1% (0.9), $p < 0.01$ (vs CSII fixed)	0.8% (MDI – CSII fixed) 1% (MDI – CSII variable)
Saurbrey, 1988[90] Random crossover *N*: 21, end of study: 19 HbA_{1c} data collected Baseline (CSII then MDI): 8.7% (1.74) Baseline (MDI then CSII) 8.8% (2.17)	Month 2.5: 7.5%	7.5%	0%
Schiffrin, 1982[91] Random crossover. *N*: 20; end of study: 16 HbA_1 data collected Baseline: 13.2% (1.1)	Month 3: 8.1% (0.6) Month 6: 8.2% (0.5)	8.4% (0.7), p = ns 8.4% (0.5), p = ns	0.3% 0.2%
Schmitz, 1989[86] Random crossover *N*: 10 HbA_{1c} data collected Baseline: 7.6% (0.9)	Month 6: 7% (1)	7.7% (1), $p = 0.002$	0.7%
Tsui, 2001[79] Parallel RCT CSII *N*:13; end of study: 12 MDI *N*: 14; end of study:14 HbA_{1c} data collected Baseline CSII: 7.73% (0.6) Baseline MDI: 8.16% (0.7)	Month 3: 6.92% Month 6: 7.19% Month 9: 7.38%	7.55%. Treatment effect (adjusted for baseline HbA_{1c}) = –0.21 (95% CI –0.59 to 0.17), $p > 0.10$ 7.62%. Treatment effect (adjusted for baseline HbA_{1c}) = –0.01 (95% CI –0.44 to 0.42), $p > 0.10$ 7.56%. Treatment effect (adjusted for baseline HbA_{1c}) = 0.25 (95% CI –0.19, 0.68), p >0.10	0.63% 0.43% 0.18%
Ziegler, 1990[84] Parallel RCT CSII *N*: 49; end of study: 36 MDI *N*: 47; end of study: 37 HbA_1 data collected Baseline CSII: 9.8% Baseline MDI: 9.5%, p = ns	Month 6: 8.2% Month 12: 8.5% Month 18: 8.5% Month 24: 8.6%	8.8%, $p < 0.05$ 8.7%, p = ns 8.4%, p = ns 8.5%, p = ns	0.6% 0.2% –0.1% –0.1%

BG, blood glucose; *N*, number of patients.

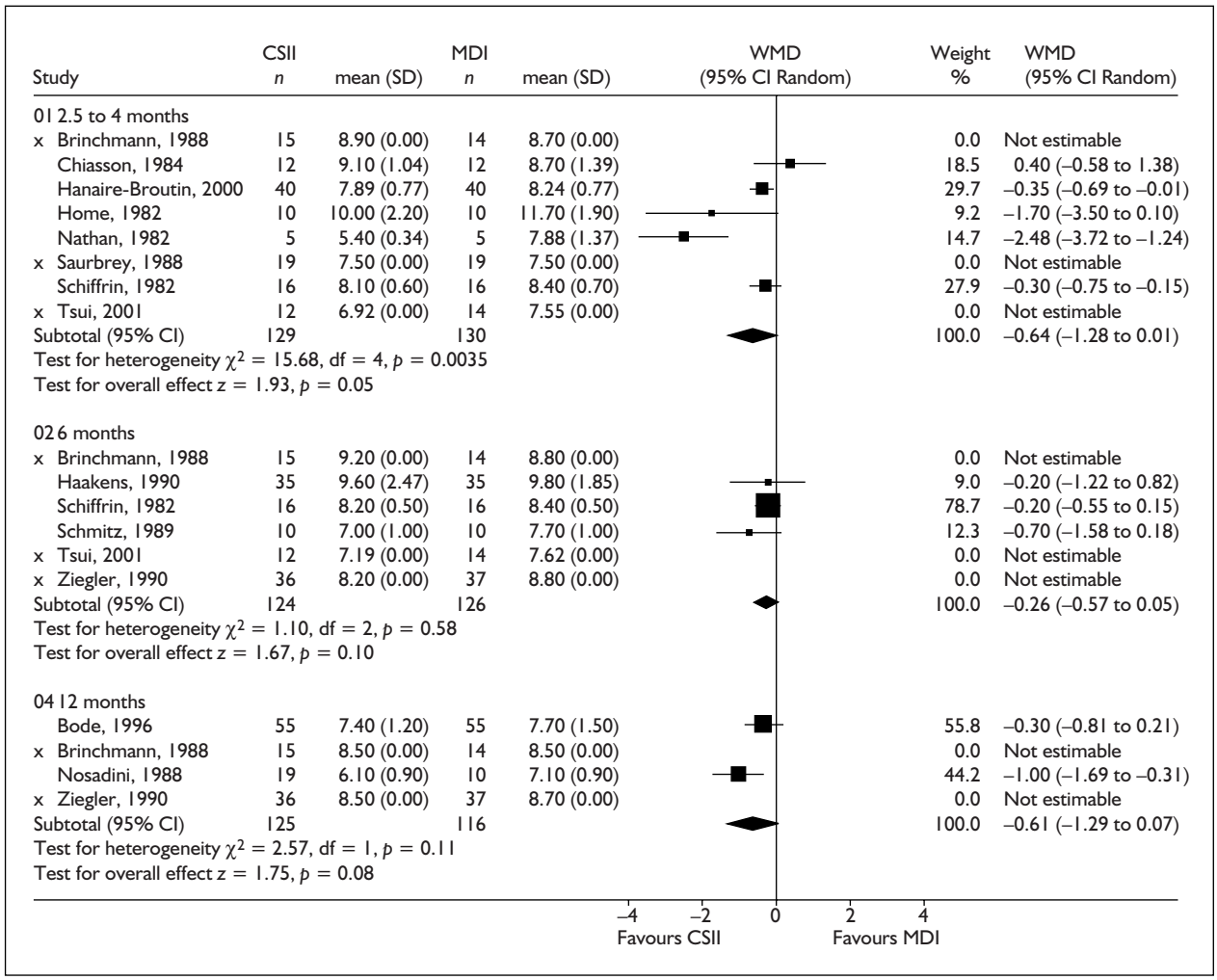

FIGURE 5 *Meta-analysis of the effect of CSII versus MDI on glycated haemoglobin in adults with Type 1 diabetes. Note: HbA_1 is reported by Brinchmann-Hansen, 1988,[76] Chiasson, 1984,[82] Haakans, 1990,[83] Home, 1982,[88] Schiffrin, 1982[91] and Ziegler, 1990.[84] HbA_{1c} is reported by Bode, 1996,[81] Hanaire-Broutin, 2000,[80] Nathan, 1982,[89] Nosadini, 1988,[85] Saurbrey, 1988,[90] Schmitz, 1989[86] and Tsui, 2001.[79]*

[means and standard deviations (SDs)] that allowed them to be combined in a meta-analysis (*Figure 5*).[80,82,88,89,91] Pooling the data using a random-effects model (χ^2 test for heterogeneity 15.68, df = 4, p = 0.0035) showed an overall reduction in glycated haemoglobin with CSII compared with MDI (–0.64, 95% CI –1.28 to 0.01). Because of the heterogeneity, these results should be viewed with some caution, but the heterogeneity was around the effect size. The study by Home and colleagues[88] used a sub-optimal MDI regime with bovine ultralente insulin, and HbA_{1c} actually worsened during MDI compared with conventional treatment at baseline, thereby exaggerating the effects of CSII. Hence there is an argument for excluding this study on the grounds that the control arm did not receive optimal MDI. Repeating the meta-analysis without this study (*Figure 6*) reduced the effect size (–0.52, 95% CI –1.19 to 0.14, p = 0.12).

Six studies reported glycated haemoglobin at 6 months follow-up (*Table 5*).[76,78,79,83,84,86,91] A mean reduction from baseline of between 0.54% and 5% was found for CSII and between –0.1 and 4.8% for MDI. Five of the studies found that glycated haemoglobin was lower with CSII than MDI, reporting a mean reduction of between 0.7% and 0.2%.[79,83,84,86,91] This difference was statistically significant in just two of the studies (0.7%, p = 0.002[86]; 0.6%, $p < 0.05$[84]). Brinchmann-Hansen and colleagues found slightly higher glycated haemoglobin with CSII than with MDI (9.2% versus 8.8%), but significance was not reported.[76,78] Three of the six studies reporting glycated haemoglobin at 6 months could be

combined in a meta-analysis (*Figure 5*).[83,86,91] Pooling the data using a random-effects model (χ^2 test for heterogeneity = 1.10, df = 2, p = 0.58) showed a non-significant reduction in glycated haemoglobin with CSII compared with MDI (–0.26, 95% CI –0.57 to 0.05).

Only one study reported glycated haemoglobin at 9 months of follow-up[79] (*Table 5*). Tsui and colleagues found a reduction from baseline of 0.35% with CSII and 0.60% with MDI. A non-significant difference between CSII and MDI was found (7.38% versus 7.56%) at 9 months of follow-up, with a treatment effect of 0.25 (95% CI –0.19 to 0.68, $p > 0.10$) adjusted for baseline glycated haemoglobin.

Four studies reported glycated haemoglobin at 12 months follow-up (*Table 5*).[76,78,81,84,85] Only two studies report baseline data, demonstrating a mean reduction from baseline of 1.3%[84] to 1.6%[76,78] for CSII and 0.8%[84] to 0.9%[76,78] for MDI. Nosadini and colleagues report significantly lower glycated haemoglobin with both fixed rate (6.3%) and variable rate (6.1%) CSII compared with MDI (7.1%, $p < 0.01$).[85] However, three studies report no difference between CSII and MDI (0% to 0.2%, p = ns).[76,78,81,84] Two of the four studies provided data that allowed them to be combined in a meta-analysis (*Figure 5*).[81,85] As the study by Nosadini and colleagues[85] had two groups with CSII, only the group with the variable insulin rate was included in the meta-analysis, as this had the lowest mean glycated haemoglobin level and may provide optimal control. Pooling the data using a random-effects model (χ^2 test for heterogeneity 2.57, df = 1, p = 0.11) revealed a non-significant result in favour of CSII (–0.61, 95% CI –1.29 to 0.07).

Two studies reported glycated haemoglobin at 24 months of follow-up (*Table 5*), showing a mean reduction from baseline of between 1.2%[84] and 1.4%[76,78] for CSII and between 0.3%[76,78] and 1%[84] for MDI. Brinchmann-Hansen and colleagues report lower glycated haemoglobin with CSII than MDI (8.7% versus 9.1%), although significance is not reported,[76,78] and Ziegler and colleagues report no significant difference between CSII and MDI (8.6% versus 8.5%, p = ns) at 12 months.[84] Studies could not be combined into a meta-analysis, as SDs were not presented.

Bode and colleagues[81] reported glycated haemoglobin at 24 (7.7%, SD 1.7), 36 (7.4%, SD 1.7) and 41 months (7.4%, SD 1.2) follow-up for CSII treatment only (*Table 5*). This was a prospective non-randomised crossover study in which patients were switched to CSII after at least 12 months with MDI.

Brinchmann-Hansen and colleagues[76,78] reported glycated haemoglobin at 41 months of follow-up (*Table 5*), demonstrating a mean reduction of 1.0% from baseline with CSII and no change with MDI. Glycated haemoglobin was lower with CSII than with MDI at 41 months of follow-up (8.7% versus 9.1%), but statistical significance was not reported.

Bak and colleagues[87] did not report glycated haemoglobin, presenting blood glucose at 12 months but not at baseline (*Table 5*). This study shows a non-significant improvement in blood glucose with CSII compared with MDI [7.7 (SD 0.7) mmol/l versus 7.9 (SD 90.7) mmol/l, p = ns).

Glycated haemoglobin: sensitivity analysis

A further meta-analysis was conducted without the three non-randomised studies (Chiasson and colleagues,[82] 3 months of follow-up; Haakens and colleagues,[83] 6 months of follow-up; and Bode and colleagues,[81] 12 months of follow-up), as there is a greater possibility of bias in non-randomised trials.

At 10 weeks to 4 months of follow-up, four randomised trials could be combined in a meta-analysis (*Figure 7*).[80,88,89,91] Pooling the data using a random-effects model (χ^2 test for heterogeneity 12.95, df = 3, p = 0.0047) showed a significant reduction in glycated haemoglobin favouring CSII compared with MDI (–0.87, 95% CI –1.59 to –0.16). This shows a slightly greater reduction with CSII compared with the earlier meta-analysis (*Figure 5*). However, even with the non-random studies excluded, significant heterogeneity was still present.

At 6 months of follow-up, two randomised trials could be combined in a meta-analysis (*Figure 7*).[86,91] Pooling the data using a random-effects model (χ^2 test for heterogeneity 1.08, df = 1, p = 0.3) showed that glycated haemoglobin was not significantly reduced with CSII compared with MDI at 6 months of follow-up (–0.28, 95% CI –0.64 to 0.08). This is similar to the earlier meta-analysis (*Figure 5*).

Removing the study by Bode and colleagues[81] at 12 months of follow-up leaves just one randomised trial presenting means and standard deviations; therefore, a meta-analysis cannot be carried out.

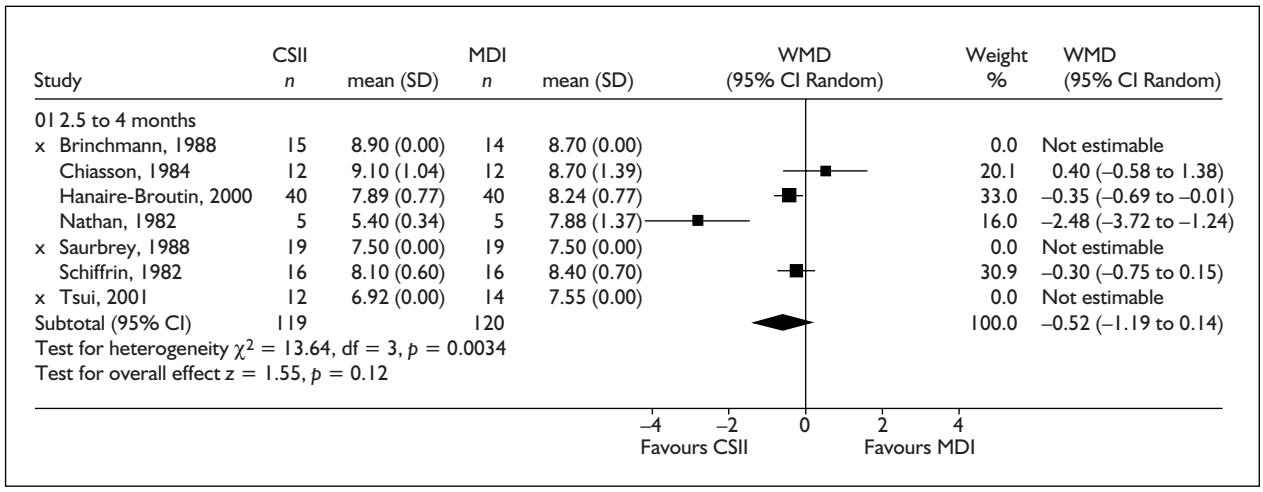

FIGURE 6 *Meta-analysis of the effect of CSII versus MDI on glycated haemoglobin in adults with Type 1 diabetes, excluding Home and colleagues.[88] Note: HbA_1 is reported by Brinchmann-Hansen, 1988,[76] Chiasson, 1984,[82] and Schiffrin, 1982.[91] HbA_{1c} is reported by Hanaire-Broutin, 2000,[80] Nathan, 1982,[89] Saurbrey, 1988[90] and Tsui, 2001.[79]*

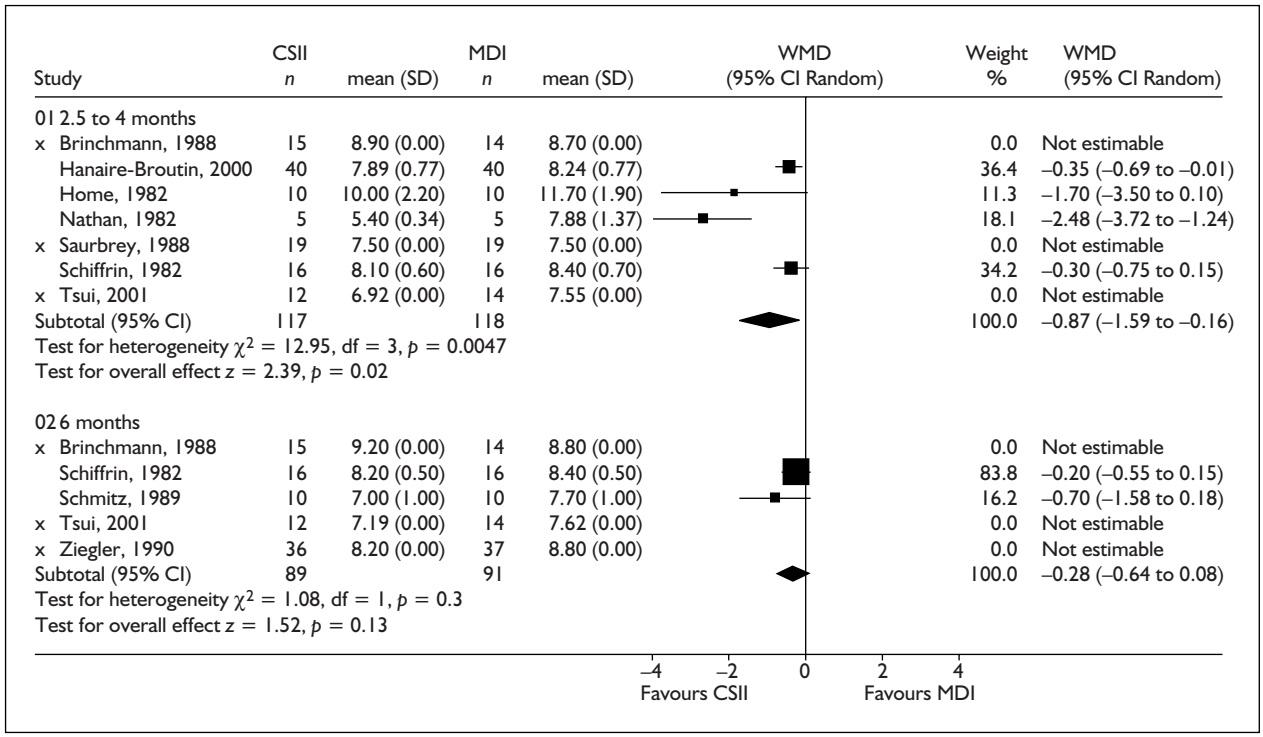

FIGURE 7 *Meta-analysis of the effect of CSII versus MDI on glycated haemoglobin in adults with Type 1 diabetes, excluding non-random studies. Note: HbA_1 is reported by Brinchmann-Hansen, 1988,[76] Home, 1982,[88] Schiffrin 1982,[91] and Ziegler, 1990.[84] HbA_{1c} is reported by Hanaire-Broutin, 2000,[80] Nathan, 1982,[89] Saurbrey, 1988,[99] Schmitz, 1989[86] and Tsui, 2001.[79]*

The shortage of long-term studies is unfortunate, since it is likely that it takes some time for optimum dosage to be worked out and for patients to become familiar with adjusting their insulin dosages, and perhaps in particular experimenting with different basal rates at different times of day and night. Nevertheless, the limited amount of data from the trials does suggest that results may improve with longer duration.

Summary

The evidence is consistent in showing an improvement in glycated haemoglobin on CSII compared with MDI, the difference averaging about 0.5%.

Caveat

As has been pointed out to us (Home, PD, Department of Diabetes, The Medical School,

Newcastle: personal communication, 2002), HbA_{1c} may not be a perfect guide to diabetes control in people who achieve good overall HbA_{1c} levels but who have problems with hypoglycaemia, since the hypoglycaemic events will reduce the HbA_{1c}. If CSII reduces the frequency of hypoglycaemia, of whatever degree, that will tend to increase HbA_{1c}, and this may conceal the extent of the improvement in control of hyperglycaemia.

Daily insulin dose

Insulin dose was reported in the studies using either units per day (U/day) or units per kilogram per day (U/kg/day), and the data are discussed here for each method separately, according to the reported length of follow-up.

Five studies reported insulin dose at 10 weeks to 4 months follow-up (*Table 6*), with four studies presenting insulin in units per day[80,82,88,89] and one study presenting insulin units per kilogram per day.[90] Compared with baseline, a mean decrease in insulin dose of 1.2–9 U/day was observed with CSII and a mean increase of 3.7–20 U/day was observed with MDI.[80,82,88,89] Three studies found significantly less insulin was required with CSII than with MDI (8.80–29 U/day).[80,82,88] The fourth study, by Nathan and colleagues, found a lower daily insulin dose with CSII compared with MDI [35.4 (SD 11.5) U/day versus 48.8 (SD 13.18) U/day] but did not report statistical significance.[89] Pooling these data into a meta-analysis using a random-effects model (χ^2 test for heterogeneity 3.78, df = 3, $p = 0.29$) shows an overall significant reduction of about 12 U/day in daily insulin dose after 10 weeks to 4 months of treatment on CSII compared with MDI (–11.90 units, 95% CI –18.16 to –5.63) (*Figure 8*). Repeating the meta-analysis without the study by Home and colleagues,[88] which used a suboptimal MDI regime with bovine insulin, (*Figure 9*) slightly reduces the effect size (–9.73, 95% CI –14.55 to –4.91), but the decrease in insulin dose with CSII remains significant.

Saurbrey and colleagues[90] found a mean reduction in insulin dose from baseline of 0.05 and 0.03 U/kg/day at 10 weeks of follow-up for CSII and MDI, respectively. Insulin use was slightly lower with CSII than MDI (0.62 versus 0.64 U/kg/day), but statistical significance was not presented.

Four studies[83,86,87,91] reported insulin dose at 6 months of follow-up (*Table 6*); two[87,91] present the data as units per day and two[83,86] units per kilogram per day. Insulin dose increased from baseline in the study by Bak and colleagues (CSII 0.6, MDI 5.9 U/day),[87] but decreased in the study by Schiffrin and colleagues (CSII –6, MDI –4 U/day).[91] Haakens and colleagues reported insulin dose for MDI with isophane and with ultralente, with a difference from baseline of –0.04 and 0.03 U/kg/day (p = ns), respectively. Insulin dose with CSII was significantly lower than at baseline (0.64 versus 0.76 U/kg/day, $p < 0.001$).[83] Schmitz and colleagues reported the mean difference from baseline for CSII as 0.05 U/kg/day ($p = 0.03$) and for MDI as 0 U/kg/day (p = ns).[86] Daily insulin dose at 6 months of follow-up was lower with CSII than with MDI: between 2.0 (p = ns)[91] and 5.30 U/day ($p < 0.05$),[87] and between 0.05 ($p = 0.02$)[86] and 0.08 U/kg/day ($p < 0.005$) for isophane and 0.15 U/kg/day ($p < 0.001$) for ultralente.[83] The difference between isophane and ultralente was also statistically significant ($p < 0.01$). A meta-analysis of insulin dose at 6 months of follow-up could not be performed as two studies did not present SDs.

Insulin dose was not often reported after 6 months of follow-up (*Table 6*). At 9 months of follow-up, Tsui and colleagues[79] found little difference compared with baseline (0.1 U/kg/day decrease for CSII and no change for MDI) or between treatments (0.1 U/kg/day, p = ns). Bode and colleagues[81] reported a non-significant decrease of 6.50 U/day with CSII compared with MDI at 12 months of follow-up, but did not report baseline values. As with glycated haemoglobin, the authors also reported insulin dose for CSII at 24 (36.6 U/day), 36 (37.7 U/day) and 48 months (37.8 U/day), but did not follow patients on MDI for this length of time.

At 24 months of follow-up, Brinchmann-Hansen and colleagues[78] found a decrease in insulin dose of 0.12 U/kg/day for CSII compared with baseline and no change for MDI (*Table 6*). There was no significant difference between CSII and MDI [0.68 U/kg/day (SD 0.19) versus 0.72 U/kg/day (SD 0.72), p = ns].

Daily insulin dose: sensitivity analysis

A further meta-analysis was conducted without the non-randomised study (Chiasson and colleagues[82]) at 10 weeks to 4 months follow-up (*Figure 10*). Pooling the three randomised studies[80,88,89] that reported data in units per day using a random-effects model (χ^2 test for heterogeneity 3.72, df = 2, $p = 0.16$) showed that the decrease in insulin dose with CSII compared with MDI remained significant (WMD –13.63, 95% CI –23.62 to –3.64).

TABLE 6 *Insulin dose in adults with Type 1 diabetes*

Study	Mean insulin dose (SD)		Difference (MDI – CSII)
	CSII	**MDI**	
Bak, 1987[87] Random crossover *N*: 20; end of study: 16 Baseline: 46 U/day (16)	Month 6: 46.6 U/day (10)	51.9 U/day (12.9), $p < 0.05$	5.3 U/day
Bode, 1996[81] Non-random crossover *N*: 55 Baseline not reported	Month 12: 36.4 U/day (12.1) Month 24: 39.6 U/day (14.4) Month 36: 37.7 U/day (13.1) Month 48: 37.8 U/day (14.2)	42.9 U/day (17.9), p = ns	6.5 U/day
Brinchmann-Hansen, 1988[78] Parallel RCT CSII *N*: 15; MDI *N*: 15 Baseline CSII: 0.8 U/kg/day (0.23) Baseline MDI: 0.72 U/kg/day (0.08)	Month 24: 0.68 U/kg/day (0.19)	0.72 U/kg/day (0.12), p = ns	0.04 U/kg/day
Chiasson, 1984[82] Non-random crossover *N*: 12 Baseline: 44.7 U/day (14.6)	Month 3: 43.9 U/day (10)	56.1 U/day (20.4), $p < 0.01$	12.2 U/day
Haakens, 1990[83] Non-random crossover *N*: 52; end of study: 35 Baseline: 0.76 U/kg/day (0.25).	Month 6: 0.64 U/kg/day (0.18)	Month 6: *MDI/human isophane* 0.72 U/kg/day (0.25), $p < 0.005$ Month 6: MDI/*human ultralente* 0.79 U/kg/day (0.25), $p < 0.001$ (isophane vs ultralente, $p < 0.01$)	0.08 U/kg/day 0.15 U/kg/day
Hanaire-Broutin, 2000[80] Random crossover *N*: 41; end of study: 40 Baseline: 43.6 U/day (13.5)	Month 4: 38.5 U/day (9.8)	47.3 U/day (14.9), $p < 0.0001$	8.8 U/day
Home, 1982[88] Random crossover *N*: 11; end of study: 10 Baseline: 60 U/day (18.97)	Month 2.5: 51 U/day (15.8)	80 U/day (28.5), $p = 0.004$	29 U/day
Nathan, 1982[89] Random crossover *N*: 5 Baseline: 42.8 U/day (16.04)	Month 3: 35.4 U/day (11.5)	48.8 U/day (13.18)	13.4 U/day
Saurbrey, 1988[90] Random crossover *N*: 21; end of study: 19 Baseline: 0.67 U/kg/day (0.4)	Month 2.5: 0.62 U/kg/day (0.17) (values collected during treatment period)	0.64 U/kg/day (0.13) (values collected during treatment period)	0.02 U/kg/day
Schiffrin, 1982[91] Random crossover *N*: 20, end of study: 16 Baseline: 48 U/day	Month 6: 42 U/day	44 U/day, p = ns	2 U/day
Schmitz, 1989[86] Random crossover *N*: 10 Baseline: 0.6 U/kg/day (0.11)	Month 6: 0.55 U/kg/day (0.1)	Month 6: 0.6 U/kg/day (0.11), $p = 0.02$	0.05 U/kg/day
Tsui, 2001[79] Parellel RCT CSII *N*: 13; end of study: 12 MDI *N*: 14, end of study: 14 Baseline CSII: 0.7 U/kg/day (0.2) Baseline MDI: 0.7 U/kg/day (0.1)	Month 9: 0.6 U/kg (0.2)	0.7 U/kg/day (0.2). Treatment effect (adjusted for baseline insulin): –0.10 (95% CI–0.26 to 0.07), $p > 0.10$	0.1 U/kg/day

continued

TABLE 6 *Insulin dose in adults with Type 1 diabetes (cont'd)*

Study	Mean insulin dose (SD)		Difference (MDI – CSII)
	CSII	MDI	
Ziegler, 1990[84] Parallel RCT CSII *N*: 49; end of study: 36 MDI *N*: 47, end of study: 37 Baseline CSII: 49 U/day (17) Baseline MDI: 48 U/day (14)	Values not reported, but it is stated that daily insulin dose was similar in CSII and MDI at entry and during follow-up		

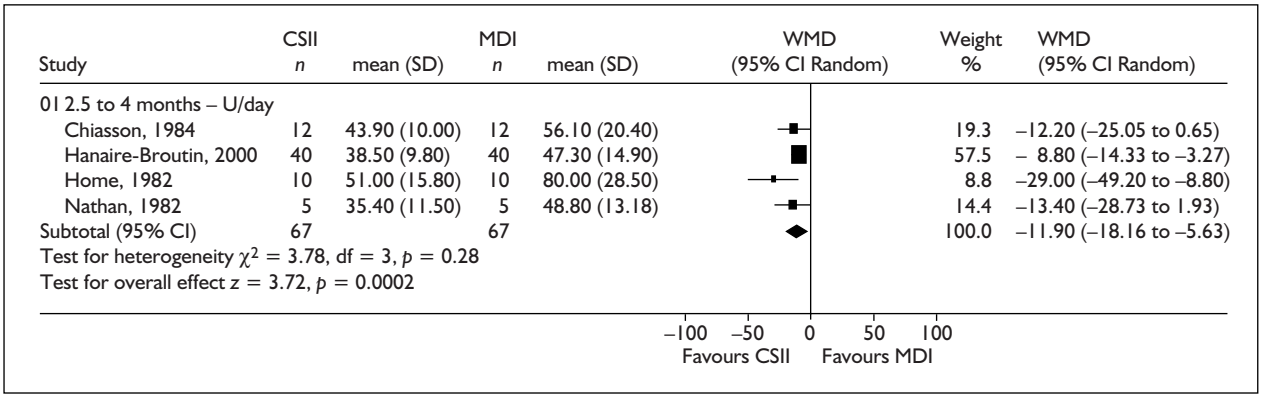

FIGURE 8 *Meta-analysis of the effects of CSII versus MDI on insulin dose (U/day) in adults with Type 1 diabetes*

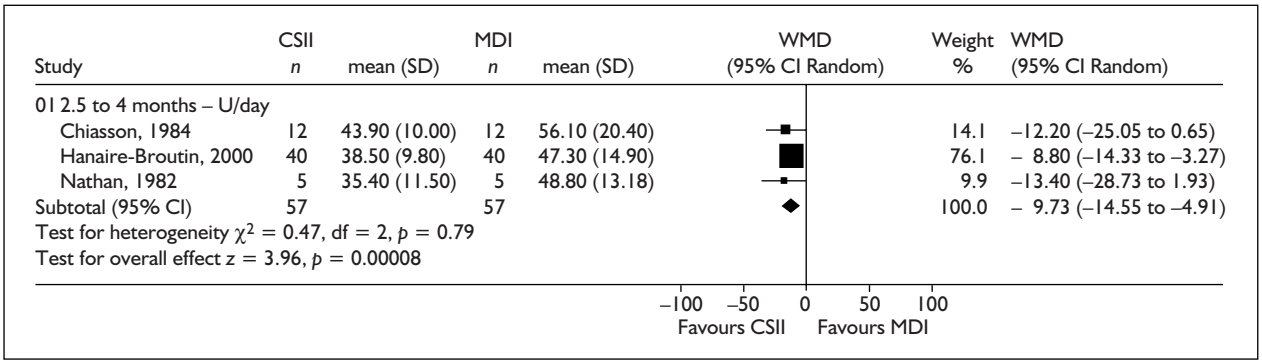

FIGURE 9 *Meta-analysis of the effects of CSII versus MDI on insulin dose (U/day) in adults with Type 1 diabetes, excluding Home and colleagues*[88]

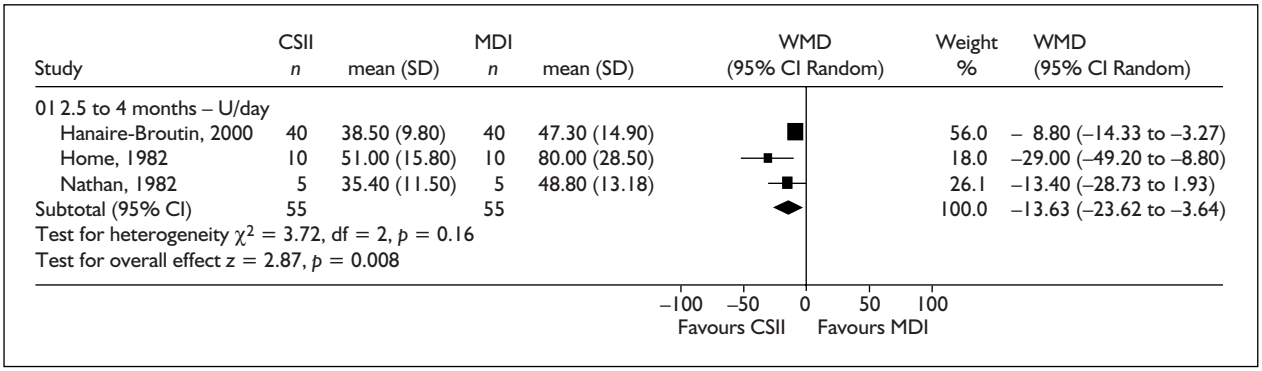

FIGURE 10 *Meta-analysis of the effects of CSII versus MDI on insulin dose in adults with Type 1 diabetes, excluding non-random studies*

Summary
In short-term studies, insulin dose is lower on CSII than on MDI, by about 12 units (20–25%), but there is little difference in longer term studies.

Body weight

Eight of the studies included in this review reported data on change in body weight in adults with Type 1 diabetes (*Table 7*).[78,80,81,83,84,86–88]

Two studies reported weight change at 10 weeks to 4 months of follow-up, with a mean increase from baseline of 0.5[80] to 1.3 kg[88] and –0.6[88] to 0.8 kg[80] for CSII and MDI, respectively. Home and colleagues[88] reported a significantly greater weight in individuals with CSII than with MDI (68.9 versus 67 kg, $p = 0.023$), whereas Hanaire-Broutin and colleagues[80] report a non-significant decrease of 0.3 kg with CSII.

Three studies reported weight change at 6 months of follow-up.[83,86,87] Body weight had increased from baseline in both groups, by 0.5 to 2.2 kg in CSII and by 0.4 to 2.0 kg in MDI.[83,86,87] Haakens and colleagues[83] reported a significantly lower weight with CSII compared with MDI (69.1 versus 70.6 kg, $p < 0.05$); conversely, Bak and colleagues[87] found that weight was lower with MDI (76.6 versus 74.8 kg, $p < 0.01$). Schmitz and colleagues[86] also found weight to be lower with MDI (73 versus 72.8 kg), but this difference was not statistically significant.

TABLE 7 *Weight change in adults with Type 1 diabetes*

Study	Mean weight (SD) (kg)		Difference (MDI – CSII) (kg)
	CSII	**MDI**	
Bak, 1987[87] Random crossover *N*: 20; end of study: 16 Baseline: 74.4 kg (9.7)	Month 6: 76.6 (9.6)	74.8 (9.7), $p < 0.01$	–1.8
Bode, 1996[81] Non-random crossover *N*: 55 Baseline not reported	Month 12: 68.1 (14.1) Month 24: 69.7 (15.2) Month 36: 70.0 (14.6) Month 48: 68 (15.2)	67.4 (14.4), p = ns	–0.7
Brinchmann-Hansen 1988[78] Parallel RCT CSII *N*: 15; MDI *N*: 15 Baseline: 68.6 kg (9.3)	Month 24: 70.5 (8.9)	75.1 (11.2), p = ns	4.6
Haakens, 1990[83] Non-random crossover *N*: 52; end of study: 35 Baseline: 68.6 kg (8.63)	Month 6: 69.1 (8.63)	70.6 (8.63), $p < 0.05$	1.5
Hanaire-Broutin, 2000[80] Random crossover *N*: 41; end of study: 40 Baseline: 68.2 kg (10)	Month 4: 68.7 (10)	69 (9.5), p = ns	0.3
Home, 1982[88] Random crossover *N*: 11, end of study: 10 Baseline: 67.6 kg (8.5)	Month 2.5: 68.9 (9.2)	67 (9.2), $p = 0.023$	–1.9
Schmitz, 1989[86] Random crossover *N*: 10 Baseline: 71.6 kg (17.2)	Month 6: 73 (17.8)	72.8 (18.4), p = ns	–0.2
Ziegler, 1990[84] Parallel RCT CSII *N*: 49; end of study: 36 MDI *N*: 47; end of study: 37 Baseline BMI: 22.1 kg/m^2	Final weight not reported Average weight gain after 2 years = 1.3 BMI (months 6–24) 22.5 kg/m^2	Final weight not reported Average weight gain after 2 years = 2.8 BMI (months 6–24) 24.2 kg/m^2, $p < 0.05$	

At 12 months of follow-up, Bode and colleagues[81] found no significant difference in body weight between CSII and MDI (68.1 versus 67.4 kg). The study also reported mean weight for CSII only at 24 (69.7 kg, SD 15.2), 36 (70.0 kg, SD 14.6) and 48 months (68 kg, SD 15.2) of follow-up, but did not follow MDI for this length of time.

Brinchmann-Hansen and colleagues[78] reported that weight had increased from baseline by 1.9 and 3.4 kg for CSII and MDI, respectively, at 24 months of follow-up. No significant difference was found between CSII and MDI (70.5 versus 75.1 kg). Ziegler and colleagues[84] also reported a non-significant mean weight gain from baseline (CSII 1.3, MDI 2.8 kg) at 24 months of follow-up. However, body mass index (BMI) was significantly lower in CSII than MDI (22.5 versus 24.2 kg/m^2, $p < 0.05$) after 6–24 months of follow-up, with a difference in BMI from baseline of –0.5 and +2.1 kg/m^2 for CSII and MDI, respectively.[84]

Summary
There was no consistent difference in weight between CSII and MDI treatment.

Lipid levels

The majority of studies included in this review did not report data on cholesterol or triglyceride levels (*Table 8*). Home and colleagues[88] found no significant difference in cholesterol after 10 weeks of either CSII or MDI [5.0 mmol/l (SD 0.6) versus 5.2 mmol/l (SD 0.6)].

Schiffrin and colleagues[91] found cholesterol to be significantly lower after 6 months of both CSII and MDI compared with baseline [CSII 163 mg/dl (SD 15) versus 190 mg/dl (SD 9), $p < 0.01$; MDI 162 mg/dl (SD 12) versus 183 mg/dl (SD 8), $p < 0.01$]. The difference between CSII and MDI was not statistically significant. Similarly, no difference in triglyceride levels was found between CSII and MDI [82 mg/dl (SD 14) versus 81 mg/dl (SD 12), p = ns].

Ziegler and colleagues[84] did not report data on cholesterol levels but stated that cholesterol levels increased within the normal range during the study without differences between groups.

Summary
There is little evidence with which to compare the effects on cholesterol levels of CSII and MDI.

Patient preference

Studies reported various forms of patient preference information, from patients' treatment preference to reasons for preference such as control, lifestyle, appearance or other reason.

Of the eight studies[80,82,83,86–88,90,91] reporting patient preference (*Table 9*), four studies[80,82,83,88] reported a greater proportion of patients preferring CSII to MDI treatment, ranging between 44% and 72.5%. Schiffrin and colleagues[91] reported no difference in the number of patients preferring to continue with CSII or MDI, with 12.5% of patients reverting to conventional treatment at the end of the study. However, three studies[86,87,90] reported a greater proportion of patients (57%–80%) preferring MDI to CSII. Two further studies[84,89] did not report patient preference but provided opinions of patients regarding treatments.

Reasons for preferring CSII included easier glycaemic control and greater flexibility of

TABLE 8 *Cholesterol and triglyceride levels in adults with Type 1 diabetes*

Study	Mean cholesterol and triglyceride level (SD)		Difference (MDI – CSII)
	CSII	**MDI**	
Home, 1982[88] Random crossover *N*: 11; end of study: 10	*Cholesterol* 2.5 months: 5 (0.6) mmol/l	5.3 (0.6) mmol/l	0.3 mmol/l
Schiffrin, 1982[91] Random crossover *N*: 20; end of study: 16	*Cholesterol* 6 months: 163 mg/dl (15) *Triglyceride* 6 months: 82 mg/dl (14)	162 mg/dl (12), p = ns 81 mg/dl (12), p = ns	–1 mg/dl –1 mg/dl
Ziegler, 1990[84] Parallel RCT CSII *N*: 49; MDI *N*: 47	Cholesterol levels increased within the normal range during the study without differences between treatment groups		

TABLE 9 *Patient preference and quality of life for adults with Type 1 diabetes*

Study	Patient preference/QoL	
	CSII	**MDI**
Bak, 1987[87] Random crossover. *N*: 20; end of study: 16	Preferring: 20% Reasons for preference: freedom from injections: 44% 75% discomforted by butterfly needle (on CSII), 56% discomforted by infuser itself at home, 21% discomforted by infuser at work QoL: not reported	80% 95% found pen easy to handle, 30% high frequency of injections a disadvantage Of total: independence of fixed mealtimes an advantage with MDI and CSII by 85%
Chiasson, 1984[82] Non-random crossover *N*: 12	Number preferring: 7 (58%) QoL: not reported	5 (42%)
Haakens, 1990[83] Non-random crossover *N*: 52; end of study: 35	Number preferring: 23/52 (44%) preferred CSII Reasons: Control Flexibility in terms of food intake allowed Avoid frequency injections: 2 (9%) Greater sense of well-being: 2 (9%) QoL: not reported	20/52 (38%) preferred MDI Reasons: Control: 17 (85%) More flexible lifestyle than CT without need to wear a device Preferred human isophane at bedtime: 16 (46%) Preferred human ultralente at bedtime: 7 (20%) No preference between bedtime insulin: 11 (31%)
Hanaire-Broutin, 2000[80] Random crossover *N*: 41; end of study: 40	Number preferring: 29 (72.5%) Of these 29, 21 previously on CSII + regular insulin and 8 on MDI QoL: not reported	11 (27.5%) Of these 11, 10 previously on CSII and 1 MDI
Home, 1982[88] Random crossover *N*: 11; end of study: 10	8 (80%) preferred pump to MDI, 4 wished to continue with it. Universally regarded as too large and uncomfortable QoL: not reported	None wished to continue with 3 daily injections owing to inconvenience
Nathan, 1982[89] Random crossover *N*: 5	Number preferring: not reported Ease of administering and adjusting insulin doses noted. A decrease in hypos and improved feeling of well-being contributed to acceptance of pump. Drawbacks: difficulty for women in dressing to accommodate pump, and removal of pump for watersports QoL: not reported	
Saurbrey, 1988[90] Random crossover *N*: 21; end of study: 19	Number preferring for future treatment: 6 (31.5%) Reasons: freedom in daily life: 11 (42%) QoL: not reported	12 (63%) 1 (5%) was unsure of preference (either ICT or CSII) Reasons: freedom in daily life: 11 (58%)

continued

TABLE 9 *Patient preference and quality of life for adults with Type 1 diabetes (cont'd)*

Study	Patient preference/QoL	
	CSII	**MDI**
Schiffrin, 1982[91] Random crossover *N*: 20; end of study: 16	Number preferring: 7 (44%) 7/16 (44%) of pts chose CSII for easier glycaemic control and also greater flexibility for meal hours and meal size CSII rejected for reasons of bulk, discomfort, a feeling of dependency on the machine and distortion of body image 70% would recommend CSII to a diabetic friend QoL: not reported	7 (44%) [2 pts reverted to conventional] 30% would recommend MDI to a diabetic friend
Schmitz, 1989[86] Random crossover *N*: 10	Number preferring: 4 (40%) QoL: not reported	6 (60%)
Tsui, 2001[79] Parallel RCT CSII *N*:13; end of study: 12 MDI *N*: 14 end of study: 14	Number preferring: not reported *QoL score: (mean)* Satisfaction 75.6 Impact: 69.9 Diabetic worry: 85.2 Social worry: 89.6 Global health: 68.2 Response rate 85%	*QoL score (mean):* 68.3 68.4 79.8 94.0 67.3 (p = ns for any of the subscales) Response rate 100%
Ziegler, 1990[84] Parallel RCT CSII *N*: 49; end of study: 36 MDI *N*: 47; end of study: 37	Number preferring: not reported 4 pts changed to MDI during study owing to technical problems with pump QoL: not reported	7 pts changed treatment group during study owing to explicit request to have a pump

pts, Patients.

meals[83,91] and freedom from injections.[87] Haakens and colleagues[83] reported that two of the 23 patients preferring CSII thought it was important to avoid frequent injections and two felt a sense of greater well-being, whereas the patients who preferred MDI found it practical and easy to administer and that it allowed a more flexible lifestyle than conventional treatment without the need to wear a pump. Nathan and colleagues[89] did not report levels of patient preference, but noted ease of administration and adjustment of insulin with CSII, and stated that a decreased number of hypoglycaemic episodes and improved feeling of well-being contributed to acceptability of the CSII. Saurbrey and colleagues[90] reported that 58% of patients felt that MDI gave the greatest freedom in daily life, compared with 42% who felt that CSII gave more freedom. Bak and colleagues[87] reported that 85% of patients found the independence of mealtimes with both CSII and MDI to be advantageous.

Home and colleagues[88] reported that eight of 10 patients preferred CSII to MDI and four of these wanted to continue with CSII rather than return to conventional treatment. However the authors noted that the pump was generally regarded as too large and uncomfortable. Similarly, the reasons given by patients in the study by Schiffrin and colleagues for not preferring CSII include the size of the device. However, both of these studies were published in 1982 when pumps were much larger than the present devices. Other drawbacks with the pump included discomfort from the needle or infuser,[87] problems of dressing to accommodate the pump for women and in watersports participation[89] and discomfort, distortion of body image and feeling of dependency on the device.[91]

Ziegler and colleagues[84] do not report level of patient preference, but do report that four patients changed to MDI from the CSII arm

owing to technical problems with the pump, and seven MDI patients explicitly requested a pump during the study.

Summary
Four of the eight studies reported that a greater proportion of patients preferred CSII, three studies found a greater proportion preferred MDI and one study found no difference. However, since some of these studies were done with older and bulkier pumps, their findings may not be relevant to today's pumps. Progress has also been made with MDI, for example the introduction of discreet 'pen' injectors. The three studies that reported that greater proportions preferred MDI were from 1987 to 1989; those where the majority preferred CSII were from 1982, 1984, 1990 and 2001.

Quality of life
Only one study (Tsui 2001)[79] reported on QoL (*Table 9*). Information was collected using the Diabetes Quality of Life (DQOL) tool. Two participants did not complete the DQOL, giving response rates of 85% for CSII and 100% for MDI, and just three of 1128 items were missing. No significant differences between CSII and MDI were found overall or on any of the subscales: satisfaction (7.3), impact (1.5), diabetic worry (5.4), global health (0.9) or social worry (–4.4).

Summary
There is little evidence with which to compare the effects of CSII and MDI on QoL.

Adverse effects
The definition of hypoglycaemic episodes varied, making comparison between studies difficult. Significantly fewer hypoglycaemic episodes with CSII therapy were observed in three studies,[81,85,87] but most studies found no statistical difference between CSII and MDI[78–80,83,89–91] (*Table 10*). Ziegler and colleagues reported significantly more episodes of blood glucose <50 mg/dl and reported symptoms of hypoglycaemia with CSII than MDI at 1–6 and 7–12 months of follow-up, but these tended to decrease in CSII so that at 19–24 months of follow-up the differences were no longer significant.[84]

Severe hypoglycaemic episodes differed little between treatments in most studies,[79,80,83,85–88,90,91] with no severe episodes occurring in two studies.[86,90] Significantly fewer severe hypoglycaemic episodes per 100 patients years occurred with CSII compared with MDI in the study by Bode and colleagues,[81] and similarly Brinchmann-Hansen and colleagues found hypoglycaemic coma occurred less frequently with CSII.[78] Ziegler and colleagues, however, found that hypoglycaemic coma was about twice as common in CSII than MDI.[84]

Two studies reported no occurrences of DKA with either treatment,[86,87] and another three studies reported no events with MDI[78,83,90] and one[83,90] or two[78] episodes with CSII. Bode and colleagues found rates of DKA to be less with CSII than MDI, although the difference was not significant (7.2 versus 14.6 events per 100 patient years). Nosadini and colleagues, however, reported significantly more ketotic events with both fixed-rate and variable rate CSII compared with MDI. About 20% of these episodes were caused by pump malfunction, and 23% of those with fixed basal rate and 27% of those with variable basal rate were caused by infective disease.[85] Ziegler and colleagues found an incidence of DKA of 9.7 events per 100 years in patients assigned to CSII and 8.1 events per 100 years in patients assigned to MDI; however, when the true therapy at the time of the event was analysed, more events occurred with CSII (14.1 versus 2.9 events per 100 years). However, it should be noted that the studies that report significant problems with DKA are the older ones.

The presence or absence of other adverse events was poorly reported in many of the studies. Pump malfunctions were reported in three studies, specified as the cause of about 20% of ketotic episodes by one study,[85] but occurring only once[88] or twice[89] in the other studies. Problems with catheters were reported in one study, in which the catheter became dislodged at night on six occasions.[89] Subcutaneous abscess occurred in one patient with CSII in two studies[83,89] and abscesses occurred in eight patients with CSII in the study by Brinchmann-Hansen and colleagues.[78] Subcutaneous infection occurred three times in one patient in another study.[90]

Caveats
In most of the RCTs, there was little difference in the frequency of severe hypoglycaemia. This evidence is in conflict with that from three other sources, namely observational studies, clinical opinion and patient experiences reported to us during this review. The observational studies include:

TABLE 10 *Adverse events for adults with Type 1 diabetes*

Study	Adverse events	
	CSII	**MDI**
Bak, 1987[87] Random crossover *N*: 20; end of study: 16	Frequency of BG values <4 mmol/l: 2.3% Severe hypos: 1 (requiring hospital treatment) DKA: 0	Frequency of background values <4 mmol/l: 4.1%, $p < 0.02$ Severe hypos: 0 DKA: 0
Bode, 1996[81] Non-random crossover *N*: 55	Severe hypos: 12 episodes (12 months) Severe hypos per 100 patient-years (*n*), significance from MDI: 12 months: 22 (55) $p < 0.0001$ 24 months: 26 (50) $p < 0.01$ 36 months: 39 (33) $p < 0.0001$ 48 months: 36 (25) $p < 0.01$ Of 25 pts with $HbA_{1c} \geq 8.0\%$, rate of severe hypos declined from 84 events per 100 patient years at baseline (MDI) to 8 events in year 1 ($p < 0.0001$). The 30 pts with baseline HbA_{1c} <8.0% also experienced a decline, from 183 to 33 severe hypos per 100 patient years ($p = 0.0005$). DKA rates were not significantly different between MDI and CSII phases (14.6 vs 7.2 events per 100 patient years, respectively)	Severe hypos: 76 episodes (12 months) Severe hypos per 100 patient years (*n*):138 (55)
Brinchmann-Hansen, 1988[78] Parallel RCT. CSII *N*: 15; MDI *N*: 15	Hypoglycaemia: mean (SEM): % of home BG <2.5 mmol/l: at randomisation = 6 (2); after 2 years = 11 (2) Symptomatic episodes/week/patient: At randomisation = 2.3 (0.6); at 2 years = 1.7 (0.3) Hypo coma: 2 (2) DKA: 2 (2) Subcutaneous abscess: 8 (6) Retinopathy: improved (14%), unchanged (29%), worsened (57%) (one patient had an allergy to fluorescein)	Hypoglycaemia: mean (SEM): % of home BG <2.5 mmol/l: at randomisation = 8 (3); after 2 years = 7 (1), vs CSII p = ns Symptomatic episodes/week/patient: At randomisation = 1.5 (0.3); at 2 years = 1.2 (0.2), vs CSII, p = ns. Hypo coma 14 (6), vs CSII $p < 0.001$. DKA 0, vs CSII p = ns Subcutaneous abscess 0, vs CSII $p < 0.01$ Retinopathy: Improved (7%), unchanged (43%), worsened (50%) (one patient had an allergy to fluorescein)
Haakens, 1990[83] Non-random crossover *N*: 52; end of study: 35	Subcutaneous abscess: 1 DKA: 1 requiring hospitalisation Severe hypos (episodes/patient/month): Total 1/7.5 (requiring glucose i.v./glucagon 1/96; assistance but not requiring glucose i.v./glucagon 1/8). No. of mild subjective hypos/week: 1.4 (SD 0.92)	Subcutaneous abscess: 0 DKA: 0 Severe hypos (episodes/patient/months): Total 1/5 (requiring glucose i.v./glucagon 1/79; assistance but not requiring glucose i.v./glucagon 1/5). CSII vs MDI p = ns. No. of mild subjective hypos/week: isophane 1.4 (SD 0.92), ultralente 1.5 (SD 1.17). CSII vs MDI p = ns.
Hanaire-Broutin, 2000[80] Random crossover *N*: 41; end of study: 40	Severe hypos: 2 pts, 3 events (severe hypos did not result in coma or seizures, external help needed to take sugar, but glucagon or glucose injection not required) Hypos during last 14 days of each treatment period: 3.9 (4.2)	Severe hypo: 1 patient, 1 event Hypos during last 14 days of each treatment period: 4.3 (3.9), p = ns

continued

TABLE 10 *Adverse events for adults with Type 1 diabetes (cont'd)*

Study	Adverse events	
	CSII	**MDI**
Home, 1982[88] Random crossover. *N*: 11; end of study: 10 Baseline hypo 1.1 (0–4) episodes per pt biweekly	Hypos: 0.6 (0–3) episodes per pt biweekly. Pump malfunction: 1 (1 pt × 3 hypo episodes in 16 h due to faulty pump) 1 patient required intravenous glucose	Hypos: 0.8 (0–7) episodes per pt biweekly
Nathan, 1982[89] Random crossover *N*: 5	During 2.5 patient years CSII: subcutaneous abscess needing oral antibiotics (1), pump malfunctions (2) catheter dislodged at night (6) Hypo reactions *n*/week at 3 months: 1 (0.25)	Hypo reactions *n*/week at 3 months: 2.5 (0.61), p = ns
Nosadini, 1988[85] Parallel RCT CSII fixed *N*: 19; MDI *N*: 15; CSII variable *N*: 10	Mean events/pt/yr: *CSII with fixed night basal rate:* Hyper: 18 (5) vs MDI, p = ns Ketotic events: 0.13 (0.02) vs MDI, $p < 0.01$ Mild hypos: 36 (10) vs MDI, $p < 0.01$ Severe hypos: 0.14 (0.05) vs MDI, $p < 0.01$ Sudden death: 0.04 (1 pt dead in bed) *CSII with variable night basal rate):* Hyper: 17 (4) vs MDI, p = ns Ketotic events: 0.16 (0.03) vs MDI, $p < 0.05$ Mild hypos: 30 (11) vs MDI, $p < 0.01$ Severe hypos: 0.16 (0.09) vs MDI, $p < 0.01$ [CSII–HOR vs CSII–FBR, all p = ns] Malfunction of pump caused about 20% of ketotic episodes in both CSII groups. 23% (CSII fixed) and 27% (CSII variable) caused by infective disease	Hyper: 20 (3) Ketotic events: 0.03 (0.01) Mild hypos: 59 (12) Severe hypos: 0.42 (0.15)
Saurbrey, 1988[90] Random crossover *N*: 21; end of study: 19	Severe hypos: 0 No. of subjective or biochemical (BG <2.5 mmol/l) hypos in each group, p = ns (values not given). Ketoacidosis = 1 (due to acute gastroenteritis and failure to take extra insulin, not pump malfunction) Subcutaneous infection (3 times) in same patient, one required surgical incision	Severe hypos: 0
Schiffrin, 1982[91] Random crossover *N*: 20; end of study: 16	Mild hypos: 186 Moderate hypos: 10 Severe hypos: 1 (due to delaying meal after bolus insulin taken – intravenous glucose was administered)	Mild hypos: 189, p = ns Moderate hypo: 11, p = ns Severe hypos: 0, p = ns
Schmitz, 1989[86] Random crossover *N*: 10	Severe hypos: 0 DKA: 0	Severe hypos: 0 DKA: 0
Tsui, 2001[79] Parallel RCT CSII *N*:13; end of study: 12 MDI *N*: 14; end of study: 14	Severe hypos: 6 Mean number of hypos each month, 8.9 (3 months), 7.2 (6 months), 7.0 (9 months), 8.0 (overall)	Severe hypos: 4, $p > 0.10$ Mean number of hypos each month, 5.0 (3 months), 9.0 (6 months), 9.2 (9 months), 7.4 (overall), all = ns vs CSII Relative treatment effect (CSII-MDI)/MDI for overall no. of hypos: +9% (95% CI –37 to +87), $p > 0.10$

continued

TABLE 10 *Adverse events for adults with Type 1 diabetes (cont'd)*

Study	Adverse events	
	CSII	**MDI**
Ziegler, 1990[84] Parallel RCT CSII *N*: 49; end of study: 36. MDI *N*: 47; end of study: 37	No. of metabolic complications/6 months mean (range). Reviewer has calculated mean of the 4 × 6 month periods to give totals below. Mild hypos (BG <50 mg/dl): 15.5 (0–70) Mild hypos (symptoms): 19.8 (0–104) Severe hypos (req. assistance): 0.091 (0–7) Severe hypos (coma): 0.101 (0–4) Ketosis (BG >200 mg/dl and ketonuria): 6.5 (0–57) Ketoacidosis: 0.046 (0–1) Frequency of pts (no. of events/100 years): Hypos requiring assistance: 13.9 (18.1) Hypos (coma): 30.6 (19.4) DKA: 13.9 (9.7) [true therapy at time of event: 15.4 (14.1)]	Mild hypos (BG <50 mg/dl): 10.6 (0–53) Mild hypos (symptoms): 10.1 (0–81) Severe hypos (requiring assistance): 0.070 (0–2) Severe hypos (coma): 0.048 (0–1) Ketosis (BG >200 mg/dl and ketonuria): 7.8 (0–85) Ketoacidosis: 0.040 (0–3) Frequency of pts (no. of events/100 years): Hypos requiring assistance: 16.2 (13.5) Hypos (coma): 13.5 (9.5) DKA: 8.1 (8.1) [true therapy at time of event: 5.9 (2.9)]

FBR, fixed basal rate; HOR, higher overnight rate; SEM, standard error of mean.

- Boland and colleagues,[98] who reported a drop in hypoglycaemic events requiring assistance from 134 per 100 person years on MDI to 76 per 100 person years on CSII, in adolescents.
- Mack-Fogg and colleagues,[99] in abstract only, report a reduction in severe hypoglycaemic events in children after transfer from MDI to CSII, from a mean of 0.55 to 0.25 per child per year.
- Rudolph and Hirsch[100] found that there were 73 severe hypoglycaemic events per 100 patient years on MDI, but only 19 on CSII.
- Haardt and colleagues,[101] in a retrospective analysis of the Hotel–Dieu cohort, found that glycated haemoglobin levels decreased 'only modestly' (from 9.3% on injections to 8.6% on CSII), but that the number of severe hypoglycaemic events fell by over 75%.

A possible explanation is that patients recruited to the trials may be roughly representative of those seen in clinics, although with a bias to the most cooperative (because of the demands of trials) who may have better control than average, whereas in routine care as reflected more in the observational studies, CSII may be used mostly in those who are having considerable problems with control, either high glycated haemoglobin or frequent hypoglycaemic events.

Summary

Hypoglycaemic events did not differ significantly between CSII and MDI in most trials, but three found fewer hypoglycaemic episodes with CSII and one study found more hypoglycaemia and hypoglycaemic coma with CSII. Observational studies found much greater reductions in the frequency of severe hypoglycaemia with CSII, but are more prone to bias.

Pregnancy

Four parallel RCTs[92–95] compared the effects of CSII with MDI in pregnancy (*Tables 4* and *11–14*, Appendices 7 and 11), although the sample size in three of the studies was small (14–32).[92–94] Carta and colleagues[94] included women with Type 1 and Type 2 diabetes diagnosed before pregnancy and analysed these groups separately. Nosari and colleagues[92] and Coustan and colleagues[93] included women with Type 1 diabetes who were pregnant or planning pregnancy, and Burkart and colleagues included women with Type 1 diabetes attending no later than the first trimester.[95]

Glycated haemoglobin

Burkart and colleagues did not report data on glycated haemoglobin, simply stating that patients in both groups had normal mean glucose and HbA_1 <7.5% at least from the end of the first trimester on.[95] During the first trimester in the other studies, glycated haemoglobin was lower

TABLE 11 *Glycated haemoglobin in pregnant women*

Study	Mean glycated haemoglobin (%) (SD)		Difference (MDI – CSII)
	CSII	**MDI**	
Burkart, 1988[95] Parallel RCT CSII *N*: 48; MDI *N*: 41 Baseline not reported	Data not reported. States that patients selected in the CSII or MDI group had normal mean glucose and HbA_1 <7.5% at least from the end of the first trimester on.		
Carta, 1986[94] Parallel RCT *Type 1* CSII *N*: 8; MDI *N*: 7 HbA_1 data collected Baseline CSII: 8.75% Baseline MDI: 9.1%, p = ns	Weeks 9–11: 7.8 Weeks 19–21: 7 Weeks 33–35: 7 Weeks ≥ 37: 6.5	8.5, p = ns 7.75, p = ns 6.95, p = ns 6.45, p = ns	0.7 0.75 –0.05 –0.05
Carta, 1986[94] Parallel RCT. *Type 2* CSII *N*: 6, MDI *N*: 8. HbA_1 data collected Baseline CSII: 8.1% Baseline MDI: 8.2%, p = ns	Weeks 9–11: 7 Weeks 19–21: 6.75 Weeks 33–35: 6.5 Weeks ≥ 37: 6	8.1, p = ns 7.2, p = ns 6.7, p = ns 6.7, p = ns	1.1 0.45 0.2 0.7
Coustan, 1986[93] Parallel RCT CSII *N*: 11; MDI *N*: 11 HbA_1 data collected Baseline CSII: 8.6% (1.7) Baseline MDI: 9.1% (1.5), p = ns	Therapy week 8: 7 Term: 6.3 (0.6)	7.5, p = ns 6.4 (0.4), p = ns	0.5 0.1
Nosari, 1993[92] Parallel RCT CSII *N*: 16; MDI *N*: 16 HbA_{1c} data collected Baseline not reported	1st trimester: 6 (3.6) 2nd trimester: 6.8 (5.6) 3rd trimester: 6.3 (2)	6.2 (1.6), $p > 0.5$ 6.1 (2.4), $p > 0.5$ 6.2 (0.8), $p > 0.5$	0.2 –0.7 –0.1

with CSII than MDI (0.2–1.1%) in both Type 1 diabetes[92,94] and Type 2 diabetes,[94] but these differences were not statistically significant (*Table 11*). Similarly, there were no significant differences between CSII and MDI during the second trimester (–0.7 to 0.75%)[92,94] or term (–0.1 to 0.7%).[94]

Insulin dose

There was no significant difference between CSII and MDI in total daily insulin dose in Type 1 diabetes[92,94] or Type 2 diabetes[94] during the first, second or third trimesters (*Table 12*). However, Coustan and colleagues[93] found that fewer insulin units per kilogram per day were required with CSII than with MDI [first trimester, 0.71 U/kg/day (SD 0.16) versus 1.01 U/kg/day (SD 0.28), p = 0.101; second trimester 1.02 U/kg/day (SD 0.53) versus 1.40 U/kg/day (SD 0.4), p = 0.027; third trimester, 1.26 U/kg/day (SD 0.49) versus 1.63 U/kg/day (SD 0.51), p = 0.041]. Daily insulin dose was not reported by Burkart and colleagues.[95]

Pregnancy outcomes

The mean duration of pregnancy was 38.1–38.9 weeks in CSII and 37.7–38.8 weeks in MDI, with no significant differences between the groups for Type 1 or Type 2 diabetes[92–95] (*Table 13*). Nosari and colleagues[92] reported three intrauterine deaths: two in the CSII group and one in the MDI group. In one case from each group, the cause of death was a severe reduction in placental blood flow; the cause of the third death was unknown. Burkart and colleagues reported two deaths in the CSII group, one intrauterine death due to cause unknown and one death at 3 months postpartum following premature delivery and maternal ketoacidosis. Three deaths occurred in the MDI group at 3 days, 5 days and 3 months postpartum due to

TABLE 12 *Insulin dose in pregnant women*

Study	Mean insulin dose (SD)		Difference (MDI – CSII)
	CSII	**MDI**	
Carta, 1986[94] Parallel RCT *Type 1* CSII *N*: 8; MDI *N*: 7 Baseline CSII: 31.5 U/day Baseline MDI: 27.8 U/day, p = ns	Month 3: 37 U/day Month 6: 42 U/day Month 9: 49.1 U/day	32 U/day, p = ns 47 U/day, p = ns 60.4 U/day, p = ns	–5 U/day 5 U/day 11.3 U/day
Carta, 1986[94] Parallel RCT *Type 2* CSII *N*: 6; MDI *N*: 8 Baseline not reported	Month 3: 23.1 U/day Month 6: 36 U/day Month 9: 52.8 U/day	28 U/day, p = ns 49 U/day, p = ns 51.2 U/day, p = ns	4.9 U/day 13 U/day –1.6 U/day
Coustan, 1986[93] Parallel RCT CSII *N*: 11; MDI *N*: 11 Baseline CSII: 0.9 U/kg/day (0.42) Baseline MDI: 1.05 U/kg/day (0.38), p = 0.381	1st trimester: 0.71 U/kg/day (0.16) 2nd trimester: 1.02 U/kg/day (0.53) 3rd trimester: 1.26 U/kg/day (0.49)	1.01 U/kg/day (0.28), p = 0.101 1.4 U/kg/day (0.4), p = 0.027 1.63 U/kg/day (0.51), p = 0.041	0.3 U/kg/day 0.38 U/kg/day 0.37 U/kg/day
Nosari, 1993[92] Parallel RCT CSII *N*: 16; MDI *N*: 16 Baseline not reported	1st trimester: 39.6 U/day (22.8) 2nd trimester: 48.1 U/day (20.8) 3rd trimester: 57.3 U/day (21.6)	36 U/day (24.4), $p > 0.5$ 43.7 U/day (35.6), $p > 0.5$ 54.7 U/day (39.2), $p > 0.5$	–3.6 U/day –4.4 U/day –2.6 U/day

toxoplasma infection, hypoplastic left heart and renal vein thrombosis, respectively.[95] No intrauterine deaths occurred in the other two studies.[93,94] The proportion of babies delivered by Caesarean section varied between the studies, but tended to be similar between CSII and MDI in Type 1 diabetes. Carta and colleagues,[94] however, reported that in Type 2 diabetes, one of nine (16.7%) women with CSII underwent Caesarean section compared with three of eight (37.5%) women with MDI. There was no significant difference in birthweight between CSII and MDI in any of the studies. A small number of preterm, small for gestational age or large for gestational age infants were observed in both groups, with little apparent difference between the groups.

Patient preference and quality of life

Patient preference and QoL were not reported by the four studies comparing CSII and MDI in pregnancy.

Adverse events

No pump malfunctions were reported, although one study reported three catheter disconnections[94] and another stated that catheter leakage or occlusion occurred infrequently and resolved quickly[93] (*Table 14*). Carta and colleagues[94] reported that among Type 2 diabetes patients, episodes of mild hypoglycaemia were few and did not occur in all patients. One severe hypoglycaemic episode occurred among the Type 1 diabetes patients, but the treatment group was not specified. Coustan and colleagues[93] found more severe hypoglycaemic episodes in the MDI group than in the CSII group (45% versus 27%), although the authors noted that the groups were too small to attain statistical significance. Two other studies, however, found slightly more severe episodes[92] and undefined hypoglycaemia[95] with CSII. Ketoacidosis occurring in CSII group but not the MDI group was reported by two studies.[92] It is important to bear in mind that even one episode of ketoacidosis could lead to fetal death.[95]

Summary

There is insufficient evidence from these studies that CSII is better than MDI in pregnancy for achieving glycaemic control. If CSII or any other form of intensified therapy is to be optimally effective in pregnancy, it would have to start before conception, partly to minimise risk of

TABLE 13 *Outcomes of pregnancy*

Study	CSII	MDI
Burkart, 1988[95] Parallel RCT CSII *N*: 48 MDI *N*: 41	Duration: mean 38.4 weeks Live births: 47/48 (97.9%) Birth weight: mean 3082.7 (units not specified) No. Caesarean: 24/48 (50%) Complications in pregnancy: Pyelonephritis 5 Premature labour 4 Premature rupture 2 Premature delivery 7 Pre-eclampsia 3 Growth retardation 3 Hypoglycaemia 5 Still birth 1 Ketoacidosis 1 Total: 12/48 pregnancies had one or more complications Fetal outcome: Healthy newborns 40 Minor symptoms 8 Major symptoms 0 Glucose i.v. 14 Overall mortality up to age 1 year = 2/48 (4.2%)	Duration: mean 38.2 weeks Live births: 100% Birth weight: mean 3319.5 (units not specified) No. Caesarean: 15/41 (36.6%), p = ns Complications in pregnancy: Pyelonephritis 6 Premature labour 3 Premature rupture 1 Premature delivery 4 Pre-eclampsia 3 Growth retardation 1 Hypoglycaemia 3 Still birth 0 Ketoacidosis 0 Total: 13/41 pregnancies had one or more complications (vs CSII p = ns) Fetal outcome: Healthy newborns 34 Minor symptoms 5 Major symptoms 2 Glucose i.v. 9 (all p = ns vs CSII) Overall mortality up to age 1 year = 3/41 (7.3%), vs CSII $p < 0.05$[a] Incidence of complications in both groups is linked to the severity of maternal diabetes (White's criteria). Birthweight reported according to White's criteria decreases with severity. Differences in mean birthweights, p = ns.
Carta, 1986[94] Parallel RCT *Type* 1 CSII *N*: 8 MDI *N*: 7	Duration: mean 266.7 days (SD 7.6) Live births: 100% Birth weight: mean 3395 g (SD 407) No. Caesarean: 3 (37.5%) 1 preterm due to hydramnios and fetal megalosomnia. 1 large for gestational age. 1 macrosomnic (>4000 g). [CSII or MDI group not specified: 2 infants depressed, 5 metabolic morbidity (hypoglycaemia, hypocalcaemia, hyperbilirubinaemia), 2 congenital cardiac malformations]	Duration: mean 263.6 days (SD 17.7) Live births: 100% Birth weight: mean 2906 g (SD 553), CSII vs MDI p = ns No. Caesarean: 3 (42.9%) 1 preterm due to metrotthagia caused by central placenta previa
Carta, 1986[94] Parallel RCT *Type* 2 CSII *N*: 6 MDI *N*: 8	Duration: mean 272 days (SD9) Live births: 100% Birth weight: mean 3292 g (SD 578) No. Caesarean: 1 (16.7%) 1 preterm due to premature rupture of membranes. 1 large for gestational age	Duration: mean 269 days (11.7) Live births: 100% Birth weight: mean 2994 g (SD 512), CSII vs MDI p = ns No. Caesarean: 3 (37.5%) 1 preterm due to premature rupture of membranes. 1 small for gestational age
Coustan, 1986[93] Parallel RCT CSII *N*: 11 MDI *N*: 11	Duration: mean 38.1 weeks (SD 2.1) Live births: 100% Birth weight: mean 3050 g (SD 675) No. Caesarean: 7 (63.6%) One birthweight above 90th percentile, 2 small for gestational age babies. Neonatal hypoglycaemia in one	Duration: mean 38.8 weeks (SD 1.4) Live births: 100% Birth weight: mean 3324 g (SD 475), CSII vs MDI p = ns No. Caesarean: 7 (63.6%) 1 baby moderate respiratory distress syndrome. Neonatal hypoglycaemia in one

continued

TABLE 13 *Outcomes of pregnancy (cont'd)*

Study	CSII	MDI
Nosari, 993[92] Parallel RCT CSII *N*: 16 MDI *N*: 16	Duration: mean 38.9 weeks (SD 7.6) Live births: 87.5% Birth weight: mean 3130 g (SD 1480) No. Caesarean: 9 (56.3%) 2 intrauterine deaths. No fetal congenital malformations, macrosomia or low Apgar scores (<7 at 5 minutes) 1 CSII large for age. Respiratory distress in 1 CSII infant. Neonatal hypo (plasma glucose <30 mg/dl) in one CSII	Duration: mean 38.2 weeks (SD 10), CSII vs MDI $p > 0.5$ Live births: 93.8% Birth weight: mean 3010 g (SD 1728), CSII vs MDI $p > 0.5$ No. Caesarean: 7 (43.8%) 1 intrauterine death. 2 MDI small for age. 1 premature MDI birth. Neonatal hypo (plasma glucose < 30 mg/dl) in one MDI

[a] The *p*-value reported in the paper appears to be incorrect, and should be statistically insignificant.

TABLE 14 *Adverse events in pregnant women*

Study details	CSII	MDI
Burkart, 1988[95] Parallel RCT CSII *N*: 48 MDI *N*: 41	Hypoglycaemia: 5 Ketoacidosis: 1	Hypoglycaemia: 3 Ketoacidosis: 0
Carta, 1986[94] Parallel RCT *Type 1* CSII *N*: 8 MDI *N*: 7	Injection site infection: 0 Pump malfunction: 0 Other: catheter disconnection: 3 In all pts, no hypo coma. One severe hypo (group not stated). Mild hypos occurred on average once every 15–20 days.	
Carta, 1986[94] Parallel RCT *Type 2* CSII *N*: 6 MDI *N*: 8	Episodes of mild hypos were few and did not occur in all patients	
Coustan, 1986[93] Parallel RCT CSII *N*: 11 MDI *N*: 11	Injection site infection: 0 Pump malfunction: 0 Mild hypos: 11 patients Moderate hypos: 6 patients Severe hypos: 3 patients (8 episodes) DKA: 0 Other: 1 hyperglycaemia and ketonuria (2 days) during viral infection Catheter leakage or occlusion occurred infrequently and resolved quickly	Mild hypo: 11 patients Moderate hypos: 10 patients Severe hypos: 5 patients (23 episodes) DKA: 0 one subject had 17 hypos related to dietary irregularities
Nosari, 1993[92] Parallel RCT CSII *N*: 16 MDI *N*:16	Severe hypos: 3 DKA: 3	Severe hypos: 1, CSII vs MDI $p > 0.5$ DKA: 0, CSII vs MDI $p > 0.1$

TABLE 15 *Glycated haemoglobin and daily insulin dose in adolescents*

Study	Mean HbA_1 (SD) (%)			Mean daily insulin dose (SD) (U/day)		
	CSII	**MDI**	**CSII + MDI**	**CSII**	**MDI**	**CSII + MDI**
Schiffrin, 1984[97] Random crossover *N*: 20 Baseline HbA_1: 13% (1) Baseline daily insulin dose: 64 U/day (14)	Month 3: 8.75 Month 4: 8.8 CSII vs MDI $p < 0.05$ CSII vs CSII + MDI $p < 0.05$	9.5 9.6	9 9.3	Month 4: 44 CSII vs MDI $p < 0.001$ CSII + MDI vs MDI $p < 0.001$	60	48
Tamborlane, 1989[96] Random crossover *N*: 10 Baseline HbA_1: 12.2% (4.11) Baseline daily insulin dose: 1.1 U/day (0.32)	Month 6: 8.5 (1.26)	8.7 (1.58), p = ns		Month 6: 1.3 (3.16)	1.4 (0.32), p = ns	

malformation and partly because it may take a few months to learn how to use the intensified regimen.

Adolescents

Two randomised crossover studies compared the effects of MDI and CSII in adolescents aged up to 20 years with Type 1 diabetes,[96,97] one of which also included treatment with CSII overnight plus MDI during the day (CSII + MDI)[97] (*Tables 4*, *15* and *16*, Appendices 8 and 12).

Glycated haemoglobin

After 1 month, glycated haemoglobin was significantly lower than baseline [13% (SD 1), $p < 0.001$] in all three groups (*Table 15*) in the study by Schiffrin and colleagues.[97] At 4 months of follow-up, glycated haemoglobin was significantly lower with CSII (8.8%) than with MDI (9.6%, $p < 0.05$) or CSII + MDI (9.3%, $p < 0.05$). The difference between CSII + MDI and MDI was not statistically significant.[97] However, although Tamborlane and colleagues also found a decrease in glycated haemoglobin with both CSII and MDI compared with baseline ($p < 0.05$), they found no significant difference between CSII and MDI after 6 months of follow-up (8.5% versus 8.7%, p = ns).[96]

Insulin

Total daily insulin dose was significantly lower during both CSII (44 U/day) and CSII + MDI (48 U/day) than at baseline [64 U/day (SD 14), $p < 0.001$] or during MDI (60 U/day, $p < 0.001$) in the study by Schiffrin and colleagues[97] (*Table 15*). Conversely, Tamborlane and colleagues found an increase in insulin dose with both CSII and MDI compared with baseline ($p < 0.05$), but no significant difference between CSII and MDI after 6 months of follow-up (1.3 versus 1.4 U/day, p = ns).[96]

Patient preference and quality of life

QoL was not reported by either study.[96,97] At the end of the study by Schiffrin and colleagues, over half of patients (55%) chose to be treated with CSII and all patients stated that they would recommend this treatment to a friend (*Table 16*). Four patients (20%) chose to continue with MDI and three (15%) with CSII + MDI, and two (10%) patients returned to using twice daily injections. MDI and CSII + MDI would be recommended to others by 66% and 70% of patients respectively.[97]

Adverse events

Both studies reported few severe hypoglycaemic episodes[96,97] (*Table 16*). Schiffrin and colleagues[97] reported that there was no difference in the number of hypoglycaemic events between treatments, although numbers are not stated, and that they were mostly mild and averaged one per week per patient. Similarly, Tamborlane and colleagues reported that episodes of mild hypoglycaemia were common during each treatment.[96] No other adverse events were reported by either study.

Summary

One study found no significant difference between CSII and MDI, whereas the other study showed a

TABLE 16 *Patient preference and adverse events among adolescents*

Study	CSII	MDI	CSII + MDI
	Patient preference		
Schiffrin, 1984[97] Random crossover *N*: 20	No. preferring: 11 (55%) 100% would recommend CSII to a friend	No. preferring: 4 (20%) 66% would recommend MDI to a friend	No. preferring: 3 (15%) 70% would recommend CSII + MDI to a friend (2 of 20 completing study reverted to twice daily injections)
	Adverse events		
	Severe hypos: 1	Severe hypos: 1 (due to inadvertent administration of extra NPH dose)	Severe hypos: 0
	Note: No difference in hypos between treatments. Mostly mild and averaged one per week per patient. Same pt had severe hypos on CSII and MDI.		
Tamborlane, 1989[96] Random crossover *N*: 10	Mild hypos were common during each treatment. States that there was only one severe hypo requiring assistance during each 6-month treatment period		

clear benefit of CSII on glycated haemoglobin and insulin dose.

CSII in children

No published randomised trials were found either by our searches or in published reviews.[65,102–104] *Table 17* summarises results from some case series. Some include both adolescents and children.

Two recent abstracts from the ADA 2002 conference were found. The first, by Fox and colleagues,[109] gives only sparse data, and it is not clear what treatment patients were on before starting CSII. They may have been newly diagnosed. Numbers are small, 10 patients to date. This study was excluded. The second abstract, by Weintrob and colleagues,[110] is further advanced, with 23 children aged 9–14 years. It is a crossover study with 3.5 months on each of CSII and MDI. There was no difference in HbA_{1c} but there were fewer hypoglycaemic episodes on CSII.

These studies suggest that CSII has a place in treatment of children with diabetes, but case series are more susceptible to bias than RCTs and better evidence is needed. In most cases, children were switched directly from CT to CSII. Nowadays, children are more likely to go from MDI to CSII. Some may have problems running out of skin sites with MDI. One small study in 10 children aged 7–10 years studied a combination of CSII from dinner until dawn and prebreakfast lispro and NPH; the comparator was three-injection MDI.[66] The study was very short, with only 4 weeks stable on each treatment. HbA_{1c} results were not available given those durations. Blood glucose results improved. For children unable to use 24-hour CSII, this may be a useful option, but further research is needed.

Overnight-only CSII in adults

There is little evidence on overnight-only CSII in adults. Olsson and colleagues in 1987[68] compared a bedtime injection of intermediate acting insulin with overnight CSII in 10 patients, but on only four nights. Kanc and colleagues[69] carried out a 2-month crossover study and reported less hypoglycaemia and improved hypoglycaemic episode awareness.

Short-term CSII in poorly controlled adults with Type 2 diabetes

There is little evidence for this. Valensi and colleagues[111] carried out a short-term study, duration 8–23 days, but CSII was combined with metformin, and with strict diet, in patients admitted to hospital. Little can be deduced about CSII from this study.

Another paper from France[112] studied all their Type 2 diabetes patients with poor control on maximal oral therapy. Many needed permanent insulin treatment, but a group of 111 remained on oral treatment apart from two 3-day periods on CSII, and their HbA_{1c} improved from 8.76% at the start of the period to 7.82% at the end, with slight weight loss. Hence there may be a place for short-term use of CSII, but further research is required.

TABLE 17 *CSII in children: case series*

Study	No. of patients	Previous treatment	Reason for starting CSII	$HbA_{1(c)}$ before	$HbA_{1(c)}$ after (%)	Discontinuation rate (%)
Brink, 1986[61]	24	CT	Poor control	14.8	13.3	30
Levy-Marchal, 1988[62]	7	CT	Trial	9.3	7.3	43 (3 pts)
Steindel, 1995[105]	6	CT	Non-compliance and brittle diabetes	9.2	9.0	–
Maniatis, 2001[106]	56, aged 7–23	Unclear	Poor control, flexibility of lifestyle, avoiding MDI	8.5	8.3	–
Bougneres, 1984[64]	6, aged 1–4 years	CT	Poor control	11.7	9.3	–
Conrad, 2002[107]	65	MDI	Various, including poor control, patient preference, hypos, dawn phenomenon	8.4	No significant difference	–
Boland, 1999[98]	75, allowed choice	CT	Post-DCCT research study		8.3 on MDI; 7.5 on CSII	Almost all continued CSII
Ahern, 2002[108]	161, aged 18 months–18 years	CT? but with some intensive features such as BG monitoring	Offered to those interested	7.1 in pre-schoolers 7.8 in 7–11 year-olds 8.1 in 12–18 year-olds	6.5 7.3 8.1	98% remained on CSII

Analogue versus soluble insulin in CSII

Quantity and quality of research

Six studies (one parallel RCT[113] and five randomised crossover studies[114–118]) comparing rapid-acting analogues with soluble insulin in CSII were included in the review and are reported in *Tables 18–23* and Appendices 9 and 13. Bode and colleagues[113] compared two analogue insulins, lispro and aspart, whereas the other studies included insulin lispro. Randomisation and allocation concealment were adequate in the parallel RCT,[113] but the method of randomisation was not reported in the five crossover studies[114–118] (*Table 18*). The similarity of the groups at baseline was reported in two studies,[113,117] and all studies reported eligibility criteria. Five studies[113,114,116–118] reported point estimates and measures of variability for the primary outcome measure; however, Schmauss and colleagues[115] reported the mean and standard error of glycated haemoglobin for each treatment at crossover and end of study, but did not combine the two periods. Raskin and colleagues[117] were the only group to perform ITT analysis. Loss to follow-up was adequately reported in two studies,[115,118] partially reported (number but not reasons, or vice versa) in one study[113] and inadequately reported (numbers not stated for each group) in two studies.[116,117] Loss to follow-up was not reported by Renner and colleagues.[114]

Adults with Type 1 diabetes

Glycated haemoglobin

Glycated haemoglobin was reported in all included studies (*Table 19*), which were combined in a meta-analysis (*Figure 11*). Pooling these data (final values and changes from baseline included as separate subgroups[119]) using a random effects model (χ^2 test for heterogeneity 9.09, df = 5, $p = 0.11$) showed a significant decrease in glycated haemoglobin with the analogue insulin lispro compared with soluble (–0.26%, 95% CI –0.47 to –0.06). The study by Bode and colleagues included a third group with insulin aspart.[113] Replacing lispro with aspart for this study in the meta-analysis made little difference to the overall treatment effect (–0.27%, 95% CI 0.44 to –0.10).

Insulin dose

Insulin requirement varied between the studies (*Table 20*); however, none of the five studies reporting insulin dose found a significant

TABLE 18 *Quality assessment of studies comparing analogue versus soluble insulin*

Study	Random	Allocation concealment	Group similarity	Eligibility criteria	Point estimates	ITT	Withdrawals
Bode, 2002[113]	Adequate	Adequate	Reported	Adequate	Adequate	Inadequate	Partial
Melki, 1998[116]	Unknown	Unknown	Unknown	Adequate	Adequate	Inadequate	Inadequate
Raskin, 2001[117]	Unknown	Unknown	Reported	Adequate	Adequate	Adequate	Inadequate
Renner, 1999[114]	Unknown	Unknown	Unknown	Adequate	Adequate	Inadequate	Unknown
Schmauss, 1998[115]	Unknown	Unknown	Unknown	Adequate	Partial	Inadequate	Adequate
Zinman 1997[118]	Unknown	Unknown	Unknown	Adequate	Adequate	Inadequate	Adequate

See Appendix 3 for description of coding.

TABLE 19 *Glycated haemoglobin with analogue and soluble insulin*

Study	Mean HbA_{1c} (SD)	
	Analogue	**Soluble**
Bode, 2002[113] Parallel RCT Lispro *N*: 28; end of study: 27 Regular *N*: 59; end of study: 50 Aspart *N*: 59; end of study: 55 Baseline lispro: 7.3% (0.7). Baseline aspart: 7.3% (0.7). Baseline soluble: 7.5% (0.8)	*Lispro* Month 4: mean change from baseline 0.18% (0.84) Aspart Month 4: mean change from baseline 0.00% (0.51)	*Soluble* Month 4: mean change from baseline 0.15% (0.63) (mean changes from baseline not significantly different between the three groups)
Melki, 1998[116] Random crossover *N*: 39; end of study: 38 Baseline: 7.84% (0.75) Baseline analogue: 7.74% (1.23) Baseline soluble: 7.97% (0.8)	Month 3: 7.11% (SD 0.92) Change from baseline –0.62 (0.8)	7.88% (SD 0.99) Change from baseline –0.09 (0.92) Lispro vs regular $p = 0.01$
Raskin, 2001[117] Random crossover *N*: 59; end of study: 58 Baseline analogue: 7.9% (1.1) Baseline soluble: 7.6% (0.8), $p = 0.234$	Month 3: 7.41% (SD 0.97) Change from baseline –0.34 (0.59)	7.65% (SD 0.85), $p = 0.004$ Change from baseline –0.09 (0.63), lispro vs regular $p = 0.004$
Renner, 1999[114] Random crossover *N*: 113 Baseline: 7.24% (1)	Month 4: 6.77% (SD 0.88)	6.9% (SD 0.97), $p < 0.02$
Schmauss, 1998[115] Random crossover *N*: 11 Baseline analogue: 6.3% (0.7) Baseline soluble: 6.7% (1.3), $p =$ ns	Month 3: 6% (SD 0.99) (Mean HbA_{1c} estimated by reviewer)	6.35% (SD 0.83), $p =$ ns
Zinman, 1997[118] Random crossover *N*: 30 Baseline: 8.03% (0.71)	Month 3: 7.66% (SD 0.71)	8% (SD 0.88), $p = 0.0041$

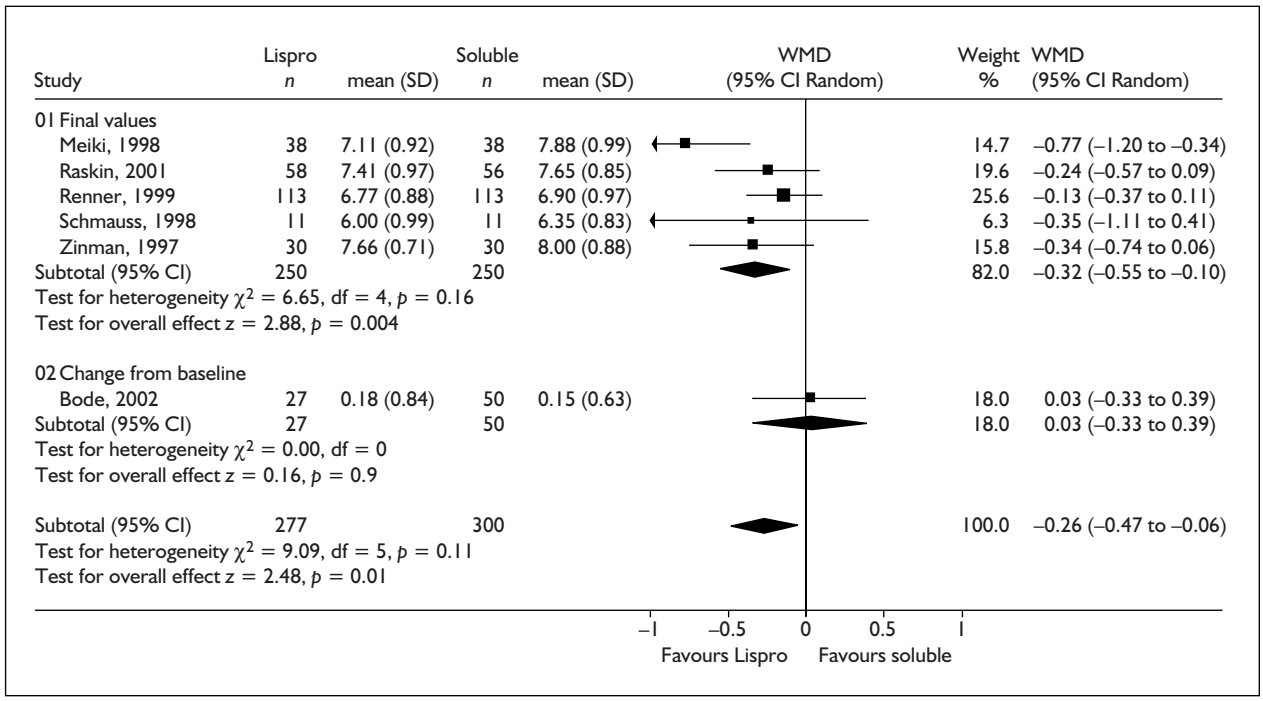

FIGURE 11 *Meta-analysis of the effect of lispro versus soluble insulin on glycated haemoglobin in Type 1 diabetes. Note: subgroup 1 'final values' include studies reporting mean HbA_{1c} at crossover or end of study (3 months with treatment). Subgroup 2 'change from baseline' includes one study reporting mean change in baseline HbA_{1c} at end of study (4 months with treatment).*

TABLE 20 *Insulin dose with analogue and soluble insulin*

Study	Mean insulin (SD)	
	Analogue	**Soluble**
Melki, 1998[116] Random crossover *N*: 39; end of study: 38 Baseline: 0.57 U/kg/day (0.12)	Month 3: 0.53 (0.12) U/kg/day	0.55 (0.12) U/kg/day, p = ns
Raskin, 2001[117] Random crossover *N*: 59; end of study: 58 Baseline not reported	Month 3: Bolus 0.28 U/kg Basal 0.35 U/kg	Basal 0.34 U/kg Bolus 0.30 U/kg
Renner, 1999[114] Random crossover *N*: 113 Baseline: 8.34 U/day	Month 4: 83.1 U/day	85.4 U/day, p = ns
Schmauss, 1998[115] Random crossover *N*: 11 Baseline not reported	Month 3: Basal 19 (6.6) U/day Bolus 1.4 (0.3) IU/12 g carbohydrate	Basal 20 (3.3) U/day, p = ns Bolus 1.5 (0.3) U/12 g carbohydrate, p = ns
Zinman, 1997[118] Random crossover *N*: 30 Baseline not reported	Month 3: 40.4 (9.3) U/day	40.8 (8.8) U/day, p = ns

TABLE 21 *Weight change with analogue and soluble insulin*

Study	Mean weight (SD) (kg)	
	Analogue	**Soluble**
Melki, 1998[116] Random crossover *N*: 39; end of study: 38 Baseline: 24.4 kg/m^2 (2.5)	Month 3: gain 0.04 (1.79)	Gain 0.48 (SD 1.6), p = ns
Raskin, 2001[117] Random crossover N:59, end of study: 58 Baseline analogue: 78.3 kg (17.9) Baseline soluble: 77.3 kg (16.7)	Month 3: 79.2 (17.1) (1 kg gained at end of period 1, vs baseline p = ns)	78.8 kg (17.3), p = 0.78 (1 kg gained at end of period 1, vs baseline p = ns)
Zinman, 1997[118] Random crossover *N*: 30 Baseline: 72.8 kg (9.9)	Month 3: 72.6 (9.9)	72.8 (9.9), p = ns

TABLE 22 *Patient preference with analogue and soluble insulin*

Study details		Analogue	Soluble
Melki, 1998[116]	*With which insulin:*		
Random crossover	Do you feel better?	34 (89.4%)	2 (5.3%)
N: 39; end of study: 38	Are daily activities easier?	32 (84.2%)	2 (5.3%)
	Do you prefer?	35 (92.1%)	2 (5.3%)
	Would you use in future?	36 (94.7%)	2 (5.3%)
	Gives most flexibility eating at home?	33 (86.8%)	2 (5.3%)
	Gives most flexibility eating outside?	32 (84.2%)	3 (7.9%)
	Best balance of glycaemia during study?	34 (89.4%)	2 (5.3%)
Renner, 1999[114]	*Diabetes Treatment Satisfaction*	*Diabetes Treatment Satisfaction Questionnaire*	
Random crossover	Questionnaire (total score possible 48):	(total score possible 48): 32.36 (5.87), $p < 0.001$	
N: 113	35.16 (4.25)		
Schmauss, 1998[115]	Continue with treatment: 11 (100%)	Continue with treatment: 0	
Random crossover	(owing to greater flexibility with lispro)		
N: 11	Reports that no significant difference in treatment satisfaction was noted		

difference between analogue and soluble insulin groups. Daily insulin dose for analogue and soluble insulin varied between 40.4[118] and 83.1 U/day[114] and between 40.8[118] and 85.4 U/day,[114] respectively, and between 0.53[116] and 0.62 U/kg[117] and between 0.55[116] and 0.65 U/kg,[117] respectively.

Weight

Three studies[116–118] presented data on weight (*Table 21*). No significant difference in weight gain[116] or weight at the end of the treatment period[117,118] was found between analogue and soluble insulin.

Patient preference and quality of life

QoL was not reported in any of the studies comparing analogue and soluble insulin.

Three studies reported patient preference. The majority of patients preferred treatment with analogue insulin than soluble, with 95–100% choosing to continue their treatment with lispro, generally owing to its greater flexibility[115,116] (*Table 22*). Although Schmauss and colleagues[115] reported that there was no significant difference in treatment satisfaction (method not stated), Renner and colleagues[114] found a statistically significant result in favour of lispro with the validated Diabetes Treatment Satisfaction Questionnaire (DTSQ).

Adverse events

Severe hypoglycaemic events occurred in 0–8% of patients using analogue insulin and 0–10% of

patients using soluble insulin, with little difference apparent between the groups[113,115–118] (*Table 23*). Bode and colleagues[113] observed a significantly lower rate of hypoglycaemic events according to symptoms (but not necessarily confirmed by blood glucose <50 mg/dl) in patients in the aspart group (6.7 episodes/patient/30 days, SD 5.4) compared with lispro (10.5 episodes/patient/30 days, SD 8.1, $p = 0.044$) or soluble (10.5 episodes/patient/30 days, SD 8.9, $p = 0.034$) groups. Nocturnal hypoglycaemia with blood glucose <50 mg/dl was also significantly lower in the aspart group than the soluble group.[113] Melki and colleagues[116] found fewer episodes of blood glucose <2.0 mmol/l with lispro [0.05 (SD 0.31) per month] than soluble [0.47 (SD 1.17) per month, $p < 0.05$], but not of episodes of blood glucose <3.0 mmol/l. Other studies found no significant difference in the number of hypoglycaemic events defined by patient symptoms or blood glucose <3 mmol/l,[117] mean number of episodes per patient defined by symptoms or blood glucose <3.5 mmol/l,[114] episodes per 30 days defined by blood glucose <3.5 mmol/l[115] or episodes per 30 days defined by symptoms or blood glucose <3.0 mmol/l.[118]

No episodes of DKA were reported in four studies. Ketosis was reported in two studies, occurring in 1.7–4.4% of patients in the lispro group and 0–3.5% of patients in the soluble group.[114,117] No significant differences in hyperglycaemia (blood glucose >350 mg/dl) between aspart, lispro and soluble insulin were reported by Bode and colleagues.[113] A similar proportion (18–23%) of patients in each group experienced catheter obstructions.[114,116] In addition, Raskin and colleagues[117] reported that eight (14%) patients using lispro and 12 (20%) patients using soluble insulin experienced 16 and 23 episodes of hyperglycaemia, respectively, caused by occlusion.[117]

Summary

Analogue insulin was associated with a 0.26% 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 events with analogue insulin, although this varied according to the definitions used.

Discontinuation rates

One way of assessing acceptability to patients is to examine how many patients continue to use pumps. However, there is a wide range of discontinuation rates and the studies need to be interpreted with care. Schifferdecker and colleagues[120] noted that discontinuation rates were higher in studies from the USA, and higher in patients with poorer control (by HbA_1) at the start. They suggest that those with poorer control were less likely to have been experienced in blood glucose self-control and insulin dose adjustment, and that discontinuation is less likely if patients have had a spell on MDI first. This is supported by Wredling and colleagues,[121] who recommend that patients be selected and prepared for CSII by means of at least 6 months of MDI, adequate experience with blood glucose self-testing, and good compliance with diabetes management.

Schifferdecker and colleagues also note a correlation between the discontinuation rate and the proportion of people with Type 1 diabetes on pumps, with a low rate in European countries such as Germany, where only 2% of Type 1 diabetes patients were on CSII,[120] but a high rate in clinics with up to 30% of Type 1 diabetes patients on pumps.[122] In the study by Knight and colleagues,[122] all patients attending the clinic were offered CSII or MDI, and most pump users (101 of 116) went straight from conventional insulin treatment with one or two injections per day to CSII. With this unselective approach, there was a high uptake (30%) of CSII but also a high early discontinuation rate by 12 months, with most of these stopping within 2 months. However, the pump used was the Graseby, and the authors comment that there was reluctance amongst patients to 'walking around with a large box attached to me all the time'. The commonest reasons for early discontinuation were pump size and discomfort. Another reason was hypoglycaemia, in patients who had been poorly controlled before CSII, had rarely experienced hypoglycaemia, and who found occasional hypoglycaemic episodes unacceptable.

Floyd and colleagues[123] reported that 33 (49%) of 68 adults starting on CSII stopped, about half within 6 months. A variety of pumps were used, including larger older ones. Factors predicting discontinuation included a high baseline HbA_1 and a low estimation by users of their ability to self-manage diabetes.

Bell and colleagues[124] found in 1988 that one of the major reasons (40%) for discontinuation was needle site abscess, but in a later paper (1993)[125] they report that the cause of the infections had been found to be the diluting fluid, and that there were no discontinuations due to abscesses in the second study.

TABLE 23 *Adverse events with analogue and soluble insulin*

Study	Adverse events	
	Analogue	**Soluble**
Bode, 2002[113] Parallel RCT Lispro *N*: 28; end of study: 27 Soluble *N*: 59; end of study: 50 Aspart *N*: 59; end of study: 55	*Lispro* Severe hypos: 0 DKA: 0 Hyperglycaemia (BG >350 mg/dl): 10, p = ns ≤ 3 clogs or blockages: 64% Hypos [episodes, rate/pt/30days (SD)]: All reported: 872, 10.5 (8.1) vs aspart p = 0.044. Hypos BG <50 mg/dl: 359, 4.4 (4.7) vs aspart p = 0.841 Nocturnal hypos BG < 50 mg/dl: 64, 0.6 (0.61) vs aspart p = 0.189 *Aspart* Severe hypos: 0 DKA: 0 Hyperglycaemia (BG >350 mg/dl): 16, p = ns 3 clogs or blockages: 75% Herpes zoster: 1 Hypos [episodes, rate/pt/30 days (SD)]: All reported: 1126, 6.7 (5.4) Hypos BG <50 mg/dl: 610, 3.7 (3.6) Nocturnal hypos BG <50 mg/dl: 96, 0.5 (0.83)	Severe hypos: 1 (1.7%) DKA: 0 Hyperglycaemia (BG > 350 mg/dl): 24, p = ns ≤ 3 clogs or blockages: 78% Hypos [episodes, rate/pt/30days (SD)]: All reported: 1663, 10.5 (8.9) vs aspart p = 0.034 Hypos BG <50 mg/dl: 770, 4.8 (4.2) vs aspart p = 0.175. Nocturnal hypos BG <50 mg/dl: 207, 0.9 (0.97) vs aspart p = 0.004
Melki, 1998[116] Random crossover *N*: 39; end of study: 38	Catheter obstructions: 9 Severe hypos: 3 (7.9%) DKA: 0 Insulin precipitation in catheter: 1 BG <3.0 mmol/l: 7.03 (5.79) per month BG <2.0 mmol/l: 0.05 (0.31) per month	Catheter obstructions: 9 Severe hypos: 4 (10.5%) patients (7 episodes) DKA: 0 Insulin precipitation in catheter: 4 BG <3.0 mmol/l: 7.94 (5.42) per month, p = ns BG <2.0 mmol/l: 0.47 (1.17) per month, p < 0.05 0 hypos resulted in coma or seizures
Raskin, 2001[117] Random crossover *N*: 59; end of study: 58	Severe hypos: 3 (5.1%) patients (3 episodes) Ketosis: 1 Hyper due to occlusion: 8 pts (16 episodes). Hypos as defined: 7 pts (8 episodes)	Severe hypos: 2 (3.4%) patients (3 episodes) DKA: 0 Hyper due to occlusion: 12 pts (23 episodes) [During study 38 pts reported 109 episodes of hyper: 39 caused by occlusion, 47 caused by other reasons, 23 no identifiable cause. Groups not specified] Hypos as defined: 7 pts (11 episodes). 1 hospitalised: fever, vomiting, dehydration
Renner, 1999[114] Random crossover *N*: 113	Injection site infection: 4 Serious adverse event not related to drug: 1 Hypos: mean 12.4 (13.9), median 8 episodes/pt Infection (cold): 19.4% Rhinitis: 15.8% Catheter occlusion: 20 (42 episodes) Ketosis: 5	Injection site infection: 2 Serious adverse event not related to drug: 6 Hypos: mean 11.0 (11.2), median 8 episodes/pt, p = ns Infection (cold): 21.1% Rhinitis: 13.8% Catheter occlusion: 21 (45 episodes), p = ns Ketosis: 4

continued

TABLE 23 *Adverse events with analogue and soluble insulin (cont'd)*

Study	Adverse events	
	Analogue	**Soluble**
Schmauss, 1998[115] Random crossover *N*: 11	Severe hypos: 0 DKA: 0 Hypos per 30 days: 4 (2.98) Note: no severe adverse events registered by either treatment	Severe hypos: 0 DKA: 0 Hypos per 30 days: 3.2 (2.3), p = ns
Zinman, 1997[118] Random crossover *N*: 30	Skin reaction: 16 Severe hypos: 0 Discoloration of insulin in reservoir or catheter (did not lead to obstruction or significant hyperglycaemia): 2 Hypos: 8.6 (7.7)/30 days (vs baseline p = 0.035) Hypos confirmed by BG: 6.0 (4.9)/30 days (vs baseline p = 0.03)	Skin reaction: 15 Severe hypos: 0 Discoloration of insulin in reservoir or catheter (did not lead to obstruction or significant hyperglycaemia): 2 Hypos 10.8 (9.9)/30 days (vs baseline and lispro p = ns) Hypos confirmed by BG: 7.6 (7.1)/30 days (vs baseline p = ns, vs lispro p = ns)

Chapter 4

The patient's perspective

The purpose of this chapter is to give an appreciation of what it means to have Type 1 diabetes that is not well controlled on insulin by injections and how CSII can change that. Although this chapter gives us access to a wider range of data than is available from the trials, it is not methodologically rigorous and findings may not be generalisable.

Caveats

The patient's perspective section is based largely on written statements from pump users, and several caveats are required. First, most comments come from people who are members of INPUT who have responded to a request for comments. They are likely to be a more highly 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 on-going costs of pumps. Third, most have had to pay for the pumps and consumables themselves, and this 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. It is apparent, for example, that some of the improvements in HbA_{1c} reported by the INPUT respondents are greater than seen in the trials. Again, this does not affect the validity of the findings, but will be relevant to discussions about the proportion of people with Type 1 diabetes who should be considered for CSII. It may also mean that CSII might be more cost-effective in 'real-life practice' than would be expected from HbA_{1c} differences seen in the trials.

The term 'control' is used in different ways. The usual use refers to control of blood glucose levels, but we need to distinguish that fairly narrow usage from control of diabetes. The broader use includes control of symptoms, hypoglycaemic episodes and other metabolic disturbances such as high cholesterol levels. Or as one of the INPUT members said, "Good diabetic control does not equal normal life."

Most of the published studies have used outcome measures such as HbA_{1c}. Some have included frequency and severity of hypoglycaemic episodes, but only one has included QoL.

It may be useful to think in terms of a spectrum of benefits in terms of ease of measurement, with the more easily measured such as HbA_{1c} at one end and benefits such as greater flexibility of lifestyle at the other. Published research tends to focus on the more easily measurable end of the spectrum, whereas it may be that the greatest amount of benefit lies at the less easily measurable, or perhaps just less frequently studied, end of the spectrum.

Since the published studies did not provide sufficient data on all outcomes of importance to patients, we have sought information from pump users, sometimes directly from individual users, but more from the pump users' group INPUT. This information has usually come from the user, but sometimes has come from their spouse or parent. For example, few of the trials have included children, and so we have specifically sought advice from a number of parents.

Such information may be from successful pump users, but when considering the resource impact, that is appropriate, since those who do not like CSII will probably cease to use it and will thereby cease to incur the extra costs. Hence the economic analysis differs from, for example, that of a drug given to a number of patients, some of whom will benefit and some not. Those who do not benefit from pumps will probably stop using them fairly quickly. The cost-effectiveness therefore depends on the costs and benefits for successful long-term users.

Space does not permit the inclusion of comments from all those members of INPUT who responded. In the quotations below, they and other pump users are identified only as 'pump user (PU)' and number. Parents are identified as, for example, 'Parent 1'.

Reasons for switching to insulin by pump

The reasons for starting CSII given in published studies have been reviewed by Pickup and Keen[39] and range from improving poor control to patient preference.

The meaning of 'poor control' and the emphasis on HbA_{1c} have been mentioned above. However, as one of our panel of experts noted:

> "HbA_{1c} is only an average of what the patient's blood glucose has been. It does not show the variations of blood glucose that any person treated with insulin will experience. These variations can often be quite wide. An HbA_1 measurement cannot show whether the patient has frequent hypoglycaemia, which is one reason for a person to opt for CSII therapy." (PU1)

Because HbA_1 is only an average, it could reflect either perfect control with blood glucose always under tight control, or a situation with both high and low blood glucose levels. As our adviser said:

> "From my own personal experience as a pump user of 20 months, if only HbA_1 was used as the measure of control, one would not be able to see how CSII therapy has altered my diabetes control. I managed to maintain a perfect, i.e. non-diabetes level using MDI treatment for a good 10 years before changing to CSII, and my HbA_1 level has not altered with pump therapy. However, CSII has had a dramatic effect on my control by reducing the frequency of hypoglycaemia." (PU1)

The value of HbA_{1c} is not in doubt as an indicator of risk of long-term complications of diabetes such as eye or kidney disease. It is less useful for large-vessel disease such as ischaemic heart disease.

The reasons given by pump users for switching to CSII included:

- To reduce problems with hypoglycaemic events; this was especially the case amongst those who had lost awareness of developing hypoglycaemia.
- To control hyperglycaemia and improve HbA_{1c}, in order to prevent longer term complications.
- To give control of wide fluctuations in glucose levels (in effect, the combination of the previous two reasons).
- To allow more flexibility in diet and insulin, particularly for those whose schedule may vary from day to day or be unpredictable (such as business people, junior doctors and schoolchildren).
- To 'regain a more normal lifestyle'.
- Less painful than multiple injections.
- To lose weight, which had been difficult on MDI because hypoglycaemic events were avoided by regular eating plus snacks when symptoms of hypoglycaemia occurred, or blood glucose testing showed lowish results.
- To control the 'dawn phenomenon', which occurs when the effect of insulin taken the evening before wears off by morning, allowing blood glucose levels to rise to high levels.
- To ensure very good control of blood glucose levels during pregnancy. (Tight control before conception and during pregnancy reduces the risk of malformation and other adverse events.)

One mother reported that her son "likes gadgets and computers" and wanted to administer his insulin with one.

Hypoglycaemic events

This was one of the main reasons for switching from MDI to pumps, and a number of respondents commented on the frequency of hypoglycaemic events on MDI and the unpredictability of the effect of long-acting insulin:

> "My quality of life has definitely improved mainly due to the reduction in hypoglycaemia. One very important improvement is that my hypoglycaemic warning signs are now much more evident, allowing me to take appropriate action in reducing the risk of severe hypoglycaemia. On MDI therapy, I had problems controlling my post-prandial blood glucose even when using the quick acting lispro insulin. The choice was either to take less insulin at meal times to avoid going hypoglycaemic several hours later, which resulted in post-prandial highs, or to take more insulin at meal times to prevent the post-prandial highs but then risk going hypo later and having to eat more food whether I was hungry or not. The pump solves this problem with the use of the different boluses available and with the continuous basal infusion." (PU1)

> "On MDI therapy, I averaged approximately 3 admissions yearly to Accident and Emergency by ambulance for severe hypoglycaemia. My wife had to administer glucagon to me on average twice a month; I have only needed one glucagon injection in 20 months since being on the pump." (PU1)

A glucagon kit, with drug, syringe and sterile water for injection, costs about £20.[126] Hence twice-monthly glucagon would cost about £480 per year.

> "At the age of 14 I began to use a basal-bolus injection regimen. . . . I remember battling exhaustion

at school due to fatigue as the result of sleep disturbance due to nocturnal hypoglycaemia. . . . I found that however hard I tried, if I aimed for normoglycaemia, I would experience frequent hypos, which left me feeling exhausted. . . . Over the next 3 years control improved again but I still suffered from frequent nocturnal hypos during which I woke up bathed in sweat. I found that reducing long-acting insulin by 2 units often had little effect and any larger reduction often resulted in morning hyperglycaemia. During my first year employed as a doctor I struggled with frequent hypos. . . . [On pump therapy] I still experience a few hypos but not to the extent of my pre pump days. . . . Overall the pump has enabled me to regain a degree of control over the condition." (PU2)

"I really do feel that for the first time in my life that I am actually controlling my diabetes rather than just letting it run constantly high so that I didn't go hypo. My hypos have become much milder and so much easier to control, so that I am not frightened to run my blood glucose in the normal range." (PU3)

"I changed to four daily injections for three years. The new regime did not help night time hypos or dawn phenomenon. I experienced severe hypos which ended up with either ambulance call-outs or emergency visits to A and E (12 in two years). . . . The pump corrected my hypos in the middle of the night and also my dawn phenomenon. Over a few months my hypo awareness returned in that I would know when my sugar levels started to drop and be able to take glucose without becoming unconscious as before. I have now been using a pump for 6 years and have not been admitted to A&E since starting on the pump." (PU4)

Several users commented that awareness of impending hypoglycaemia (see 'Introduction' for explanation) had returned once they had been on CSII for a couple of months, probably because they had had periods of relative freedom from hypoglycaemic episodes.

Control of blood glucose

A number of respondents commented that MDI did not provide satisfactory control.

"I was diagnosed age 12. Years ago I went on to a multiple injection regime, which used long-acting insulin as a background dose, with injections of short-acting insulin before each meal – a total of six injections a day. My diabetes has always been difficult to control. Six injections a day and very regular blood testing (5–7 tests a day) backed up by sensible and regular eating and hardly any lifestyle 'excesses' did not enable me to achieve reasonable blood sugar control. Every single day I would have a problem with either high or low blood sugars. On pump therapy although my sugars still fluctuate, on most days I can hope to get through the day without a significant problem." (PU 5)

"My diabetes control had been erratic for some years due to problems with insulin absorption after 28 years of injections. After I had used the pump for 4 months, blood test results decreased by some 20%, which if sustained should lead to decreased morbidity and risk of complications. . . ." (PU6)

"When I was on MDI blood glucoses were erratic. In one day I could easily go from being hypo to being over 20. On the pump, I have very few highs and lows. When I do, I can explain each and every one. I can look back and see that I have misjudged a meal bolus, or that I didn't reduce my basal rate enough while exercising. Diabetes is a constant balancing act. . . . because of this you have to make small changes to your diabetes control all the time and with pump therapy this is very simple and very easy." (PU7)

"My HbA_{1c} results, which date back 4 years before starting pump therapy, were at best 7.4% and at worst 11.8%, with an average of 8.9%. Within 3 months of commencing pump therapy, I achieved 6.8%, and on my last test it was down to 6.1% – excellent control." (PU8)

Some respondents had additional comments on the difference between MDI and CSII:

"To a certain extent some of these things could be partially accomplished using lispro insulin on MDI therapy. However, the difficulty lies with the injection of intermediate/long acting basal insulin. For me, I found that its action from day to day would peak at imprecise times probably due to the variable absorption of the unused injected insulin. It is also impossible with this insulin to adjust for changes in insulin needs and sensitivity throughout the day, e.g. dawn phenomenon. For myself with the pump, I set four different basal rates throughout a 24 hour day, ranging from 0.1 units/hour for most of my working day, to 0.4, 0.5 and 0.6 units for the evening, night and early morning, respectively. This would be very difficult to do with MDI therapy." (PU1).

Flexibility of lifestyle

The advantages of pumps in allowing greater flexibility of lifestyle and working patterns were referred to by a number of respondents:

"Living with diabetes is not an easy situation. Anything that allows the individual person to take control and manage a medical condition must be beneficial both to the patient and the carers. The proper use of an insulin pump allows this to happen.

From my own perspective the pump has allowed me to lead a full and active life where I control my diabetes rather than the diabetes control 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." (PU9)

"Freedom, flexibility, pleasure and peace of mind in one's daily life, almost like being a non-diabetic, compared with the uncertainty of the MDI regime." (PU10).

"I can live a much more flexible lifestyle where I have the freedom to eat when and what I please without compromising on my glycaemic control, whereas before, on MDI, the insulin was controlling my eating habits. Now I can more easily regulate the insulin by taking whatever is needed according to when and what I eat. I can even skip meals or take a second helping." (PU1)

"As I have a very busy life the remote control of my pump helps me to be able to eat on the go and give a couple of units of insulin for the carbohydrate that I eat." (PU3)

"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." (PU4).

"I have just completed the first 6 months of an intensive degree course, which has meant balancing family life with controlling my blood sugars and working literally all hours in order to complete my projects in time. My last three projects involved my working through the night. . . . I couldn't imagine doing that without the support of a pump." (PU5; a working mother with young children).

Other comments

The respondents mentioned a number of benefits relating to their reasons for going on to pump therapy, but they also gave details of benefits that they did not seem to have expected:

" I feel more energetic and more able to cope with the demands of work."

"The pump is extremely predictable; I have never had a problem with mine. Using the pen, the absorption of insulin was erratic and everything was left to guesswork. . . . "

"For the first time in my life I almost feel normal. I am not constantly looking for drink and food."

"My injection sites were hard and painful and I would have to alternate these. With the pump I do not have these."

"I do not have to carry syringes with me everywhere or inject in restaurants or loos before eating".

"My condition is much less visible, in that I can take insulin without anyone being aware of what I am doing."

"On the pump I backpacked through Guatemala, Belize and Honduras for 3 months, scuba diving, climbing volcanoes, doing all sorts of activities for the first time. I could apply my pump knowledge to any situation and come out the other end with good BGs. I could conceal my pump so didn't get needles out where locals may have seen and suspected. It would have been a lot harder on injections and more worrying and stressful."

"It all goes back to being in control of your condition rather than the condition controlling you".

"The extra weight has been lost."

Disadvantages

The commonest reported problem was cost.

Other problems included concern about being attached to a pump 24 hours per day every day:

"At first I was very apprehensive about this form of therapy since it would mean being connected to a pump for 24 h/7 days a week which I didn't really think was for me," but after being on the pump, "Always being connected to a device is certainly not an ideal way to live. Its advantages however far outweigh the inconvenience of wearing it. It can easily and quickly be removed for taking a shower, bath, and swimming or for sex."

"It certainly made me more aware of my diabetes. In fact to be honest, I had the feeling that I was a disabled person, something I had never felt before. This feeling of being disabled is no longer present."

"In the 20 months since using the pump, I have experienced on 3–4 occasions interruptions of insulin delivery which were not detected by the pump's security alarm system, and only later detected by testing my blood sugar and finding an unexpected high. I later discovered the causes for these as either being a large bubble forming in the infusion line or that the infusion site cannula had slipped out. This has reinforced the need for frequent monitoring of my blood sugar."

"The only problems that I see with the pumps are the red marks that the infusion sets leave on my abdomen, and that I can't swim with it."

> "Curiously enough, I have never found the actual wearing of the pump to be the slightest problem. The pump and its tubing are easily disconnected at the site (this takes about a second) should I wish to be without it for a short period. It is small and clips to the waistband of whatever I am wearing and the short length of tubing is simply tucked under my clothes. The only time I have found the wearing of the pump to be a problem was when I was on holiday, wearing a swimsuit and having to keep the pump in a small coolbag so that the sun did not overheat the insulin."

> "The only problem occurred shortly after I started using it and was unused to it. One evening I inadvertently knocked out the cannula from under my skin and went to bed. I then had no insulin delivery until the morning."

The alarm on the pump will go off if the pump fails to pump out insulin, but as long as the insulin is being pumped out, whether into the patient or the bed, the alarm will not go off.

Pump users need to remember that they have no reserves of insulin:

> "Anyone contemplating pump therapy needs to understand that, because one is using only short-acting insulin, if for any reason the supply of insulin is unexpectedly interrupted, the body has no reserve of long-acting insulin, and so sugars can rise sharply."

and that they have to monitor their blood sugar levels:

> "Anyone on a pump has to accept that they have to keep a reasonably close eye on their blood sugars, by doing regular blood tests during the day. This way, any unexpected fluctuations can be investigated."

and

> "If the pump is to work for you, you need to be prepared to work with it. It relies on good programming by the user and you need to be motivated in order to get the best out of it, as it will not solve all your problems without any input from you".

With CSII, there is a needle through the skin all the time, although the site will be changed every few days. There is therefore a small but real risk of infection:

> "The only disadvantage I have found is the very rare occurrence of infection at the insertion site. In my case I have suffered this on four occasions in 20 years when I have needed antibiotics. However, it is easy to recognise how I got infections. It was the direct result of leaving the infusion line in place for too long. This of course happens because I have to pay for all the ancillary supplies, costing about £1200 per annum, a cost that would double if I changed the reservoirs and infusion lines as often as recommended by the suppliers."

Children and CSII

All the comments above came from adult pump users. Fourteen submissions were obtained by INPUT from parents of children (some now older teenagers) with experience of pumps. The number of children on pumps in the UK appears to be low [currently over 100 children on pumps (Davis J, INPUT: personal communication, 2002)] and this has been a problem for some families:

> "Because there are currently so few others in the same situation, we had to follow a steep learning curve for the first few weeks, making up a number of ground rules for ourselves. We have joined a growing support group of pump users. . . . " (P1)

Space prohibits more than a few quotations from the submissions, but a few examples give an illustration of before and after pump therapy.

Before:

> "The two words that best summed up living with the condition are 'discipline' and 'stress'. Discipline relates to the way our lives had to be structured around Sam's diabetes. This included arranging injections to fit in with meal times (i.e. just before breakfast and just before tea, in general), working out a fairly rigid regime of snacks and regular meals, trying to ensure that a young child eats just the right amount at just the right time, forward planning to make sure that all trips away from home were adequately prepared for any eventuality. . . . It had been very frustrating to put so much effort into looking after him, only to see wide fluctuations in his blood glucose levels partly due to the uncertainties in insulin absorption from injections."

(This child developed diabetes at the age of two, and switched to the pump when he was 7.)

After:

> "We can definitely say that it has been beneficial for all of us. The first few weeks were very hard work, but once the various insulin delivery rates had been established, we quickly settled into a routine.
>
> Meal times are no longer rigid or stressful. Sam can eat what he wants (within reason) whenever he wants – we simply add up the amount of carbohydrate in each meal, convert this to an insulin amount using

> our own conversion chart, and program the bolus on the pump. It did not take Sam very long to work out how to do this himself and it has made an enormous difference to his independence and self-esteem." (P1)

From a child switched to CSII from MDI:

> "better control on multiple injections than on two a day (HbA_1 8.6%) but even better on pump (7%). Pump gives back part of the quality of life that was destroyed when he first became diabetic – he may not be 'normal' or 'better', but he can live a more or less normal life with a pump."

This child had severe problems with hypoglycaemic unawareness and hypoglycaemic events, had had hypoglycaemic event-induced seizures and had episodes of unconsciousness at school events:

> "He was deeply affected by having collapsed at school, in a public hall, on stage in front of all the other schools in the town with everyone having seen." [He is a saxophone player.] "He was not allowed his snack on a school trip and he collapsed hypo on the outing."

After:

> "I no longer have the child alarm in his room in case he goes hypo in his sleep because I am confident he is not likely to. Having spoken to other parents whose child has fitted [i.e. had an epileptic-like convulsion due to hypoglycaemia], it is an experience you never, ever, forget, but on a pump you are able to sleep nights, and so is your child, confident that he will wake up in the morning." (P2)

Hypoglycaemic episodes affect not just the child but the family. From the parent of a child who developed diabetes at 1 year old and is now 4 years old:

> "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 9.30 and by 11 am they can phone me up because he has gone low, and I have to go back to the school." (P3)

Most of the respondents noted improvements in HbA_{1c}, but it should be noted that half the children were on conventional insulin treatment with two injections a day:

> "Her HbA_{1c} levels dropped from 10.6 to 8.2, and her mood and personality dramatically changed – we got our little girl back again." (P8).

In some cases, treatment with conventional therapy rather than MDI was preferred by the hospital clinic, and one parent switched to MDI herself after studying Internet sites and books:

> "In a 12 week period, I listed all Jamie's readings – 78 hypers, 63 hypos and 69 normal readings. Went on multiple injections – I telephoned the hospital and said that I would be starting it, as they had failed to respond to my requests for many weeks, and it would be helpful if they could tell me how to work out the dosage, but that even if they did not, we would be doing it." (P2)

Several commented on reduced emergency hospital visits:

> "... Has not been admitted to hospital since going on the pump. On four injections a day had four admissions over 2 years." (P6)

There were comments on the pros and cons of MDI versus CSII:

> "We wouldn't consider having 12 injections every 3 days when we can have only 1 and the ability to correct a hyper at the touch of a button with no more injections." (P8)

> "I don't think multiple injections do anything for a child's mental state. Their lives would be governed by the clock. Syringes would always have to be carried on the person which is not socially acceptable (school, discos, etc.) plus the safe carriage of a vial of insulin." (P9)

Some of the benefits are social rather than medical:

> "Steven feels more like his peers now [on the pump]. He can eat with them [instead of going in to dinner early] and he can eat the same things as them." (P10)

> "Had to move school due to bullying as other pupils could not accept Nicola eating at certain times of the day. ..."

> "Diabetes [on pump] is now not obvious to anyone as Nicola does not need to eat during class and does not have so many hypo attacks." (P9)

Some children had snacks stolen; one had his blood glucose meter stolen.

Disadvantages mentioned included:

- more daily blood tests than on CT, and more parental input to collate tests and insulin boluses
- cost
- the need for vigilance in case any thing goes wrong with the pump
- misunderstandings by other people – "On a few occasions, people have thought he was playing with a Game Boy while he was programming a bolus"
- being connected to a device 24 hours a day.

However, most respondents said there were no disadvantages.

Common themes

Sources of information

The majority of parents got their information from non-NHS sources, the two main ones being the Internet, and *Balance*, the magazine of Diabetes UK (formerly the British Diabetic Association). Several encountered resistance from the NHS, and sometimes wrong information:

> "We had to go to a private doctor instead of the NHS." (P4)

> "Every avenue had been explored to try to stabilise her condition (different insulins and regimes) but nothing worked. The pump was a plea from me to see whether or not it would help, as the consultant did not know what else to try. Nurse educator from company put her on the pump; hospital consultant did not get involved as he has no knowledge of this therapy. It worked, thankfully." (P9)

> "Consultant was patronising, dismissive and combative." (P11).

> "Consultant thought pumps were dangerous." (P2)

Training needs

Most parents commented that much support was needed in the first few weeks. This was sometimes provided by the local clinic, but often by nurses from the pump companies.

Training needs sometimes varied between parents and children:

> "Started pump therapy after a week of training for me and his father – Jamie of course had already worked out how to use the pump from talking to another child with one and from reading all the manuals." (P2).

Jamie started using the pump aged 11 years; he likes computers and other gadgets.

Funding

Of the 14 respondents, eight were funding the pump and consumables themselves; one had support from a hospital league of friends; five were funded by the NHS, some with little trouble, others after much correspondence with the NHS, MPs and the media. It appears that most health authorities do not fund pumps for children. One health authority funded the pump for 2 years then stopped funding.

Problems with schools

There were many problems with schools. Some are not relevant to this review, but the testimonies are consistent in reporting that schools cope much better with children on pumps than those on injections – although to some extent this is because the children find it easier to look after themselves, have fewer hypoglycaemic episodes, do not need to eat at special times, can miss meals if necessary and do not need to carry insulin syringes and vials.

Conclusions

The evidence above differs in type from that seen in traditional systematic reviews, being anecdotal and subject to selection biases, but it does provide valuable information that is not available from the published literature, and is very useful. Data on many of the outcomes could be collected in trials. The problem for this review is that such data have not been collected in good-quality studies from which one can extract utility data to feed into cost per QALY calculations.

Nevertheless, the submissions have been very useful, and provide information that is currently not available anywhere else.

Chapter 5
Economic analysis

Introduction

The economic assessment of CSII versus MDI is an evaluation of differing forms of delivery for intensive insulin therapy, and this type of comparison has received little, if any, attention in the scientific literature in terms of cost-effectiveness analysis. Much of the economics literature pertaining to diabetes is related to either cost-of-illness studies[127,128] or the cost-effectiveness of intensive diabetic therapy versus conventional diabetic therapy (e.g. DCCT[129] UKPDS[130]). We have not identified any studies informing on the economic consequences of CSII versus MDI. Therefore, we have to see what can be extrapolated from the studies of the benefits of improved control, and we begin by outlining some of the key studies, both trials and epidemiological literature, which have been used to support economic analysis in diabetes, and Type 1 diabetes in particular.

A brief outline of the DCCT,[19] UKPDS[131] and Wisconsin Epidemiologic Study of Disease Retinopathy (WESDR)[132] studies is given below, and in the section 'Economic models for Type 1 diabetes' (p. 66) we review the main economic modelling approaches published to date. These studies are used to illustrate the problems of creating an economic model to estimate the cost-effectiveness of CSII.

The section 'Literature review: economic evaluations and quality of life comparisons' (p. 54) refers to the methodology and findings of the literature search to identify economic studies relevant to the evaluation of CSII versus MDI. The section 'Costs associated with CSII (versus MDI)' (p. 55) presents the cost analysis for CSII. The section 'The benefits of CSII' (p. 59) provides an assessment of the benefits and QoL issues associated with CSII. The sections 'Economic models for Type 1 diabetes' (p. 66) and 'Cost-effectiveness of CSII versus MDI' (p. 71) explore the opportunities to estimate the cost-effectiveness of CSII using available models and through the synthesis of available cost and outcome data.

The Diabetes Control and Complications Trial (DCCT)

The DCCT[19] was a multi-centre randomised clinical trial designed to compare the effects of intensive diabetes therapy with those of conventional diabetes therapy on the development and/or long-term progression of diabetes complications of IDDM. The intensive therapy was designed to achieve blood glucose values as close to normal range as possible with three or more daily insulin injections or treatment with an insulin pump. Conventional therapy consisted of one or two insulin injections per day (note that conventional insulin therapy was probably less than in the UK, where most patients would get two injections of mixtures per day). Two cohorts of patients were studied, a primary prevention cohort, to consider whether intensive therapy would prevent the development of complications, and a secondary cohort, to consider whether intensive therapy would affect the progression of early complications. Retinopathy was the principal study outcome, but renal, neurological and cardiovascular outcomes were also studied, as were the adverse effects of the two regimens. The results of the DCCT demonstrated that intensive treatment led to a significant risk reduction in the onset and progression of retinopathy, nephropathy and neuropathy. However, intensive therapy (compared with conventional therapy) was associated with a threefold increase in the risk of severe hypoglycaemia.[19] Analyses did not demonstrate differences in the QoL outcomes between the treatment groups. Most economics assessments in the field of diabetes have been undertaken using largely homogeneous modelling methods, which utilise the data from the DCCT.

The model developed and presented by the DCCT Research Group[129] examined the cost-effectiveness of alternative approaches to the management of IDDM. The model was used to consider all persons with IDDM in the USA who would meet the DCCT eligibility criteria, in order to provide estimates of the lifetime benefits and costs of intensive therapy, and to address whether more costly intensive therapy would be preferable to conventional therapy from the perspective of the healthcare system. The model used data collected as part of the DCCT, together with data from other clinical trials and epidemiological studies – detail on the model is presented later in *Table 35*. The DCCT Research Group present

findings from the model to demonstrate that intensive therapy reduces complications and can be expected to increase length of life. The authors also state that from a healthcare system perspective, intensive therapy is well within the range of cost-effectiveness considered to represent good value[129] – although the marginal benefits of the intensified treatment will vary depending on the level of control achieved with whatever conventional treatment is used.

The DCCT data are not appropriate to assess the relative benefits of CSII and MDI, because the intensive treatment group was treated with either MDI or CSII with non-randomised allocation. However, the study does provide evidence on the relationship between HbA_{1c} and health outcomes (long-term complications), and on some of the QoL issues related to intensive therapy and hypoglycaemia. The DCCT also offers a general foundation for modelling the cost-effectiveness of therapies in IDDM.

The United Kingdom Prospective Diabetes Study (UKPDS)

The UKPDS, started in 1977, was designed to establish whether, in patients with Type 2 diabetes, intensive blood glucose control reduced the risk of macro- or microvascular complications, and to investigate the benefits of the therapeutic options. Studies within the UKPDS have reported on blood glucose control with sulphonylureas or insulin compared with conventional therapy,[9] control with metformin on complications in overweight patients[133] and cost-effectiveness analysis for both of these comparisons,[130,134] amongst others. The UKPDS has reported that intensive blood glucose control in patients with Type 2 diabetes can substantially reduce the cost of diabetic complications and increase the time free of complications. Findings from the UKPDS support those findings presented in the DCCT concerning the benefits of improved control.

As with the DCCT, the UKPDS presents findings from comparisons of intensive versus conventional therapy. For example, the UKPDS[9] reports a 0.9% difference in HbA_{1c} between intensive (7.0%) and conventional (7.9%) groups over 10 years (an 11% reduction), and data showed a significant 25% reduction in microvascular endpoints ($p = 0.0099$), most of which was a risk reduction of 21% for retinopathy. The study suggests that the risk reduction is due to improved glycaemic control, rather than the method by which it was achieved, as there were no significant differences between the three types of drug treatment.

However, the link between glycaemic control and outcome is complex as the HbA_{1c} levels progressively increased over time, although the differences between the more intensively treated and control groups was maintained.[9]

As part of the UKPDS,[130] a model was developed to estimate cost and effect. The model is a discrete event simulation model, looking at cost per event-free year; however, it does not have a direct link to the HbA_{1c} input variable.

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)

The WESDR is a population-based study of the prevalence and incidence of diabetic retinopathy.[129] The study population consisted of a sample selected from 10,135 patients with diabetes who received primary care in an 11-county area in southern Wisconsin from 1979 to 1980. The study reports on 'younger onset' Type 1 diabetic patients diagnosed before 30 years of age. The study provides unique long-term population-based information. Within the sample studied the 14-year rate of progression of retinopathy was 86%, regression of retinopathy was 17%, progression of proliferative retinopathy (PDR) was 37% and the incidence of macular oedema was 26%. Data from the study suggest relatively high 14-year rates of progression of retinopathy and that a reduction of hyperglycaemia and hypertension may result in a beneficial decrease in the progression to proliferative retinopathy. Data from WESDR have been applied in disease progression models used for the purpose of economic evaluation [e.g. Palmer and colleagues,[135] discussed further in the section 'Economic models for Type 1 diabetes' (p. 66)].

Literature review: economic evaluations and quality of life comparisons

Methods

Literature searches were undertaken using search terms related to the technology and to economics and QoL. Searches were carried out in a range of databases (see Appendix 2).

Summary of findings on cost-effectiveness

There were no studies identified via the literature search that reported on the cost-effectiveness of CSII versus MDI. Experts were also consulted in order to identify any literature on the cost-effectiveness of CSII, but no further studies were

TABLE 24 *Supplies used in diabetes treatment by intensive MDI therapy or CSII therapy*

Supply item	Needed for MDI?	Needed for CSII?	Additional costs for CSII compared with MDI
Lancets	Yes, ≥ 3 per day	Yes, ≥ 4 per day	No
Glucose test strips	Yes, ≥ 3 per day	Yes, ≥ 4 per day	No
Glucometer	Yes	Yes	No
Insulin	Yes, short-acting and other intermediate- and long-acting preparations; unit requirements vary	Yes, short-acting insulin; unit requirements vary	Reduced insulin use in CSII users
Insulin syringes or insulin pen	Yes, ≥ 3 per day	Yes	No (minor cost saving in CSII users)
Insulin infusion pump	No	Yes (see pump costs for details)	Yes
Insulin cartridge/reservoirs	No	Yes	Yes
Adaptors for insulin cartridge/reservoirs	No	Yes, depending on type of insulin pump	Yes
Infusion sets	No	Yes, one set every 3 days	Yes
Batteries	No	Yes, battery life varies by pump type	Yes

identified. Furthermore, we did not identify any literature covering the costs associated with CSII.

Summary of findings on quality of life comparisons

The literature searches provided only one RCT comparing QoL outcomes of CSII versus MDI. This study[79] found no significant differences between the two interventions [see the section 'CSII versus MDI' (p. 14)]. Some descriptive and observational studies that assist with the understanding of the QoL consequences of CSII are discussed in the section 'The benefits of CSII' (p. 59).

Costs associated with CSII (versus MDI)

Additional costs associated with CSII have been estimated based on the perspective of the NHS and personal social services sector. The cost analysis here aims to identify cost differences between CSII and MDI. Costs components comprise (i) intervention costs, (ii) differences in insulin costs, (iii) differences in the general management of patients, (iv) the costs associated with additional education for pump users and (v) costs associated with adverse events and complications. From these, we provide an overall estimate of the additional costs associated with CSII. Cost estimates are based on data from a number of sources (i.e. manufacturers, patient groups and expert opinion from two diabetes centres with expertise in management of patients on CSII therapy). As previously mentioned, we found no cost data in the published literature.

Intervention costs

Table 24 shows the differences in the supplies required for CSII and MDI therapy, indicating where the intervention costs differ.

Insulin pump costs

In the UK there are currently three insulin pumps available for diabetic patients, Disetronic H-Tron, Disetronic D-Tron and MiniMed 508. *Table 25* provides the costs associated with the purchase and maintenance of the insulin pumps available.

One aspect of the cost analysis is the assumption on the expected life of the insulin pump. The guaranteed life of those insulin pumps available in the UK is 4 years, whereas indications from INPUT and insulin pump manufacturers are around an expected life of 7–8 years. This analysis will use as a base case a pump life of 4 years, reflecting the guaranteed life where no maintenance costs are payable. Further cost comparisons and sensitivity analysis will explore alternative periods of expected pump life (e.g. 8 years).

TABLE 25 *Costs associated with purchase and maintenance of insulin pumps*

Type of insulin pump	Initial cost (£)	Expected life (years)	Guaranteed pump life (years)	Maintenance cost: average cost per year following warranty life (£)
Disetronic H-Tron	2350	4–8	2 pumps at 2 years each (total 4)	176.25
Disetronic D-Tron	2468	4–8	4	176.25
MiniMed 508	2562	4–8	4	381.88 for 2 years

Costs are inclusive of VAT.
Source: INPUT[136] and pump manufacturers.

TABLE 26 *Cost for consumable items required by insulin pump users*

Item	Unit cost (excluding VAT) (£)	Requirements	Cost per year (including VAT) (£)
Insulin cartridge/reservoirs:			
Disetronic H-Tron	41.25 per 25	Depend on dose	51.47
Disetronic D-Tron	35.00 per 10	Depend on dose	N/A[a]
MiniMed 508	40.80 per 24	Depend on dose	53.60
Adaptors for insulin cartridge/reservoirs:			
Disetronic D-Tron	35.00 per 10	Weekly (approx.)	220.10
Infusion sets:			
Disetronic H-Tron and D-Tron	Varies: 4.04/4.96/5.25	1 every 2 or 3 days	950.15[b]
MiniMed 508	Varies: 3.70–7.05	1 every 2 or 3 days	847.60[c]
Batteries:			
Disetronic H-Tron	10.30 per set	1 set every 5 weeks	126.21
Disetronic D-Tron	11.00 per set	1 set every 12 weeks	56.17
MiniMed 508	4.50 per set	1 set every 6 weeks	45.95
Estimated annual cost for consumable items (including VAT):			
Disetronic H-Tron			1127.83
Disetronic D-Tron			1226.42
MiniMed 508			947.15

[a] Disetronic D-Tron is able to use 3-ml Humalog insulin cartridges.
[b] Weighted annual cost from Disetronic/Abacus.
[c] Weighted annual cost based on average cost for Teflon needles and proportions of 0.55 and 0.45 for Teflon and steel needles used.
Source: cost data from INPUT 2001,[136] unless stated otherwise.

Estimates of the cost for consumable items required as part of CSII therapy are presented in *Table 26*. All pumps require batteries, infusion sets and insulin cartridges and/or adaptors.

Insulin costs

The clinical review has shown a reduction in the daily insulin dose with CSII. *Table 27* uses the findings from the meta-analysis [see the section 'CSII versus MDI' (p. 14)] to estimate the cost implications of the reduced insulin requirement.

Cost for general patient management

Diabetic patients on MDI are typically managed on an outpatient basis at a local diabetes centre. Patients typically (where no complications occur) attend for a regular annual outpatient appointment with the consultant physician, and at 6-monthly intervals they attend for an appointment with a DSN (two visits per year). They should be able to have HbA_{1c} measured every 3–4 months. Patients also have access to advice by telephone to the medical team at their

TABLE 27 *Reduction in insulin dose and associated costs*

Reduction in daily insulin dose: mean (95% CI)	Source	Insulin/cost per unit[a]	Annual cost reduction (£)
–9.73 (–14.5 to –4.91)	Meta-analysis 2.5–4 months (all appropriate trials)	Humalog: 5 × 3-ml cartridge (100 units per ml) = £26.78	66.33
		Soluble: Actrapid, 10-ml vial (100 units per vial) = £10.50	37.29
–13.63 (–23.62 to –3.64)	Meta-analysis 2.5–4 months (RCT data only)	Humalog: 5 × 3-ml cartridge (100 units per ml) = £26.78	88.72
		Soluble: Actrapid, 10-ml vial (100 units per vial) = £10.50	52.57

[a] Source of cost data: BNF, March 2002.

diabetes centre (normally their DSN). This level of care is not expected to be any different once a patient has started CSII therapy (assuming that education support is adequate for those on MDI, otherwise there would be an added cost) and has been through the education and training required as part of CSII therapy. However, in the early stages of CSII therapy it would be reasonable to expect that one extra visit to the DSN may be necessary (in addition to the education required at the start of CSII therapy), at 3 months after the start of pump therapy (source: expert opinion) (*Table 28*). These extra visits probably do not apply in the case of children, who are usually seen more often (every 3 months).

Where complications do occur, the treatment patterns/care pathways will be the same for both MDI and CSII patients.

Costs associated with education for CSII

Education for CSII: patient level

Where patients are switched from MDI to CSII they must undertake a programme of education to familiarise themselves with the use of the insulin pump and its use in the management of their diabetes. There are no published data on the costs associated with insulin pump education. We consulted Bournemouth Diabetes and Endocrine Centre, a leading centre for insulin pump use, and their practice indicates that all patients on MDI should have been through diabetes education as part of the management of their diabetes. The typical education package at the Bournemouth Centre, for MDI, would entail an education programme comprising attendance at four 6-hour sessions, in a consecutive 4-week programme. These programmes typically cater for groups of 5–6 patients and involve a DSN and dietitian throughout the programme, with a consultant physician devoting up to 3 hours of contact time over the complete programme.

TABLE 28 *Additional resources for general patient management: CSII versus MDI*

Additional resource items	Additional cost (£)
1 additional outpatient appointment in year 1	74
Source: PSSRU, 2001.	

Diabetic education will differ across centres from formal packages of education, as provided in Bournemouth, to more informal and *ad hoc* patient education programmes. The issue in this review is the additional education required by patients when switching to CSII. Again we have drawn on current practice at the Bournemouth Centre, which we believe provides a reasonable estimate (a relatively thorough package of education and training) of the education necessary for insulin pump users. When a patient initiates CSII, additional education is provided at both group and individual patient levels. Patients attend for both group and individual education sessions. Education is delivered to groups of 3–5 patients (minimum, maximum) and comprises input from a DSN, at 9-hour group level, and thereafter patients typically attend for 3 hours of education with the DSN at an individual patient level. The typical programme would comprise a 6-hour group session, a 3-hour group session and individual education (3 hours) thereafter. Input from a dietitian would be variable, from 0–6 hours, depending on the level of prior education within the group (i.e. MDI education package outlined above) and the time that had

TABLE 29 *Patient-level education for CSII therapy*

Input to education programme	Hours	Staff inputs: cost per hour[a] (£)	Cost per patient (assuming a group of 4 patients) (£)
DSN – group	9	21.75	48.94
Dietitian – group	6	22.23	33.35
DSN – individual	3	21.75	65.25
Additional education cost per patient switching to CSII			147.54

[a] See Appendix 14 for details.

TABLE 30 *CSII – education and training for professionals*

Cost/resource inputs per centre	Number (minimum)	Cost per day[a] (£)	No. of days	Cost estimate (£)
Physician	1	578	3	1734
DSN	1	163	3	489
Dietitian	1	164	3	492
Course fees (NHS transfers)		N/A		N/A
Estimate of the costs associated with education for professionals				2715

[a] See Appendix 14 for details.

lapsed since the delivery of prior education programmes. In the estimate provided in *Table 29* we assume the maximum expected 6 hours of dietitian input. In paediatric care, because of smaller numbers, group sessions may not be possible.

Education for CSII: institutional level

Staff in diabetes centres providing CSII therapy will also require additional education and training where it is lacking. There is an organisation set up in the UK, Pump Management for Professionals (PUMP), a collaboration between Bournemouth Diabetes and Endocrine Centre and the Harrogate Diabetes Centre, that delivers education to professionals to facilitate the wider use of insulin pump therapy. PUMP recommends that for each centre managing patients on insulin pumps a minimum of three persons be educated on CSII: one physician, one dietitian and one DSN. The educational programmes offered currently comprise a 3-day teaching programme. *Table 30* presents details of the costs associated with the education of diabetes centres.

Information from PUMP indicates that 90 diabetes centres currently have some patients (one or more) on CSII and 25 centres have 10 or more patients. It is difficult to estimate the number of centres that would require CSII education for health care professionals. It may be that some of those centres already managing CSII patients would still require some degree of professional education. At one end of the spectrum we could assume that all 218 NHS Trusts in England and Wales that offer diabetic care, as listed in the Directory of Diabetes Care,[137] require the minimum education detailed in *Table 30*. This would result in an estimate of about £590,000 to cover education as described in the above table. However, it is unlikely that all centres would be responsible for the management of CSII patients, with the setting up of local or regional CSII centres being a possibility, which would reduce costs.

Costs associated with severe hypoglycaemia

The clinical review suggests that there will be slightly fewer severe hypoglycaemic events on CSII than MDI. Severe hypoglycaemia could have an economic impact, owing to the costs associated with treatment and the potential impact on patient QoL. However, indications from the two diabetes centres assisting with our review (Bournemouth and Harrogate) are that most instances of severe hypoglycaemia are treated by patients and carers and do not result in significant NHS resource implications. There is little literature on the cost consequences of severe hypoglycaemia. We detail below the insights available from the limited literature and the findings from consultation with two diabetes centres. We use these in *Table 31* to give an estimate of the cost per severe hypoglycaemic event, based on the assumptions on treatment

TABLE 31 *Cost estimate for treatment of severe hypoglycaemic event*

Treatment	Unit cost (£) (source)	Proportion of events treated in this way (%)	Proportionate cost (£)
Glucagon	19.95 (BNF[126])	100	19.95
DSN/outpatient attendance	74.00 (PSSRU[138])	10	7.40
Paramedic/ambulance attendance	247.00 (PSSRU[138])	5	12.35
Average cost for severe hypo			39.70

given in the third column. Based on discussion with the diabetes centres the cost profile for severe hypoglycaemic events assumes that in most cases there is no input from NHS staff, with patients or carers administering glucagon. In a number of instances patients are expected to attend or report the event to a DSN and we have made an assumption that this occurs in 10% of cases. Also, we have made an assumption that in 5% of cases an ambulance is called out to a patient experiencing an event, although these cases do not result in a hospital admission. These are conservative assumptions, and in reality there may be fewer instances of glucagon use, fewer visits/reports to the DSN and fewer ambulance callouts than those detailed in the cost profile.

The NHS Reference Costs Data[139] offer estimates for two health-related resource groups (HRGs) (K11, K12) associated with emergency hypoglycaemia in diabetic patients. K11 refers to 'Diabetes with Hypoglycaemic Emergency >69 or w cc' and K12 refers to 'Diabetes with Hypoglycaemic Emergency <70 w/o cc'. The cost database provides estimates for elective inpatient (ELIP) costs, non-elective inpatient (NELIP) costs and day case (DC) costs. Although elective inpatients stays (costing £1395 for K11 and £796 for K12) do not seem correct for emergency hypoglycaemia, 48 such events are listed as finished clinical episodes (FCEs) in the Reference Costs Database and 198 for K12. It is possible that they have been mis-coded as elective, or that patients have been admitted as semi-elective cases in order to review treatment and improve control. For NELIP costs are £954 and £567, respectively (activity data show 3027 and 2416 FCEs). For DC cost estimates are £222 and £352, respectively (16 and 97 FCEs). These HRG costs do not reflect the costs of the average severe hypoglycaemic event. It is possible that the cost estimates given in the NHS Reference Costs refer to severe hypoglycaemia complicated by uncommon related events, possibly hypoglycaemia associated with seizure or coma. Although relevant, they are probably sufficiently rare to have little effect on the average cost of a severe hypoglycaemic event.

A Scandinavian study by Nordfelt and Jonsson[140] reports a 12-month prospective follow-up of diabetic patients and estimates the costs associated with diabetes, providing an estimate of the costs associated with severe hypoglycaemia. The study assesses costs and other short-term effects of severe hypoglycaemia in 129 children and adolescents with Type 1 diabetes. Data were collected on 111 events of severe hypoglycaemia (16 were events involving unconsciousness and 95 were non-unconscious events). The average cost per event is reported at €239 (2047 SEK) for events involving unconsciousness and €63 (543 SEK) for events not involving unconsciousness (n = 95). These estimates include indirect costs (e.g. time lost from the workplace), and the estimates with healthcare costs only are substantially lower at €151 and €28, respectively (approximately £94 and £17.50, using an exchange rate of €1.6 per £). The study by Nordfelt and Jonsson, although in children and adolescents, adds support to our cost assumptions for severe hypoglycaemia (as above).

In a study available in abstract only, Leese and colleagues from the population-based DARTS collaboration reported that over a 12-month period, 7% of patients with Type 1 diabetes had severe hypoglycaemic events ('severe' being defined as needing emergency assistance from NHS personnel). One in three episodes (of all cases, Type 1 and Type 2 diabetes) were dealt with solely by the ambulance crew. The average cost was around £377.[141]

Estimated marginal cost for CSII

Based on the cost estimates presented above, the additional costs of CSII are as given in *Table 32*.

The benefits of CSII

From the clinical effectiveness evidence and the users' submissions, the benefits of CSII over MDI include:

TABLE 32 *Estimated marginal cost associated with CSII compared with MDI*

Cost consequence of CSII versus MDI	Disetronic D-Tron (£)	Disetronic H-Tron (£)	MiniMed 508 (£)
Intervention costs:			
Pump	2,468	2,350	2,562
Consumables	1,226.42	1,127.83	947.15
General patient management	74	74	74
Patient education costs	147.54	147.54	147.54
Difference in treatment cost for severe hypos (assuming a reduction of 1 event per year)	–39.70	–39.70	–39.70
Difference in insulin cost[a]	–88.72	–88.72	–88.72
Total net cost for CSII:			
Year 1	3,878	3,571	3,602
Cumulative cost, assuming 4-year pump life:			
Years 1–4 (discounted)[b]	7,081 (6,722)	6,569 (6,242)	6,058 (5,790)
Mean non-discounted cost per year (costs spread over 4 years)	1,770	1,642	1,514
Years 1–8 (discounted)[b]	13,941 (11,871)	12,917 (11,011)	11,894 (10,201)
Mean non-discounted cost per year (costs spread over 8 years)	1,743	1,615	1,487
Cumulative cost, assuming 8-year pump life:			
Years 1–8 (discounted)[b]	12,178 (10,429)	11,272 (9,663)	10,096 (8,728)
Mean non-discounted cost per year (costs spread over 8 years)	1,522	1,409	1,262
Education for professionals	~2,715 per centre, year 1 only	~2,715 per centre, year 1 only	~2,715 per centre, year 1 only

[a] Using data from meta-analysis including RCTs alone.
[b] Figures in parentheses indicate where discounting of future costs has been undertaken using a discount rate of 6%.

- QoL gains from greater lifestyle flexibility
- improved diabetes control as reflected in HbA_{1c}, which might be expected to reduce long-term complications
- a reduction in hypoglycaemic events, which would be expected to be associated with a reduction in the fear of hypoglycaemic events
- an improvement in hypoglycaemic event awareness, which will feed into both the previous benefits.

However, all these benefits can feed into an improved quality and quantity of life.

This section starts with an overview of diabetes and QoL and then considers individual benefits.

Diabetes and quality of life

A recent review of QoL associated with diabetes[142] characterises the nature of diabetes (generally) by reporting that people with diabetes often feel challenged by their disease and its day-to-day management demands, finding that these demands are substantial. Patients with diabetes must deal with their diabetes all day, every day, making countless decisions in an often futile effort to approximate the non-diabetic metabolic state. Diabetes therapy, such as taking insulin, can substantially affect QoL either positively, by reducing symptoms of high blood sugar, or negatively, by symptoms of low blood sugar. The psychosocial toll of living with diabetes is often a heavy one, and this toll can often affect self-care behaviour and, ultimately, long-term glycaemic control, the risk of developing long-term complications and overall QoL.[142]

However, to place diabetes in context, the authors of the above review report that 'people with diabetes have a worse QoL than people with no chronic illness, but a better QoL than people with most other serious chronic diseases' (p. 205). The review is a useful one, albeit general, and presents findings on a range of issues affecting the

relationship between QoL and diabetes, for example, type of diabetes, treatment regimen, glycaemic control, demography and patient characteristics. The review highlights some of the associations and uncertainties evident in the literature covering the assessment of QoL in diabetic patients generally.

A number of the above issues impact on the assessment of CSII, which may affect glycaemic control, adverse events and lifestyle issues associated with managing diabetes. Within this assessment of CSII versus MDI, the prime concern is the difference between the two therapeutic options. With respect to QoL, there are few insights as to any potential differences between the two options. From the clinical review only one study has reported QoL as a trial outcome, by Tsui and colleagues,[79] and that study failed to find a significant difference between CSII and MDI (using DQOL). Further literature searches did not identify any studies (randomised or crossover studies) comparing QoL outcomes in CSII and MDI. A number of descriptive studies may assist in forming a view on the QoL consequences of CSII, and these are discussed below. However, we must be aware that the findings from these studies may not be generalisable and may introduce bias from a variety of sources, such as patient selection and study design.

From the clinical review findings in Chapter 3, the small, but significant, difference in HbA_{1c} and the reduction in the event rate for severe hypoglycaemia are deserving of attention in terms of their impact on the QoL of patients (CSII versus MDI). These issues are discussed below.

Glycaemic control (HbA_{1c})

Data from long-term trials and epidemiological studies have provided evidence that 'good' metabolic control protects diabetic patients against chronic complications (e.g. DCCT Research Group,[19] WESDR[132] and UKPDS[130]).

The DCCT Research Group[143] have presented findings on the relationship of glycaemic exposure (glycated haemoglobin/HbA_{1c}) to the risk of development of progression of retinopathy in the DCCT. The DCCT demonstrated a marked reduction in the risks of development and progression of retinopathy and other complications of IDDM with intensive treatment compared with conventional treatment. They also present findings[143] from an epidemiological assessment of the association between levels of HbA_{1c}, before and during the DCCT, with the risk of retinopathy progression. The DCCT data do not provide a definitive assessment of the causal relationship between specific levels of glycaemic exposure (HbA_{1c}) and the risk of complications,[143] as confounding is possible from a number of sources. However, the findings from the epidemiological assessment lead the DCCT group to believe that the mean HbA_{1c} (i.e. improved HbA_{1c}) is the dominant predictor of the reduced risk of complications in the intensive treatment group, and that data on the total exposure to glycaemia (based on HbA_{1c} at screening and the level during the trial), the baseline duration of IDDM and the time in the study provide a strong, although indirect, affirmation of the glucose hypothesis (i.e. lower levels of glycaemia would reduce the development and progression of complications).

The DCCT Research Group use a number of different statistical models (proportional hazards, Poisson and Logit models) to show that the risk of complications increases with increases in the model variables reflecting glycaemic exposure. It is from these sources that the recent meta-analysis by Pickup and colleagues,[40] comparing CSII with MDI, postulates that a difference in HbA_{1c} of 0.5% approximates to a reduction of 0.5 cases of sustained retinopathy progression per 100 patient years (such a difference would be reflected by a reduction in the probability of sustained retinopathy progression of $p = 0.005$, or 0.5% per patient per year). Although these statistical models are helpful, they do not lend themselves to an application in economic models, as the difference in HbA_{1c} cannot be translated into a transit probability from meaningful health state descriptions [i.e. a Markov or decision analytic model requires a pathway of disease from one health state to another and the DCCT statistical models do not offer this opportunity, based on the published literature. This point is discussed further below, in the section 'Cost-effectiveness of CSII versus MDI' (p. 71), as we assess the general findings from the DCCT statistical models that predict the absolute risk of onset of sustained retinopathy progression].

Data from WESDR demonstrated the general relationship of glycaemic control to the incidence of diabetic complications.[144] WESDR health outcomes data suggest that higher levels of glycaemia are related to a decreasing QoL, but the investigators expect this to be because of the increased incidence of complications.[145]

Hypoglycaemia

Hypoglycaemia is the most common complication of therapy for Type 1 diabetes, and the reported incidence varies considerably (from four to 65 episodes per 100 patient years).[146] The consequences of hypoglycaemia vary from mild symptoms and signs to profound sequelae of neuroglycopenia including coma and seizures.[146] Effects on motor coordination, cognitive function and judgement can impair performance of complex functions such as driving a car, and also simple tasks, such as treating hypoglycaemia with oral carbohydrate. Mild hypoglycaemia can be rapidly corrected by food intake or sugary drinks, and has little clinical impact. However, severe hypoglycaemia, generally defined as requiring assistance from another person, can be serious, involving the potential for harm to patients and others. Severe hypoglycaemic events may also result in coma or seizure.

Severe hypoglycaemia is common in all patients with Type 1 diabetes with almost one-third of patients experiencing one or more episodes each year (EURODIAB IDDM Complications Study Group[147]). Severe hypoglycaemic events are themselves short-term events, with acute effects lasting no more than 1–2 days in most cases. However, the fear of experiencing a hypoglycaemic event is a further characteristic of the disease.

The clinical review [see the section 'Results in adults with Type 1 diabetes' (p. 16)] found that the rate of severe hypoglycaemic episodes differed little between treatments in most studies,[79,80,83,85–88,90,91] with no severe episodes occurring in two studies.[86,90] However, significantly fewer severe hypoglycaemic events per 100 patients years occurred with CSII compared with MDI in the study by Bode and colleagues.[81] Therefore, the impact of this potential reduction in the rate of severe events on the QoL of patients may be an important factor in the comparison of the two treatment options. As discussed in Chapter 3, it is possible that the RCTs underestimate the benefits of CSII for those with recurrent severe hypoglycaemia.

Findings from the DCCT showed that although hypoglycaemia is an important adverse event for IDDM, the relationship between hypoglycaemia and QoL is not clear. The DCCT presents findings on the relationship between hypoglycaemia and QoL as measured within the trial. QoL in the DCCT was assessed through the completion of the DQOL measure, the Symptom Checklist-90R (SCL-90R), the Short Form with 36 Items (SF-36) and psychosocial events observed in the trial. QoL data were collected from patients at annual visits. Initial analyses did not demonstrate differences in the QoL of outcomes between the treatment groups,[19] even though there was a marked increase in hypoglycaemia in the intensive intervention group. Subsequent analyses have supported this finding.[148] End of study assessments showed that the scores on all scales did not differ between the treatment groups. Subsequent analyses were undertaken to assess the relationship between hypoglycaemia and QoL outcomes. The DCCT Research Group[148] modelled the relationship of hypoglycaemia to the SCL-90R and DQOL outcomes. Data showed that the occurrence of severe hypoglycaemia was not consistently associated with a subsequent increase in symptomatic distress or decline in diabetes-related QoL. Models using the SCL-90R showed that only where patients had repeated severe hypoglycaemia, resulting in coma or seizure, did they tend to be at increased risk of measurable symptomatic distress. The models using the DQOL score as the outcome did not demonstrate an association of hypoglycaemia with an adverse change in QoL. The authors draw attention to some of the factors that may account for these findings (e.g. lack of power to detect an association between hypoglycaemia and QoL as measured by the DQOL), but present the findings as an indication that patients on intensive therapy did not face a deterioration in QoL, despite increasing demands of their diabetes care and the frequency of hypoglycaemia (for further detail, see the DCCT references listed).

Although severe hypoglycaemia is seen as a major complication by diabetic patients, other studies seem to support the supposition from the DCCT analysis that hypoglycaemia may not have a significant impact on the patients' reported QoL assessments. Ferguson and colleagues[149] in a study to investigate the potential of insulin Lispro to limit the frequency of severe hypoglycaemia, in a cohort of patients with Type 1 diabetes who are at a high risk of severe hypoglycaemia, present some indicative findings on the relationship between severe hypoglycaemia and QoL. The study (an open-label design) used the DTSQ and Hypoglycaemia Fear Survey (HFS) to assess QoL, and reported that overall, considering both treatment groups together, the 55% of study participants (18 of 33 patients) who experienced severe hypoglycaemia during the 48 weeks of study follow-up scored significantly higher on the HFS scales for worry ($p = 0.049$) and behaviour ($p = 0.015$), and these patients also had significantly

lower DTSQ scores ($p = 0.040$). Analysis across all patients in the study showed an increase in exposure to severe hypoglycaemia correlated with greater anxiety ($r = 0.55$, $p = 0.001$) and worry ($r = 0.58$, $p = 0.001$), depression ($r = 0.45$, $p = 0.010$) and lower levels of energy ($r = –0.52$, $p = 0.002$). However, where one treatment group showed a reduced incidence of severe hypoglycaemia (insulin Lispro treatment), there were no significant improvements in QoL measures between the two treatment groups.

Boland and colleagues[98] present findings from a prospective follow-up study in 75 adolescents and young adults with Type 1 diabetes, where patients chose between CSII and MDI prior to follow-up in the study. Rates for all hypoglycaemic events requiring assistance or resulting in coma were reduced by almost 50% in the CSII group (134 versus 76 per 100 patient years, $p < 0.05$), and patients in the CSII group found coping with diabetes to be less difficult than patients using MDI ($p = 0.05$). However, QoL assessed using the DQOLY (a version of the DCCT DQOL instrument) showed no differences between the two groups. The study also reports no difference between groups in terms of depression (assessed using psychosocial assessments), and self-efficacy assessments. (Note that this study was a non-randomised prospective study, and subject to selection bias, and so was not included in our clinical review.)

Nordfelt and Jonsson[140] present findings from a descriptive study to describe costs and other short-term effects of severe hypoglycaemia in children and adolescents with Type 1 diabetes. The study is predominantly a cost-of-illness study, with a 12-month prospective follow-up. The study does not assess CSII and the study sample group ($n = 129$) are patients treated intensively with multiple insulin therapy, based on active self-control, problem-based learning and psychosocial support. The interest in this study is the focus on hypoglycaemia and general comments on QoL issues associated with severe hypoglycaemia. The study used a questionnaire containing 20 detailed questions regarding short-term effects after each event of severe hypoglycaemia (during January to December 1988). Questionnaires were obtained from 50 patients who had reported one or more events of severe hypoglycaemia. Nine patients (7%) reported severe hypoglycaemia with unconsciousness (U) and 45 (35%) reported severe hypoglycaemia without unconsciousness but needing assistance of another person (NU). Four patients had both U and NU events. Data were collected on 111 events of severe hypoglycaemia (16 were U and 95 were NU events). With respect to QoL, patients indicated cancellations of planned activities in 11 events (10%), tiredness/headache in seven events (6%), schoolwork affected in five events (5%) and anger, sadness, minor wounds or bed/clothes wetting in two events. Other effects were reported for parents/families; increased worry after nine events (8%), poor sleep/tired during the day after eight events. As can be seen from the questionnaire response data, the assessment appears to have been primarily assessing QoL issues related to activities of daily living and psychosocial impacts; the authors do not offer further detail on the questionnaire administered.

Nordfelt and Jonsson[140] also present brief detail on a health state valuation exercise undertaken as part of their study. The study used the EQ-5D instrument in a postal survey of patients with a duration of diabetes longer than 1 year. The EQ-5D scores indicated lower global QoL for the patients with severe hypoglycaemia in 1997 compared with those without the severe hypoglycaemia: median 0.85 versus 1.0, $p = 0.0114$. The authors do not offer further detail on their findings or methods. The EQ-5D typically measures QoL on a scale of 0–1, with 0 representing the worst imaginable health and 1 reflecting the best imaginable health, whereby respondents are asked to place a rating for their own health state on a visual analogue scale (VAS) from 0 to 100. Further detail is required on this paper before findings can be generalised, as some ambiguities exist as to the comparator groups and the methods employed to obtain values (presumably the study used the VAS section of the EQ-5D instrument).

The association between severe hypoglycaemia and QoL differences is not apparent from the literature. The literature does not offer a reasonable estimate of health state values/utilities associated with health states involving severe hypoglycaemia. Some insights are available and these will be explored in the section 'Economic models for Type 1 diabetes' (p. 66).

Fear of hypoglycaemia

Because of the ever-present threats from hypoglycaemia (physical symptoms, negative mood states, cognitive dysfunction and the risk of seizures or death), many patients acknowledge substantial anxiety and fear concerning hypoglycaemia.[150] Fear of hypoglycaemia may itself be associated with poor metabolic control (e.g. deliberately maintaining high glucose levels

or over-treating early symptoms).[150] A survey instrument, the Hypoglycaemia Fear Survey (HFS),[151] has been developed to assess patients' fear. The HFS is a 27-item questionnaire, with a five-point Likert scale format. The HFS was used in a study by Ferguson and colleagues,[149] discussed above. However, the literature on the relative effectiveness of CSII versus MDI does not offer any detail on any differences in hypoglycaemic fear between the treatment groups.

In the appraisal of long-acting insulin analogues (insulin glargine), the NICE Appraisal Committee accepted that episodes of hypoglycaemia are detrimental to QoL, partly owing to fear of such episodes. The Committee accepted that reduction in fear of hypoglycaemia could have a significant effect on QoL, additional to that obtained from reducing the QoL losses from the actual episodes. Specific QoL and utility values are not given in the appraisal consultation document for long-acting analogues, but it appears that the cost-effectiveness estimates were significantly influenced by a reduction in fear of hypoglycaemia (NICE website at www.nice.org.uk, accessed 18 October 2002).

Hypoglycaemic awareness

Impaired awareness of hypoglycaemia, defined as a reduced ability to perceive the onset of hypoglycaemia, is common in patients with Type 1 diabetes, affecting around 25% of patients,[152] with prevalence increasing with duration of diabetes.[149] Up to 50% of IDDM patients 15–20 years post-diagnosis report having lost their ability to perceive autonomic symptoms associated with low blood glucose levels and thus often fail to act to prevent severe hypoglycaemia.[152] Severe hypoglycaemia has been reported to occur up to five times more frequently in patients with reduced awareness of hypoglycaemia. One of the benefits of better control through CSII may be the return of awareness of impending hypoglycaemia.

Clarke and colleagues[152] have developed a survey instrument to assess patient awareness of hypoglycaemia, and report a prospective study in 78 IDDM patients. The study concluded that IDDM subjects who believed they had reduced awareness of hypoglycaemia were generally correct. As part of this work, Clarke and colleagues[152] report that reduced awareness led to a greater number of moderate and severe hypoglycaemic events (results were from prospective diary records and were statistically significant at p values of 0.026 and 0.0062, respectively). In support of this finding, Gold and colleagues[153] (cited by Bode and colleagues[81]) report a sixfold higher incidence of severe hypoglycaemia in patients with hypoglycaemic unawareness compared with patients without impaired awareness. The literature review on the effectiveness of CSII versus MDI does not offer any detail on differences in hypoglycaemic awareness between the treatment groups.

CSII versus MDI: quality of life assessment

The search of the literature on QoL associated with CSII identified only one study that included QoL as an outcome in a randomised trial comparing CSII with MDI.[79] Tsui and colleagues[79] randomly assigned 27 patients with Type 1 diabetes to CSII or MDI. This study reports a QoL assessment at baseline and 9 months, as a secondary outcome, using the DQOL questionnaire. The study did not observe any significant differences in DQOL scores between the two groups (see detail on the study in Appendices 6 and 10).

There were no further findings on QoL comparisons between CSII and MDI from randomised or controlled trials, identified as part of the literature review. However, we have consulted a number of general and cross-sectional studies to provide an insight to the health status associated with CSII treatment. We have discussed above a number of studies that address issues related to severe hypoglycaemia and QoL and offer brief detail below of studies by Chantelau and colleagues[154] and Lewis and colleagues[155] that considered general QoL issues in the context of CSII. However, these studies are not randomised or crossover designs, and the quality of the studies (often descriptive in nature) is variable; caution should be exercised in the interpretation and generalisation of any findings.

The study by Chantelau and colleagues[154] presents findings from a prospective cohort study with a 6-month follow-up. The study uses the DCCT DQOL questionnaire to consider QoL in IDDM. The study considers two groups. Group A were patients who had moved to a more intensive therapy (one group is CSII). The study reports no change on scales for social worries or diabetes-related worries, the scale for impact of disease showed a reduction and the score for patient satisfaction increased. CSII indicated fewer hypoglycaemic events. (The DQOL instrument has 46 items, four subscales, scored on five-point Likert scales.) Group B comprised a comparison of pens versus pumps, and pen therapy scored relatively low on the satisfaction subscale, mean

3.61 (SD 0.06), and higher on the impact subscale, mean 2.20 (SD 0.06). CSII significantly improved ($p = 0.02$) these subscale scorings only [satisfaction up to 4.02 (SD 0.06) and impact down to 2.03 (SD 0.05)], with the scales for social worries and diabetes-related worries unchanged.

Within subgroup analysis, pump users (Group B subgroup B1) scored significantly improved QoL with regard to hypoglycaemia, whereas pen users (Group A subgroup A1) did not (those changing from pen to pump, B1, reported less frequent hypoglycaemia, as opposed to those changing from traditional therapy to intensive pump therapy who reported hypoglycaemia as 'unchanged').

Lewis and colleagues[155] present a Treatment Satisfaction Scale for IDDM diabetes, with three subscales. The authors offer support for the scale and some experimental results, which indicate that CSII has better QoL than other treatment groups. However, the authors also raise concerns over the generalisability of the study findings.

In a general review of QoL issues associated with diabetes, Rubin and Peyrot[142] state that it is not possible to conclude that QoL differences (i.e. diabetes versus non-diabetes) are due to diabetes *per se* rather than some other characteristics associated with diabetes. The authors sum up by stating that better glycaemic control is associated with better QoL, but it is the complications of diabetes that are the most important disease-specific determinant of QoL. This position appears to be the position of the WESDR and DCCT investigators also. Based on findings on QoL from these long-term studies, and from what we can learn from the limited empirical evidence available elsewhere, it would seem reasonable to assume that differences between CSII and MDI in terms of the rates of severe hypoglycaemia may not in themselves result in a difference in QoL, as assessed using instruments such as DQOL and SCL-90R.

As highlighted in the patients' perspective section of this report, hypoglycaemia is undoubtedly a serious concern for diabetic patients, with potentially severe consequences, yet the overall impact does not appear to be captured in the general assessment of QoL. This may be due to the lack of sensitivity in the instruments used, or it may be due to the short-term nature of the events themselves, or the fact that the difference between CSII and MDI may, on average, only reflect a reduction of one event or less per patient per year. These considerations are mere speculation and should be the subject of further research efforts.

CSII may result in a more flexible lifestyle with regard to meal schedules, work and recreation, with flexibility over the timing and content of meals. CSII may offer variability in timing and dose selection for insulin therapy and it may allow patients to follow a flexible lifestyle, offering the capability easily to correct blood glucose values by altering infusion rates to meet swings in these values.[156] However, there is no evidence base to demonstrate how a reduction in the rate of severe hypoglycaemia impacts on patients' QoL. Likewise, although the fear of hypoglycaemia and the reduced awareness of hypoglycaemia are very real issues for a number of patients, it is not possible at present to quantify the impact of CSII on the fear of hypoglycaemia or the effect of CSII on the ability of patients to perceive the onset of hypoglycaemia (let alone the QoL issues associated with such impacts).

Health state values/utilities for CSII

The literature identified did not contain any insight as to the values, or health state utilities, that patients ascribe to the use of CSII. Furthermore, we found more generally that the literature on health state values associated with diabetes was also sparse, although this was subject to *ad hoc* searches only and by a systematic review of the literature.

Wu and colleagues[157] present analyses on health state values for diabetes derived via a mapping process, from SF-36 responses to the values available from the QWB Scale. The findings are based on analysis from a sample of 89 (non-diabetic) respondents completing the SF-36. The paper is a methods paper and can be classed as experimental; however, the presentation of estimates of QWB scores associated with a move from 'general population health state values' to a condition in which patients are 'Type 1 diabetics, with no complications', and from the 'no complications' diabetic state to a state involving 'diabetic retinopathy' may be helpful for the development of illustrative analysis within this review. *Table 33* presents outline findings from the study by Wu and colleagues. Caution must be exercised when considering the data presented in this study.

Data from Wu and colleagues[157] indicate that health state values associated with different states show only small differences in valuations (e.g. for a move from 'no complications' to 'retinopathy state' we see a change of 0.03, 0.04 and 0.02 for the groups in *Table 33*). The clinical significance of these differences is dubious, and retinopathy

TABLE 33 *Age- and health-specific QWB scores. (Copyright © 1998 American Diabetes Association. From* Diabetes Care *1998;* ***21****: 275–31.*[157] *Reprinted with permission from The American Diabetes Association.)*

Age (years)	General population[a]	Type 1 diabetic, no complications	Type 1 diabetic, with retinopathy only	Other[b]
<45	0.82	0.73 ± 0.07	0.76 ± 0.05	0.70 ± 0.08
45–64	0.75	0.68 ± 0.09	0.72 ± 0.09	0.66 ± 0.07
≥ 65	0.70	0.64 ± 0.08	0.62 ± 0.07	0.55 ± 0.05

[a] Data on general population are from previous studies; see Wu *et al.*[157] for detail.
[b] Type 1 diabetic individuals with diabetic neuropathy or nephropathy alone, or with other complications.

would only affect QoL if it impaired vision, or if it led to anxiety though the diagnosis *per se*, or from disutility from treatment given.

With regard to diabetic retinopathy, Brown and colleagues[158] assessed the utility values associated with varying degrees of visual loss due to diabetic retinopathy. The study presents utility values, elicited using standard gamble (SG) and time trade-off (TTO) techniques, across five subgroups with varying degrees of visual loss, ranging from 0.85 to 0.59 for TTO and from 0.70 to 0.90 for SG scores. Overall, in the sample of 95 respondents the TTO values were 0.77 and the SG scores were 0.88 (with visual acuity ranging from 20/20 vision to hand motion visual acuity in the best eye).

Kiberd and Jindal,[159] in a study on screening to prevent renal failure in insulin-dependent diabetic patients, present an estimate of the health state utility for patients with diabetes; they report a value of 0.838, commenting that traditionally utilities vary between 1.0 (perfect health) and 0 (death). The authors, finding no published literature to inform on health state values, determined these values using a TTO format in a sample of 17 healthcare workers not associated with their study (this sample consisted of nephrologists, clinical house staff, nurses and one social worker). The sample of healthcare workers estimated values for six health states, one of which was 'insulin-dependent diabetes alone'. The authors do not report any further detail on the health state valuation exercise.

The above studies have no direct relevance to the comparison of CSII and MDI, but they do offer some idea of the magnitude of the health state valuation differences between diabetes-related health states, and may offer an opportunity to consider how the difference between CSII and MDI might relate to the differences associated with (i) a non-diabetic state versus a diabetic state or (ii) a diabetic state with no complications versus a diabetic state with retinopathy complications. Once again, in raising these matters for consideration we stress that caution must be exercised in generalising from these essentially experimental studies or using the information for anything other than illustrative purposes.

Economic models for Type 1 diabetes

Review of economic models for Type 1 diabetes mellitus (IDDM)

Given the limited data available to inform on the cost-effectiveness of CSII versus MDI, a general topic search of the diabetes literature was undertaken to identify literature on the model-based economic assessments within Type 1 diabetes (IDDM). Only a limited number of model-based approaches have been identified that assess economic outcomes for Type 1 diabetes. *Table 34* provides summary detail on the modelling approaches associated with Type 1 diabetes. Models are described in outline, with a particular focus on diabetic retinopathy and hypoglycaemia, where they form part of the model structure. The models are described to offer background to the assessment of CSII but do not directly assist with the assessment of CSII versus MDI.

DCCT Research Group

The DCCT has been discussed above. The DCCT model[129] describes and compares the lifetime benefits and costs of conventional and intensive therapy as implemented in the DCCT. The model is a Monte Carlo simulation model, used to predict the incidence of microvascular and neurological complications in a hypothetical sample of 10,000 persons with IDDM. It randomly selects from the hypothetical population (either a primary prevention cohort, or secondary prevention) and assigns characteristics (e.g. age, disease characteristics). It then uses 12 health

TABLE 34 *Approaches to model the cost-effectiveness of Type 1 diabetes*

Study	Study design	Approach	Intervention
DCCT, 1996[129]	Modelling	Cost-effectiveness	Conventional versus intensive therapy
Palmer, 2000[135]	Modelling	Cost-effectiveness	Conventional versus intensive therapy (various treatment options)
Tomar, 1998[160]	Modelling (based on DCCT model above)	Cost-effectiveness	Conventional versus Intensive therapy (plus costing study)

states to capture disease characteristics, grouped according to the three major complications studied in the DCCT (retinopathy, neuropathy, nephropathy). The model simulates the course of the patient's disease over their expected lifetime. The model uses 1-year cycles and at each cycle an individual is in one of five retinopathy health states, one of four nephropathy health states and one of three neuropathy health states. The probability that a patient will advance to a more severe stage of disease in a given year depends on the patient's current state of health, treatment regime (i.e. intensive versus conventional insulin therapy) and treatment duration. The model cycles through time at a patient level, until the patient exits the model (due to death) and then the next patient is selected from the hypothetical sample. This process is repeated in the DCCT analysis for a sample of 10,000 individuals. At the end of the modelling process (the simulation), the time spent in each of the treatments and health states and the time spent alive are calculated, costs are assigned and mean statistics are calculated by treatment group (conventional versus intensive). The DCCT model does not consider hypoglycaemic events.

The DCCT model uses empirical data on disease progression, over 9 years, from the DCCT and a series of statistical models (Weibull models) to predict the probability of patients advancing to background diabetic retinopathy (BDR) and proliferative diabetic retinopathy (PDR) [e.g. Weibull model, $\alpha \times \beta \times t(\alpha - 1)$, where α and β are statistical parameters determined by the study and t is the parameter for duration of treatment; different α and β parameters were determined to reflect conventional and intensive treatment probabilities of progression of disease]. These methods are not transferable to the assessment of CSII versus MDI. *Table 35* offers outline detail on the DCCT model structure.

Palmer and colleagues

The diabetes disease model developed by Palmer and colleagues[135] considers the cost-effectiveness of a range of intensive interventions for Type 1 diabetes (IDDM) compared with conventional therapy, to consider optimal lifetime treatment patterns. A variant of this model has been used in an earlier NICE submission on pioglitazone in Type 2 diabetes.[171] (Chilcott and colleagues, 2001). The Type 1 model of Palmer and colleagues is a microsimulation model, simulating the experiences of individual patients (the modelling process is similar to the process described above for the DCCT model). The data for the model are generally drawn from the DCCT and WESDR studies. The authors cite an early WESDR study[144] and the main DCCT study[19] as evidence that the rate of disease progression from no retinopathy to BDR is dependent on duration of diabetes and the HbA_{1c} value;[135] yet the model uses DCCT methods surrounding duration of diabetes to predict transit probabilities for BDR.[19]

Palmer and colleagues' model comprises a series of Markov submodels, representing the development and consequences of renal disease, retinopathy, amputation, myocardial infarction, stroke, major hypoglycaemic events and DKA. The data used in the model on hypoglycaemic events are data (event rates) from the DCCT, reflecting a greater risk of severe hypoglycaemic events for the intensive treatment group versus conventional therapy.

The submodel for hypoglycaemia (*Figure 12*) is a simple transition from an entry state involving no major hypoglycaemic event to a health state whereby patients experience an event requiring assistance (severe hypoglycaemia) and then transit back to either the health state of no hypoglycaemia or hypoglycaemic death (the model assumes a very small probability of death as a consequence of hypoglycaemia, a death rate of 0.0001).

The submodel for diabetic retinopathy is described in *Figure 13*.

For retinopathy, the pattern of disease progression is from no retinopathy to BDR, to PDR and on to

blindness (*Figure 13*). As the simulation progresses each year (1-year model cycles), patients may continue in their present health states or transit to the next stage of disease progression or a non-specific mortality state. Transit probabilities are based on DCCT data and are dependent on duration of diabetes. Therefore, the methodology is not transferable to an evaluation of CSII versus MDI. The retinopathy submodel does not include macular oedema. The retinopathy submodel makes assumptions surrounding screening and treatment for diabetic retinopathy.

The model examines the course of the development of diabetes complications under a set of intervention scenarios and examines the treatment effects in terms of a time series of clinical events and outcomes (e.g. incidence of complications, mortality). It produces results for a typical cohort of 19-year-old diabetic patients, with no baseline complications (to reflect a typical cohort of Swiss male patients). It does not have a separate submodel for mortality, as mortality is included within each of the complication specific submodels. However, it is not clear how the mortality rates have been determined. *Table 35* offers outline detail on the model structure.

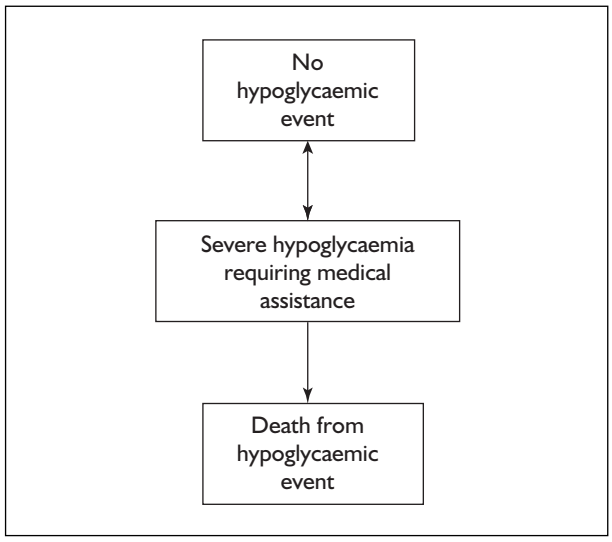

FIGURE 12 *Hypoglycaemia submodel from Palmer and colleagues*[135]

Tomar and colleagues

The model by Tomar and colleagues[160] is not described in this report as it is based on the approach documented by the DCCT Research Group (as above), and does not offer additional data to inform on the modelling of diabetes for CSII versus MDI. See the cited reference for further detail.

Suitability of economic models for evaluation of CSII versus MDI

The modelling approaches discussed above do not offer an opportunity to transfer methods to the assessment of CSII versus MDI. The model-based approaches described for Type 1 diabetes (and much of the Type 2 diabetes literature) are configured to assess the impact of intensive therapy compared with conventional therapy, whereas the assessment of CSII versus MDI is a comparison of different treatment options for the delivery of intensive therapy.

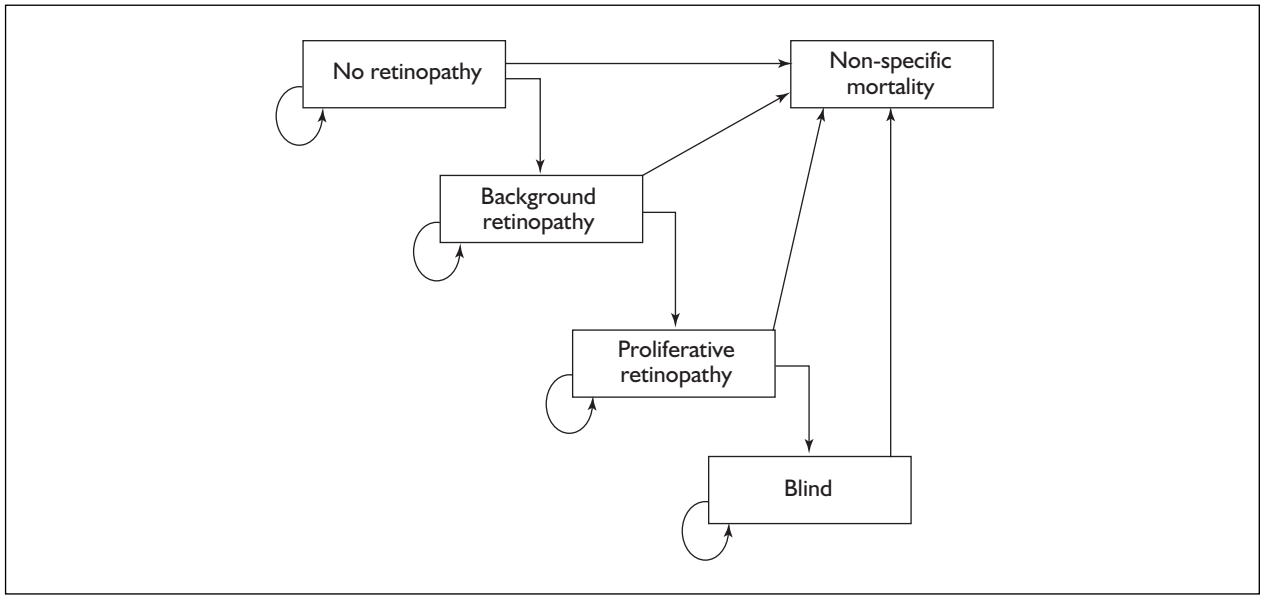

FIGURE 13 *Retinopathy submodel from Palmer and colleagues*[135]

TABLE 35 *Models for IDDM and model characteristics*

Detail	Modelling studies	
	DCCT Research Group[129]	**Palmer and colleagues[135]**
Study design	Modelling	Modelling
Economic outcomes	Cost-effectiveness	Cost-effectiveness
Intervention	Intensive insulin therapy	Intensive therapy combinations
Type of modelling	Microsimulation (Monte Carlo, patient level, 1-year cycles)	Microsimulation (Monte Carlo, patient level, 1-year cycles)
	Markov model	Markov model
Decision analysis	Yes	Yes
Cohort/age	Two cohorts aged 13–39 years (primary/secondary prevention)	Swiss cohort of 19-year-old diabetics patients
Source of cohort information	WESDR	
Complications:		
Retinopathy	✓	✓
Neuropathy	✓	✓
Nephropathy	✓	✓
Heart Disease	–	✓
Stroke	–	✓
Hypoglycaemia	–	✓
Ketoacidosis	–	✓
Data inputs for retinopathy	WESDR	DCCT/WESDR
Data inputs for hypo	–	DCCT

Illustrative analysis of the relationship between HbA_{1c} reductions and the incidence of diabetic retinopathy

Given the lack of models with which to compare directly the cost-effectiveness of CSII with MDI, one option is to use the observed mean reduction in HbA_{1c} in combination with the DCCT model for a somewhat speculative estimate of reduction in future retinopathy.

The DCCT Research Group demonstrated that a regimen of intensive therapy aimed at maintaining near normal blood glucose values markedly reduces the risk of development and progression of retinopathy and other complications of IDDM when compared with a conventional treatment regimen.[19] The DCCT Research Group also present a further epidemiological assessment of the association between levels of glycaemic exposure (HbA_{1c}) before and during the DCCT with risk of retinopathy progression within each treatment group.[143] Total glycaemic exposure (HbA_{1c} and the duration of exposure) was the dominant factor associated with the risk of retinopathy progression.[143] When examined simultaneously within each treatment group, each of the components of pre-DCCT HbA_{1c}, pre-DCCT duration of IDDM, mean HbA_{1c} during the study, time in the study and their interaction, was significantly associated with risk of retinopathy progression.[143] However, the DCCT data cannot provide a definitive assessment of the causal relationship between specific levels of glycaemic exposure and the risk of complications. The study was designed to assess whether an intensive regimen aimed at lower levels of glycaemia would yield the desired effects (i.e. reduced complications), recognising that any effects observed could theoretically be attributable to any of the effects of such therapy.[143] However, the DCCT Group do state that the epidemiological assessment of data conclusively demonstrates that the updated mean HbA_{1c} (i.e. following intervention) during the trial and the years of follow-up in the study are the most important predictors of the risk of complications in the conventional treatment group, and that the updated mean HbA_{1c} was the dominant predictor of risk of complications in the intensive treatment group. Although glycaemic exposure was the dominant predictor, the updated mean HbA_{1c} did not completely explain the risk of progression.

The DCCT Research Group[143] investigated whether there was a threshold for glycaemia below which there was no further reduction in risk of

Absolute risk at time (t) = f (HbA_{1c}, log of duration of IDDM on entry to the study, time)

$$\lambda(t) = \exp\{\alpha + \beta_1 (H) + \beta_2 \ln(D) + \beta_3 (t) + \beta_4 \ln(A) + [\beta_5(t) \times \ln(A)]\} \quad (1)$$

where $\lambda(t)$ is the absolute risk at time t, α is an intercept term, β_1 is the screen HbA_{1c} coefficient, H is the screening HbA_{1c}, β_2 is the duration coefficient, D is the duration of IDDM (in years) on entry, β_3 is the time coefficient, t is the study time and β_4 and β_5 are interaction coefficients. Hence,

λ (risk of onset of sustained retinopathy progression at t) = $\exp\{\alpha + \beta_1$ (screen HbA_{1c}) + β_2 (log duration of IDDM on entry) + β_3 (time) + β_4 (log mean updated HbA_{1c}) + $[(\beta_5 \times$ time) $\times$ (log mean HbA_{1c})]} (2)

FIGURE 14 *DCCT regression model used for illustrative analysis*

TABLE 36 *From DCCT[143] Table 9: regression models of sustained retinopathy progression as a function of total glycaemic exposure*

	Intensive – treatment		
Total glycaemic exposure, Poisson model	**Estimate**	**95% CI**	***p***
Intercept	–10.871	–16.964 to –4.779	<0.001
Screening HbA_{1c} (%)	0.215	0.061 to 0.37	–
Log (duration) (years)	1.055	0.656 to 1.454	–
Pre-DCCT exposure (2 df)	–	–	<0.001
Time (years)	– 1.710	–3.120 to –0.300	–
Log (mean HbA_{1c})	1.541	–1.46 to 4.541	–
Log (mean HbA_{1c}) × time	0.809	0.136 to 1.483	<0.019

complications, finding that over the range of values for intensive treatment, there was a gradual decline in risk with each additional reduction in HbA_{1c} (i.e. no threshold was seen below which the risk of retinopathy was eliminated entirely). The authors present a number of statistical models (regression models) used to predict the risk of retinopathy progression. In *Figure 14* we apply one of these models in an illustrative analysis to assess the predicted risk of retinopathy progression amongst patient groups subject to CSII or MDI.

Coefficients for this model are presented by the DCCT Group as shown in *Table 36*.

The exploratory model (see *Figure 15*), uses a time horizon of 10 years (10 years has been used as the analysis does not accommodate mortality concerns) to simulate patient level experiences for CSII and MDI therapies against differing HbA_{1c} profiles, to reflect the efficacy parameters expected from CSII versus MDI. A simple Excel spreadsheet model has been used, using Crystal Ball software (Decisioneering®) to produce a simulation.

We have applied the above statistical model [equation (1)] to predict the probability of onset of sustained progression of diabetic retinopathy in a population defined by baseline HbA_{1c} and duration of IDDM at the start of therapy. The cohort is assumed to be a primary prevention cohort, free from diabetic retinopathy. Cohort data have been gathered from studies within the clinical review described above (see *Figure 15* for detail). The efficacy data from the clinical review have been used to reflect a difference in baseline HbA_{1c} and follow-up HbA_{1c}. To simulate the progression of disease over time, the model uses the transit probabilities determined through use of the statistical model and appropriate model coefficients, together with a series of random numbers, with the onset of disease based on the balance of probabilities within the patient cohort. The onset of sustained progression of disease is as defined in the DCCT study.

A simple simulation has been run over the 10-year time frame, to predict the experiences of a patient cohort with CSII (reflecting a reduced level of HbA_{1c}) and a patient cohort on MDI (i.e. no reduction in HbA_{1c}), using the same series of random numbers to cycle both patient groups through the model/simulation. A simulation has been carried out using a group of 10,000 patients. Results generated from specific input parameters (i.e. HbA_{1c} and duration of IDDM) are presented in *Table 37*, for illustrative purposes only [this

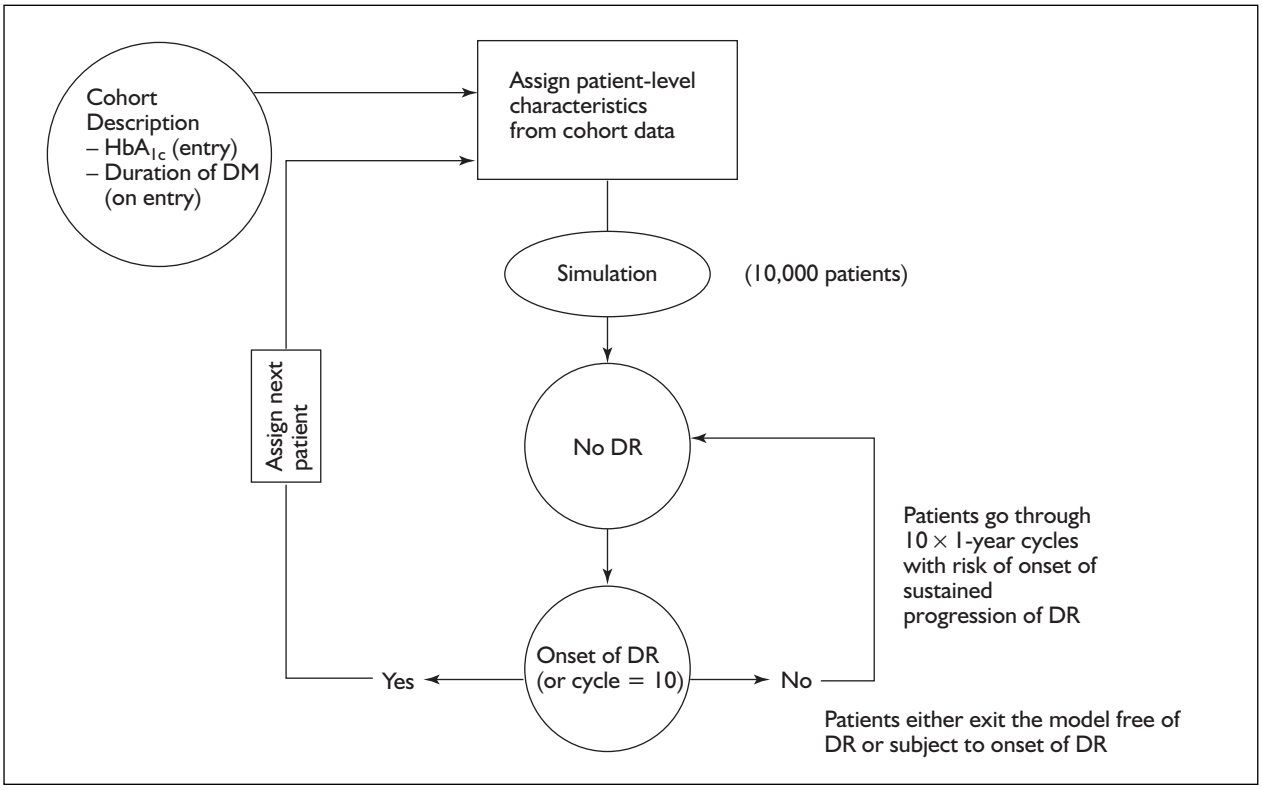

FIGURE 15 *Structure of exploratory model to assess risk of onset of sustained progression of diabetic retinopathy (DR)*

exploratory analysis is based on an assumption of primary prevention cohorts (diabetic retinopathy), assuming that patient cohorts are free from disease].

Cost-effectiveness of CSII versus MDI

We have discussed above the difficulties associated with modelling cost-effectiveness via a disease progression model using glycated haemoglobin (HbA_{1c}), the main effectiveness outcome from the comparison of CSII and MDI. From our exploration of the literature and available modelling technologies, it is not possible to produce a meaningful incremental cost-effectiveness ratio. We have produced a cost analysis to determine the short-term and medium-term costs associated with CSII. However, we have not been able to identify comprehensive estimates of meaningful health outcomes from the clinical evidence available. The link between HbA_{1c} and longer term complications (e.g. eye and kidney disease) would have to be assumed. There is an absence of data linking the use of pumps with any longer term complication or mortality data. To our knowledge there are no long-term trials of CSII versus MDI planned for the future.

Below we make some assumptions surrounding the benefits associated with CSII. However, based on the lack of an evidence base to support these assumptions, the examples are purely illustrative.

Outcomes associated with CSII

Long-term complications

We have discussed above the general belief that a reduction in HbA_{1c} is a good thing, with a reduction in HbA_{1c} expected to contribute to a reduction in the incidence of complications such as diabetic retinopathy (DCCT,[19] UKPDS,[131] WESDR[132]). However, in previous studies assessing the cost-effectiveness of interventions for Type 1 diabetes (DCCT,[129] Palmer and colleagues[135]), hazard rates and statistical parameters have been used that have been determined from particular study and intervention groups, in order to estimate future rates for complications and the subsequent reduction in risk associated with diabetic interventions (e.g. intensive therapy versus conventional therapy). Pickup and colleagues[40] in a recent meta-analysis of CSII have alluded to a potential reduction in the onset of sustained retinopathy progression and we have undertaken some exploratory analysis to assess whether their claims are supported by the data from the DCCT. Using a statistical model to assess the absolute risk of sustained onset of retinopathy

TABLE 37 *Illustrative examples of the reduction in risk of onset of progression of diabetic retinopathy in a cohort of patients free from retinopathy*

Cohort characteristics			**Source of characteristics**	**MDI – onset of disease: 10-year probability (%)**	**CSII – onset of disease: 10-year probability (%)**	**Risk reduction**	
Baseline HbA_{1c}: mean (SD) [assumption: normal distribution]	**Duration of diabetes: mean (SD; range) [assumption: log-normal distribution]**	**Efficacy parameter (reduction in HbA_{1c}) [assumption: normal distribution]**				**10-year (%)**	**Average annual reduction (%)**
8.39 (0.87)	20 (11.2; 4–42)	–0.52[a]	Hannaire-Broutine *et al.*[80]	52.23	42.29	9.94	0.99
10.4 (1.85)	9.2 (5.55)	–0.52[a]	Haakens *et al.*[83]	70.94	64.41	6.53	0.65
7.73 (0.6)	17 (10; 8–37)	–0.52[a]	Tsui *et al.*[79] – CSII cohort characteristics	30.82	23.15	7.67	0.77
8.16 (0.7)	15 (9; 4–28)	–0.52[a]	Tsui *et al.*[79] – MDI cohort characteristics	37.96	29.01	8.95	0.90
Some validation of the model used has been attempted through estimation of the risk for the DCCT primary prevention cohort, based on data available in DCCT:[19,129]							
9.1 (1.6)	2.6 (1.4)	–1.9% (assume SD of 0.19)	DCCT – intensive treatment, primary prevention cohort	Model predicts 15% risk of onset (over 10 years) based on cohort characteristics, and mean efficacy data. The data presented in the DCCT indicated a rate of 1.2 per 100 patient years, therefore the model is not far from this estimate (i.e. 1.5% from the model versus 1.2% from the DCCT data presented by the DCCT Group[19])			
Other studies, e.g. Nosadini *et al.*,[85] Bode *et al.*,[81] Schiffrin *et al.*,[97] Ziegler *et al.*,[84] data available do not allow investigation.							

[a] Efficacy data from the meta-analysis presented in Chapter 3, covering trial data over 10 weeks to 4 months, from included RCTs and CCTs; mean reduction 0.52% (SD of 0.22 assumed to reflect the reported 95% CIs of –1.19 to 0.14).

progression, a Poisson model detailed by the DCCT Research Group, we would concur with the suggestion of Pickup and colleagues that a 0.5% reduction in HbA_{1c} would result in a reduction in the region of 0.5 cases of sustained retinopathy progression per 100 patient years.

The analysis we have undertaken to relate the effect of HbA_{1c} changes to the incidence of long-term complications is illustrative. The statistical model used does not differentiate between the nature of the outcome expected, sustained retinopathy progression. BDR, which would comprise most, if not all, of this forecast reduction in the risk of diabetic retinopathy, is very different from PDR in terms of both its economic implications and the implications for the diabetic patient. The onset of BDR does not involve additional NHS resources as there is no treatment other than insulin therapy to manage glycaemic control. All diabetic patients should be subject to eye screening to detect onset and progression of diabetic retinopathy. The probability of onset of BDR is relatively high compared to the progression from BDR to PDR, hence our concern over the ability of the statistical model available to model disease progression. Our exploratory analysis of the methods presented by the DCCT Research Group[143] involved a simulation of patient groups defined by levels of HbA_{1c} and duration of diabetes over a 10-year period to detect onset of BDR from a population assumed to be free from BDR. From the clinical studies identified to inform on the effectiveness of CSII versus MDI we used patient characteristics, together with the mean effectiveness on HbA_{1c} identified via the meta-analysis reported above (we assume a reduction in HbA_{1c} of 0.52%). Findings indicate that a reduction in the risk of onset of BDR is somewhere between 0.5% and 1% per patient per year. The effect of such a reduction in the onset of sustained retinopathy progression requires consideration in the context of the overall incidence of disease and the impact of disease. The incidence of BDR is reported to be dependent on the duration of diabetes (WESDR,[132] DCCT[19]), and an estimate of the annual incidence of BDR from 'no retinopathy' would be in the region of 22% per year, based on data from WESDR, reported in their study on the 4-year incidence of diabetic retinopathy (data showed an incidence rate of 59% over 4 years). The DCCT Research Group[19] report in their primary prevention cohort a rate of 1.2 events per 100 patient years for onset of BDR. However, this group consisted of recently diagnosed patients with a mean duration of diabetes of 2.6 years (±1.4), hence a low-risk group.

In our opinion, it would seem reasonable to assume a small reduction in the onset of sustained retinopathy progression, predominantly from no disease to BDR; however, the impact of any such effect would be small on any cost-effectiveness findings for a population or patient analysis. Further effects on other long-term complications such as nephropathy (kidney disease) may be relevant, although we are not able to identify any literature concerning the consequences for such events in the context of the size of difference in HbA_{1c} related to the comparison of CSII and MDI.

It might also be worth noting that the move to systematic screening for early retinopathy, followed by laser photocoagulation, will diminish the incidence of visual loss. Hence the benefits of tighter control will, at least for retinopathy, be less than in past decades.

Adverse events – severe hypoglycaemia

The impact of severe hypoglycaemic events on QoL is not known. Indications from the limited literature indicate that overall QoL, as measured by instruments such as the DQOL, is not affected by events. Events are very short term, with the acute impact of a severe hypoglycaemic event lasting for 24 hours, at most, in most cases.

In order to assess the impact of severe hypoglycaemic events on the health state utility experienced by the diabetic patient, we can consider illustrative examples in a number of ways:

1. We could take the data reported by Nordfelt and Jonsson[140] showing a reduction of 0.15 (on a health metric scale of 0–1), between a state characterised by severe hypoglycaemia and one which is not. As mentioned earlier, these data are not supported by detail on methods within the paper, so caution must be exercised. However, it could be assumed that the health gain associated with preventing one event could be characterised by dividing 0.15 (the health gain) by 365 days to ascertain the associated impact for the 24-hour acute period. This obviously results in a very small difference in overall health utility, and even assuming that the effect of the severe hypoglycaemic event covered a period of 4 days, the health utility gained from preventing an event would be 0.00164, less than a 0.2% difference.
2. We could consider the health state values offered as part of the EQ-5D tariff[161] and assume that the effect of a severe hypoglycaemic event would be reflected in a movement in the EQ-5D health

TABLE 38 *Estimated additional costs associated with CSII versus MDI: mean patient-level costs for 1, 4 and 8 years (figures in parentheses where future costs have been discounted at 6%)*

Total net cost for CSII	Disetronic D-Tron (£)	Disetronic H-Tron (£)	MiniMed 508 (£)
Year 1	3,878	3,571	3,602
Assuming 4-year pump life:			
Years 1–4 (discounted)	7,081 (6,722)	6,569 (6,242)	6,058 (5,790)
Years 1–8 (discounted)	13,941 (11,871)	12,917 (11,011)	11,894 (10,201)
Assuming 8-year pump life:			
years 1–8 (discounted)	12,178 (10,429)	11,272 (9,663)	10,096 (8,728)

descriptive system against the dimensions of anxiety/depression and/or usual activities, as intuitively both dimensions may be affected by an episode of severe hypoglycaemia. Considering that an event may cause a movement on the EQ-5D algorithm from a moderate to a severe level (level 2 to level 3), or from a level associated with no problems or anxiety to a level associated with a moderate level of anxiety/depression and/or some problems with usual activities (level 1 to level 2). In such a way we can estimate the health gain associated with preventing one severe hypoglycaemic event. The health gain identified in this hypothetical manner would still be very small, assuming that an acute affect from an event covers a 24-hour period. Assuming that a patient moves from an EQ-5D health state described as having no anxiety and depression and no problems with usual activities to a health state characterised by extreme anxiety/depression and unable to do usual activities (all other dimensions remaining constant), the EQ-5D tariff values would reflect a difference in health utility/value of 0.294 quality-adjusted life-years (QALYs). Applying such a change to a short-term experience such as a severe hypoglycaemic event lasting 24 hours, we have 0.294/365, which is 0.0008 QALYs per event.

3. Even if we were crudely to assume that a patient experiencing a severe hypoglycaemic event were to move, on the health metric scale of 0–1 (where 1 represents full health), from full health (score of 1) to worst imaginable health (score of 0), it would still only reflect a health gain (QALY value) of 0.00274 per event (assuming the event were to last for 24 hours).

The above considerations are purely speculative and have no basis in the published literature, and combining these assumptions with available cost estimates (in effect assuming that the reduction in hypoglycaemic events was the only benefit of CSII) would result in very extreme, and potentially unrealistic, cost-effectiveness findings (~£400,000–500,000 per QALY).

Other benefits of CSII

Chapter 4 indicated that CSII is reported by some patients to offer lifestyle benefits and opportunities to manage their diabetes in a more flexible way. In this review we have been unable to quantify such benefits for the purpose of economic analysis. This does not mean that such benefits are not of importance for the patients themselves, but just that the research necessary to quantify any relative utility values has not been undertaken.

Estimating the cost-effectiveness of CSII versus MDI

Cost estimates have been detailed above (see summary in *Table 38*). In order to present cost-effectiveness estimates, data on meaningful health outcomes are required. We have been unable to identify health outcomes that can be quantified for the purposes of cost-effectiveness analysis. Based on the cost estimates calculated as part of this review, and the speculation as to the health gain associated with the prevention of severe hypoglycaemia (for example, a reduction of one event per year), with estimated QALY values per event ranging from 0.00164 to 0.00274, any cost-effectiveness estimates would be circa ~400,000–500,000 per QALY. A summary of benefits/outcomes from CSII versus MDI is presented in *Table 39*.

Cost-effectiveness

Cost per severe hypoglycaemic event avoided

The evidence on the rate of severe hypoglycaemic events, CSII versus MDI, is conflicting. Using data from Bode and colleagues,[81] which cover the reduction in events associated with CSII in a patient group that has a relatively high risk of events (i.e. a relatively high estimate of

TABLE 39 *Summary of benefits/outcomes from CSII versus MDI*

Benefit/outcome	Quantifiable	Related to cost-effectiveness
Reduction in HbA_{1c}	Yes	Not able to link directly to diabetic complications
Reduction in severe hypoglycaemia	Yes	Not able to link to cost-effectiveness in a meaningful manner (i.e. only able to consider cost per event avoided). Not able to establish QoL impact associated with the reduction in severe hypoglycaemic events
Long-term complications (e.g. diabetic retinopathy)	No	Not able to link HbA_{1c} directly to diabetic complications (illustrative analysis provided). Small reduction in incidence of microvascular complications expected
QoL benefits	No	Insufficient data to make a judgement on overall QoL differences between CSII and MDI
Lifestyle benefits/flexibility	No	No research available with quantifiable utility effects

TABLE 40 *Cost per severe hypoglycaemic event avoided*

Time horizon for analysis	Cost per severe hypoglycaemic event avoided (£)[a]
Year 1	3078–3264
4-year time horizon (years 1–4)[b]	1305–1526 [1275–1481][c]
8-year time horizon (years 1–8)[b]	1281–1502 [1157–1346][c]

[a] Range reflects the differences between the three insulin pumps available.
[b] Assuming an insulin pump life of 4 years.
[c] Where future costs have been discounted at 6% and future outcomes discounted at 1.5%.

effectiveness), there is an assumed reduction of 1.16 severe hypoglycaemic events per patient per year (12-month data showed 22 events for CSII compared with 138 events for MDI). Applying the cost data in *Table 38* to the data on severe hypoglycaemia from Bode and colleagues offers an estimate of the cost per severe hypoglycaemic event avoided. However, this is an intermediate outcome and does not describe the health impact with respect to a severe hypoglycaemic event.

Estimates are also presented based on an estimate of effectiveness that is expected to be at the high end of the expected benefits from CSII therapy.

Cost per severe hypoglycaemic event avoided is presented in *Table 40*.

Further estimates on the cost-effectiveness of CSII versus MDI are not possible given the data available.

Chapter 6

Implementation

The cost to the NHS would depend mainly on the proportion, and therefore the number, of patients who used pumps. The largest cost, as shown in Chapter 5, would be those of the consumables such as infusion sets, with the pump being second. These two together cost from around £1075 per annum assuming an 8-year life of pump and the cheapest of the three, to £1423 per annum assuming a 4-year life and the most expensive model.

Numbers would be limited. CSII is not just a pump, but a package of self-care involving frequent self-monitoring of blood glucose and willingness to accept further training and responsibility. The presence of the device for 24 hours will deter some people. Conversely, the younger generation of children familiar with pocket technologies such as games, phones and hand-held computers might have a faster uptake.

Various guides to identifying patients most able to benefit have been produced. Those from the Diabetes Federation of Ireland note that the decision is often made by patients:

> "Patient selection
>
> - Patients tend to self-select for pumps. They are exclusively patients with Type 1 diabetes who are highly motivated and have developed an expertise in their own condition.
> - Most will have been using MDI but have not achieved their desired level of control.
> - Many have early complications such as retinopathy, nephropathy or large vessel disease, which contribute to the patient's personal motivation to take control of the condition. This is a motivator, not a criterion, as ideally intensive insulin therapy should aim to prevent complications.
> - Patients make an important trade-off in accepting the long-term attachment to the pump in exchange for better control and a lower risk of complications."
>
> T. O'Sullivan, Diabetes Federation of Ireland, September 2001

Similar thoughts were expressed by Gerich in 1985,[162] who added that patients must be capable of accurate self-monitoring of blood glucose levels and must be willing to do this several times a day.

It is unlikely that more than a small proportion of people with Type 1 diabetes would become pump users, but this proportion is not known with accuracy. Experience from the first few years of the West Kent service, provided by the Guy's Hospital trust, suggests that perhaps only 2% will move to CSII (Pickup J: personal communication). It is likely that CSII would be used mainly by those with particular problems with control of hypoglycaemia, rather than high HbA_{1c}. It seems safe to assume that patients with Type 2 diabetes will not be treated with CSII, except as part of research projects on reversing insulin resistance. *Figure 16* shows the system used in the service provided to West Kent Health Authority (Pickup J: personal communication) and *Table 41* gives the criteria used to assess suitability.

There are about 330,000 people with Type 1 diabetes in England and Wales. The annual costs for varying percentages are shown in *Table 42*. However these figures may be too conservative. It is reported that in Sweden in 1999, 7.5% of children and teenagers were on CSII, but that this has now increased to 12%.[163]

Costs other than disposables and pumps are minor. There will be modest savings in insulin dosage and from reduced hypoglycaemic events. In the longer term, there will probably be savings from reduced long-term complications, although these are difficult to quantify (see Chapters 5 and 7). There will also be education costs, for both patients and staff. We have included these in our costings.

One issue would be the number of centres that provide a CSII service. Should all large diabetes clinics provide a service, or should there be a limited number, with perhaps one pumps clinic per 500,000 population, except in less densely populated areas where that would impose travel costs on patients? One might expect that services would be better if they looked after a minimum number of pump users, but there is no hard evidence for that, or for what the minimum number should be. The converse argument is that all hospitals providing a diabetes clinic should offer pump therapy, since it is just another way of giving insulin. Furthermore, if pump services were

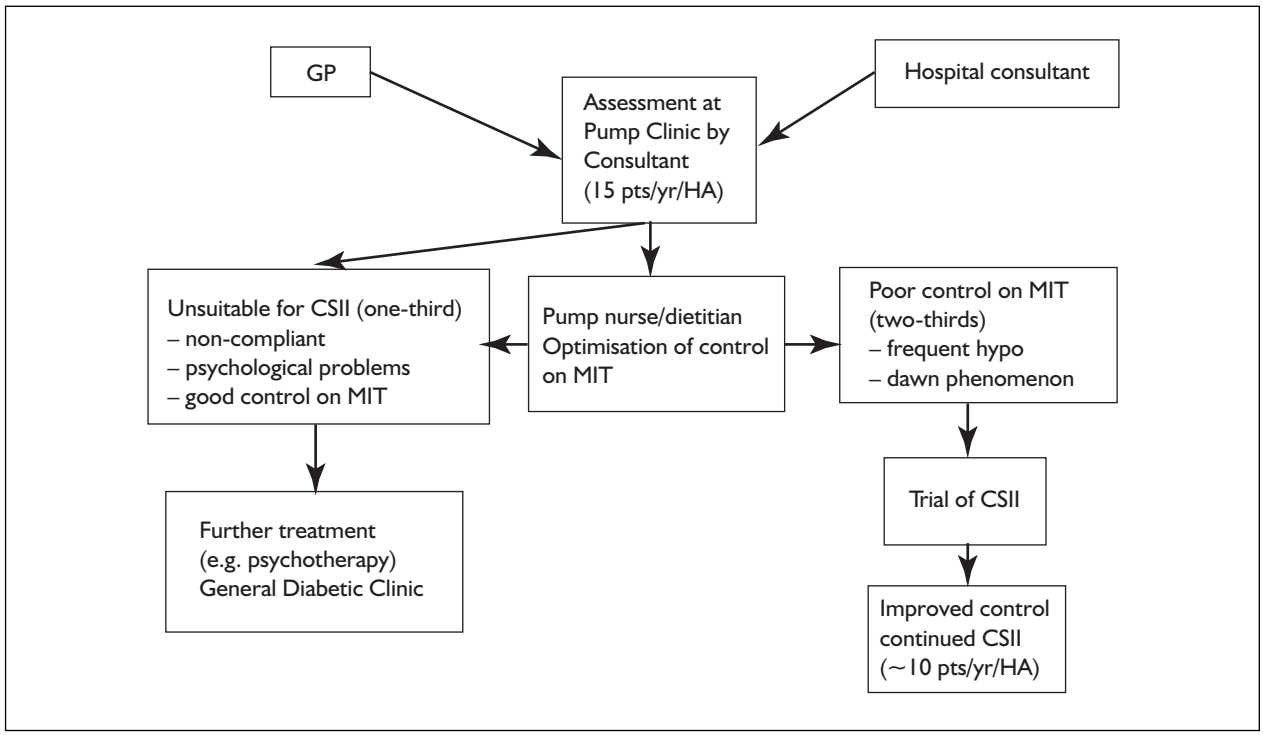

FIGURE 16 *Strategy for management of potential insulin pump patients*

TABLE 41 *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.

NB. We find that in patients with unpredictable and wide swings in blood glucose levels during injection therapy, disabling hypoglycaemia may develop as injection therapy is intensified. These patients would then become candidates for CSII, as indicated above.

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.

Patients who are likely to do poorly on pump therapy

- 'brittle' diabetic subjects characterised by recurrent DKA
- patients who are poorly compliant on injection therapy
- patients with significant psychological and psychiatric problems, or those who otherwise do not meet the prerequisites.

Source: Pickup and Keen, 2001.[38]

TABLE 42 *Annual costs of Type 1 diabetes*

All Type 1s (including children) (%)	Number	Annual cost (£)
1	3,300	3.5 million
3	9,900	10.5 million
5	16,500	17.5 million

provided at a limited number of 'area' locations, this would disadvantage those living in rural areas with poor public transport, particularly bearing in mind that they are more likely to be unable to drive than people without diabetes. One option would be for each area to start with one centre and roll out the service according to demand.

Barriers to implementation

Use of CSII in the UK appears to have been limited by two main factors. First, the cost has limited use in those diabetes clinics where consultants believed in their value. Second, the prevailing clinical impression seems to have been that the risks might outweigh the benefits. That impression probably dates from the days of the early pumps, but has not been superseded perhaps because there has been little experience with newer and more reliable pumps. A circular scenario may have been operating: because the value of CSII was doubted by many diabetologists, there has been little pressure for more funds; because funds have been limited, there has been little experience with newer pumps, and the conservative attitude has not been countered by new experience.

Unpublished (as of early August 2003; Matsuoka K, Oxford: personal communication, 2003) research from one English health authority provides very useful information on the barriers to implementation if NICE approved the use of insulin pumps in selected individuals. The problems include:

- A lack of knowledge about CSII.
- A perception amongst many in diabetes care that the evidence base for CSII was weak; this seemed to be based on knowledge of the early trials. The diabetologists with this belief did not think that pumps had improved, or did not know whether they had or not.
- Lack of resources, coupled with competing demands, so that CSII would not be a top priority even if funding became available.
- Concern about the training needs – it was believed that heavy initial investment would be required for education and backup in the first few weeks.

The three barriers reported most often were lack of a skills base (80%), insufficient staff for follow-up care (63%) and lack of funding. There was particular concern about a shortage of DSNs, which was not just about funding, but about the availability of trained people.

This research project also noted that there was an inequitable distribution of pumps users across socioeconomic areas, with very little use in the more deprived areas. This is only partly explained by the fact that 50% of users fund their own pumps.

Chapter 7

Discussion: analysis of uncertainties

This chapter reviews the key issues, and where appropriate, the uncertainties involved in each.

Efficacy

The potential benefits of CSII are threefold:

1. Glycaemic control: the evidence suggests a modest improvement in control of high blood glucose levels, as reflected in glycated haemoglobin. This may lead to reduced long-term complications, but evidence is lacking from the studies included in this review.
2. Frequency of hypoglycaemic episodes: although most studies found no difference in the frequency of hypoglycaemia between CSII and MDI, some found decreases with CSII and one study found an increase with CSII. There may also be benefits from reduced fear of hypoglycaemia, but this has not been quantified by the studies.
3. Well-being and QoL: QoL was assessed by just one eligible study, which reported no differences between CSII and MDI. Statements from patients who are successful pump users suggest an improvement in well-being and QoL, partly from greater flexibility of lifestyle. The effects have not been quantified in utility terms.

There is good evidence that CSII is acceptable to users (partly because those who do not like using it stop, and thereby incur no further added costs). The fact that many pump users are meeting the costs themselves implies that they value it. There is also good evidence of a useful reduction in glycated haemoglobin levels and of a small drop in the frequency of serious hypoglycaemia.

There is strong anecdotal evidence from users from INPUT and elsewhere that CSII improves QoL, but the RCTs have neglected this and have focused on measuring the more easily measurable outcomes such as HbA_{1c}. This is unfortunate: as one of our users commented, "there is more to control of diabetes than HbA_1".

One problem with assessing the effect of CSII on glycated haemoglobin is that those who take part in trials, or whose results are reported in some observational studies, may be highly motivated individuals whose HbA_{1c} is already better than average, so that there is less scope for improvement. Conversely, in some studies patients may have been poorly controlled with more to gain, both in terms of glycated haemoglobin and reduction in hypoglycaemic events. For example, in the study by Boland and colleagues,[98] the rate of severe hypoglycaemic episodes was reduced by 50% ($p = 0.01$), and Bode and colleagues[81] also reported much greater reductions in hypoglycaemia with CSII compared with MDI. Hence in routine care results may be better than in the trials, because there is greater selection of patients with problems. Numbers of patients going on to CSII may be small partly because the clinics that use CSII most are also vigorous in trying to achieve better control on MDI, so that only those who still have problems go on to CSII.

Two studies included in the meta-analysis by Pickup and colleagues[40] were excluded from the present meta-analysis. In the study by Marshall and colleagues,[164] most patients (10 out of 12) used twice-daily injections while on the injection phase of the crossover study, and although the authors described the trial as being of "CSII versus optimised injection therapy", it seemed more like optimised conventional therapy rather than optimised modern MDI, and was therefore excluded. Because it was a very small study of only 10 patients, inclusion would not have changed the results of our meta-analysis.

The other study, by Helve and colleagues,[165] was again of conventional therapy versus CSII. Although the authors say that conventional therapy could be optimised by changing the number and timing of daily injections, no data are given to show the extent to which this was done. They report that daily insulin dose did not change during the conventional phase (whereas it dropped during CSII), suggesting that in practice there was little change in the intensity of the conventional treatment. Most patients were on two injections per day at the start, and a few were on only one.

Comparators

We have assumed that patients progress from conventional insulin treatment to MDI and then to CSII, and that the key comparator for CSII is optimised MDI. However, given that there are varying intensities of MDI, it is possible that in terms of convenience to patients, changing to CSII might be worthwhile for some patients before all options with MDI had been tried. That is, that some patients might be able to achieve good control, as reflected in HbA_{1c}, on MDI but only at a level of inconvenience that made it worthwhile switching to CSII before that level of control was reached. This implies that patient convenience becomes an independent indicator for CSII. The expectation is that that would only apply to patients on MDI, but there could be some on conventional therapy (twice-daily mixture injections) who would request a change to CSII.

We do not have good data on the proportions of people with Type 1 diabetes who achieve adequate control at present. Data from young people with diabetes in Scotland (SSGCYD) indicates that only a minority succeed, but the proportion would be expected to be higher in adults, especially the over-30s. Nevertheless, it may be worth bearing in mind that most people (perhaps 80%) with Type 1 diabetes are not adequately controlled.[166]

There is a new, long-acting analogue insulin, glargine, on the market and another, detemir, is following. Glargine has been the subject of another review.[167] It may have advantages over the current long-acting insulins,[168] and might be regarded as a stronger competitor to CSII, by providing a better (less hypoglycaemia) form of MDI. However, CSII has the advantage of being able to provide several different basal insulin rates over 24 hours, whereas glargine provides only a constant basal level. A recent abstract reported that CSII gave better glycaemic control than glargine, but conclusions must await the full study, which was not an RCT.[169]

Cost-effectiveness and cost per QALY

There is general agreement that reducing HbA_{1c} improves long-term outcomes, and this has been shown in the meta-analysis of smaller trials by Wang and colleagues[18] (which pooled results from 681 patients) and by the DCCT study[19] (1441 patients). One problem in many of these studies is that they report changes in relative risks, rather than giving absolute differences. However, they do provide evidence of delays in the onset of complications such as renal disease, which should lead to life years gained in due course, although these may be 20 years down the line and hence offset by the rules on discounting. There should also be future savings in healthcare, but these will be much more reduced by discounting at 6%. It may be worth noting that the main evidence to date from the DCCT was of delaying rather than preventing complications.

However, it has not proved possible to go from reduction in HbA_{1c} to a simple cost per QALY for several reasons. First, there is insufficient evidence on the utility value of some of the benefits most appreciated by patients, such as flexibility of lifestyle and freedom from the fear of hypoglycaemic events.

Second, there is the issue of the improvement in HbA_{1c} and the expected consequent reduction in the risk of long-term complications. There are several problems with estimating the cost-effectiveness implications of these factors:

- Trials such as DCCT compare packages of care. The intensive arm of DCCT had CSII or MDI, more intensive self-monitoring of blood glucose with targets to achieve, more education on diet and exercise, more visits to clinics and frequent advice by telephone. It is unsafe to attribute all the benefits seen in the intensive group to the reduction in HbA_{1c}. For example, their cholesterol results were better; it may be that some benefits were due to aspects other than the insulin regimen. What other confounding factors are there in each trial? Did smoking rates or blood pressure levels change?
- There were clear differences in HbA_{1c} levels. However, can we extrapolate from the benefits of, a drop of, for example, 1.4% (from Wang and colleagues' meta-analysis) to one of 0.6% (in the CSII analysis here)? If a drop of 1.4% in HbA_{1c} gives an odds ratio of 0.32 for renal disease progression, would the odds ratio for a drop of 0.65 be in proportion?
- There are differences in how these drops in HbA_{1c} were obtained. Does a drop based on a switch from conventional twice daily insulin to CSII have the same implication as one achieved by switching from MDI to CSII?
- There is also the issue of baseline HbA_{1c}. Would a drop from 10% to 9.4% carry the same implications as one from 8.0 to 7.4%? Even if the relative risk reduction was the same, the lower absolute risks would affect the cost-effectiveness equations.

A third problem in producing a cost per QALY is that we do not have good data on the representativeness of patients in the trials. Those patients who enter trials may do better whatever treatment they use. If their results on MDI are better than average, there may be less scope for improvement on CSII, which would reduce the power of the studies to show benefits with CSII. It may be that there are other patients who would struggle with an intensive MDI regimen but who would cope with a pump. Pumps would be more cost-effective in the latter group because there would be a greater potential gain in HbA_{1c}.

A fourth problem might be that CSII is not just a pump, but a package. However, since this also applies to MDI, this should not invalidate the meta-analysis of CSII versus MDI.

Costs

The costs and uncertainties involved include the following:

- The NHS costs of those with inadequate control on MDI – will there be savings after transfer to CSII? Possibly, but probably small in the short-term. The cost to the NHS of hypoglycaemic events is small in monetary terms.
- The cost of pumps. The number of pump users in the UK is small at present. If a much greater number were to be used, could the NHS secure significantly lower prices by bulk purchase?
- The cost of disposables such as infusion sets. Could these be reduced, perhaps by longer use? How much would that increase the risk of infections?
- The cost of insulin – good evidence of a modest but useful reduction in the short term leading to savings of around £90 per patient per annum

Duration of studies

Most of the present studies are fairly short term. We do not know what benefits will accrue after, for example, 20 years of CSII.

Strengths and limitations of review

The systematic review has the following strengths:

- The systematic review is independent of any vested interests.
- The systematic review brings together the evidence for the effectiveness of insulin pumps applying consistent methods of critical appraisal.
- The review was guided by the principles for undertaking systematic reviews. Before undertaking the review the methods were set out in research protocol (Appendix 1), which was commented on by an advisory group. The protocol defined the research question, inclusion criteria, quality criteria, data extraction process and methods used to undertake the different stages of the review.
- An advisory group has informed the review from its initiation, through the development of the research protocol and completion of the report.

In contrast, there were certain limitations placed upon the review:

- Owing to time constraints placed upon the review, there was a lack of follow-up with authors of studies to clarify methodological details and results from the primary studies.
- The systematic review was limited to parallel RCTs and randomised and non-randomised crossover studies. However, for areas where no eligible studies were identified, selected observational studies were discussed [see the sections 'CSII in children' (p. 37), 'Overnight-only CSII in adults' (p. 37), 'Short-term CSII in poorly controlled adults with Type 2 diabetes' (p. 37) and 'Discontinuation rates' (p. 42)].
- Abstracts and conference proceedings were excluded from the review as these usually fail to provide adequate details of the methods of the study and their results, and inclusion was limited to English language due to time constraints. A previous meta-analysis found evidence of some publication bias for glycated haemoglobin.[40]

Other issues

- Parallel RCTs and crossover studies have been combined in meta-analyses in this systematic review. In a recently published paper, Elbourne and colleagues suggest that combining crossover and parallel trials in this way is conservative, as it ignores the within-patient correlation.[170]
- Due to the nature of the interventions compared, blinding of patients and treating clinicians in clinical trials is difficult, if not impossible. Although a lack of blinding may provide the opportunity for observer bias, it was felt that as the primary outcome measure assessed was an objective measure, that of

glycated haemoglobin, any potential bias would have a limited effect.

- As part of a new development to help support the NICE appraisal process, the report included a section examining the patients' perspective on the condition suffered and their reflections on the different technologies assessed. Although considered useful, it should be recognised that it is not methodologically rigorous and has limitations that mean it is not generalisable. The information originates from members of a specific user group, who are enthusiasts for the technology, may have paid for it themselves and have had problems with previous forms of managing the condition. Research is under way to provide guidance on the most appropriate methods for representing such patient views in health technology assessments.

Research needs

1. We need much more evidence on the gains in QoL from CSII, which was one of the hindrances in analysing cost-effectiveness. In particular, there is a need for trials focused on patients with good control as recorded by glycated haemoglobin, but with specific problems such as recurrent severe hypoglycaemia.
2. There is a need for good randomised trials in children, of different ages, and of different patterns of use, such as 24-hour use under parental supervision for the 0–4-years-olds, overnight only use in the 4–8-years age range and independent use in the over-8-years-olds.
3. Research is needed on the role of CSII in teenagers, who often have poor diabetic control. Could pumps improve compliance with treatment?
4. We need RCTs in pregnancy, starting preconceptually, and compared with MDI.
5. There may be a place for short-term use in insulin-resistant adults with Type 2 diabetes, but this is unproven. Trials should control for other interventions such as diet, and should be done on outpatients.
6. There may be a need for further trials of CSII versus MDI using longer acting analogues such as glargine, but we need to see the full details of the current glargine trials first.

Chapter 8
Conclusions

Pump technology has advanced considerably since the early days, and pumps are now much more portable and reliable. In randomised trials, they show definite but modest benefits. In observational studies, greater benefits are reported, probably because the patients in those are selected because of particular problems and have more scope to benefit. In routine practice, patients who go on to pumps are carefully selected and to a large degree self-selected.

However, pumps are used much less in the UK than in other Western nations. This may be partly because of cost and partly because of early adverse experiences. The lack of use may mean that the adverse experiences have in most centres not been replaced by positive ones, hence allowing pessimism to prevail.

It is unlikely that insulin pumps would be used by more than a small percentage of people with Type 1 diabetes, but the exact proportion is uncertain.

Acknowledgements

We are grateful to the advisory panel who provided expert advice and comments on the research protocol and/or a draft of this report:

Professor Stephanie Amiel (Professor of Diabetic Medicine), King's College School of Medicine, London. Miss Ann Brooker (Paediatric Diabetes Clinical Nurse Specialist), St Luke's Hospital, Bradford. Mr John Davis, INPUT, Lymington, Hampshire. Sister Joan Everett (Diabetes Specialist Nurse), Royal Bournemouth Hospital, Dorset. Dr Stephen Greene (Reader in Child and Adolescent Health), Tayside Institute of Child Health, Ninewells Hospital and Medical School, Dundee. Professor Philip Home, Department of Diabetes, The Medical School, Newcastle upon Tyne. Dr Abigail King, Haverfordwest, Pembrokeshire. Dr John Pickup (Reader) Guy's, King's and St Thomas School of Medicine, London. Mrs Gill Salt (Paediatric Diabetes Nurse Specialist), New Cross Hospital, Wolverhampton. Dr Ken Tieszen, Department of Diabetes, Hope Hospital, Salford.

We would like to thank the following people and organisations for information or other assistance: Dr Pam Royle (Senior Researcher/Information Scientist), Wessex Institute of Health Research and Development. Professor Harry Keen, Guy's Hospital, London. Karen Matsuoka, Oxford. Lorraine Rothery, Halifax. Professor William Tamborlane, School of Medicine, Yale University. Bournemouth Diabetes and Endocrine Centre. Diabetes Resource Centre, Harrogate District Hospital. INPUT, UK, and in particular all those pump users who provided personal experiences. Royal College of Nursing Paediatric and Adolescent Diabetes group. Royal College of Physicians of London.

We are also grateful to Disetronic and Medtronic for kindly supplying photographs of their insulin pumps.

This report was commissioned by the NHS R&D HTA Programme on behalf of NICE. The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme. The report remains the responsibility of the Southampton Health Technology Assessments Centre, Wessex Institute for Health Research and Development, University of Southampton. Any errors are the responsibility of the authors.

Contributions of authors

JL Colquitt (Senior Researcher) assessed studies for inclusion, extracted and synthesised clinical effectiveness data, and contributed to drafting the report. C Green (Senior Research Fellow) was responsible for the cost-effectiveness section, and contributed to drafting the report. MK Sidhu (Researcher) assisted with study selection, data extraction and drafting the clinical effectiveness section. D Hartwell (Researcher) assisted with study selection, data extraction and drafting the report. N Waugh (Professor of Public Health) drafted the protocol, contributed to drafting the report, and was responsible for writing the patient's perspective chapter.

References

1. Rangasami JJ, Greenwood DC, McSporran B, Smail PJ, Patterson CC, Waugh NR. Rising incidence of type 1 diabetes in Scottish children, 1984–93. The Scottish Study Group for the Care of Young Diabetics. *Arch Dis Child* 1997;**77**:210–13.
2. Bingley PJ, Gale EA. Incidence of insulin dependent diabetes in England: a study in the Oxford region, 1985–6. *BMJ* 1989;**298**:558–60.
3. Zhao HX, Stenhouse E, Soper C, Hughes P, Sanderson E, Baumer JH, *et al*. Incidence of childhood-onset type 1 diabetes mellitus in Devon and Cornwall, England, 1975–1996. *Diabet Med* 1999;**16**:1030–5.
4. Burden AC, Hearnshaw JR, Swift PG. Childhood diabetes mellitus: an increasing incidence. *Diabet Med* 1989;**6**:334–6.
5. Patterson CC, Thorogood M, Smith PG, Heasman MA, Clarke JA, Mann JI. Epidemiology of type 1 (insulin-dependent) diabetes in Scotland 1968–1976: evidence of an increasing incidence. *Diabetologia* 1983;**24**:238–43.
6. Patterson CC, Smith PG, Webb J, Heasman MA, Mann JI. Geographical variation in the incidence of diabetes mellitus in Scottish children during the period 1977–1983. *Diabet Med* 1988;**5**:160–5.
7. Staines A, Bodansky HJ, Lilley HE, Stephenson C, McNally RJ, Cartwright RA. The epidemiology of diabetes mellitus in the United Kingdom: the Yorkshire Regional Childhood Diabetes Register. *Diabetologia* 1993;**36**:1282–7.
8. Green A, Gale EA, Patterson CC. Incidence of childhood-onset insulin-dependent diabetes mellitus: the EURODIAB ACE Study. *Lancet* 1992;**339**:905–9.
9. UKPDS Study Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;**352**:837–53.
10. Neil HA, Gatling W, Mather HM. The Oxford Community Diabetes Study: evidence for an increase in the prevalence of known diabetes in Great Britain. *Diabet Med* 1987;**4**:539–43.
11. Gatling W, Budd S, Walters D, Mulle MA, Goddard JR, Hill RD. Evidence of an increasing prevalence of diagnosed diabetes in the Poole area from 1983 to 1996. *Diabet Med* 1998;**15**:1015–21.
12. Mather HM, Keen H. The Southall Diabetes Survey: prevalence of known diabetes in Asians and Europeans. *BMJ* 1985;**291**:1081–4.
13. Newnham A, Ryan R, Khunti K, Majeed A. Prevalence of diagnosed diabetes mellitus in general practice in England and Wales, 1940 to 1998. *Health Stat Q* 2002;**14**:5–13.
14. Turner R, Cull C, Holman R, for the United Kingdom Prospective Diabetes Study. UKPDS 17: A 9-year update of a randomised controlled trial of the effect of improved metabolic control on complications in non-insulin-dependant diabetes mellitus. *Ann Intern Med* 1996;**124**:136–45.
15. Waugh NR, Jung RT, Newton RW. The Dundee prevalence study of insulin-treated diabetes; intervals between diagnosis and start of insulin therapy. *Diabet Med* 1989;**6**:346–50.
16. Humphrey ARG, McCarty DJ, Mackay IR, Rowley MJ, Dwyer T, Zimmet P. Autoantibodies to glutamic acid decarboxylase and phentotypic features associated with early insulin treatment in individuals with adult-onset diabetes. *Diabet Med* 1998;**15**:113–19.
17. Office for National Statistics. *Key health statistics from general practice 1998*. London: Office for National Statistics; 2000.
18. Wang PH, Lau J, Chalmers TC. Meta-analysis of effects of intensive blood-glucose control on late complications of type I diabetes. *Lancet* 1993;**341**:1306–9.
19. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;**329**:977–86.
20. Reichard P, Nilsson B-Y, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 1993;**329**:304–9.
21. The Diabetes Control and Complications Trial. The effect of intensive diabetes treatment on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus. *Arch Ophthalmol* 1995;**113**:36–51.
22. Egger M, Davey-Smith G, Stettler C, Diem P. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. *Diabet Med* 1997;**14**:919–28.

23. Gold AE, Frier BM. Hypoglycaemia: practical and clinical implications. In Kelnar CJH, editor. *Childhood and adolescent diabetes*, London: Chapman and Hall; 1995. pp. 351–66.

24. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 1997;**46**:271–86.

25. Muhlhauser I, Berger M, Sonnenberg G, Koch J, Jorgens V, Schernthaner G, *et al*. Incidence and management of severe hypoglycemia in 434 adults with insulin-dependent diabetes mellitus. *Diabetes Care* 1985;**8**:268–73.

26. Rewers A, Chase HP, Mackenzie T, Walravens P, Roback M, Rewers M, *et al*. Predictors of acute complications in children with type 1 diabetes. *JAMA* 2002;**287**:2511–18.

27. Emilien G, Maloteaux JM, Ponchon M. Pharmacological management of diabetes: recent progress and future perspective in daily drug treatment. *Pharmacol Ther* 1999;**81**:37–51.

28. Swift PGF. Insulin: types and regimens. *Childhood and adolescent diabetes*. London: Chapman and Hall; 1995. pp. 253–66.

29. Morris AD, Boyle DIR, McMahon AD, for the DARTS/MEMO Collaboration. Adherence to insulin treatment, glycaemic control and ketoacidosis in IDDM. *Lancet* 1997;**350**:1505–10.

30. Scottish Study Group for the Care of the Young Diabetic. Factors influencing glycemic control in young people with type 1 diabetes in Scotland. A population-based study (DIABAUD2). *Diabetes Care* 2001;**24**:239–44.

31. Atkinson MA, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. *Lancet* 2001;**358**:221–9.

32. Pickup JC, Keen H, Parsons JA, Alberti KGMM. Continuous subcutaneous insulin infusion: an approach to achieving normoglycaemia. *BMJ* 1978;**i**:204–7.

33. Tamborlane WV, Sherwin RS, Genel M, Felig P. Reduction to normal of plasma glucose in juvenile diabetes by subcutaneous administration of insulin with a portable infusion pump. *N Engl J Med* 1979;**300**:573–8.

34. Thorp FK. Insulin pump therapy reconsidered. *JAMA* 1986;**255**:645–6.

35. Davies AG, Baum JD. A decade of insulin infusion pumps. *Arch Dis Child* 1988;**63**:329–32.

36. Lenhard MJ, Reeves GD. Continuous subcutaneous insulin infusion: a comprehensive review of insulin pump therapy. *Arch Intern Med* 2001;**161**:2293–300.

37. American Diabetes Association. Continuous subcutaneous insulin infusion. *Diabetes Care* 2002;**25**:S116.

38. Pickup J, Keen H. Continuous subcutaneous insulin infusion in type 1 diabetes is beneficial in selected patients and should be more widely available. *BMJ* 2001;**322**:1263–4.

39. Pickup J, Keen H. Continuous subcutaneous insulin infusion at 25 years: Evidence base for the expanding use of insulin pump therapy in type 1 diabetes. *Diabetes Care* 2002;**25**:593–8.

40. Pickup J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ* 2002;**324**:705–8.

41. Pons JMV. *Continuous subcutaneous infusion of insulin with portable pump in diabetes type 1 patients*. Barcelona: CAHTA; 2000. No. IN01/2000.

42. Munoz A, Saz Z, Amate JM. *Efficacy of insulin infusion pumps. Impact on the quality of live of certain patients*. Spain: AETS; 2000.

43. Hotta SS, Adams D. Reassessment of external insulin infusion pumps. *Health Technol Assess Reports* 1990;(9):1–9.

44. Graff MR, Rubin RR, Walker EA. How diabetes specialists treat their own diabetes: findings from a study of the AADE and ADA membership. *Diabetes Educ* 2000;**26**:460–7.

45. Wredling R, Lin PE, Adamson U. Pump 'run-away' causing severe hypoglycaemia. *Lancet* 1989;**ii**:273.

46. Tritos NA, Casper K, King G. Museum visit leading to insulin pump malfunction. *Ann Intern Med* 1997;**126**:746.

47. Darmon P, Guillaume V, Wiart J, Dutour A, Oliver C. Do mobile cellular phones interfere with portable insulin pumps? *Diabetes Care* 1998; **21**:1775.

48. Prendergast JJ, Dorsey C, Elsea V. Over-delivery of insulin by insulin pumps. *Diabetes Care* 1995; **18**:1201–2.

49. Mecklenburg RS, Benson EA, Benson JW, Fredlund PN, Guinn T, Metz RJ, *et al*. Acute complications associated with insulin infusion pump therapy. Report of experience with 161 patients. *JAMA* 1984;**252**:3265–9.

50. Teutsch SM, Herman WH, Dwyer DM, Lane JM. Mortality among diabetic patients using continuous subcutaneous insulin-infusion pumps. *N Engl J Med* 1984;**310**:361–8.

51. Knight G, Jennings AM, Boulton AJ, Tomlinson S, Ward JD. Severe hyperkalaemia and ketoacidosis during routine treatment with an insulin pump. *BMJ* 1985;**291**:371–2.

52. The Kroc Collaborative Study Group. Blood glucose control and the evolution of diabetic retinopathy and albuminuria. A preliminary multicenter trial. *N Engl J Med* 1984;**311**:365–72.

53. Steel JM, West CP. Intrauterine death during continuous subcutaneous infusion of insulin. *BMJ* 1985;**290**:1787.

54. Bradley C, Gamsu DS, Knight G, Boulton AJ, Ward JD. Predicting risk of diabetic ketoacidosis in patients using continuous subcutaneous insulin infusion. *BMJ* 1986;**293**:242–3.

55. Bending JJ, Pickup JC, Keen H. Frequency of diabetic ketoacidosis and hypoglycemic coma during treatment with continuous subcutaneous insulin infusion. Audit of medical care. *Am J Med* 1985;**79**:685–91.

56. Chantelau E, Spraul N, Mhuhlhauser I, Gause R, Beger M. Long-term safety, efficacy and side-effects of continuous subcutaneous insulin infusion treatment for type 1 (insulin-dependent) diabetes mellitus: a one centre experience. *Diabetologia* 1989;**32**:421–6.

57. Raskin P. Treatment of type 1 diabetes with portable insulin pumps. *Diabetes Care* 1982;**5** (Suppl 1):48–52.

58. Toth EL, Boychuk LR, Kirkland PA. Recurrent infection of continuous subcutaneous insulin infusion sites with *Mycobacterium fortuitum*. *Diabetes Care* 1995;**18**:1284–5.

59. Pagnoux C, Nassif X, Boitard C, Timsit J. Infection of continuous subcutaneous insulin infusion site with *Mycobacterium peregrinum*. *Diabetes Care* 1998;**21**:191–2.

60. New insulin pump forum launched in UK. *Pract Diab Int* 2000;**17**:278–9.

61. Brink SJ, Stewart C. Insulin pump treatment in insulin-dependent diabetes mellitus. Children, adolescents, and young adults. *JAMA* 1986; **255**:617–21.

62. Levy-Marchal C, Czernichow P. Feasibility of continuous subcutaneous insulin infusion in young diabetic patients. *Diabetes Metab* 1988;**14**:108–13.

63. Knight G, Boulton AJ, Ward JD. Experience of continuous subcutaneous insulin infusion in the outpatient management of diabetic teenagers. *Diabet Med* 1986;**3**:82–4.

64. Bougneres PF, Landier F, Lemmel C, Mensire A, Chaussain JL. Insulin pump therapy in young children with type 1 diabetes. *J Pediatr* 1984; **105**:212–7.

65. De Beaufort CE, Bruining GJ. Continuous subcutaneous insulin infusion in children. *Diabet Med* 1987;**4**:103–8.

66. Kaufman FR, Halvorson M, Kim C, Pitukcheewanont P. Use of insulin pump therapy at nighttime only for children 7–10 years of age with type 1 diabetes. *Diabetes Care* 2000;**23**:579–82.

67. Schiffrin A. Nighttime continuous subcutaneous insulin infusion revisited: a strategy for improving insulin delivery. *Diabetes Care* 2000;**23**:571–3.

68. Olsson P, Arnqvist H, Von Schenck H, Ottosson AM. Overnight metabolic control with bedtime injection of intermediate-acting insulin or continuous subcutaneous insulin fusion. *Diabetes Care* 1987;**10**:702–6.

69. Kanc K, Janssen MM, Keulen ET, Jacobs MA, Popp-Snijders C, Snoek FJ, *et al*. Substitution of night-time continuous subcutaneous insulin infusion therapy for bedtime NPH insulin in a multiple injection regimen improves counterregulatory hormonal responses and warning symptoms of hypoglycaemia in IDDM. *Diabetologia* 1998;**41**:322–9.

70. Gabbe SG. New concepts and applications in the use of the insulin pump during pregnancy. *J Matern Fetal Med* 2000;**9**:42–5.

71. Aucott SW, Williams TG, Hertz RH, Kalhan SC. Rigorous management of insulin-dependent diabetes mellitus during pregnancy. *Acta Diabetol* 1994;**31**:126–9.

72. Caruso A, Lanzone A, Bianchi V, Massidda M, Castelli MP, Fulghesu AM, *et al*. Continuous subcutaneous insulin infusion (CSII) in pregnant diabetic patients. *Prenat Diagn* 1987;**7**:41–50.

73. Jensen BM, Kuhl C, Molsted-Pedersen L, Saurbrey N, Fog-Pedersen J. Preconceptional treatment with insulin infusion pumps in insulin-dependent diabetic women with particular reference to prevention of congenital malformations. *Acta Endocrinol Suppl (Copenh)* 1986;**277**:81–5.

74. Rudolf MC, Coustan DR, Sherwin RS, Bates SE, Felig P, Genel M, *et al*. Efficacy of the insulin pump in the home treatment of pregnant diabetics. *Diabetes* 1981;**30**:891–5.

75. Simmons D, Thompson CF, Conroy C, Scott DJ. Use of insulin pumps in pregnancies complicated by Type 2 diabetes and gestational diabetes in a multiethnic community. *Diabetes Care* 2001;**24**:2078–82.

76. Brinchmann-Hansen O, Dahl-Jorgensen K, Hanssen KF, Sandvik L. The response of diabetic retinopathy to 41 months of multiple insulin injections, insulin pumps, and conventional insulin therapy. *Arch Ophthalmol* 1988;**106**:1242–6.

77. Dahl-Jorgensen K, Hanssen KF, Kierulf P, Bjoro T, Sandvik L, Aagenaes O. Reduction of urinary albumin excretion after 4 years of continuous subcutaneous insulin infusion in insulin-dependent diabetes mellitus. The Oslo Study. *Acta Endocrinologica* 1988;**117**:19–25.

78. Dahl-Jorgensen K, Brinchmann-Hansen O, Hanssen KF, Ganes T, Kierulf P, Smeland E, *et al*. Effect of near normoglycaemia for two years on progression of early diabetic retinopathy, nephropathy, and neuropathy: the Oslo study. *BMJ* 1986;**293**:1195–9.

79. Tsui E, Barnie A, Ross S, Parkes R, Zinman B. Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. *Diabetes Care* 2001;**24**:1722–7.

80. Hanaire-Broutin H, Melki V, Bessieres-Lacombe S, Tauber JP. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in type 1 diabetic patients on intensified treatment: a randomized study. The Study Group for the Development of Pump Therapy in Diabetes. *Diabetes Care* 2000;**23**:1232–5.

81. Bode BW, Steed RD, Davidson PC. Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type I diabetes. *Diabetes Care* 1996;**19**:324–7.

82. Chiasson JL, Ducros F, Poliquin HM, Lopez D, Lecavalier L, Hamet P. Continuous subcutaneous insulin infusion (Mill-Hill Infuser) versus multiple injections (Medi-Jector) in the treatment of insulin-dependent diabetes mellitus and the effect of metabolic control on microangiopathy. *Diabetes Care* 1984;**7**:331–7.

83. Haakens K, Hanssen KF, Dahl-Jorgensen K, Vaaler S, Aagenaes O, Mosand R. Continuous subcutaneous insulin infusion (CSII), multiple injections (MI) and conventional insulin therapy (CT) in self-selecting insulin-dependent diabetic patients. A comparison of metabolic control, acute complications and patient preferences. *J Intern Med* 1990;**228**:457–64.

84. Ziegler D, Dannehl K, Koschinsky T, Toeller M, Gries FA. Comparison of continuous subcutaneous insulin infusion and intensified conventional therapy in the treatment of type I diabetes: a two-year randomized study. *Diabetes Nutr Metab Clin Exp* 1990;**3**:203–13.

85. Nosadini R, Velussi M, Fioretto P, Doria A, Avogaro A, Trevisan R, *et al*. Frequency of hypoglycaemic and hyperglycaemic–ketotic episodes during conventional and subcutaneous continuous insulin infusion therapy in IDDM. *Diabetes Nutr Metab* 1988;**1**:289–96.

86. Schmitz A, Christiansen JS, Christensen CK, Hermansen K, Mogensen CE. Effect of pump versus pen treatment on glycaemic control and kidney function in long-term uncomplicated insulin-dependent diabetes mellitus (IDDM). *Dan Med Bull* 1989;**36**:176–8.

87. Bak JF, Nielsen OH, Pedersen O, Beck-Nielsen H. Multiple insulin injections using a pen injector versus insulin pump treatment in young diabetic patients. *Diabetes Res* 1987;**6**:155–8.

88. Home PD, Capaldo B, Burrin JM, Worth R, Alberti KG. A crossover comparison of continuous subcutaneous insulin infusion (CSII) against multiple insulin injections in insulin-dependent diabetic subjects: improved control with CSII. *Diabetes Care* 1982;**5**:466–71.

89. Nathan DM, Lou PAJ. Intensive conventional and insulin pump therapy in adult type 1 diabetes. A crossover study. *Ann Intern Med* 1982;**97**:31–6.

90. Saurbrey N, Arnold-Larsen S, Moller-Jensen B, Kuhl C. Comparison of continuous subcutaneous insulin infusion with multiple insulin injections using the NovoPen. *Diabet Med* 1988;**5**:150–3.

91. Schiffrin A, Belmonte MM. Comparison between continuous subcutaneous insulin infusion and multiple injection of insulin. A one-year prospective study. *Diabetes* 1982;**31**:255–64.

92. Nosari I, Maglio ML, Lepore G. Is continuous subcutaneous insulin infusion more effective than intensive conventional insulin therapy in the treatment of pregnant diabetic women? *Diabetes Nutr Metab* 1993;**6**:33–7.

93. Coustan DR, Reece EA, Sherwin RS, Rudolf MC, Bates SE, Sockin SM, *et al*. A randomized clinical trial of the insulin pump vs intensive conventional therapy in diabetic pregnancies. *JAMA* 1986;**255**:631–6.

94. Carta Q, Meriggi E, Trossarelli GF, Catella G, Dal Molin V, Menato G, *et al*. Continuous subcutaneous insulin infusion versus intensive conventional insulin therapy in type I and type II diabetic pregnancy. *Diabetes Metab* 1986;**12**:121–9.

95. Burkart W, Hanker JP, Schneider HP. Complications and fetal outcome in diabetic pregnancy. Intensified conventional versus insulin pump therapy. *Gynecol Obstet Invest* 1988; **26**:104–12.

96. Tamborlane WV, Batas SE, Rudolf MC. Comparison of continuous subcutaneous insulin infusion versus multiple daily injections in adolescents with insulin-dependent diabetes. *Adv Diabetol* 1989;**2** (Suppl 1):24–7.

97. Schiffrin AD, Desrosiers M, Aleyassine H, Belmonte MM. Intensified insulin therapy in the type 1 diabetic adolescent: a controlled trial. *Diabetes Care* 1984;**7**:107–13.

98. Boland EA, Grey M, Oesterle A, Fredrickson L, Tamborlane WV. Continuous subcutaneous insulin infusion. A new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. *Diabetes Care* 1999;**22**:1779–84.

99. Mack-Fogg J, Bates S, Faro B, Sciera M, Ippolito K, Orlowski CC, *et al*. Safe and effective use of continuous subcutaneous insulin infusion in young children with type 1 diabetes mellitus. *Diabetes* 2002;**51** (Suppl 1, poster 712):122A.

100. Rudolf JW, Hirsch IB. An assessment of continuous subcutaneous insulin infusion therapy

in an academic diabetes clinic. *Diabetes* 2000; **49** (Suppl 1, poster 501-P):A124.

101. Haardt MJ, Berne C, Dorange C, Slama G, Selam JL. Efficacy and indications of CSII revisited: the Hotel-Dieu cohort. *Diabet Med* 1997;**14**:407–8.

102. Tamborlane WV, Bonfig W, Boland E. Recent advances in treatment of youth with type 1 diabetes: better care through technology. *Diabet Med* 2001;**18**:864–70.

103. Kaufman FR, Halvorson M, Miller D, Mackenzie M, Fisher LK, Pitukcheewanont P. Insulin pump therapy in type 1 pediatric patients: now and into the year 2000. *Diabetes Metab Res Rev* 1999;**15**:338–52.

104. Plotnick L, Clark L. Insulin pumps in children and adolescents. *Endocrinologist* 2001;**11**:112–17.

105. Steindel BS, Roe TR, Costin G, Carlson M, Kaufman FR. Continuous subcutaneous insulin infusion (CSII) in children and adolescents with chronic poorly controlled type 1 diabetes mellitus. *Diabetes Res Clin Pract* 1995;**27**:199–204.

106. Maniatis AK, Klingensmith GJ, Slover RH, Mowry CJ, Chase HP. Continuous subcutaneous insulin infusion therapy for children and adolescents: an option for routine diabetes care. *Pediatrics* 2001;**107**:351–6.

107. Conrad SC, McGrath MT, Gitelman SE. Transition from multiple daily injections to continuous subcutaneous insulin infusion in type 1 diabetes mellitus. *J Pediatr* 2002;**140**:235–40.

108. Ahern JA, Boland E, Doane R, Ahern JJ, Rose P, Vincent M, *et al*. Insulin pump therapy in pediatrics: a therapeutic alternative to safely lower HbA_{1c} levels across all age groups. *Pediatr Diabetes* 2002;**3**:10–15.

109. Fox LA, Wilkinson K, Buckloh L, Wysocki T, Mauras N. A randomized trial of insulin pump therapy in preschool age children with type 1 diabetes mellitus: preliminary results. *Diabetes* 2002;**51** (Suppl 2, poster 1751):426A.

110. Weintrob N, Benzaquen H, Galatzer A, Shalitin S, Lazar L, Fayman G, *et al*. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens in children with type 1 diabetes: a randomised controlled trial. *Diabetes* 2002;**51** (Suppl 2, poster 1969).

111. Valensi P, Moura I, Le Magoarou M, Paries J, Perret G, Attali JR. Short-term effects of continuous subcutaneous insulin infusion treatment on insulin secretion in non-insulin-dependent overweight patients with poor glycaemic control despite maximal oral anti-diabetic treatment. *Diabetes Metab* 1997;**23**:51–7.

112. Dupuy O, Mayaudon H, Palou M, Sarret D, Bordier L, Bauduceau B. Optimized transient insulin infusion in uncontrolled type 2 diabetes: evaluation of a pragmatic attitude. *Diabetes Metab* 2000;**26**:371–5.

113. Bode B, Weinstein R, Bell D, McGill J, Nadeau D, Raskin P, *et al*. Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: a randomized study in type 1 diabetes. *Diabetes Care* 2002;**25**:439–44.

114. Renner R, Pfutzner A, Trautmann M, Harzer O, Sauter K, Landgraf R. Use of insulin lispro in continuous subcutaneous insulin infusion treatment. Results of a multicenter trial. German Humalog-CSII Study Group. *Diabetes Care* 1999; **22**:784–8.

115. Schmauss S, Konig A, Landgraf R. Human insulin analogue [LYS(B28), PRO(B29)]: the ideal pump insulin? *Diabet Med* 1998;**15**:247–9.

116. Melki V, Renard E, Lassmann-Vague V, Boivin S, Guerci B, Hanaire-Broutin H, *et al*. Improvement of HbA_{1c} and blood glucose stability in IDDM patients treated with lispro insulin analog in external pumps. *Diabetes Care* 1998;**21**:977–82.

117. Raskin P, Holcombe JH, Tamborlane WV, Malone JI, Strowig S, Ahern JA, *et al*. A comparison of insulin lispro and buffered regular human insulin administered via continuous subcutaneous insulin infusion pump. *J Diabetes Complications* 2001; **15**:295–300.

118. Zinman B, Tildesley H, Chiasson JL, Tsui E, Strack T. Insulin lispro in CSII: results of a double-blind crossover study. *Diabetes* 1997;**46**:440–3.

119. Green S, Deeks J, Savio F. The ends and the means: continuous data in Cochrane reviews. Poster presentation at Cochrane Colloquium, 2001.

120. Schifferdecker E, Schmidt K, Boehm BO, Schatz H. Long-term compliance of intensified insulin therapy. *Diabetes Res Clin Pract* 1994;**23**:17–23.

121. Wredling R, Lins PE, Adamson U. Factors influencing the clinical outcome of continuous subcutaneous insulin infusion in routine practice. *Diabetes Res Clin Pract* 1993;**19**:59–67.

122. Knight G, Boulton AJ, Drury J, Gamsu DS, Moses JL, Bradley C, *et al*. A feasibility study of the use of continuous subcutaneous insulin infusion in a diabetic clinic: patients' choice of treatment. *Diabet Med* 1984;**1**:267–72.

123. Floyd JC, Cornell RG, Jacober SJ, Griffith LE, Funnell MM, Wolf LL, *et al*. A prospective study identifying risk factors for discontinuance of insulin pump therapy. *Diabetes Care* 1993; **16**:1470–8.

124. Bell DS, Ackerson C, Cutter G, Clements RS. Factors associated with discontinuation of continuous subcutaneous insulin infusion. *Am J Med Sci* 1988;**295**:23–8.

125. Bell DSH, Cutter G, Clements J. The feasibility of long-term treatment of diabetes with continuous subcutaneous insulin infusion. *Diabetes Nutr Metab Clin Exp* 1993;**6**:57–60.

126. *British National Formulary*. London: British National Formulary; 2002.

127. Herman WH, Eastman RC. The effects of treatment on the direct costs of diabetes. *Diabetes Care* 1998;**21**:C19–24.

128. American Diabetes Association. Economic consequences of diabetes mellitus in the U.S. in 1997. *Diabetes Care* 1998;**21**:296–309.

129. Lifetime benefits and costs of intensive therapy as practiced in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. *JAMA* 1996;**276**:1409–15.

130. Gray A, Raikou M, McGuire A, Fenn P, Stevens R, Cull C, *et al*. Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomised controlled trial (UKPDS 41). United Kingdom Prospective Diabetes Study Group. *BMJ* 2000;**320**:1373–8.

131. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, *et al*. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;**321**:405–12.

132. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. *Ophthalmology* 1998;**105**:1801–15.

133. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;**352**:854–65.

134. Clark P, Gray A, Adler A, Stevens R, Raikou M, Cull C, *et al*. Cost-effective analysis of intensive blood glucose control with metformin in overweight patients with type 2 diabetes (UKPDS 51). *Diabetologia* 2001;**44**:298–304.

135. Palmer AJ, Weiss C, Sendi PP, Neeser K, Brandt A, Singh G, *et al*. The cost-effectiveness of different management strategies for type I diabetes: a Swiss perspective. *Diabetologia* 2000;**43**:13–26.

136. INPUT. *INsulin PUmp Therapy*. 2001.

137. *Directory of diabetes care*. Cambridge: CMA Medical Data; 2001.

138. Netten A, Rees T, Harrison G. *Unit costs of health and social care, 2001*. Canterbury: Personal Social Services Research Unit, University of Kent at Canterbury; 2002.

139. NHS. *NHS reference costs*. London: Department of Health; 2000.

140. Nordfeldt S, Jonsson D. Short-term effects of severe hypoglycaemia in children and adolescents with type 1 diabetes. A cost-of-illness study. *Acta Paediatr* 2001;**90**:137–42.

141. Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, *et al*. Incidence of severe hypoglycaemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. *Diabet Med* 2002;**19** (Suppl 2):12–3.

142. Rubin RR, Peyrot M. Quality of life and diabetes. *Diabetes Metab Res Rev* 1999;**15**:205–18.

143. The Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA_{1c}) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes* 1995;**44**:968–83.

144. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. Glycosylated hemoglobin predicts the incidence and progression of diabetic retinopathy. *JAMA* 1988;**260**:2864–71.

145. Klein R, Klein BE. Relation of glycemic control to diabetic complications and health outcomes. *Diabetes Care* 1998;**21** (Suppl 3):C39–43.

146. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. The DCCT Research Group. *Am J Med* 1991;**90**:450–9.

147. Microvascular and acute complications in IDDM patients: the EURODIAB IDDM Complications Study. *Diabetologia* 1994;**37**:278–85.

148. Influence of intensive diabetes treatment on quality-of-life outcomes in the diabetes control and complications trial. *Diabetes Care* 1996;**19**:195–203.

149. Ferguson SC, Strachan MW, Janes JM, Frier BM. Severe hypoglycaemia in patients with type 1 diabetes and impaired awareness of hypoglycaemia: a comparative study of insulin lispro and regular human insulin. *Diabetes Metab Res Rev* 2001;**17**:285–91.

150. Marrero DG, Guare JC, Vandagriff JL, Fineberg NS. Fear of hypoglycemia in the parents of children and adolescents with diabetes: maladaptive or healthy response? *Diabetes Educ* 1997;**23**:281–6.

151. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of hypoglycaemia: quantification, validation and utilisation. *Diabetes Care* 1987;**10**:6717–621.

152. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and

associated symptoms. *Diabetes Care* 1995; **18**:517–22.

153. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycaemia in patients with type 1 diabetes with impaired awareness of hypoglycaemia. *Diabetes Care* 1994;**17**:697–703.

154. Chantelau E, Schiffers T, Schutze J, Hansen B. Effect of patient-selected intensive insulin therapy on quality of life. *Patient Educ Couns* 1997;**30**:167–73.

155. Lewis KS, Bradley C, Knight G, Boulton AJM, Ward JD. A measure of treatment satisfaction designed specifically for people with insulin-dependent diabetes. *Diabet Med* 1988;**5**:235–42.

156. Johansson UB, Adamson UC, Lins PE, Wredling RA. Improved blood glucose variability, HbA_{1c} insuman Infusat and less insulin requirement in IDDM patients using insulin lispro in CSII. The Swedish Multicenter Lispro Insulin Study. *Diabetes Metab* 2000;**26**:192–6.

157. Wu S, Sainfort F, Tomar R, Tollios JL, Fryback DG. Development and application of a model to estimate the impact of type 1 diabetes on health-related quality of life. *Diabetes Care* 1998;**21**:725–31.

158. Brown MM, Brown GC, Sharma S, Shah G. Utility values and diabetic retinopathy. *Am J Ophthalmol* 1999;**128**:324–30.

159. Kiberd BA, Jindal KK. Screening to prevent renal failure in insulin dependent diabetic patients: an economic evaluation. *BMJ* 1995;**311**:1595–9.

160. Tomar R, Lee S, Wu S, Klein R, Moss SE, Fryback DG, *et al*. Disease progression and cost of insulin dependent diabetes mellitus: development and application of simulation model. *J Soc Health Syst* 1998;**5**:24–37.

161. Dolan P. Modelling valuations for EuroQol health states. *Med Care* 1997;**35**:1095–108.

162. Gerich JE. Selection of patients for intensive insulin therapy. *Arch Intern Med* 1985;**145**:1383–4.

163. Hanas R. Selection for and initiation of continuous subcutaneous insulin infusion. Proceedings from a workshop. *Horm Res* 2002;**57** (Suppl 1):101–4.

164. Marshall SM, Home PD, Taylor R, Alberti KG. Continuous subcutaneous insulin infusion versus injection therapy: a randomised cross-over trial under usual diabetic clinic conditions. *Diabet Med* 1987;**4**:521–5.

165. Helve E, Koivisto VA, Lehtonen A, Pelkonen R, Huttunen JK, Nikkila EA. A crossover comparison of continuous insulin infusion and conventional injection treatment of type I diabetes. *Acta Med Scand* 1987;**221**:385–93.

166. Scottish Study Group for the Care of the Young Diabetic. Factors influencing glycemic control in young people with type 1 diabetes in Scotland. *Diabetes Care* 2001;**24**:239–44.

167. Warren E, Weatherley-Jones E, Chilcott J, Beverley C. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. *Health Technol Assess* 2004;**8** (in press).

168. Schober E, Schoenle E, van Dyk J, Wernike-Panten K. Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes. *Diabetes Care* 2001;**24**:2005–6.

169. Armstrong DU, King AB. Basal insulin: continuous glucose monitoring reveals less overnight hypoglycaemia with continuous subcutaneous insulin infusion than with glargine. *Diabetes* 2002;**51** (Suppl 2, poster 373):92A.

170. Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol* 2002;**31**:140–9.

171. Chilcott J, Wight J, Lloyd Jones M, Tappenden P. The clinical effectiveness and cost effectiveness of pioglitazone in Type 2 diabetes mellitus: a rapid and systematic review. *Health Technol Assess* 2001;**5**(19).

Appendix 1

Rapid review methods from the research protocol

Full title of research question

Research aim: to assess the clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion (CSII) using insulin pumps in the treatment of patients with insulin-treated diabetes, whether Type 1 or Type 2, in whom diabetes control is unsatisfactory, and to consider which groups of patients could benefit most.

Clarification of research question and scope

Conventional insulin treatment in people with Type 1 diabetes involves two injections per day, usually giving a mixture of short- and longer acting insulins [this will be referred to henceforth as conventional therapy (CT)]. CT provides satisfactory control as assessed by glycosylated haemoglobin (HbA_{1c}) in only a minority of patients. Furthermore, some of those who do achieve an acceptable average blood glucose level only do so by having a mixture of high and low glucose levels, and may have lives made difficult by hypoglycaemic attacks. The HbA_{1c} level can therefore be used only as a guide and needs to be used in conjunction with information on fluctuations in blood glucose, such as number of hypoglycaemic episodes, and results of blood tests, in order to establish how the HbA_{1c} level has been achieved.

After CT, the current next best regimen is 'basal plus bolus', now often referred to as 'meal-time plus basal', wherein patients receive one or two injections of long-acting insulins to provide the low level of insulin needed throughout the day and night, with additional injections of short-acting insulins to cover the steep rises in blood glucose that would otherwise occur after meals. This is sometimes referred to as MDI, for multiple daily injections, and can be regarded as a form of intensified treatment. However, there can be different degrees of intensity. Our initial searches show variations in the meanings of conventional and intensive. The term 'optimised MDI' has been used to describe the situation where control with MDI is thought to be as good as can be achieved. This may involve four or more injections each day, usually accompanied by frequent self-testing of blood sugar levels using reagent strips and meters.

CSII is usually used to provide intensive treatment in a different way to MDI, with a needle under the skin all day long, but with different amounts of insulin being given at different times – a slow basal infusion all day long, but with the infusion rate being boosted to cover meals. It is therefore another way of providing basal plus bolus, but has advantages in that both basal and bolus dosage can be adjusted more easily and that because only short-acting insulin is used, there is less chance of hypoglycaemic episodes from unpredictable absorption from injections of long-acting insulins. There can also be different basal rates at different times of day.

The main clinical question is the extent to which CSII using insulin pumps provides any clinical advantages over management of Type 1 diabetes with optimised MDI. The benefits could be better control of blood glucose as reflected in HbA_1, or a similar level of control but with other advantages such as fewer problems with hypoglycaemia, or greater flexibility of lifestyle and hence better QoL. If MDI is particularly intensive (e.g. 5–7 injections a day), then CSII may in effect be less intensive.

Multiple injections can be given by syringe or more often by insulin pen injectors or a combination thereof.

It is expected that CSII will be part of a package of care delivered by specialist clinics.

The cost-effectiveness question is whether the benefits are commensurate with the marginal cost.

Subsidiary questions to be addressed include:

- Do rapid-acting analogue insulins have advantages over older short-acting (soluble) insulins?
- Should CSII be used for women with Type 1 diabetes preconceptually and during pregnancy?

Where possible, cost issues will be considered for these questions.

Studies giving data on discontinuation rates will be used as a guide to patient acceptability and other data on patient experiences and perspective will be obtained from users and past users.

Studies on safety with modern pumps will be sought. With the older pumps in the past, there were problems with device failure leading to DKA.

Two other possible questions have been identified during initial literature searches, but where little research seems to have been done. These will only be addressed if time, resources and evidence permit. Our initial impression is that the present evidence will be insufficient as a basis for guidance and that these may be topics to be identified only as areas for future research. They are:

- What is the value of short periods of CSII in patients with Type 2 diabetes who are very resistant to oral drugs?
- What is the role of overnight-only CSII (in patients who would take injections as usual by day)? This method might be particularly relevant to children, but could apply to some adults as well.

These questions will not be subjected to economic analysis.

Implantable pumps will not be covered by the review. We believe these to be a different technology at an earlier stage of application. Pumps used for external intravenous infusion in hospital care will also be excluded.

It is assumed that the usual sequence is to start on conventional insulin treatment and to move to intensive treatment with MDI if control is inadequate, and so the main question for this review is whether it is worth moving from optimised MDI to CSII.

We will define intensive or MDI as a combination of short-acting insulins (soluble or analogue) to cover meals with long-acting insulins (intermediate ultralente or long-acting analogues such as glargine) to provide basal insulin. In practice, MDI will mean a minimum of three injections per day.

Report methods

Search strategy

In order to capture not only RCTs for efficacy analysis, but also information on problems with pumps and reasons for discontinuation, economic studies, patient experiences and long-term outcomes, a very sensitive search will be carried out. Filtering will then be done by reading the abstracts (this has been done for MEDLINE; 1349 abstracts have been checked, and about 110 studies identified for review of the full paper). Reference lists of retrieved studies will be checked for others. Our expert advisers will be asked to comment on the comprehensiveness of our review. The Cochrane Metabolic and Endocrine Diseases Group based in Düsseldorf will be consulted.

Inclusion and exclusion criteria

Exclusions will include: conventional therapy; treatment of newly diagnosed patients; implantable pumps; very short-term studies; and hospital in-patient pumps.

Because the key measure of blood glucose control is glycosylated haemoglobin (HbA_{1c}), studies of <10 weeks duration on each treatment will be excluded from any HbA_{1c} analysis.

Inclusion and exclusion criteria will be applied by one reviewer and checked by a second. Any disagreement will be resolved by discussion.

Data extraction strategy

Data will be extracted by one person and checked by a second. Any discordances will be resolved by discussion or by checking by a third person.

Quality assessment strategy

This will be done in accordance with Chapter II.5 of CRD Report 4 (2nd edition). A locally developed system will be used to assess QoL studies. Criteria will be applied by one reviewer and checked by a second.

Patient perspectives

Our expert panel will include several users of CSII, and we will explore with INPUT how best to include information on patient experiences with CSII.

Methods of analysis/synthesis

Clinical effectiveness will be synthesised through a narrative review with tabulation of results of included studies.

Combination of studies into a Review Manager meta-analysis will be considered. This could form the basis for a collaborative Cochrane review.

Economic appraisal

The costs and effects of CSII will be compared with MDI in Type 1 diabetes patients. Costs will be

obtained from published literature, NHS sources, *ad hoc* studies and industry submissions. Costs to be considered will include NHS resource use before and after CSII (e.g. insulin pumps, pump maintenance, disposables, extra hospital contacts); educational needs (at both institutional and patient level); and insulin requirements. If there is evidence of differences in long-term outcomes such as eye or kidney disease, the economic consequences of these outcomes will be considered. The likely numbers of patients who might be treated with CSII will be considered. The perspective of the economic analysis will be that of the NHS and Personal and Social Services decision-maker.

Data on clinical and QoL benefits will be sought from the literature. Cost-effectiveness analysis will compare CSII and MDI on the basis of the primary outcome measures specified as part of the literature review (e.g. HbA_{1c}, severe hypoglycaemic events and diabetes-related complications) and additional QoL outcomes where documented as part of the review findings. Information from the patient impact assessment will also be considered.

Economic analysis will consider

- Short-term benefits such as reduction in hypoglycaemic events, greater flexibility of lifestyle and quality of life
- Short-term disbenefits such as acute events due to pump failure, cosmetic problems, interference with leisure activities
- Intermediate benefits such as improved blood glucose control as measured by HbA_{1c}, likely to lead to a reduction in long-term complications.

If evidence showed that CSII was cost-effective on short-term outcomes alone, the benefits of longer term outcomes would not need to be precisely quantified and they would simply be listed as additional benefits.

Cost per QALY values will be estimated if the data provide evidence of cost-effectiveness gains.

Published cost-effectiveness studies will be reviewed. All papers that present findings on the cost-effectiveness of CSII when compared with MDI (as defined above) will be reviewed in detail, comprising a narrative review with tabulation of results where appropriate.

Company submission(s)

We will use company and other submissions to check on completeness of ascertainment of relevant trials, for costs of pumps and CSII and for data on current use of insulin pumps in England and Wales. We will compare results of cost-effectiveness analysis from industry models with the Southampton Health Technology Assessment Centre one, but in line with our contract the time spent on industry models may be limited to 5 person days. This may not allow sufficient time for a detailed critique of industry models.

Appendix 2

Sources of information, including databases searched and search terms

The databases were searched for published studies and recently completed and ongoing research. All searches were limited to English language only.

Clinical effectiveness search strategies

Cochrane Library (Issue 2, 2002) and National Research Register (Issue 2, 2002):
#1 (INSULIN near PUMP*)
#2 CSII
#3 ((CONTINUOUS near INSULIN) near INFUSION)
#4 ((SUBCUTANEOUS near INSULIN) near INFUSION)
#5 ((EXTERNAL and PUMP*) AND (DIABET* near INSULIN*))
#6 ((((#1 or #2) or #3) or #4) or #5)

MEDLINE (WebSPIRS), 1985–June 2002:
((explode 'Diabetes-Mellitus-Insulin-Dependent' / all subheadings in MIME,MJME) and ((insulin near pump*) or (csii) or (continuous near insulin near infusion) or (subcutaneous near insulin near infusion) or (external pump* and diabet* and insulin*))) and (English in la)

Embase (WebSPIRS), 1980–May 2002:
(((insulin near3 pump*) or ((pump* near therapy) and diabet*) or (csii) or (subcutaneous near insulin near infusion) or (external pump near insulin) or (continuous near insulin near infusion) or (external pump near diabet*)) and (English in la)) or ((external pumps near insulin) and (English in la))

PubMED (Internet version), records added from 20 June 2001 to 25 June 2002:
insulin pumps* OR CSII OR continuous insulin infusion OR subcutaneous insulin infusion

Science Citation Index, 1990–26 June 2002:
insulin pump* or csii or insulin infusion (restricted to document type = meeting abstracts)

BIOSIS, 1999–26 June 2002:
((insulin and pump*) or csii or continuous subcutaneous insulin)) and random* (restricted to document type = meeting abstracts)

Web of Science Proceedings,1990–26 June 2002:
(insulin pump* or csii or insulin infusion) and random*

DARE and HTA Databases (web version), searched on 29 June 2002:
csii or insulin pump$ or insulin infusion

Libcat (in-house library catalogue):
insulin pump* or csii or insulin infusion

A flowchart of identification of studies for inclusion in the review of clinical effectiveness is given in *Figure 17*.

Cost effectiveness and quality of life searches

MEDLINE (WebSPIRS), 1981–June 2002:
((insulin near3 pump*) or csii or (insulin near infusion)) and ((cost* or economic*) or (explode 'Economics-' / all subheadings in MIME,MJME) or (explode 'Health-Status' / all subheadings in MIME,MJME) or (explode 'Outcome-Assessment-Health-Care' / all subheadings in MIME,MJME) or (explode 'Quality-of-Life' / all subheadings in MIME,MJME) or (wellbeing or well-being) or (health near3 outcome*))

EMBASE (WebSPIRS), 1980–May 2002:
(((insulin near pump*) or (csii or (insulin near infusion))) and (((explode 'health-economics' / all subheadings) or (explode 'economics-' / all subheadings) or (explode 'quality-of-life' / all subheadings) or (quality near3 life) or (cost* or economic*) or (health near3 status) or (health near3 outcome*)) or (wellbeing or well-being))) and (English in la)

PubMED (Internet version, records added from 20 June 2001 to 29 June 2002:
insulin pumps* OR CSII OR continuous insulin infusion OR subcutaneous insulin infusion

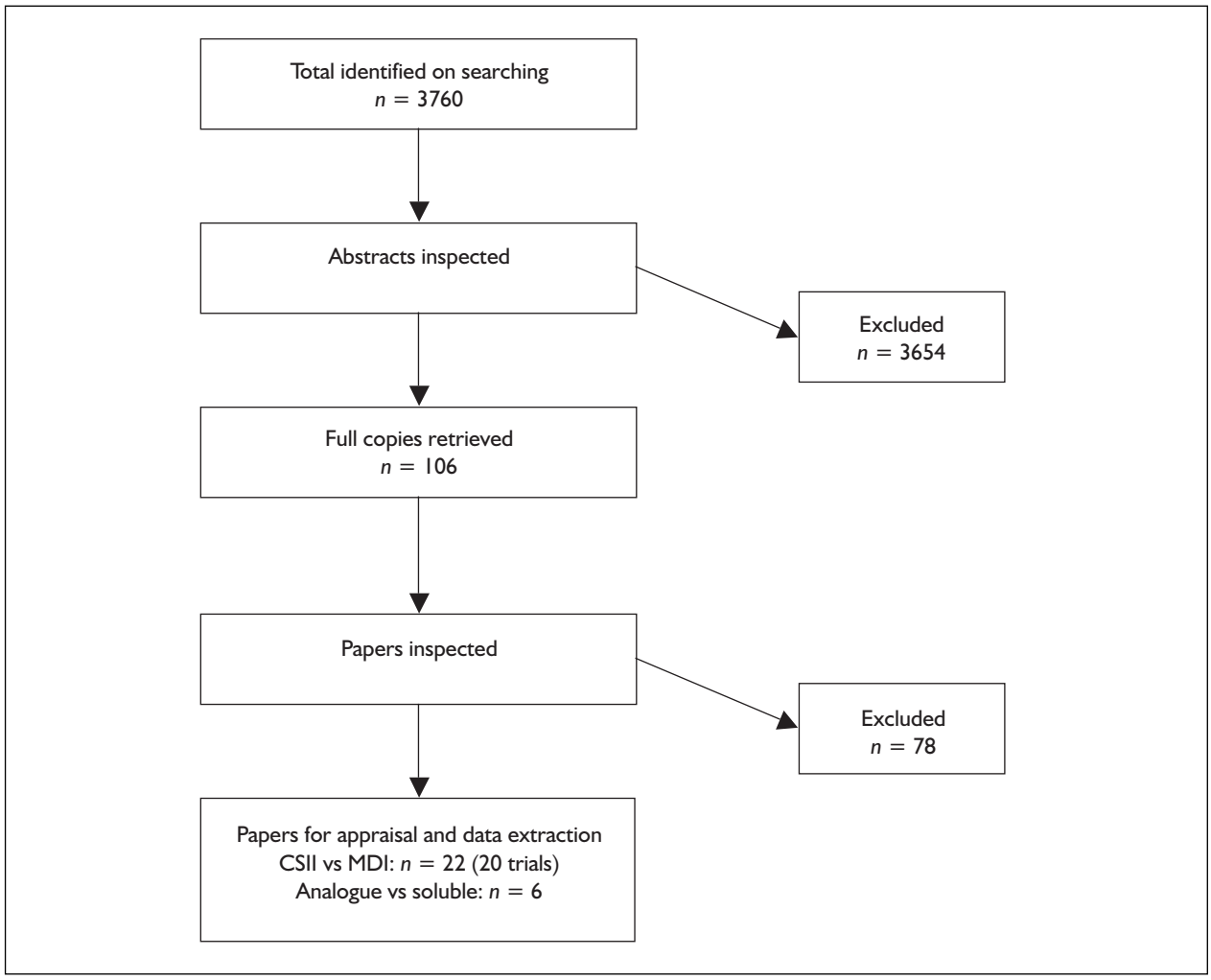

FIGURE 17 *Flowchart of identification of studies for inclusion in the review of clinical effectiveness*

PsycINFO (WebSPIRS), 1984–June 2002:
(insulin near pump*) or (csii or (insulin near infusion))

CINAHL (WebSPIRS), 1982–December 2001:
((insulin near pump*) or csii or (insulin near infusion)) and ((cost* or economic*) or (explode 'Economics-' / all topical subheadings / all age subheadings in DE) or (explode 'Health-Status' / all topical subheadings / all age subheadings in DE) or (explode 'Quality-of-Life' / all topical subheadings / all age subheadings in DE) or (wellbeing or well-being) or (explode 'Outcomes-Health-Care' / all topical subheadings / all age subheadings in DE) or (health near3 outcome*))

NHS EED (web version), searched on 29 June 2002:
csii or insulin pump$ or insulin infusion

EconLit (WebSPIRS): 1969–May 2002
csii or insulin pump* or insulin infusion

Additional searching

Bibliographies: all references of articles for which full papers were retrieved were checked to ensure that no eligible studies had been missed.

Industry submissions to NICE were examined for any further studies that met the inclusion criteria.

Appendix 3

Quality assessment scale

This is adapted from CRD Report 4 (2nd edition).

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?
2. Was the treatment allocation concealed?
3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were the point estimates and measure of variability presented for the primary outcome measure?
6. Did the analyses include an intention-to-treat analysis?
7. Were withdrawals and dropouts completely described?

Some instructions for using a checklist for RCTs

Quality item	Coding	Explanation
1. Was the assignment to the treatment groups really random?		
Random sequence generation	**Adequate** **Partial** **Inadequate** **Unknown**	**Adequate**: random numbers table or computer and central office or coded packages **Partial**: (sealed) envelopes without further description or serially numbered opaque, sealed envelopes **Inadequate**: alternation, case record number, birth date or similar procedures **Unknown**: just the term 'randomised' or 'randomly allocated' etc.
2. Was the treatment allocation concealed?		
Concealment of randomisation The person(s) who decide on eligibility should not be able to know or be able to predict with reasonable accuracy to which treatment group a patient will be allocated. In trials that use good placebos this should normally be the case; however, different modes or timing of drug administration in combination with the use of small block sizes of known size may present opportunities for clinicians who are also involved in the inclusion procedure to make accurate guesses and selectively exclude eligible patients in the light of their most likely treatment allocation; in centres with very low inclusion frequencies combined with very brief follow-up times this may also present a potential problem because the outcome of the previous patient may serve as a predictor of the next likely allocation	**Adequate** **Inadequate** **Unknown**	**Adequate**: when a paper convinces you that allocation cannot be predicted [separate persons, placebo really indistinguishable, clever use of block sizes (large or variable)]. Adequate approaches might include centralised or pharmacy-controlled randomisation, serially numbered identical containers, on-site computer-based system with a randomisation sequence that is not readable until allocation and other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients **Inadequate**: this option is often difficult. You have to visualise the procedure and think how people might be able to circumvent it. Inadequate approaches might include use of alternation, case record numbers, birth dates or week days, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation) and any other measures that cannot prevent foreknowledge of group allocation **Unknown**: no details in text. Disagreements or lack of clarity should be discussed in the review team

continued

Quality item	Coding	Explanation
3. Were the groups similar at baseline regarding the prognostic factors?		
Baseline characteristics Main aim is to enable the reviewer to see which patients were actually recruited. It enables one to get a rough idea on prognostic comparability. A real check on comparability requires multivariable stratification (seldom shown)	**Reported** **Unknown**	Consult the list of prognostic factors or baseline characteristics (not included in this Appendix). Reviewer decides
4. Were the eligibility criteria specified?		
	Adequate **Partial** **Inadequate** **Unknown**	
5. Were the point estimates and measure of variability presented for the primary outcome measure?		
Results for the primary outcome measure	**Adequate** **Partial** **Inadequate** **Unknown**	**Adequate**: mean outcome in each group together with mean difference and its standard error (SE) or standard deviation (SD) or any CI around it or the possibility to calculate those from the paper. Survival curve with log-rank test and patient numbers at later time points **Partial**: partially reported **Inadequate**: no SE or SD, or SD without *N* (SE = SD/*N*) **Unknown**: very unlikely
6. Did the analysis include an intention to treat analysis?		
Intention-to-treat analysis (ITT) Early dropout can make this very difficult. Strictest requirement is sensitivity analysis including early dropouts	**Adequate** **Inadequate**	Reviewers should not just look for the term ITT but assure themselves that the calculations were according to the ITT principle
7. Loss to follow-up		
This item examines both numbers and reasons; typically an item that needs checking in the methods section and the marginal totals in the tables. Note that it may differ for different outcome phenomena or time points. Some reasons may be reasons given by the patient when asked and may not be the true reason. There is no satisfactory solution for this	**Adequate** **Partial** **Inadequate** **Unknown**	**Adequate**: number randomised must be stated. Number(s) lost to follow-up (dropped out) stated or deducible (from tables) for each group and reasons summarised for each group **Partial**: numbers, but not the reasons (or vice versa) **Inadequate**: numbers randomised not stated or not specified for each group **Unknown**: no details in text

Appendix 4

List of excluded studies

Arias P, Kerner W, Zier H, Navascues I, Pfeiffer EF. Incidence of hypoglycemic episodes in diabetic patients under continuous subcutaneous insulin infusion and intensified conventional insulin treatment: assessment by means of semiambulatory 24-hour continuous blood glucose monitoring. *Diabetes Care* 1985;**8**:134–40. [Study design]

Barbosa J, Menth L, Eaton J, Sutherland D, Freier EF, Najarian J. Long-term, ambulatory, subcutaneous insulin infusion versus multiple daily injections in brittle diabetic patients. *Diabetes Care* 1981;**4**:269–74. [Insufficient follow-up]

Beck-Nielsen H, Richelsen B, Schwartz-Sorensen N, Hother-Nielsen O. Insulin pump treatment: effect on glucose homeostasis, metabolites, hormones, insulin antibodies and quality of life. *Diabetes Res* 1985;**2**:37–43. [Not intensive therapy]

Bell DS, Ovalle F. Improved glycemic control with use of continuous subcutaneous insulin infusion compared with multiple insulin injection therapy. *Endocr Pract* 2000; **6**:357–60. [Study design]

Blackett PR. Insulin pump treatment for recurrent ketoacidosis in adolescence. *Diabetes Care* 1995; **18**:881–2. [Study design]

Bode BW, Strange P. Efficacy, safety, and pump compatibility of insulin aspart used in continuous subcutaneous insulin infusion therapy in patients with type 1 diabetes. *Diabetes Care* 2001;**24**:69–72. [Insufficient follow-up]

Boland EA, Grey M, Oesterle A, Fredrickson L, Tamborlane WV. Continuous subcutaneous insulin infusion. A new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. *Diabetes Care* 1999;**22**:1779–84. [Study design]

De Beaufort CE, Houtzagers CM, Bruining GJ, Aarsen RS, den Boer NC, Grose WF, *et al*. Continuous subcutaneous insulin infusion (CSII) versus conventional injection therapy in newly diagnosed diabetic children: two-year follow-up of a randomized, prospective trial. *Diabet Med* 1989;**6**:766–71. [Not intensive therapy]

Garg SK, Anderson JH, Gerard LA, Mackenzie TA, Gottlieb PA, Jennings MK, *et al*. Impact of insulin lispro on HbA_{1c} values in insulin pump users. *Diabetes Obesity Metab* 2000;**2**:307–11. [Study design]

Helve E, Koivisto VA, Lehtonen A, Pelkonen R, Huttunen JK, Nikkila EA. A crossover comparison of continuous insulin infusion and conventional injection treatment of type I diabetes. *Acta Med Scand* 1987; **221**:385–93. [Not intensive therapy]

Jennings AM, Lewis KS, Murdoch S, Talbot JF, Bradley C, Ward JD. Randomized trial comparing continuous subcutaneous insulin infusion and conventional insulin therapy in type II diabetic patients poorly controlled with sulfonylureas. *Diabetes Care* 1991;**14**:738–44. [Not intensive therapy]

Johansson UB, Adamson UC, Lins PE, Wredling RA. Improved blood glucose variability, HbA_{1c} insuman Infusat and less insulin requirement in IDDM patients using insulin lispro in CSII. The Swedish Multicenter Lispro Insulin Study. *Diabetes Metab* 2000;**26**:192–6. [Insufficient follow-up]

Laatikainen L, Teramo K, Hieta-Heikurainen H, Koivisto V, Pelkonen R. A controlled study of the influence of continuous subcutaneous insulin infusion treatment on diabetic retinopathy during pregnancy. *Acta Med Scand* 1987;**221**:367–76. [Not intensive therapy]

Lauritzen T, Frost LK, Larsen HW, Deckert T. Effect of 1 year of near-normal blood glucose levels on retinopathy in insulin-dependent diabetics. *Lancet* 1983;**i**:200–4. [Not intensive therapy]

Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, *et al*. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 2000;**49**:2142–8. [Insufficient follow-up]

Mancuso S, Caruso A, Lanzone A, Bianchi V, Massidda M, Codipietro F, *et al*. Continuous subcutaneous insulin infusion (CSII) in pregnant diabetic women. *Acta Endocrinol Suppl (Copenh)* 1986; **277**:112–16. [Study design]

Marshall SM, Home PD, Taylor R, Alberti KG. Continuous subcutaneous insulin infusion versus injection therapy: a randomised cross-over trial under usual diabetic clinic conditions. *Diabet Med* 1987;**4**:521–5. [Not intensive therapy]

Ng-Tang FS, Pickup JC, Bending JJ, Collins AC, Keen H, Dalton N. Hypoglycemia and counterregulation in insulin-dependent diabetic patients: a comparison of continuous subcutaneous insulin infusion and conventional insulin injection therapy. *Diabetes Care* 1986;**9**:221–7. [Not intensive therapy]

Olsen T, Ehlers N, Nielsen CB, Beck-Nielsen H. Diabetic retinopathy after one year of improved metabolic control obtained by continuous subcutaneous insulin infusion (CSII). *Acta Ophthalmol (Copenh)* 1985;**63**:315–19. [Not intensive therapy]

Olsen T, Richelsen B, Ehlers N, Beck-Nielsen H. Diabetic retinopathy after 3 years' treatment with continuous subcutaneous insulin infusion (CSII). *Acta Ophthalmol (Copenh)* 1987;**65**:185–9. [Not intensive therapy]

Ooi C, Mullen P, Williams G. Insulin lispro: the ideal pump insulin for patients with severe hypoglycemic unawareness? *Diabetes Care* 1999;**22**:1598–9. [Study design]

Reeves ML, Seigler DE, Ryan EA, Skyler JS. Glycemic control in insulin-dependent diabetes mellitus. Comparison of outpatient intensified conventional therapy with continuous subcutaneous insulin infusion. *Am J Med* 1982;**72**:673–80. [Insufficient follow-up]

Rizza RA, Gerich JE, Haymond MW, Westland RE, Hall LD, Clemens AH, *et al*. Control of blood sugar in insulin-dependent diabetes: comparison of an artificial endocrine pancreas, continuous subcutaneous insulin infusion, and intensified conventional insulin therapy. *N Engl J Med* 1980;**303**:1313–8. [Insufficient follow-up]

The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;**329**:977–86. [Study design]

Appendix 5

List of recent abstracts

Bode B, McCulloch K, Strange P. Insulin aspart efficacy and safety compared to buffered regular insulin (Velosulin®) for continuous subcutaneous insulin infusion. *Diabetes* 2000;**49**:394.

Chase HP, Saib SZ, MacKenzie T, Hansen M, Garg SK. Postprandial glucose excursions following four methods of bolus insulin administration using an insulin pump. *Diabetes* 2001;**50**:A92.

Conway RJ, Milliken JA. Option or essential tool? Insulin pump therapy in young women. *Diabetes* 2002;**51** (Suppl 2):1921.

Devries JH, Snoek FJ, Kostense PJ, Masurel N, Heine RJ. CSII improves glycaemic control and quality of life in type 1 diabetic patients with long standing poor glycaemic control. A randomized trial. *Diabetes* 2002; **51** (Suppl 2):520.

Galatzer A, Weintrob N, Cohen D, Benzaquen H, Rimer A, Ofan R, *et al*. Treatment satisfaction of type 1 diabetic patients: CSII v MDI. *Diabetes* 2002;**51** (Suppl 2):2570.

Laffel L, Loughlin C, Ramchandani N, Butler D, Laffel N, Levine BS, *et al*. Glycemic challenges of pump therapy (CSII) in youth with type 1 diabetes (T1DM). *Diabetes* 2001;**50**:A66–7.

Lenhard MJ, Maser RE. Continuous subcutaneous insulin infusion (CSII) in patients with type 2 diabetes. *Diabetes* 2001;**50**:A440–1.

Lepore M, Pampanelli S, Fanelli CG, Porcellati F, Brunetti P, Bolli GB. Pharmacokinetics and dynamics of s.c. injection of insulin glargine, NPH and ultralente in T1DM: comparison with CSII. *Diabetes* 2000;**49**:36.

Linkeschova R, Raoul M, Bott U, Berger M, Spraul M. Better diabetes control, quality of life and less severe hypoglycaemias with insulin pump treatment. *Diabetologia* 2000;**43**:748.

Litton J, Rice A, Friedman N, Oden J, Lee M, Freemark M. Insulin pump therapy in infants and preschool children with type 1 diabetes. *Paediatr Res* 2002;**51** (Suppl 1):748.

Mack-Fogg J, Bates S, Faro B, Sciera M, Ippolito K, Orlowski CC, *et al*. Safe and effective use of CSII in young children with type 1 diabetes mellitus: *Paediatr Res* 2002;**51** (Suppl 1):712.

Raskin P, Bode B, Marks JB, Hirsch IB, Weinstein R, McGill J, *et al*. Insulin aspart (IAsp) is as effective in continuous subcutaneous insulin infusion as in multiple daily injections for patients with type 2 diabetes. *Diabetes* 2001;**50**:A128.

Reid SM, Lawson ML. Comparison of CSII versus conventional treatment of diabetes with respect to metabolic control. Quality of life and treatment satisfaction. *Paediatr Res* 2002;**51** (Suppl 1):713.

Rudolph JW, Hirsck IB. An assessment of continuous subcutaneous insulin infusion therapy in an academic diabetes clinic. *Diabetes* 2000;**49**:501.

Tubiana-Rufi N, Coutand R, Bloch J, Munz-Licha G, Delcroix C, Limal JM, *et al*. Efficacy and tolerance of insulin lispro in young diabetic children treated with CSII. *Diabetologia* 2000;**43**:762.

Turrentine LA, Wallander JL, Roth DL, Bode BW, Trippe BS, Bell DS. The influence on quality of life of continuous subcutaneous insulin infusion (CSII) therapy. *Diabetes* 2001;**50**:A49.

Wainstein J, Cohen Y, Gilad R, Raz I, Wexler ID. Treatment of severe insulin resistance in type 2 diabetics with insulin pumps. *Diabetologia* 2000;**43**:789.

Wainstein J, Metzger M, Menuchin O, Cohen Y, Yaffe A, Ravid M, *et al*. Insulin pump therapy versus multiple daily injections in obese type 2 diabetic patients. *Diabetologia* 2001;**44**:94.

Weintrob N, Benzaquen H, Shalitin S, Fayman G, Galatzer A, Dickerman Z, *et al*. Continuous subcutaneous insulin infusion versus multiple daily injections in children with type 1 diabetes. *Diabetologia* 2001;**44**:95.

White NH, Hollander AS, Sadler M, Daniels L. Risks and benefits of continuous subcutaneous insulin infusion (CSII) therapy in children. *Diabetes* 2001; **50**:A66.

Zloczower M, Cohen J, Zaidise I, Kanter Y. Insulin pump in pregnancy. *Diabetes* 2000;**49**:1885.

Appendix 6

Summary of methodology: adults with Type 1 diabetes

Study	Interventions	Subjects	Outcome measures	Methodology
Bak *et al.*, 1987[87] Denmark, single-centre, randomised crossover Duration: CSII 6 months, MDI 6 months	Treatment 1: CSII + soluble. Graseby MS36 Treatment 2: MDI + regular (3 × soluble, 1 × NPH). Pen injector (NovoPen) Reason for CSII: not reported	Population: young adults; IDDM with duration of >2.5 y, diagnosed before the age of 30 y. Criteria: no sign of neuropathy, hypertension or advanced retinopathy, absence of albuminuria, diastolic blood pressure <95 mmHg, absence of cataract, retinal proliferations, haemorrhages or exudates, <5 micro-aneurysms in the retina. C-peptide –ve Participants: *N*: 20 End of study: 16 Female: 6.25% Mean age (±SD): 24 (±2) y Diabetes duration mean (±SD): 5.8 (±3.8) y *Baseline values: mean (±SD):* Insulin: 46 (±16) IU/day Weight: 74.4 (±9.7) kg Previous regimen: previously treated conventionally with intermediate insulin alone or in combination with short-acting insulin once or twice daily	Assessment of outcomes: hypos estimated by the M-value of Schlictkrull, and also frequency of BG values <4 mmol/l – both calculated from home-recorded BG profiles during last 3 months on each treatment regimen. Patient preference by questionnaire at end of study	Allocation to treatment groups: randomised, half to each treatment. No further details Run-in/wash-out period: transition to CSII or MDI made during hospitalisation. No run-in or wash-out period specified Comparability of treatment groups: not reported Analysis: Wilcoxon's test for paired differences (2-tailed). Means (SD) presented Sample size/power calculation: not reported Generalisability: mainly young male adults with Type 1 Outcome measures: HbA_1 not reported. Duration of diabetes reported in months. Mean glucose values during last 3 months of each treatment regimen reported. Average daily insulin requirement at optimum insulin dosage reported Reasons for withdrawals: incompatibility with pump regimen (4 CSII) Patient preference: % wanting to continue with treatment presented, numerator and denominator not reported Conflict of interest: NOVO Industri, Denmark provided NovoPen injectors and infusers, and performed laboratory analyses. Supported by Aarus University, Danish Diabetic Association and Danish Medical Research Council

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Bode *et al.*, 1996[81] USA, single-centre, non-randomised crossover Duration: CSII mean 37 months, MDI min. of 12 months	Treatment 1: CSII + soluble Minimed 506/504 Treatment 2: MDI + regular Reason for CSII: (1) suboptimal glycaemic control as shown by fluctuating BG levels thought to be associated with poor response to intermediate acting insulin; (2) HbA_{1c} >8.0%; (3) a history of recurrent severe hypoglycaemia (defined as ≥ 1 episodes/y of hypos requiring assistance); or (4) hypoglycaemic unawareness	Population: Patients currently on CSII Criteria: from a population of 255 pts using CSII: min. of 12 months on intensive therapy with MDIs before switching to CSII; and a min. of 12 months on CSII after crossover Participants: *N*: 55 End of study: 55 Female: 64% Mean age (±SD): 39.2 (±12.9) y Diabetes duration mean (±SD): 22.2 (±9.7) y Previous regimen: MDI	Assessment of outcomes: weight and HbA_{1c} recorded quarterly at each visit. BG recorded when severe hypo experienced. Hypos/daily insulin/self-monitoring frequency/DKA = obtained at each visit from patients' personal log sheet	Allocation to treatment groups: patients not randomised Run-in/wash-out period: all started on CSII as in-patients on diabetes unit; no washout period Comparability of treatment groups: not reported Analysis: baseline values = last HbA_{1c}, body weight and total daily insulin dose recorded when patients on MDI before crossing over to CSII (at least 12 months). Single-sample Student's *t*-test to evaluate change from baseline. Sign test to evaluate changes in event rates of hypos and DKA from the MDI to the CSII period Sample size/power calculation: not reported Generalisability: adults previously on MDI changed to CSII. History of severe hypos and/or hypo unawareness Outcome measures: HbA_{1c}, body weight and total insulin dose values. Number of severe hypos and DKA episodes during MDI year and during each CSII year Conflict of interest: 1 author has received honoraria for speaking engagements from Minimed, Inc., and has received grant support for the Minimed Implantable Pump study

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Brinchmann-Hansen *et al*., 1988[76] Other publications: Dahl-Jorgensen *et al.*,1988[77] and Dahl-Jorgensen *et al.*, 1986[78] Norway, multi-centre, RCT (parallel) (Study = conventional vs MDI vs CSII; data extracted on MDI and CSII only) Duration: CSII mean 40 months (range 24–60), MDI mean 41 months (range 21–47)	Treatment 1: CSII + soluble. Nordisk Infuser, Autosyringe AS6C, Eulgy, Graseby MS36 and Nipro. Treatment 2: MDI + regular (4 × soluble, 1 × long-acting) Reason for CSII: not reported	Population: insulin-dependent diabetic patients Inclusion criteria: age 18–45 y, diabetes before 30 y old; duration of disease >6 and <30 y; no clinical signs of nephropathy or systemic hypertension; no history of neuropathy; tested negative for C-peptide. Pts with proliferative retinopathy were not included CSII participants: *N*: 15 End of study: 15 Female: 53% Mean age (min.–max.): 26 (18–38) y Diabetes duration mean (min.–max.): 12.8 (6.4–23.3) y *Baseline values: mean (±SD):* HbA_1: 10.1 (±1.55)% , range 8.0–12.9 Insulin: 0.8 (±0.23) U/kg Weight: 68.6 (±9.3) kg MDI participants: *N*: 15 End of study: 14 Female: 53% Mean age (min.–max.): 26 (19-42) y Diabetes duration mean (min.–max.): 12.8 (6.8–20.8) y *Baseline values: mean (±SD):* HbA_1: 9.4 (±1.55)% , range 7.0–11.7, p = ns Insulin: 0.72 (±0.08) U/kg Weight: 71.7 (±10.1) kg, p = ns Previous regimen: two injections of insulin	Assessment of outcome: subjective hypos recorded by patient. HbA_1 determined every month for first year and every second month thereafter	Allocation to treatment groups: block randomisation with computerised matching of clinical background characteristics Run-in/wash-out period: home glucose monitoring during 2 months before randomisation significantly reduced HbA_1 ($p < 0.01$) in all groups. Comparability of treatment groups: HbA_1, body weight, insulin requirement, age, sex and duration of diabetes comparable Analysis: 2-sided Wilcoxon rank-sum test to compare values between treatment groups and 2-sided Wilcoxon signed rank test to compare values within treatment groups. Level of significance = 5%. HbA_1 data extracted from figure by reviewer (except 2-y data). SEM presented, SD calculated by reviewer. Data at 2 y extracted from Dahl-Jorgensen, 1986 (table). Multicentre variability not assessed Sample size/power calculation: not reported Generalisability: adult insulin dependent diabetics Other: frequency of home BG monitoring was reduced after 1st 12 months and caused a trend for increase in HbA_1 in all groups Reasons for withdrawals: severe hypoglycaemia (1 MDI) Conflict of interest: study supported by grants from the Norwegian Council for Science and Humanities, Oslo; the Norwegian Diabetes Association, Oslo; the Norwegian Council on Cardiovascular diseases, Oslo; the University of Oslo; the Anders Jahres Medical Foundation, Oslo; and Nordisk Gentofte A/S

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Chiasson *et al.*, 1984[82] Canada, single-centre, non-randomised crossover Duration: CSII 3 months, MDI 3 months	Treatment 1: CSII + soluble. Mill Hill infuser Treatment 2: CSII + soluble (soluble, plus 1 ultralente). MDI administered by automatic jet injector (Medi-Jector). Boluses before meals and snack with >20 g carbohydrate Reason for CSII: not reported	Population: insulin-dependent diabetics, all had signs of retinopathy, all within 20% of ideal body weight Inclusion criteria: not reported Participants: *N*: 12 End of study: 12 Female: 58.3% Mean age (min.–max.): 26.8 (18–40) y Diabetes duration mean (min.–max.): 15.3 (4–23) y *Baseline values: mean (±SD):* HbA_1: 11.9 (±2.08)% Insulin: 44.7 (±14.6) IU/d Previous regimen: conventional therapy	Assessment of outcomes: diabetic diary: incl. insulin dose (collected before start of study and at end of 3-month period). Glycosylated haemoglobin measured at end of each 3-month period	Allocation to treatment groups: randomisation mentioned in abstract but not in paper, which states half started with CSII and half with MDI. Method not stated Run-in/wash-out period: no wash-out period indicated. Patients were hospitalised (unknown period) where they learned to operate the intervention, modify insulin and calculate carbohydrate content Comparability of treatment groups: individual patient data presented for age, sex, duration of diabetes, but treatment group not given Analysis: statistical comparisons were made by means of paired *t*-test SEM presented, SD calculated by reviewer Sample size/power calculation: not reported Generalisability: adults with insulin-dependent diabetes with signs of retinopathy, previously on conventional therapy Outcome measures: HbA_1, daily insulin dose Other: number of injections in MDI not stated Conflict of interest: study funded in part by grants from Medical Research Council (MA 7211), the Conseil de la Recherché en Santé du Québec and the NIH (2R01 AM 2199-05)

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Haakens *et al.*, 1990[83] Norway, single-centre, non-randomised crossover (Study = conventional vs MDI vs CSII; data extracted on MDI and CSII only) Duration: CSII 6 months, MDI 6 months	Treatment 1: CSII + soluble. Nordisk infuser/ (n = 50), autosyringe AS 8MP (n = 2) Treatment 2: MDI + regular [4 × soluble (via Novopen); 1 × intermediate (ultralente and isophane used via syringe)] Reason for CSII: not reported	Population: insulin-dependent diabetic patients aged 16–50 y, attending outpatient clinic at hospital Exclusion criteria: on intensified insulin therapy; pregnant or planning pregnancy; diabetes duration <1 y; total daily insulin dose <24 U; serum creatinine > 150 μmol/l; proliferative/preproliferative retinopathy; macrovascular complications; severely affected ability to recognise hypoglycaemia, as evidenced by multiple hypoglycaemic comas without warning symptoms during the last few years; malignant disease; known alcohol/drug abuse; psychosis; mental retardation Participants: *N*: 52 End of study: 35 Female: 63% Mean age (±SD): 24.9 (±6.78) y Diabetes duration mean (±SD): 9.2 (±5.55) y *Baseline values: mean (±SD):* HbA_1: 10.4 (±1.85)%. Insulin: 0.76 (±0.25) IU/day BMI: 23.2 (±2.47) kg/m^2 (at entry to study) Weight: 68.6 (±8.63) kg. HbA_1 at beginning of pre-period = 10.7 (±2.47)	Assessment of outcomes: outpatient clinic visits = 6 weeks, occurrence of mild and serious hypos, DKA, injection/infusion site infections, results of home BG monitoring recorded	Allocation to treatment groups: individuals not randomised Run-in/wash-out period: run-in period = 3–9 months Comparability of treatment groups: no baseline characteristics provided to allow comparisons. No statistical significance between subjects who entered the study and those who didn't with regard to HbA_1 (11.1 ± 0.29% vs. 10.9 ± 0.16%) or age (24.4 ± 1.0 y vs 25.5 ± 0.5 y) Analysis: not ITT analysis. Results given as means ± SEM. Reviewer calculated SD. 2-sided Wilcoxon signed-rank test for paired data used to compare different treatment modes. Spearman's rank correlation coefficient used. Statistical significance set to $p < 0.05$. Sample size/power calculation: not reported. Generalisability: adults (16–50 y) with insulin-dependent diabetes for >1 y, with no proliferative/preproliferative retinopathy Outcome measures: stable HbA_1 = reference range 5.4–7.6% Reasons for withdrawals: serious hypo (1 MDI), unable to control BG (2 MDI), discontinued after 1.5 months – uncomfortable (6 CSII), medical reasons (2 CSII), refused to give up pump to go on MDI (4), refused trial of CSII (2) Conflict of interest: Norwegian Diabetic Association provided financial support

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Hanaire-Broutin *et al.*, 2000[80] France, single-centre, randomised crossover Duration: CSII 4 months, MDI 4 months	Treatment 1: CSII + lispro. Minimed 506/507, Disetronic Htron D/V Treatment 2: MDI + lispro [3 × lispro, 2 × NPH (mean 2.65 injections at end of MDI)] Reason for CSII: not reported	Population: Type 1 diabetic patients aged 21–65 y. Inclusion criteria: HbA_{1c} < 10.0%, C-peptide –ve and experience of intensified insulin therapy. None had untreated retinopathy, impaired renal function, gastric neuropathy, BMI >30 kg/m^2, daily insulin dose >2 U/kg, history of hypoglycaemia unawareness, or any severe disease Participants: *N*: 41 End of study: 40 Female: 48.8% Mean age (±SD): 43.5 (±10.3) y, min. 21, max. 65.4 y Diabetes duration mean (±SD): 20 (±11.3 y), min. 4, max. 42 y *Baseline values: mean (±SD):* HbA_{1c}: 8.39 (±0.87)% Insulin: 43.6 (±13.5) U/day BMI: 24 (±2.4) kg/m^2 Weight: 68.2 (±10) kg Previous regimen: at enrolment 32 were treated with CSII + regular insulin and 9 by MDI with regular insulin or lispro	Assessment of outcomes: daily BG measurements – in event of hypoglycaemic symptoms. Pts recorded all episodes of hypoglycaemia and any other technical or metabolic incident. Visits every 2 months, insulin dose and adverse events noted. Patient preference at end of study. HbA_{1c} determined at end of each period Hypos (BG <60 mg/dl) during last 14 days	Allocation to treatment groups: randomised after run-in period, method not stated. Allocation concealment unclear, open-label design Run-in/wash-out period: all pts had 6 weeks run-in with CSII + regular insulin. No wash-out period. States that no carryover effect was observed Comparability of treatment groups: not reported Analysis: results given as means and SD. All tests were 2-tailed, and *p* values <0.05 = statistically significant. Changes in continuous criteria studied by analysis of variance applied to crossover study with period, treatment group, and interaction factors. Categorical criteria (adverse events) were compared with χ^2 test. Sample size/power calculation: not reported Generalisability: adults with Type 1 diabetes and experience of intensified therapy (CSII or MDI) Outcome measures: HbA_{1c} at 4 months, insulin dose, hypo episodes during last 14 days Reasons for withdrawals: difficulties with MDI (pts on CSII before enrolment) (1 MDI) Conflict of interest: study was supported by Lilly France and Bayer France

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Home *et al.*, 1982[88] UK, single-centre, randomised crossover Duration: CSII 2.5 months, MDI 2.5 months	Treatment 1: CSII + soluble. Mill Hill 1001HM, Autosyringe AS*6C Treatment 2: MDI + regular (2 × soluble, 1 × ultralente) Reason for CSII: not reported	Population: insulin-dependent, C-peptide –ve, adults whose control had been previously optimised on twice-daily injection therapy. Criteria: not specified. 1 (of 12) patient excluded due to ischaemic heart disease Participants: *N*: 12 consented (see methodology) End of study: 10 Female: 40% Mean age (min.–max.): 40.4 (29–52) y Diabetes duration mean (min.–max.): 22.3 (7–34) y *Baseline values: mean (±SD):* HbA_1: 10.7 (±1.9)% Insulin: 60 (±18.97) IU/day Weight: 67.6 (±8.5) kg Previous regimen: optimised on twice-daily injections	Assessment of outcomes: number of hypos requiring oral glucose recorded at biweekly clinic visits Patient preference by questionnaire at end of study	Allocation to treatment groups: states regimens in 'random order' but no further details Run-in/wash-out period: not reported Comparability of treatment groups: not reported Analysis: not ITT. Data presented on 10 pts who completed study. Mean (SE) presented. SD calculated by reviewer. Student's paired *t*-test Sample size/power calculation: not reported Generalisability: adults with insulin-dependent diabetes Outcome measures: blood taken for HbA_1 biweekly and for cholesterol at end of each treatment. Hypos recorded at clinic visit, therefore subject to recall bias. Questionnaire for patient preference. Reasons for withdrawals: 1 pt excluded because of ischaemic heart disease (not clear whether this was before or after randomisation); 1 pt had myocardial infarction before completing study Conflict of interest: personal support from Novo Laboratories Limited. Financial support from British Diabetic Association

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Nathan and Lou, 1982[89] USA, single-centre, randomised crossover Duration: each period 8–12 weeks duration; 1 subject on MDI for <10 weeks. 1 subject crossed-over 3 times (MDI 8 weeks, CSII 12 weeks, MDI 8 weeks, CSII 4 weeks	Treatment 1: CSII + soluble. Autosyringe AS*6C Treatment 2: MDI + regular (3 × soluble, 2 × NPH or 1 × ultralente). Reason for CSII: not reported	Population: motivated adults with Type I diabetes Criteria: pts had history of ketosis-prone, insulin-dependent diabetes. None had significant neuropathy nephropathy, retinopathy or vascular disease at study outset. All pts within 10% of ideal body weight Participants: *N*: 5 End of study: 5 Female: 60% Mean age (min.–max.): 31 (27–41) y Diabetes duration mean (min.–max.): 7.4 (5–9) y *Baseline values: mean (±SD):* HbA_{1c}: 9.03 (±1.43)%. Insulin: 42.8 (±16.04) IU/day Hypoglycaemic reactions (*n*/week) = 1.8 (±0.84) Previous insulin regimen: regular + NPH (2 × daily) (3 pts); NPH (2 × daily) (1 pt); regular + NPH (1 pt)	Assessment of outcomes: diary: insulin dose adjustments, hypoglycaemic reactions, unusual activities, complications of therapy. Hypoglycaemia: combination of symptoms of palpitations, diaphoresis, hunger, light-headedness or confusion occurring with BG < 60 mg/dl and relieved by carbohydrate ingestion Acceptability of treatment assessed with questionnaire	Allocation to treatment groups: randomised after baseline data obtained. Method not stated. Concealment of allocation not indicated 1 pt participated in a double-blind crossover trial of both therapies (3 weeks per arm) Run-in/wash-out period: No indication of wash-out period. Pts admitted to IP for 2–3 days after each treatment started and after crossover. After completing first leg of trial, pts had all baseline studies again, inpatient monitoring was carried out and pts were swapped over to the alternative therapy Comparability of treatment groups: baseline data table given, though comparability between groups (those on MDI first vs CSII first) not given Analysis: Student's paired 2-tailed *t*-test. Individual pt data presented, means calculated by reviewer. Baseline and insulin and HbA_{1c} (for treatments) SD calculated by reviewer Sample size/power calculation: not reported Generalisability: motivated adults with Type I diabetes, previously on NPH and regular insulin regimes Outcome measures: appropriate outcome measures (HbA_{1c}, hypoglycaemic episodes) used Conflict of interest: grant support: in part by Corning Medical and Scientific, Medfield, MA; the Murial McLauthlin Fund, Massachusetts General Hospital; and the General Clinical Research Centre grant RR01066, National Institutes of Health. One author is the Capps Scholar of Harvard University; one author is an investigator for the Howard Hughes Medical Institute

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Nosadini *et al.*, 1988[85] Italy, single centre, RCT (parallel) [4 arms: conventional vs MDI vs CSII with fixed basal rate (FBR) vs CSII with higher dawn insulin (HOR). Data on conventional arm not extracted] Duration: 12 months	Treatment 1: CSII + soluble (FBR). Microjet MC 20 Treatment 2: MDI + regular (3 × soluble, 1 × long-acting) Treatment 3: CSII + soluble (HOR). Betatron II Reason for CSII: not reported	Population: insulin-dependent diabetics Inclusion criteria: C-peptide –ve CSII FBR participants: *N*: 19 End of study: 19 Female: 42.1% Mean age (±SD): 36 (±6) y Diabetes duration mean (±SD): 8 (±3) y *Baseline values: mean (±SD):* Weight: 77 (±7) kg MDI participants: *N*: 15 End of study: 15 Female: 26.7% Mean age (±SD): 32 (±9) y Diabetes duration mean (±SD): 7 (±4) y *Baseline values: mean (±SD):* Weight: 71 (±6) kg CSII HOR participants: *N*: 10 End of study: 10 Female: 40% Mean age (±SD): 34 (±3) y Diabetes duration mean (±SD): 7 (±3) y *Baseline values: mean (±SD):* Weight: 70 (±7) kg Previous regimen: 2–3 injections/day, mixed regular and long-acting insulin preparations	Assessment of outcomes: BG measured when hyper and hypo episodes suspected. Events assessed from twice-weekly profiles, hospital BG and pt records of suspected events. Hyper = BG up to 350 mg/dl with acetonuria assessed by pt, no medical advice. Ketotic events = BG >400 mg/dl and ketone body levels >1.5 mmol/l with clinical symptoms requiring admission to ward. Hypo = BG <60 mg/dl with clinical symptoms without help from others. Severe hypo = BG<60 mg/dl requiring glucagon or glucose parenteral administration from others	Allocation to treatment groups: 96 pts recruited and divided into 4 groups: male, female, duration of disease >5 y, <5 y. Subjects of each group were assigned 'blindly' to each of 4 treatments. Method not stated. Sealed envelopes opened by pts. Consent obtained after randomisation Run-in/wash-out period: after randomisation, metabolic data collected for 3 months on previous traditional therapy. A week in hospital was spent teaching self-monitoring and self-regulation of insulin Comparability of treatment groups: states similar insulin daily dose and number of injections, and HbA_{1c} Analysis: no crossover within treatments occurred. Multivariate ANOVA for repeated measures used for differences within the 4 insulin regimens and between time 0 and each regimen. Unpaired *t*-test analysis and Bonferroni *t*-test for diffs between single values when ANOVA revealed significant difference Sample size/power calculation: not reported Generalisability: insulin-dependent diabetics receiving conventional therapy Outcome measures: baseline values collected in month preceding time 0. Hypos expressed as mean value/pt/year Conflict of interest: supported by CNR grants and CNR International Research Programme

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Saurbrey *et al.*, 1988[90] Denmark, single-centre, randomised crossover Duration: CSII 2.5 months, MDI 2.5 months	Treatment 1: CSII + soluble. Autosyringe AS-6C ($n = 6$), Medix 209 ($n = 13$). Treatment 2: MDI + regular [3 × soluble (Novopen), 1 × intermediate (syringe)]. Reason for CSII: not reported	Population: adults with insulin dependent diabetes; assumed that most of the pts C-peptide –ve. All were treated with twice daily injections of short-acting plus intermediate- or long-acting insulin. Background retinopathy (12), proliferative retinopathy (0), incipient sensory neuropathy (4), intermittent proteinuria (3) Inclusion criteria: insulin-dependent diabetes; able to comply with intensive insulin regime Participants: *N*: 21 End of study: 19 Female: 43% Mean age (±SD): 32 (±2.1) y, min. 20, max. 53 Diabetes duration mean (±SD): 14.5 (±1.4) y *Baseline values: mean (±SD):* Group starting with CSII, HbA_{1c}: 8.7 (±1.74)% Group starting with MDI HbA_{1c}: 8.8 (±2.17)%, p = ns Insulin: 0.67 (±0.4) IU/day	Assessment of outcomes: twice weekly = 7-point BG profiles. Number of hypos recorded. No further details. Blood samples for HbA_{1c} taken after run-in and after each treatment period At all outpatient visits = injections sites inspected and body weight recorded. Patient attitude questionnaire completed at end of study	Allocation to treatment groups: pts randomised, but no indication of method of randomisation. No mention of concealment of allocation Run-in/wash-out period: pts had a 3-week run-in Comparability of treatment groups: not reported Analysis: Mean and ± SE values provided. Reviewer calculated SD for HbA_{1c} and insulin. Results compared statistically by Student's t-test and differences resulting in p-values <0.05 were considered significant. HbA_{1c} data extracted from figure by reviewer Sample size/power calculation: not reported Generalisability: adults with insulin-dependent diabetes who had previously been on injection insulin therapy. Outcome measures: appropriate outcome measures used (HbA_{1c} and hypos), although no indication of recording method of hypos Reasons for withdrawals: pump wearing unacceptable (2) Conflict of interest: Novo Industri A/S supplied NovoPens

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Schiffrin and Belmonte, 1982[91] Canada, single-centre, randomised crossover Duration: CSII 6 months, MDI 6 months	Treatment 1: CSII + soluble. Mill Hill 1001 GM Treatment 2: MDI + regular (3 × soluble, 1 × NPH). Reason for CSII: not reported	Population: insulin-dependent diabetics with severe insulin deficiency documented by absent C-peptide response to glucagon stimulation. Aged 14–41 y. Inclusion criteria: not reported Participants: *N*: 20 End of study: 16 Female: 70% Mean age (min.–max.): 24.95 (14–41) y Diabetes duration mean (min.–max.): 10.35 (6–21) y *Baseline values: mean (±SD):* HbA_1: 13.2 (±1.1)% Insulin: 48 IU/day BMI: 22.81 kg/m^2 Weight: 61.86 kg Previous regimen: conventional treatment of regular and intermediate-acting insulin. 2 injections/day (n = 16), 3 injections/day (n = 3), 4 injections/day (n = 1)	Assessment of outcomes: Hypos: mild = recognised by sensation of hunger, fatigue, irritability, headache. Moderate = cold sweating, palpitations, tremours, blurred vision, impaired voluntary movements or memory loss. Severe = loss of consciousness. Method of collecting pt preference data not reported. HbA_1 and cholesterol measured monthly	Allocation to treatment groups: pts randomised, half to each therapy, but no indication of method of randomisation. Allocation concealment unclear Run-in/wash-out period: pts remained on conventional treatment prior to study. Pts starting on CSII were given practice for 1 week prior to study. No wash-out period reported Comparability of treatment groups: not reported Analysis: not ITT analysis. Mean ± SD provided. Data analysed by paired Student's t-test. When values did not have a normal distribution, a paired t-test was performed on the logarithmic transform of the data. Baseline and 6-month insulin values extrapolated from graph (Figure 4) by reviewer. Baseline weight and BMI calculated from Table 1 by reviewer Sample size/power calculation: not reported Generalisability: insulin-dependent diabetics aged 14–41 y who had previously been on conventional injection insulin therapy Outcome measures: HbA_1 reported monthly for months 0–6. Data extracted for months 0, 3 and 6 only. Method of recording hypos not clear. Pts followed their usual diabetic diet: 30–40% fat, 15–20% protein, 40–45% CHO in the form of 3 meals and bedtime snack. Reasons for withdrawals: 1 CSII, 1 MDI after 4 weeks of therapy (reason not specified); 1 after 2 weeks and 1 after 2 months of both CSII and MDI Conflict of interest: Boehringher Mannheim Canada loaned the reflectance meters (for BG measurement). Funded by Diabetic Children's Foundation, Quebec and the Montreal Children's Hospital Research Institute

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Schmitz *et al.*, 1989[86] Denmark, single-centre, randomised crossover Duration: CSII 6 months, MDI 6 months	Treatment 1: CSII + soluble. Nordisk Treatment 2: MDI + regular (3–4 × soluble, 1 × NPH. Insuject pen+) Reason for CSII: not reported	Population: otherwise healthy insulin-dependent diabetics, aged 26–50 y. Diabetes in 'good control' before entrance to the study Inclusion criteria: diabetes duration ≥ 20 y, absence of severe diabetic complications, i.e. urinary albumin excretion rate ≤ 20 μg/min, normal blood pressure and serum creatinine and no proliferative retinopathy. Also, no medication other than insulin taken Participants: *N*: 10 End of study: 10 Female: 60% Mean age (±SD): 36.5 (±7.9) y, min. 26, max. 50 Diabetes duration mean (±SD): 23.7 (±2.9) y, min. 21, max. 30 *Baseline values: mean (±SD):* HbA_{1c}: 7.6 (±0.9)% Insulin: 0.6 (±0.11) IU/kg/day BMI: 23 kg/m^2 (calculated by reviewer) Weight: 71.6 (±17.2) kg Previous regimen: conventional treatment (no further details)	Assessment of outcomes: Method of recording hypos not recorded. Pts chose their preferential treatment at end of study; method not recorded	Allocation to treatment groups: pts randomised, but no indication of method of randomisation. Allocation concealment unclear Run-in/wash-out period: not reported Comparability of treatment groups: not reported Analysis: Means ± assume SD (not specified). Differences judged by Student's paired *t*-test. HbA_{1c} measured at 0 months and monthly and mean of values during last 3 months of each study period calculated. Weight and insulin dose calculated as mean of values during 3 months prior to study and during last 3 months of each study period Sample size/power calculation: not reported Generalisability: adults with long-term uncomplicated insulin-dependent diabetes. In good control before entrance to study Outcome measures: pts seen monthly in outpatient clinic. Very little information on hypos – only reports that 'no severe hypos occurred' Conflict of interest: none reported

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Tsui *et al.*, 2001[79] Canada, single-centre, RCT (parallel) Duration: 9 months	Treatment 1: CSII + lispro. Minimed 507 Treatment 2: MDI + lispro (also 1 × NPH). Reason for CSII: not reported	Population: adults aged 18–60 y with endocrine diagnosed Type I diabetes Inclusion criteria: diabetic for >2 y, onset of diabetes on or before 40 y, able to comply with treatment regimen, currently receiving two or more injections per day and interested and motivated to use CSII Exclusion: history of >2 severe hypos (coma, seizure, loss of consciousness) in the last year, haemoglobinopathy, insulin resistance, extreme obesity (BMI >35), severe late complications of diabetes, evidence of significant cardiovascular, hepatic disease, cancer, or cerebrovascular or severe peripheral vascular disease, alcohol or drug abuse, and/or participation in another clinical trial in past 4 weeks. Pregnant women or those likely to become pregnant. 1 excluded as too hirsute for pump adhesive to stick CSII participants: *N*: 13 End of study: 12 Female: 38% Mean age (±SD): 36 (±12) yrs Median age (min-max): 38 (19-57) y Diabetes duration mean (±SD): 17 (±10), min. 8, max. 37 y *Baseline values: mean (±SD):* HbA_{1c}: 7.73 (±0.6)% Insulin: 0.7 (±0.2) IU/day BMI: 27 (±4) kg/m^2 MDI participants: *N*: 14 End of study: 14 Female: 29% Mean age (±SD): 36 (±10) y Median age (min-max): 35 (21–58) y Diabetes duration mean (±SD): 15 (±9), min. 4, max. 28 yrs *Baseline values: mean (±SD):* HbA_{1c}: 8.16 (±0.7)% , 95% CI –0.94 to +0.09, $p >$ 0.10. Insulin: 0.7 (±0.1) IU/day BMI: 26 (±3) kg/m^2	Assessment of outcomes: Adverse events such as DKA recorded by patients. HbA_{1c} measured monthly. Hypoglycaemia: symptoms relieved by ingestion of glucose and/or BG ≤ 3 mmol/l; severe hypoglycaemia: requires assistance or in coma	Allocation to treatment groups: pts randomised after a 2-week screening period by sealed envelopes, prepared independently using computer-generated randomisation schedule Run-in/wash-out period: not reported Comparability of treatment groups: pts similar at baseline Difference in HbA_{1c}: not statistically significant Analysis: HbA_{1c} analysed by random-effects regression model; monthly hypos analysed by Poisson regression, baseline HbA_{1c} used as a covariate in model. Multivariate linear modelling used for subscale of DQOL and multivariate analysis of variance globally, each treatment group tested on its own and with age, sex, disease duration, baseline HbA_{1c}, total no. of hypos, and no. of severe hypos included separately and combined as covariates. 95% CI and *p*-values calculated. *p*-value of 0.05 used as significance, not adjusted for multiple comparisons. Pts analysed according to randomisation group Sample size/power calculation: 28 pts recruited but only 27 randomised – 1 was unsuitable. Statistical power of 86% to detect a clinically important overall difference of ±0.5 in HbA_{1c} between two treatment groups using two-tailed alpha of 0.05 Generalisability: adults aged 18–60 y with insulin-dependent diabetes Outcome measures: recorded adverse events such as DKA, HbA_{1c}, monthly Other: At end of 9 months study 12 MDI crossed to CSII and followed for 6 months. First 3 months excluded from analysis, but study done *post hoc* and potential for bias due to period effect Reasons for withdrawals: 1 CSII dropped out after 3 months (reason not given) Conflict of interest: 1 author received research support, honoraria and consultant fees from Eli Lilly, one author is a certified trainer from MiniMed. Study supported by research grant from Eli Lilly. Pumps and disposable supplies by MiniMed. Humalog and NPH by Eli Lilly

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Ziegler *et al.*, 1990[84] Germany, single-centre, RCT (parallel) Duration: 24 months	Treatment 1: CSII + soluble. Nordisk Infuser, Betatron I and II, autosyringe 8MP, or Promedos E1 Treatment 2: MDI + regular (2–4 injections daily: 2 injections (standard) = combinations of regular and NPH. 3 injections (increased fasting BG) = 2 × NPH + regular, and 2–3 × regular. 4 injections (irregular lifestyle) = 1–2 × NPH and 3–4 × regular). Reason for CSII: not reported	Population: C-peptide –ve, poorly controlled Type 1 diabetes pts with clinical symptoms of at least 1 chronic diabetic complication, who were unselected as to intelligence and education. Aged 18–60 y. Inclusion criteria: ≥ 18 y and ≤ 60 y; Type 1 diabetes; manifestation of diabetes <35 y of age; diabetes duration >1 y, stimulated serum C-peptide <0.3 ng/ml; HbA_1 ≥ 8.0% under conventional insulin therapy; at least 1 chronic diabetic complication (retinopathy, nephropathy or neuropathy) Exclusion: malignancies; previous cardiac infarction; endocrine disorders; primary dyslipoproteinaemia; amaurosis; hypoglycaemic unawareness; serum creatinine >3 mg/dl; psychosis; chronic alcohol abuse; informed consent refused CSII participants: *N*: 49 End of study: 36 Female: 38.8% Median age (min.–max.): 32 (18–54) y Diabetes duration median (min.–max.): 18.0 (3–44) y *Baseline values: mean (±SD):* HbA_1: 9.8% HbA_1 1 month prior to randomisation 10.6 (±2.2) Insulin: 49 (±17) IU/day BMI: 23 kg/m^2 MDI participants: *N*: 47 End of study: 37 Female: 51.1% Median age (min.–max.): 32 (18–55) y Diabetes duration median (min.–max.): 14.8 (3–42) y *Baseline values: mean (±SD):* HbA_1: 9.5%, p = ns HbA_1 1 month prior to randomisation 10.2 (±1.6), p = ns Insulin: 48 (±14) IU/day, p = ns BMI: 22.1 kg/m^2 Previous regimen: conventional insulin therapy, defined as daily injections of long-acting or fixed combinations of intermediate- and short-acting insulin at given doses without regular BG self-monitoring and self-adjustment of therapy	Assessment of outcomes: systematic assessment of hypo- and hyperglycaemic episodes based on pts' daily records and on inquiries at each monthly clinic visit. Mild hypo = BG <50 mg/dl without symptoms, or the appearance of typical symptoms that could be self-managed. Severe hypo = events requiring assistance by other persons, or coma when glucose or glucagon injections were required. Hyperglycaemic ketosis = BG >200 mg/dl and positive urine acetone. Ketoacidosis = venous blood pH <7.3 at hospital admission. HbA_1 determined monthly	Allocation to treatment groups: pts randomised, but no indication of method of randomisation. Allocation concealment unclear Run-in/wash-out period: for 1 month prior to randomisation, all pts were put on intensified conventional injection therapy. Also 1-week teaching programme Comparability of treatment groups: clinical characteristics at randomisation given for both groups. Similar age, BMI, duration of diabetes, insulin dose and HbA_1. Analysis: method states data are mean ± SD, but graphs are SE. Adverse effects are mean (range). Baseline data are median (min.–max.). Student's *t*-test (2-sided) for independent groups. Fisher's exact probability test (2-sided) to analyse qualitative variables. Reviewer has extrapolated graph for all HbA_1 values. Where pts changed treatment group, they were retained in the originally assigned group for statistical analysis Sample size/power calculation: not reported Generalisability: poorly controlled Type 1 pts with clinical symptoms of at least 1 chronic diabetic complication Outcome measures: HbA_1 examined at baseline and monthly thereafter. No. of adverse events calculated for each pt per 6 months. Total no. of severe hypo and DKA per 24 months extrapolated to 100 y (no events/100 y). Reasons for withdrawal: participation offered to 208, 108 refused due to study protocol or distance to centre. 4 excluded at end of recruitment phase as did not meet criteria. Withdrawals: adverse effects (not specified) (1 CSII); refusal to continue on therapy (1 CSII, 1 MDI); burden of study (e.g. regular BG self-monitoring) (6 CSII, 5 MDI); reasons unrelated to study (e.g. moved house) (5 CSII, 4 MDI) Other: 11 pts (4 CSII, 7 MDI) changed to other treatment. In both groups changers equally distributed throughout study period. 1 pt with autonomic neuropathy died from sudden death without evidence of hypo of DKA – assumed they are included in the group of withdrawals 'unrelated to study' Conflict of interest: supported by grants from Deutsche Forschungsgemeinschaft, Bonn FRG (SFB 113), the Bundesminister für Gesundheit and the Minister für Wissenschaft und Forschung, NRW

ANOVA, analysis of variance.

Appendix 7

Summary of methodology: pregnancy

Study	Interventions	Subjects	Outcome measures	Methodology
Burkart *et al.*, 1988[95] Germany, single-centre, RCT (parallel) Duration: 9 months (Also compared with a conventional treatment group – data not extracted)	Treatment 1: CSII + soluble. 'Open loop infusion system' – no further details Treatment 2: MDI + regular. Described as 'intensified insulin therapy' by 'conventional syringe technique'. Reason for CSII: not reported	Population: pregnant women with Type 1 diabetes who attended the hospital no later than the first trimester Exclusion criteria: Type 2 and gestational diabetes, patients who attended the hospital later than in the first trimester CSII participants: *N*: 48 End of study: 48 Female: 100% Mean age (±SD): 28.4 (±5.3) y Diabetes duration mean (±SD): 11.7 (±7.4) y MDI participants: *N*: 41 End of study: 41 Female: 100% Mean age (±SD): 28.7 (±4.7) y Diabetes duration mean (±SD): 9.9 (±8.9) y *Baseline values*: not given. States that patients selected in the CSII or MDI group had normal mean glucose and HbA_1 <7.5% at least from the end of the first trimester on. Previous regimen: not stated for either group	Assessment of outcomes: Data presented according to severity of maternal diabetes (White's classification). Mean birthweight and gestational age for each group estimated from the means reported for each of White's classification. Fetal morbidity: healthy newborns – i.v. glucose <48 h, 1 minor symptom; minor symptoms – i.v. glucose >48 h, <5 days, one or more of polycythaemia, hyperbilirubinaemia, hypocalcaemia, light respiratory distress syndrome, birthweight >90th percentile; major symptoms – 2 or more symptoms of birthweight >95th percentile, cardiomyopathy, hepatosplenomegaly, severe respiratory distress syndrome, spasms, i.v. glucose usually >5 days. Premature - delivery before end of gestational week 37	Allocation to treatment groups: patients 'randomly selected to each of the procedures'. No further details. No details of allocation concealment Run-in-wash out period: not applicable Comparability of treatment groups: age and duration of diabetes similar. CSII had more class D ($p < 0.05$) and less class B ($p < 0.005$) than MDI (White's classification). Similarity of baseline HbA_1 and other variables not reported Analysis: States 'routine statistical methods' used. No further details. Units for birthweight: not given Sample size/power calculation: not reported Generalisability: pregnant women with Type 1 diabetes Outcome measures: pregnancy complications, fetal outcome. Blood glucose, HbA_1 and insulin dose not reported Conflict of interest: none stated

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Carta *et al.*, 1986[94] Italy, single-centre, RCT (parallel) Duration: 9 months	Treatment 1: CSII + soluble. Microjet MC 20 Treatment 2: MDI + regular (Actrapid × 4 only). Reason for CSII: not reported	Population: pregnant diabetic women – classified as Type 1 (15) and Type 2 (14) before pregnancy Criteria: not reported Type 1 CSII participants: *N*: 8 End of study: 8 Female: 100% Mean age (min.–max.): 24.6 (17-37) y *Baseline values: mean (±SD):* HbA_1: 8.75% Insulin: 31.5 IU/day Type 1 MDI participants: *N*: 7 End of study: 7 Female: 100% Mean age (min.–max.): 25.9 (19–32) y *Baseline values: mean (±SD):* HbA_1: 9.1%, p = ns Insulin: 27.8 IU/day, p = ns Type 1 previous regimen: 13 previously on conventional, 2 CSII started 3–4 months before conception Type 2 CSII participants: *N*: 6 End of study: 6 Female: 100% Mean age (min.–max.): 31.3 (25-39) y *Baseline values: mean (±SD):* HbA_1: 8.1% Type 2 MDI participants: *N*: 8 End of study: 8 Female: 100% Mean age (min.–max.): 29.4 (20–46) y *Baseline values: mean (±SD):* HbA_1: 8.2%, p = ns Type 2 previous regimen: 4 taking oral hypoglycaemics before pregnancy, 10 treated by dietary measures only	Assessment of outcomes: HbA_1 measured each trimester	Allocation to treatment groups: no indication of method of randomisation Run-in/wash-out period: not applicable Comparability of treatment groups: similar age. Baseline HbA_1 not significantly different for CSII vs MDI arms in both Type 1 and Type 2. Baseline insulin requirements not significantly different in Type 1, but not presented for Type 2 Analysis: significance of difference between results assessed by means of 2-tailed Students *t*-test for unpaired data. Baseline HbA_1 and HbA_1 and some insulin values extracted from figure by reviewer. Individual patient baseline data presented, means calculated by reviewer Sample size/power calculation: not reported Generalisability: Pregnant women with Type 1 and 2 diabetes (analysed separately) who had diabetes before pregnancy Outcome measures: insulin requirement, perinatal outcome and glycaemic control. Weekly visits to outpatients where insulin dose adjusted Conflict of interest: supported by Grant of Regione Piemonte

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Coustan *et al.*, 1986[93] USA, single-centre, RCT (parallel) Duration: 9 months	Treatment 1: CSII + soluble. Autosyringe AS-2C, 6C, 6C(U100); Lilly CPI-9100 Treatment 2: MDI + regular (2–4 intermediate or rapid-acting insulin) Reason for CSII: not reported	Population: insulin-dependent diabetes. Women – pregnant (15) or planning pregnancy (7). 21 women with 22 pregnancies Criteria: not specified CSII participants: *N*: 11 End of study: 11 Female: 100% Mean age (±SD): 29 (±3) yrs, min. 26, max. 32 *Baseline values: mean (±SD):* HbA_1: 8.6 (±1.7) % Insulin: 0.9 (±0.42) IU/day % obese (>20% over ideal body weight) = 2 MDI participants: *N*: 11 End of study: 11 Female: 100% Mean age (±SD): 28 (±4) y, min. 24, max. 32 *Baseline values: mean (±SD):* HbA_1: 9.1 (±1.5) % , p = ns Insulin: 1.05 (±0.38) IU/day, $p = 0.381$ % obese (>20% over ideal body weight) = 2 Previous regimen: at least 2 daily injections of a mixture of rapid- and intermediate-acting insulins (100%)	Assessment of outcomes: subjective hypos recorded in diary: mild (responded to self-administered snack), moderate (requiring another person's assistance), severe (required glucagon or intravenous glucose, usually in emergency room setting). HbA_1 measured at weekly clinic visits. Pts switched to continuous intravenous glucose and insulin infusion when admitted to labour, elective labour or Caesarean section	Allocation to treatment groups: pts randomised using sealed envelopes. The subject studied during 2 pregnancies was randomised independently each time and treated with CSII during one pregnancy and MDI during other Run-in/wash-out period: 48 h on existing regimen as inpatient for baseline data. After randomisation remained in inpatient for up to 7 days to optimise control on assigned treatment Comparability of treatment groups: table of baseline characteristics shows groups to be comparable, reports no significant differences. Analysis: means and SD presented. Student's *t*-test (paired and unpaired). Wilcoxon non-paired rank-sum test. HbA_1 month 2 data extracted from figure Sample size/power calculation: sample size 22 pregnancies allowing detection of a difference in average circulating glucose levels between the two groups of 17.9 mg/dl at 0.05 level of significance and 80% power, assuming an SD of 15 mg/dl. Groups too small for statistically significant difference in moderate and severe hypos to be attained – with a power of 80% if 50% in one group and 90% in the other group reported symptoms 29 patients would be required in each group Generalisability: pregnant insulin dependent women Outcome measures: HbA_1 reported. Hypos recorded by patients. Conflict of interest: study supported by grant 6-260 from the March of Dimes Birth Defects Foundation, grants RR125 and AM20495 from the NIH and grants from the Juvenile Diabetes Foundation, American Diabetes Association and the Diabetes Association of Greater Fall River, Massachusetts. Insulin provided by Squibb-Novo

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Nosari *et al.*, 1993[92] Italy, single-centre, RCT (parallel) Duration: 9 months	Treatment 1: CSII + soluble. Microjet 20 or Dahedi BV Treatment 2: MDI + regular (3 × soluble, 1 × intermediate) Reason for CSII: referred for intensive treatment because pregnant (28) or planning to become pregnant (4)	Population: classified with Type 1 diabetes before pregnancy. 31 women with 32 pregnancies (16 in each arm) included. Criteria: not reported CSII participants: *N*: 16 End of study: 16 Mean age (±SD): 25.5 (±7.2) y Diabetes duration: min. 3.0, max. 16.0 y *Baseline values: mean (±SD):* BMI: 21.8 (±1.6) kg/m^2 MDI participants: *N*: 16 End of study: 16 Mean age (±SD): 27.3 (±12) y Diabetes duration: min. 3.0, max. 16.0 y *Baseline values: mean (±SD):* BMI: 21.6 (±2.4) kg/m^2 Previous regimen: one started CSII 2–4 months prior to conception, 15 had at least 2 daily injections	Assessment of outcomes: hypos classified as severe when characterised by coma or seizure or requiring hospitalisation or intravenous glucose or glucagon	Allocation to treatment groups: randomly allocated using sealed envelopes. No further information reported Run-in/wash-out period: not applicable Comparability of treatment groups: similar age and BMI, but baseline HbA_{1c}, mean insulin dose, duration of pregnancy of randomisation not reported Analysis: student's *t*-test or χ^2 analysis Sample size/power calculation: not reported Generalisability: pregnant women with Type 1 diabetes Outcome measures: HbA_{1c} reported. Birthweight assessed in relation to gestational age, according to the national nomogram of intrauterine fetal growth Other: 28 women were pregnant when referred, but duration of pregnancy when randomised not reported Conflict of interest: none stated

Appendix 8

Summary of methodology: adolescents

Study	Interventions	Subjects	Outcome measures	Methodology
Schiffrin *et al.*, 1984[97] Canada, single-centre, randomised crossover [3 arms – MDI, CSII, or CSII at night with preprandial short-acting insulin during the day (CSII + MDI)] Duration: CSII 4 months, MDI 4 months, CSII+MDI 4 months	Treatment 1: CSII + soluble. Mill Hill 2703 Treatment 2: MDI + regular (3–4 × soluble, 1 × NPH). Treatment 3: CSII + MDI. CSII overnight with preprandial injections of short-acting insulin during the day. Pump used for prebreakfast bolus Other interventions: pts followed the Canadian Diabetes Association Food choices diet system Reason for CSII: not reported	Population: Type 1 pts aged 13–20 y. Previously had failed to respond to twice-daily injections with home BG monitoring regime. Pts had not been on intensive therapy in the past and were not significantly obese Criteria: not reported Participants: *N*: 24 End of study: 20 Age (min.–max.): 13–20 y Diabetes duration, mean: 9 y *Baseline values: mean (±SD):* HbA_1: 13 (±1)% Insulin: 64 (±14) IU/day Previous regimen: twice-daily injections	Assessment of outcomes: once-monthly fasting blood samples obtained for HbA_1 Severe hypos – required glucagon	Allocation to treatment groups: pts were said to be randomised, but no indication of randomisation method. No indication of allocation concealment Run-in/wash-out period: none Comparability of treatment groups: not reported Analysis: treatment comparisons were done by 2-way ANOVA followed by the Newman–Keuls test and Student's *t*-test for paired data. ITT analysis not carried out. HbA_1 data presented in figure only. HbA_1 data extracted from figure by reviewer Sample size/power calculation: not reported Generalisability: adolescents with Type 1 diabetes Outcome measures: HbA_1 reported Reasons for withdrawal: 1 CSII after 3 months and 1 MDI after 1 week (reason not specified); refused to cross over from CSII (n = 2) Conflict of interest: grant from the Juvenile Diabetes Foundation and the Canadian Diabetes Association

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Tamborlane *et al.*, 1989[96] USA, single-centre, randomised crossover Duration: CSII 6 months, MDI 6 months	Treatment 1: CSII + soluble. Pump type not reported Treatment 2: MDI + regular. Insulin type and frequency not reported Reason for CSII: not reported	Population: non-obese adolescents with Type 1 diabetes, aged 11–20 y, had diabetes for 2–12 y. Heights were within range of normal with one exception. One subject had attained full pubertal development Inclusion criteria: pts were drawn from the Yale Children's Diabetes Clinic and were included if they were deemed to be able to carry out the tasks and responsibilities demanded by the study protocol Exclusion criteria: pts taking more than 2 daily insulin injections or performing frequent self-blood glucose measurements prior to enrolment Participants: *N*: 10 Female: 50% Age (min.–max.): 11–20 y Diabetes duration (min.–max.): 2–12 y Baseline values: mean (±SD): HbA_1: 12.2 (±4.1)% Insulin: 1.1 (±0.32) U/day Previous regimen: conventional insulin treatment of not more than 2 injections/day	Not reported	Allocation to treatment groups: randomly assigned to CSII or MDI after baseline assessments obtained and pts admitted to Yale Children's Clinical Research Centre. No further details. Allocation concealment not reported Run-in/wash-out period: pts remained in hospital 5–7 days to optimise control on assigned treatment regimen. Pts readmitted to research centre to crossover treatments. No wash-out period or analysis of treatment effects Comparability of treatment groups: not reported Analysis: data presented as mean (SE). SE converted to SD by reviewer. Analysis of variance used Sample size/power calculation: not reported Generalisability: non-obese adolescents who were previously taking ≤ 2 daily insulin injections and not performing frequent blood glucose monitoring, therefore likely to be poorly controlled Outcome measures: HbA_1 and daily insulin dose reported Dropouts/withdrawals: not reported Conflict of interest: supported by grants from the National Institutes of Health and the Juvenile Diabetes Foundation International

Appendix 9

Summary of methodology: analogue versus soluble insulin

Study	Interventions	Subjects	Outcome measures	Methodology
Bode *et al.*, 2002[113] USA, multi-centre, RCT (parallel) Duration: 4 months	Treatment 1: CSII + lispro Treatment 2: CSII + buffered regular Treatment 3: CSII + aspart Minimed/ Disetronic 506 or 507 Reason for CSII: not reported	Population: adults aged 18–71 y with Type 1 diabetes >12 months and treated with CSII continuously for previous 3 months Exclusion criteria: impaired hepatic, renal, or cardiac function or recurrent hypoglycaemia. Women pregnant, breast-feeding, or not using contraception Lispro participants: *N*: 28 End of study: 27 Female: 68% Mean age (±SD): 39.9 (±11.1) y *Baseline values: mean (±SD):* HbA_{1c}: 7.3 (±0.7)% Insulin: 0.5 (±0.19) U/kg BMI: 26.3 (±3.2) kg/m^2 Buffered regular participants: *N*: 59 End of study: 50 Female: 68% Mean age (±SD): 43.1 (±9.4) y *Baseline values: mean (±SD):* HbA_{1c}: 7.5 (±0.8)%. Insulin: 0.6 (±0.18) U/kg BMI: 25.9 (±3.8) kg/m^2 Aspart participants: *N*: 59 End of study: 55 Female: 61% Mean age (±SD): 42.3 (±12) y *Baseline values: mean (±SD):* HbA_{1c}: 7.3 (±0.7)%. Insulin: 0.7 (±0.76) U/kg BMI: 26.7 (±3.8) kg/m^2	Assessment of outcomes: HbA_{1c} taken at week 16. Total daily insulin dose for week before baseline and last week of treatment. Hypo symptoms and adverse events recorded in diary. Minor hypo = symptoms (palpitations, tiredness, sweating, strong hunger, dizziness, tremor, etc.) confirmed by BG <50 mg/dl and able to deal with it on own. Major hypo = BG <50 mg/dl and severe central nervous system dysfunction preventing them treating themselves or administration of parenteral glucose or glucagon	Allocation to treatment groups: randomly assigned after run-in (2:2:1) to lowest available randomisation number to aspart, lispro or regular. Randomisation code provided by Novo Nordisk to ensure that investigator and subject were blinded at point of randomisation Run-in/wash-out period: 4-week run-in with buffered regular. Dose adjustment period during 4 weeks after randomisation. Comparability of treatment groups: patients appear similar in age, sex, BMI, HbA_{1c}, insulin dose but statistics not presented Analysis: between-treatment comparisons, except insulin used, made with ANCOVA model with treatment and centre as fixed effects and corresponding baseline measurement as covariate. Last observation carried forward used in analysis of HbA_{1c}, weight and lipid profile. Sample size/power calculation: not reported. Generalisability: adults with Type 1 diabetes with at least 3 months CSII experience Outcome measures: final HbA_{1c} measures and SD/SEM/CI not presented, changes from baseline only. Rate of hypos = mean number (SD) of hypos reported by subject per 30 days for all subjects in the treatment group. 'All reported hypos' = regardless of BG value. Data extracted for maintenance period only (entire trial and dose-adjustment period values also reported) Reasons for withdrawal: withdrawal of consent, lack of compliance, loss to follow-up, ineffective therapy (numbers for each reason not specified): lispro (1), buffered regular (9), aspart (3); adverse event – herpes zoster (1 aspart). Conflict of interest: sponsored by Novo Nordisk Pharmaceuticals, Princeton, NJ

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Melki *et al.*, 1998[116] France, multi-centre, randomised crossover Duration: soluble 3 months, lispro 3 months	Treatment 1: CSII + soluble (Actrapid) Treatment 2: CSII + lispro (Humalog) Minimed 506 Reason for CSII: not reported	Population: adults with Type 1 diabetes aged 18–60 y, treated by CSII with regular insulin for at least 1 y before enrolment Criteria: HbA_{1c} <8.5%, negative C-peptide response, anti-insulin antibodies <70%. None had untreated retinopathy, impaired renal function, gastric neuropathy, BMI >30, daily insulin dose >2 IU/kg, history of hypo unawareness or severe disease that could interfere with study Participants: *N*: 39 End of study: 38 Female: 43.6% Mean age (±SD): 39.4 (±9.4) y Diabetes duration mean (±SD): 22.5 (±10) y *Baseline values: mean (±SD):* HbA_{1c}: 7.84 (±0.75)% (HbA_{1c} soluble 7.74 ±1.23; lispro 7.97 ±0.8) Insulin: 0.57 (±0.12) IU/day BMI: 24.4 (±2.5) kg/m^2	Assessment of outcomes: hypos, technical or metabolic incidents, e.g. ketonuria, recorded in notebook. Number of hypos defined by BG < 3.0 mmol/l or very low BG < 2.0 mmol/l noted at monthly visits. Satisfaction questionnaire at end of study. Last 30 days of 1st period analysed	Allocation to treatment groups: randomised after run-in. No further details Run-in/wash-out period: 4 week run-in of CSII + regular prior to randomisation. Analysis of HbA_{1c} performed only during first period due to a carryover effect. Analysis of hypos restricted to last 30 days of first period to avoid confusion due to carryover effect Comparability of treatment groups: HbA_{1c} reported for each group at baseline, no further details. Possibility of bias as second period ignored for analysis of hypos and HbA_{1c} Analysis: not ITT analysis. Means (SE) reported. SD calculated by reviewer. All tests 2-tailed. Comparisons for baseline characteristics used χ^2 or Fisher's exact test. ANOVA for continuous variables applied for crossover study with period, treatment group and interaction factors. In case of significant interaction or carryover effect, only the first period was used in comparisons. Categorical data compared by sign test between periods and between treatment groups. Study conducted in 5 centres, intercentre variability not assessed Sample size/power calculation: not reported Generalisability: adults with Type 1 diabetes who have used a pump for at least 1 year Reasons for withdrawal: personal reasons and lack of protocol compliance (n = 1) Conflict of interest: study supported by Lilly France

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Raskin *et al.*, 2001[117] USA, multicentre, randomised crossover Duration: lispro 3 months, soluble 3 months	Treatment 1:CSII + lispro (Humalog) Treatment 2: CSII + soluble (Velosulin) Minimed 504, 504-S, 506 or 507 Reason for CSII: not reported	Population: Type 1 diabetes age 13–60 y who had achieved acceptable compliance with insulin pumps therapy and a nutritional regimen and had been treated with CSII for at least 6 months Exclusion criteria: total glycated haemoglobin values or HbA_{1c} >2.0 times upper limit of normal range, clinically significant renal, hepatic or cardiac disease, cancer, drug or alcohol abuse, insulin allergy, recurrent severe hypoglycaemia, anaemia, life expectancy <3 y, lactating, pregnant or intending to become pregnant or require dilution of insulin in pump. 3 pts discontinued before randomisation (2 for personal reasons, 1 failed to meet criteria) *N*: 59 End of study: 58. Sequence lispro then regular insulin: End of study: 28 Female: 42.9% Mean age (±SD): 40.5 (±8.7) y Diabetes duration mean (±SD): 18.8 (±7.6) y *Baseline values: mean (±SD):* HbA_{1c}: 7.9 (±1.1)% Weight: 78.3 (±17.9) kg. Sequence regular then insulin lispro: End of study: 30 Female: 53.3% Mean age (±SD): 37.8 (±9.7) y Diabetes duration mean (±SD): 17.4 (±8.5) y *Baseline values: mean (±SD):* HbA_{1c}: 7.6 (±0.8)%, $p = 0.234$. Weight: 77.3 (±16.7) kg Previous regimen: 2–4 weeks run-in with CSII + regular insulin	Assessment of outcomes: hypos recorded in diary: pt believed (or other person observed) they were experiencing at least one sign or symptom associated with hypo, or BG <3.0 mmol/l. Hyper = 2 or more BG >13.8 mmol/l in 2–4 h not responding to insulin boluses or otherwise unexplained	Allocation to treatment groups: randomised after run-in. States that 'randomisation was such that there would be approximately equal numbers of pts in each treatment sequence at each investigative site'. No further details given Run-in/wash-out period: 2–4 week run-in with regular insulin. No wash-out period. No carryover or investigator effects discovered by ANOVA, therefore data from treatment periods combined Comparability of treatment groups: data presented for both groups. Similar in proportion of females, age, weight and duration of diabetes, but statistical analysis not presented. No significant difference in HbA_{1c} Analysis: states that ITT analysis performed. 2-tailed tests, significance level 0.05. ANOVA used to examine for carryover, investigator or treatment effects. Multicentre: investigator effects assessed by ANOVA and none identified Sample size/power calculation: not reported Generalisability: Type 1 diabetes with acceptable compliance and at least 6 months with CSII Outcome measures: HbA_{1c} measured at end of each treatment period. Insulin doses used on day before each clinic visit (every 6 weeks) recorded in diary Reasons for withdrawal: personal reasons ($n = 1$). Conflict of interest: Sponsored by Eli Lilly and Company

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Renner *et al.*, 1999[114] Germany, multicentre, randomised crossover Duration: lispro 4 months, soluble 4 months	Treatment 1:CSII + lispro (Humalog). Minimed 506 Treatment 2: CSII + soluble (Huminsulin). Disetronic Htron-100 Reason for CSII: not reported	Population: Type 1 diabetes >2 y and treatment with CSII for at least 6 months Exclusion criteria: known insulin allergy, cardiovascular or cerebrovascular symptoms of athersclerosis, cancer, renal or hepatic failure, signs of drug abuse, life-threatening disease, pregnant, lactating or planning pregnancy Participants: *N*: 113 End of study: 113 Female: 46.9% Mean age (±SD): 37.1 (±11.6) y Diabetes duration mean (±SD): 19.1 (±9.2) y *Baseline values: mean (±SD):* HbA_{1c}: 7.24 (±1)% Insulin: 83.4 IU/day (calculated by reviewer) BMI: 24.7 (±1.1) kg/m^2 Previous regimen: CSII, duration 5.3 ±3.9 y	Assessment of outcomes: hypo: <3.5 mmol/l and/or symptoms, recorded in diary. Diabetes Treatment Satisfaction Questionnaire completed at beginning and end of each treatment arm, maximum score 48	Allocation to treatment groups: randomised after run-in. No further details Run-in/wash-out period: 4 weeks run-in with CSII + regular insulin. No wash-out. Treatment order effect not reported Comparability of treatment groups: not reported Analysis: ANOVA with pts, treatment and period terms. Friedman's rank-sum test if not normally distributed (HbA_{1c}, patient preference). Frequency of hypos and catheter occlusions used McNemar's test. Insulin dose calculated by reviewer from means of 7 reported meal-related basal and bolus values. Total baseline and 4-month insulin calculated by reviewer Sample size/power calculation: not reported Generalisability: well-controlled Type 1 diabetes with at least 6 months CSII use Outcome measures: Diabetes Treatment Satisfaction Questionnaire reported to be validated Other: total insulin dose calculated by reviewer from basal breakfast, lunch and dinner; bolus breakfast lunch and dinner; and snacks Conflict of interest: 2 authors hold stock in and/or received honoraria from MiniMed and/or Eli Lilly. A 3rd author received grant and research support from Eli Lilly

continued

Study	Interventions	Subjects	Outcome measures	Methodology
Schmauss *et al.*, 1998[115] Germany, single-centre, randomised crossover Duration: lispro 3 months, soluble 3 months	Treatment 1: CSII + lispro (Humalog) Treatment 2: CSII + soluble (Humulin) Disetronic Htron V100 Reason for CSII: not reported	Population: well-controlled Type 1 diabetes, use of intensified insulin therapy at least 2 y, with CSII for at least 6 months prior to study. Age 18–65 y. Exclusion criteria: known allergy to insulin, severe complications of diabetes, inadequate metabolic control (HbA_{1c} >10%), life-threatening disease, drug abuse, women pregnant or planning pregnancy Participants: *N*: 11 End of study: 11 Female: 54.5% Mean age (±SD): 30 (±8.3) y Diabetes duration mean (±SD): 14 (±3.3) y *Baseline values: mean (±SD):* Lispro HbA_{1c}: 6.3 (±0.7)% Soluble HbA_{1c}: 6.7 (±1.3)%, p = ns BMI: 24 (±3.3) kg/m^2	Assessment of outcomes: hypos and adverse events recorded at clinic visits. Hypos = BG <3.5 mmol/l	Allocation to treatment groups: randomised after run-in, no further details Run-in/wash-out period: run-in period 4 weeks. No wash-out Treatment order effect: not discussed Comparability of treatment groups: HbA_{1c} at randomisation given for each group, no further details Analysis: ANOVA with repeated measures applied to evaluate the influence of group and time on continuous variables. Wilcoxon rank test for hypos. Mean (SEM) presented. SD calculated by reviewer. HbA_{1c} at end of periods 1 and 2 for each treatment averaged by reviewer Sample size/power calculation: not reported Generalisability: adults with well-controlled Type 1 diabetes, with at least 6 months CSII use and no severe diabetic complications Outcome measures: HbA_{1c} recorded at end of run-in, crossover and end of study Conflict of interest: supported by an unrestricted research grant from Eli Lilly, Germany
Zinman *et al.*, 1997[118] Canada, single-centre, randomised crossover Duration: lispro 3 months, soluble 3 months	Treatment 1: CSII + lispro Treatment 2: CSII + soluble (Humulin) Disetronic Htron V100. Reason for CSII: not reported	Population: adults with Type 1 diabetes and at least 3 months with CSII. None had significant endogenous insulin secretion as assessed by the measurement of fasting C-peptide (<0.02 nmol/l) Exclusion criteria: severe retinopathy or neuropathy, >1 severe past year. Mild to moderate retinopathy was present in 16 (53%), mild to moderate neuropathy in 12 (40%) Participants: *N*: 30 End of study: 30 Female: 56.7% Mean age (±SD): 35.1 (±8.2) y, min. 26, max. 51 Diabetes duration mean (±SD): 17.5 (±8.8) y, min. 6, max. 44 *Baseline values: mean (±SD):* HbA_{1c}: 8.03 (±0.71)% BMI: 24.8 (±2.7) kg/m^2 Weight: 72.7 (±9.9) kg Previous regimen: 14 on CSII >3 months. Intensified insulin therapy with pen (7) or syringe (9) before switching to CSII + regular insulin 3 months prior to randomisation	Assessment of outcomes: insulin dose and hypos recorded in diary. HbA_{1c} measured monthly. Hypo = BG <3 mmol/l or symptoms. Before randomisation frequency 12.7 (8.8) episodes/30 days, or if confirmed by BG 8.4 (7.1)/30 days. Severe hypos as defined by DCCT	Allocation to treatment groups: double-blind. Randomised after run-in Run-in/wash-out period: 16 pts on MDI switched to CSII + regular 3 months before randomisation. All pts received CSII + regular for 1 month run-in Comparability of treatment groups: not reported Analysis: ANOVA used models with treatment sequence (study group), period and treatment terms. Ordinal variables with Wilcoxon's rank-sum test (treatment sequence, period and treatment term evaluated in three separate analyses). Categorical variables used χ^2, McNemar's and/or Fisher's exact tests Sample size/power calculation: not reported Generalisability: adults with Type 1 diabetes previously on intensive insulin therapy or CSII Conflict of interest: supported by an unrestricted research grant from Eli Lilly Canada

Appendix 10

Summary of results: adults with Type 1 diabetes

Study	Treatment	Glycated Hb	Insulin dose	Weight	Lipids	Patient preference/quality of life	Adverse events
Bak *et al.*, 1987[87] Randomised crossover Duration: CSII 6 months, MDI 6 months *N*: 20 End of study: 16	CSII + soluble	Glycated Hb: not reported Blood glucose: Month: 6 Mean: 7.7 SD: 0.7	Month: 6 Mean: 46.6 U/day SD: 10	Month: 6 Mean: 76.6 kg SD: 9.6	Not reported	No. preferring: not reported Freedom from injections: 44% 75% discomforted by butterfly needle (on CSII), 56% discomforted by infuser itself at home, 21% discomforted by infuser at work QoL: not reported	Moderate hypo: 2.3 (% of BG values below 4 mmol/l) Severe hypo: 1 (requiring hospital treatment) DKA: 0
	MDI + regular	Blood Glucose: Month: 6 Mean: 7.9 SD: 0.7 Significance: p = ns	Month: 6 Mean: 51.9 U/day SD: 12.9 Significance: $p < 0.05$	Month: 6 Mean: 74.8 kg SD: 9.7 Significance: $p < 0.01$	Not reported	Preferring: 80% wanted to continue with MDI 95% found pen easy to handle, 30% high frequency of injections disadvantage Of total: independence of fixed mealtimes an advantage with MDI and CSII by 85% QoL: not reported	Moderate hypo: 4.1 (% of BG values below 4 mmol/l), $p < 0.02$ Severe hypo: 0 DKA: 0
Bode *et al.*, 1996[81] Non-randomised crossover Duration: MDI min. of 12 months. CSII mean 37 months. *N*: 55	CSII + soluble	HbA_{1c} reported Month: 12 Mean: 7.4% SD: 1.2 Month: 24 Mean: 7.7% SD: 1.7 Month: 36 Mean: 7.4% SD: 1.7 Month: 48 Mean: 7.4% SD: 1.2 Note: $N = 55$ (12 months); 41 (24 months); 26 (36 months); 20 (48 months)	Month: 12 Mean: 36.4 U/day SD: 12.1 Month: 24 Mean: 39.6 U/day SD: 14.4 Month: 36 Mean: 37.7 U/day SD: 13.1 Month: 48 Mean: 37.8 U/day SD: 14.2 Note: $N = 54$ (12 months); 38 (24 months); 25 (36 months); 19 (48 months)	Month: 12 Mean: 68.1 kg SD: 14.1 Month: 24 Mean: 69.7 kg SD: 15.2 Month: 36 Mean: 70.0 kg SD: 14.6 Month: 48 Mean: 68 kg SD: 15.2 Note: $N = 55$ (12 months); 41 (24 months); 25 (36 months); 19 (48 months)	Not reported	No. preferring: not reported QoL: not reported	Severe hypo: 12 Note: hypo events per 100 patient years (n), significance from MDI: 12 months 22 (55), $p < 0.0001$; 24 months 26 (50), $p < 0.01$; 36 months 39 (33), $p < 0.0001$; 48 months 36 (25), $p < 0.01$. Of 25 pts with $HbA_{1c} \geq 8.0\%$, rate of severe hypos declined significantly, from 84 events per 100 patient years at baseline (MDI) to 8 events in year 1 ($p < 0.0001$). The 30 pts with baseline HbA_{1c} <8.0% also experienced a decline, from 183 to 33 severe hypos per 100 patient years ($p = 0.0005$). DKA rates were not significantly different between MDI and CSII phases (14.6 vs 7.2 events per 100 patient years, respectively)

continued

Study	Treatment	Glycated Hb	Insulin dose	Weight	Lipids	Patient preference/quality of life	Adverse events
	MDI + regular	HbA_{1c} reported Month: 12 Mean: 7.7% SD: 1.5 Significance: p = ns Note: a significant improvement in mean HbA_{1c} from baseline (MDI) to year 1 was seen with patients who had unacceptable glycaemic control at baseline (MDI), defined as $HbA_{1c} \geq$ 8.0% (8.9 ± 0.8% vs 8.1 ± 1.0%, p = 0.0004). In contrast, the 30 patients who had better glycaemic control at baseline, defined as HbA_{1c} <8.0% showed no significant difference in control from baseline to year 1 (6.7 ± 1.1% vs 6.8 ± 1.2%, p = ns)	Month: 12 Mean: 42.9 U/day SD: 17.9 Significance: p = ns	Month: 12 Mean: 67.4 kg SD: 14.4 Significance: p = ns	Not reported	No. preferring: not reported QoL: not reported	Severe hypo: 76 MDI: hypo events per 100 patient years (n):138 (55)

continued

Study	Treatment	Glycated Hb	Insulin dose	Weight	Lipids	Patient preference/quality of life	Adverse events
Brinchmann-Hansen *et al.*, 1988[76,78] RCT (parallel) Duration: CSII mean 40 months (24–60). MDI mean 41 months (21–47) CSII *N*: 15 MDI *N*: 15	CSII + soluble	HbA_1 reported Month: 3 Mean: 8.9% Month: 6 Mean: 9.2% Month: 12 Mean: 8.5% Month: 24 Mean: 8.7% SD: 1.16 Month: 41 Mean: 9.1%	Month: 24 Mean: 0.68 U/kg SD: 0.19 (SEM 0.05)	Month: 24 Mean: 70.5 kg SD: 8.9 (SEM 2.3)	Not reported	No. preferring: not reported QoL: not reported	Hypoglycaemia mean (SEM) values: (% of home BG <2.5 mmol/l): at randomisation = 6 (2), after 2 years = 11 (2), $p < 0.05$. Symptomatic episodes/week/patient: at randomisation = 2.3 (0.6); at 2 years = 1.7 (0.3) Hypo coma: 2 (2) DKA: 2 Subcutaneous abscess: 8 (6) Retinopathy = improved (14%), unchanged (29%), worsened (57%) (one patient had an allergy to fluorescein)
	MDI + regular	HbA_1 reported Month: 3 Mean: 8.7% Month: 6 Mean: 8.8% Month: 12 Mean: 8.5% Month: 24 Mean: 9.1% SD: 1.55 Month: 41 Mean: 9.4%	Month: 24 Mean: 0.72 U/kg SD: 0.12 (SEM 0.03) Significance: p = ns	Month: 24 Mean: 75.1 kg SD: 11.2 (SEM 2.9) Significance: p = ns	Not reported	No. preferring: not reported QoL: not reported	Hypoglycaemia mean (SEM) values: (% of home BG <2.5 mmol/l): at randomisation = 8 (3), after 2 years = 7 (1), p = ns. Symptomatic episodes/week/patient: at randomisation = 1.5 (0.3); at 2 years = 1.2 (0.2). Hypo coma: 14 (6) vs CSII, $p < 0.001$. DKA: 0 (vs CSII, p = ns) Subcutaneous abscess: 0 vs CSII, $p < 0.01$ Retinopathy = improved (7%), unchanged (43%), worsened (50%) (one patient had an allergy to fluorescein)

continued

Study	Treatment	Glycated Hb	Insulin dose	Weight	Lipids	Patient preference/quality of life	Adverse events
Chiasson, *et al.*, 1984[82] Non-randomised crossover Duration: CSII 3 months, MDI 3 months *N* = 12	CSII + soluble	HbA_1 reported Month: 3 Mean: 9.1% SD: 1.04	Month: 3 Mean: 43.9 U/day SD: 10	Not reported	Not reported	No. preferring: 7 (58%) QoL: not reported	Not reported
	MDI + regular	HbA_1 reported Month: 3 Mean: 8.7% SD: 1.39 Significance: p = ns	Month: 3 Mean: 56.1 U/day SD: 20.4 Significance: $p < 0.01$	Not reported	Not reported	No. preferring: 5 (42%) QoL: not reported	Not reported
Haakens *et al.*, 1990[83] Non-randomised crossover Duration: CSII 6 months, MDI 6 months *N*: 52 End of study: 35	CSII + soluble	HbA_1 reported Month: 6 Mean: 9.6% SD: 2.47	Month: 6 Mean: 0.64 U/kg/day SD: 0.18 CSII significantly lower than during CT ($p < 0.001$), MDI/human ultralente ($p < 0.001$), MDI/human isophane ($p < 0.005$)	Month: 6 Mean: 69.1 kg SD: 8.63 Start of CSII vs end of CSII (start of MDI), p = ns	Not reported	23/52 (44%) preferred CSII: Reasons: Control Flexibility in terms of food intake allowed Avoid frequent injections: 2 (9%) Greater sense of well-being: 2 (9%) QoL: not reported	Injection site infection: 1 DKA: 1 Severe hypos (episodes/patient/month) = 1/7.5; requiring glucose i.v./glucagon = 1/96, assistance but not requiring glucose i.v./glucagon = 1/8. No. of mild subjective hypos/week: 1.4 (SD 0.92)
	MDI + regular	HbA_1 reported Month: 6 Mean: 9.8% SD: 1.85 Significance: p = ns	Month: 6 MDI/human isophane Mean: 0.72 SD: 0.25 Significance: $p < 0.005$ MI/human ultralente Mean: 0.79 SD: 0.25 Significance: $p > 0.001$ (isophane vs ultralente, $p < 0.01$)	Month: 6 Mean: 70.6 kg SD: 8.63 Significance: $p < 0.05$ Start of CSII vs end of MDI, $p < 0.02$	Not reported	20/52 (38%) preferred MDI. Reasons: Control: 17 More flexible lifestyle than CT without need to wear a device Preferred human isophane at bedtime: 16 (46%) Preferred human ultralente at bedtime: 7 (20%) No preference between bedtime insulin: 11 (31%) QoL: not reported	Injection site infection: 0 DKA: 0 Severe hypos (episodes/patient/month) = 1/5; requiring glucose i.v./glucagon = 1/79, assistance but not requiring glucose i.v./glucagon = 1/5. No. of mild subjective hypos/week: isophane 1.4 (SD 0.92), ultralente 1.5 (SD 1.17)

continued

Study	Treatment	Glycated Hb	Insulin dose	Weight	Lipids	Patient preference/quality of life	Adverse events
Hanaire-Broutin *et al.*, 2000[80] Randomised crossover Duration: CSII 4 months, MDI 4 months *N*: 41 End of study: 40	CSII + lispro	HbA_{1c} reported Month: 4 Mean: 7.89% SD: 0.77 Note: mean value over 4 months	Month: 4 Mean: 38.5 U/day SD: 9.8 Note: mean value over 4 months	Month: 4 Mean: 68.7 kg SD: 10	Not reported	No. preferring: 29 (72.5%) Of these 29, 21 previously on CSII + regular and 8 on MDI QoL: not reported	Severe hypo: 3 events, 2 pts Note: hypos during last 14 days of each treatment period: 3.9 (4.2). Severe hypos did not result in coma or seizures, external help needed to take sugar, but glucagon or glucose injection not required
	MDI + lispro	HbA_{1c} reported Month: 4 Mean: 8.24% SD: 0.77 Significance: $p < 0.001$ Note: mean value over 4 months	Month: 4 Mean: 47.3 U/day SD: 14.9 Significance: $p < 0.0001$ Note: mean number of NPH injections = 2.65 day at end of MDI period	Month: 4 Mean: 69 kg SD: 9.5 Significance: p = ns	Not reported	No. preferring: 11 (27.5%) Of these 11, 10 previously on CSII and 1 MDI QoL: not reported	Severe hypo: 1 event, 1 pt Note: hypos during last 14 days of each treatment period = 4.3 (3.9), p = ns. Severe hypos did not result in coma or seizures, external help needed to take sugar, but glucagon or glucose injection not required
Home *et al.*, 1982[88] Randomised crossover Duration: CSII 2.5 months, MDI 2.5 months *N*: 11 End of study: 10	CSII + soluble	HbA_1 reported Month: 2.5 Mean: 10% SD: 2.2 Note: 5 reached normal (<8.2%) at some point during pumps	Month: 2.5 Mean: 51 U/day SD: 15.8 Note: Individual changes +21% to –43% of twice-daily injection dose. Requirements remained steady from 2nd week	Month: 2.5 Mean: 68.9 kg SD: 9.2 Note: weight gain clinically significant problem on CSII, on occasion limiting adjustment of insulin dosage	Cholesterol: end of study Mean: 5 SD: 0.6	No. preferring: 8 (80%) preferred pump to MDI, 4 wished to continue with it. Universally regarded as too large and uncomfortable QoL: not reported	Pump malfunction: 1 (1 pt × 3 episodes in 16 h due to faulty pump) Severe hypo: 0.6 (0–3) episodes per pt biweekly [Baseline hypo 1.1 (0–4) episodes per pt biweekly] 1 pt required intravenous glucose
	MDI + regular	HbA_1 reported Month: 2.5 Mean: 11.7% SD: 1.9 Significance: $p = 0.026$ Note: 1 pt reached normal during MDI	Month: 2.5 Mean: 80 U/day SD: 28.5 Significance: $p = 0.004$ Note: difference CSII – MDI due to difference in basal insulin requirements [CSII 29 (3) U/day vs MDI 53 (9) U/day, $p = 0.013$]. Individual increases compared with pump: +20% to +120%, twice daily: +14% to +74%	Month: 2.5 Mean: 67 kg SD: 9.2 Significance: $p = 0.023$	Cholesterol: End of study Mean: 5.3 SD: 0.6	No. preferring: 0 None wished to continue with 3× injections due to inconvenience QoL: not reported	Severe hypo: 0.8 (0–7) episodes per pt biweekly

continued

Study	Treatment	Glycated Hb	Insulin dose	Weight	Lipids	Patient preference/quality of life	Adverse events
Nathan and Lou, 1982[89] Randomised crossover Duration: Each period 8–12 weeks *N*: 5	CSII + soluble	HbA_{1c} reported Month: 3 Mean: 5.4% SD: 0.34	Month: 3 Mean: 35.4 U/day SD: 11.5	Not reported	Not reported	No. preferring: not reported Note: ease of administering and adjusting insulin doses – noted. A decrease in hypos and improved feeling of well-being contributed to acceptance of pump; drawbacks = difficulty for women in dressing to accommodate pump and removal of pump for water sports QoL: not reported	During 2.5 patient-years CSII = subcutaneous abscess needing oral antibiotics (1), pump malfunctions (2) catheter dislodged at night (6) Hypo reactions *n*/week at 3 months = 1 (0.25)
	MDI + regular	HbA_{1c} reported Month: 3 Mean: 7.88% SD: 1.37 Significance: *p* not reported Note: *n* = 4	Month: 3 Mean: 48.8 U/day SD: 13.8	Not reported	Not reported	No. preferring: not reported QoL: not reported	Hypo reactions *n*/week at 3 months = 2.5 (0.61)
Nosadini *et al.*, 1988[85] RCT (parallel) Duration: 12 months CSII fixed basal rate (FBR): 19 MDI: 15 CSII higher dawn insulin (HOR): 10	CSII + soluble (FBR)	HbA_{1c} reported Month: 12 Mean: 6.3% SD: 0.7	Not reported	Not reported	Not reported	No. preferring: not reported QoL: not reported	Mean events/pt/y: Hyper 18 (5) Ketotic events 0.13 (0.02) Mild hypo 36 (10) Severe hypo 0.14 (0.05) Sudden death 0.04 (1 pt dead in bed). Malfunction of pump caused about 20% of ketotic episodes in both CSII groups. 23% (FBR) and 27% (HOR) caused by infective disease
	MDI + regular	HbA_{1c} reported Month: 12 Mean: 7.1% SD: 0.9 Significance: $p < 0.01$ MDI vs CSII–FBR and CSII–HOR, $p < 0.01$	Not reported	Not reported	Not reported	No. preferring: not reported QoL: not reported	Hyper 20 (3), p = ns. Ketotic events 0.03 (0.01), $p < 0.01$ Mild hypo 59 (12), $p < 0.01$ Severe hypo 0.42 (0.15), $p < 0.01$ (all vs CSII–FBR)

continued

Study	Treatment	Glycated Hb	Insulin dose	Weight	Lipids	Patient preference/quality of life	Adverse events
	CSII + soluble (HOR)	HbA_{1c} reported Month: 12 Mean: 6.1% SD: 0.9 Note: vs MDI $p < 0.01$	Not reported	Not reported	Not reported	No. preferring: not reported QoL: not reported	Hyper 17 (4) vs MDI, p = ns Ketotic events 0.16 (0.03) vs MDI, $p < 0.05$ Mild hypo 30 (11) vs MDI, $p < 0.01$ Severe hypo 0.16 (0.09) vs MDI, $p < 0.01$ CSII–HOR vs CSII-FBR, all p = ns
Saurbrey *et al.*, 1988[90] Randomised crossover Duration: CSII 2.5 months, MDI 2.5 months *N*: 21 End of study: 19	CSII + soluble	HbA_{1c} reported Month: 2.5 Mean: 7.5%	Collected during treatment period Mean: 0.62 U/day SD: 0.17	Not reported	Not reported	No. preferring: 6 (31.5%) Reasons Lifestyle: 42 QoL: not reported	Severe hypo: 0 No. of subjective or biochemical (BG <2.5 mmol/l) hypos in each group, p = ns Ketoacidosis = 1 (due to acute gastroenteritis and failure to take extra insulin, not pump malfunction) Subcutaneous infection (3 times) in same patient, one required surgical incision
	MDI + regular	HbA_{1c} reported Month: 2.5 Mean: 7.5%	Collected during study Mean: 0.64 U/day SD: 0.13	Not reported	Not reported	No. preferring: 12 (63%) Reasons: Lifestyle: 58 1 (5%) were unsure of preference (either ICT or CSII) QoL: not reported	Severe hypo: 0

continued

Study	Treatment	Glycated Hb	Insulin dose	Weight	Lipids	Patient preference/quality of life	Adverse events
Schiffrin and Belmonte, 1982[91] Randomised crossover Duration: CSII 6 months, MDI 6 months. N: 20 End of study: 16	CSII + soluble	HbA_1 reported Month: 3 Mean: 8.1% SD: 0.6 Month: 6 Mean: 8.2% SD: 0.5 Note: HbA_1 reported monthly. Data for months 3 and 6 extracted only	Month: 6 Mean: 42 U/day	Not reported	Cholesterol: End of study Mean: 163 mg/dl SD: 15 Baseline: 190 (9) mg/dl Triglyceride: end of study Mean: 82 mg/dl SD: 15	No. preferring: 7/16 (44%) of pts chose CSII for easier glycaemic control and also greater flexibility for meal hours and meal size CSII rejected for reasons of bulk, discomfort, a feeling of dependency on the machine & distortion of body image 70% would recommend CSII to a diabetic friend QoL: not reported	Mild hypo: 186 Moderate hypo: 10 Severe hypo: 1 (severe hypo in 1 pt due to delaying meal after bolus insulin taken – intravenous glucose was administered)
	MDI + regular	HbA_1 reported Month: 3 Mean: 8.4% SD: 0.7 Significance: p = ns Month: 6 Mean: 8.4% SD: 0.5 Significance: p = ns	Month: 6 Mean: 44 U/day Significance: p = ns	Not reported	Cholesterol: end of study Mean: 162 mg/dl SD: 12 Baseline: 183 (8) mg/dl. Mean baseline cholesterol for whole group: 186.5 (70–200). Baseline value vs CSII and MDI at end of study, $p < 0.01$ Triglyceride: end of study Mean: 81 mg/dl SD: 12, p = ns	No. preferring: 7 (44%) 30% would recommend MDI to a diabetic friend. (2 pts reverted to conventional) QoL: not reported	Mild hypo: 189, p = ns Moderate hypo: 11 p = ns Severe hypo: 0, p = ns

continued

Study	Treatment	Glycated Hb	Insulin dose	Weight	Lipids	Patient preference/quality of life	Adverse events
Schmitz *et al.*, 1989[86] Randomised crossover Duration: CSII 6 months, MDI 6 months $N = 10$	CSII + soluble	HbA_{1c} reported Month: 6 Mean: 7% SD: 1 Baseline vs CSII, $p = 0.03$	Month: 6 Mean: 0.55 U/kg/day SD: 0.1 Baseline vs CSII, $p = 0.03$	Month: 6 Mean: 73 kg SD: 17.8 Baseline vs CSII, $p = 0.01$	Not reported	No. preferring: 4 (40%) QoL: not reported	Severe hypo: 0 DKA: 0
	MDI + regular	HbA_{1c} reported Month: 6 Mean: 7.7% SD: 1 Significance: $p = 0.002$ Baseline vs MDI, $p =$ ns	Month: 6 Mean: 0.6 U/kg/day SD: 0.11 Significance: $p = 0.02$ Note: baseline vs MDI, $p =$ ns	Month: 6 Mean: 72.8 kg SD: 18.4 Significance: $p =$ ns Baseline vs MDI, $p =$ ns	Not reported	No. preferring: 6 (60%) QoL: not reported	Severe hypo: 0 DKA: 0
Tsui *et al.*, 2001[79] RCT (parallel) Duration: 9 months. CSII: 13 End of study: 12 MDI: 14 End of study: 14	CSII + lispro	HbA_{1c} reported Month: 3 Mean: 6.92% Month: 6 Mean: 7.19% Month: 9 Mean: 7.38% Pooled estimates of parallel and crossover study: difference CSII and MDI = 0.09% (95%CI –0.09 to +0.26), $p > 0.1$. Probability that true treatment effect is more extreme than ±0.5% is < 0.00001	Month: 9 Mean: 0.6 U/kg SD: 0.2	Not reported	Not reported	No. preferring: not reported QoL score: Satisfaction 75.6 Impact: 69.9 Diabetic worry: 85.2 Social worry: 89.6 Global Health : 68.2 Response rate: 85%	Severe hypo: 6 Mean number of hypos each month, 8.9 (3 months), 7.2 (6 months), 7.0 (9 months), 8.0 (overall), all $p =$ ns

continued

Study	Treatment	Glycated Hb	Insulin dose	Weight	Lipids	Patient preference/quality of life	Adverse events
	MDI + lispro	HbA_{1c} reported Month: 3 Mean: 7.55% Treatment effect (adjusted for baseline): –0.21 (95% CI –0.59 to 0.17), $p > 0.10$ Month: 6 Mean: 7.62% Treatment effect (adjusted for baseline): –0.01 (95% CI –0.44 to 0.42), $p > 0.10$ Month: 9 Mean: 7.56% Treatment effect (adjusted for baseline): 0.25 (95% CI –0.19 to 0.68), $p > 0.10$ Note: treatment effect CSII – MDI shown corrected for baseline differences	Month: 9 Mean: 0.7 U/kg SD: 0.2 Treatment effect (adjusted for baseline): –0.10 (85% CI –0.26 to 0.07), $p > 0.10$ Significance given for different CSII – MDI –0.10	Not reported	Not reported	No. preferring: not reported QoL: Satisfaction: 68.3 Impact: 68.4 Diabetic worry: 79.8 Social worry: 94.0 Global Health : 67.3 p = ns for any of the subscales Response rate: 100%	Severe hypo: 4, $p > 0.10$ Mean number of hypos each month, 5.0 (3 months), 9.0 (6 months), 9.2 (9 months), 7.4 (overall), all p = ns vs CSII Relative treatment effect (CSII–MDI)/MDI for overall no. of hypos = +9% (95% CI –37 to +87) $p > 0.10$

continued

Study	Treatment	Glycated Hb	Insulin dose	Weight	Lipids	Patient preference/quality of life	Adverse events
Ziegler *et al.*, 1990[84] RCT (parallel) Duration: 24 months CSII: 49 End of study: 36 MDI: 47 End of study: 37	CSII + soluble	HbA_1 reported Month: 6 Mean: 8.2% Month: 12 Mean: 8.5% Month: 18 Mean: 8.5% Month: 24 Mean: 8.6	No values given, but p = ns during follow-up	No values given, but noted in discussion that average weight gain after 2 y = 1.3 kg. BMI at months 6–24 = 22.5	No values given, but noted in discussion that cholesterol levels increased within the normal range during the study without differences between treatment groups	No. preferring: not reported 4 pts changed to MDI during study due to technical problems with pump QoL: not reported	No. of metabolic complications/6 months mean (range). Reviewer has calculated mean of the 4 × 6-month periods to give totals below Mild hypo (BG <50 mg/dl): 15.5 (0–70) Mild hypo (symptoms): 19.8 (0–104) Severe hypo (requiring assistance): 0.091 (0–7) Severe hypo (coma): 0.101 (0–4) Ketosis (BG >200 mg/dl and ketonuria): 6.5 (0–57) Ketoacidosis: 0.046 (0–1) Frequency of pts (no. of events/100 y) Hypo requiring assistance: 13.9 (18.1) Hypo coma: 30.6 (19.4) DKA: 13.9 (9.7) [true therapy at time of event: 15.4 (14.1)]
	MDI + regular	HbA_1 reported Month: 6 Mean: 8.8% Significance: $p < 0.05$ Month: 12 Mean: 8.7% Significance: p = ns Month: 18 Mean: 8.4% Significance: p = ns Month: 24 Mean: 8.5 Significance: p = ns	No values given, but p = ns during follow-up	As for CSII, average weight gain after 2 y = 2.8 kg. BMI at months 6–24 = 24.2, $p < 0.05$		No. preferring: not reported 7 pts changed treatment group during study due to explicit request to have a pump QoL: Not reported	Mild hypo (BG <50 mg/dl): 10.6 (0–53) Mild hypo (symptoms): 10.1 (0–81) Severe hypo (requiring assistance): 0.070 (0–2) Severe hypo (coma): 0.048 (0–1) Ketosis (BG >200 mg/dl and ketonuria): 7.8 (0–85) Ketoacidosis: 0.040 (0–3) Frequency of pts (no. of events/100 y) Hypo requiring assistance: 16.2 (13.5) Hypo coma: 13.5 (9.5) DKA: 8.1 (8.1) [true therapy at time of event: 5.9 (2.9)]

Appendix 11

Summary of results: pregnancy

Study	Treatment	Glycated Hb	Insulin dose	Pregnancy outcomes	Patient preference	Adverse events
Burkart *et al.*, 1988[95] RCT (parallel) Duration: 9 months CSII: 48 MDI: 41	CSII + soluble	Not reported. States that patients selected in the CSII or MDI group had normal mean glucose and HbA_1 <7.5% at least from the end of the first trimester on	Not reported	Mean duration: 38.4 weeks Live births: 47/48 (97.9%) Mean birth weight: 3082.7 (units not specified) No. Caesarean: 24/48 Complications in pregnancy: Pyelonephritis: 5 Premature labour: 4 Premature rupture: 2 Premature delivery: 7 Pre-eclampsia: 3 Growth retardation: 3 Hypoglycaemia: 5 Still birth: 1 Ketoacidosis: 1 Total: 12/48 pregnancies had one or more complications Incidence of complications in both groups is linked to the severity of maternal diabetes (White's criteria). Birthweight decreases with severity. Differences in mean birthweights, p = ns Fetal outcome: Healthy newborns: 40 Minor symptoms: 8 Major symptoms: 0 I.v. glucose: 14 Overall mortality up to age 1 y = 2/48	No. preferring: not reported QoL: not reported	See complications in pregnancy

continued

Study	Treatment	Glycated Hb	Insulin dose	Pregnancy outcomes	Patient preference	Adverse events
	CSII + regular		Not reported	Mean duration: 38.2 weeks Live births: 100% Mean birth weight: 3319.5 (units not specified) No. Caesarean: 15/41 (p = ns) Complications in pregnancy: Pyelonephritis: 6 Premature labour: 3 Premature rupture: 1 Premature delivery: 4 Pre-eclampsia: 3 Growth retardation: 1 Hypoglycaemia: 3 Still birth: 0 Ketoacidosis: 0 Total: 13/41 pregnancies had one or more complications (vs CSII, p = ns) Fetal outcome: Healthy newborns: 34 Minor symptoms: 5 Major symptoms: 2 I.v. glucose 9 (all p = ns vs CSII) Overall mortality up to age 1 y = 3/41, vs CSII $p < 0.05$. (Note: the p-value reported by the paper appears to be incorrect, and should be insignificant)	No. preferring: not reported QoL: not reported	See complications in pregnancy

continued

Study	Treatment	Glycated Hb	Insulin dose	Pregnancy outcomes	Patient preference	Adverse events
Carta *et al.*, 1986[94] RCT (parallel) Duration: 9 months Type 1 diabetes: CSII: 8 MDI:7	CSII + soluble	Month: 3 Mean: 7.8% Month: 5 Mean: 7% Month: 8 Mean: 7% Month: 9 Mean: 6.5%	Month: 3 Mean: 37 U/day Month: 6 Mean: 42 U/day Month: 9 Mean: 49.1 U/day	Mean duration: 266.7 days SD: 7.6 Live births: 100% Mean birth weight: 3395 g SD: 407 No. Caesarean: 3 (37.5%) 1 preterm due to hydramnios and fetal megalosomnia. 1 large for gestational age. 1 macrosomnic (>4000 g). [Arms not specified: 2 infants depressed, 5 metabolic morbidity (hypoglycaemia, hypocalcaemia, hyperbilirubinaemia), 2 congenital cardiac malformations]	No. preferring: not reported QoL: not reported	Injection site infection: 0 Pump malfunction: 0 Catheter disconnection: 3 In all pts: no hypo coma. 1 severe hypo (group not stated). Mild hypos occurred on average once every 15–20 days
	MDI + regular	Month: 3 Mean: 8.5% Significance: p = ns Month: 5 Mean: 7.75% Significance: p = ns Month: 8 Mean: 6.95% Significance: p = ns Month: 9 Mean: 6.45% Significance: p = ns	Month: 3 Mean: 32 U/day Significance: p = ns Month: 6 Mean: 47 U/day Significance: p = ns Month: 9 Mean: 60.4 U/day Significance: p = ns	Mean duration: 263.6 days SD: 17.7 Live births: 100% Mean birth weight: 2906 g SD: 553 Significance: p = ns No. Caesarean: 3 (42.9%) 1 preterm due to metrotthagia caused by central placenta previa	No. preferring: not reported QoL: not reported	

continued

Study	Treatment	Glycated Hb	Insulin dose	Pregnancy outcomes	Patient preference	Adverse events
Carta *et al.*, 1986[94] RCT (parallel) Duration: 9 months Type 2 diabetes: CSII: 6 MDI: 8	CSII + soluble	Month: 3 Mean: 7% Month: 5 Mean: 6.75% Month: 8 Mean: 6.5% Month: 9 Mean: 6%	Month: 3 Mean: 23.1 U/day Month: 6 Mean: 36 U/day Month: 9 Mean: 52.8 U/day	Mean duration: 272 days SD: 9 Live births: 100% Mean birth weight: 3292 g SD: 578 No. Caesarean: 1 (16.7%) 1 preterm due to premature rupture of membranes. 1 large for gestational age	No. preferring: not reported QoL: not reported	Episodes of mild hypos were few and did not occur in all pts
	MDI + regular	Month: 3 Mean: 8.1% Significance: p = ns Month: 5 Mean: 7.2% Significance: p = ns Month: 8 Mean: 6.7% Significance: p = ns Month: 9 Mean: 6.7% Significance: p = ns	Month: 3 Mean: 28 U/day Significance: p = ns Month: 6 Mean: 49 U/day Significance: p = ns Month: 9 Mean: 51.2 U/day Significance: p = ns	Mean duration: 269 days SD: 11.7 Live births: 100% Mean birth weight: 2994 g SD: 512 Significance: p = ns No. Caesarean: 3 (37.5%) 1 preterm due to premature rupture of membranes. 1 small for gestational age	No. preferring: not reported QoL: not reported	

continued

Study	Treatment	Glycated Hb	Insulin dose	Pregnancy outcomes	Patient preference	Adverse events
Couston *et al.*, 1986[93] RCT (parallel) Duration: 9 months CSII: 11 MDI: 11	CSII + lispro	Month: 2 Mean: 7% Month: 9 Mean: 6.3% SD: 0.6 Note: Significance reduction from baseline ($p < 0.05$)	Month: 3 Mean: 0.71 U/kg/day SD: 0.16 Month: 6 Mean: 1.02 U/kg/day SD: 0.53 Month: 9 Mean: 1.26 U/kg/day SD: 0.49	Mean duration: 38.1 weeks SD: 2.1 Live births: 100% Mean birth weight: 3050 g SD: 675 No. Caesarean: 7 (63.6%) 1 birthweight above 90th percentile, 2 small for gestational age babies. Neonatal hypoglycaemia in 1	No. preferring: not reported QoL: not reported	Injection site infection: 0 Pump malfunction: 0 Mild hypo: 11 pts Moderate hypo: 6 pts Severe hypo: 3 pts (8 episodes) DKA: 0 1 hyperglycaemia and ketonuria (2 days) during viral infection. Catheter leakage or occlusion occurred infrequently and resolved quickly
	MDI + lispro	Month: 2 Mean: 7.5% Significance: p = ns Month: 9 Mean: 6.4% SD: 0.4 Significance: p = ns Note: significance reduction from baseline ($p < 0.05$)	Month: 3 Mean: 1.01 U//kg/day SD: 0.28 Significance: $p = 0.101$ Month: 6 Mean: 1.4 U//kg/day SD: 0.4 Significance: $p = 0.027$ Month: 9 Mean: 1.63 U//kg/day SD: 0.51 Significance: $p = 0.041$	Mean duration: 38.8 weeks SD: 1.4 Live births: 100% Mean birth weight: 3324 g SD: 475 Significance: p = ns No. Caesarean: 7 (63.6%) 1 baby moderate respiratory distress syndrome. Neonatal hypoglycaemia in 1	No. preferring: not reported QoL: not reported	Mild hypo: 11 pts Moderate hypo: 10 pts Severe hypo: 5 pts (23 episodes) DKA: 0 1 subject had 17 hypos related to dietary irregularities

continued

Study	Treatment	Glycated Hb	Insulin dose	Pregnancy outcomes	Patient preference	Adverse events
Nosari *et al.*, 1993[92] RCT (parallel) Duration: 9 months CSII: 16 MDI: 16	CSII + soluble	Month: 3 Mean: 6% SD: 3.6 Month: 6 Mean: 6.8% SD: 5.6 Month: 9 Mean: 6.3% SD: 2 Note: data at 1st, 2nd, 3rd trimester	Month: 3 Mean: 39.6 U/day SD: 22.8 Month: 6 Mean: 48.1 U/day SD: 20.8 Month: 9 Mean: 57.3 U/day SD: 21.6 Note: data at 1st, 2nd, 3rd trimester	Mean duration: 38.9 weeks SD: 7.6 Live births: 87.5% Mean birth weight: 3130 g SD: 1480 No. Caesarean: 9 (56.3%) 2 intrauterine deaths. Gestational age at delivery (pregnancy duration) $p > 0.5$, birthweight $p > 0.5$. Fetal congenital malformations, macrosomia, low Apgar scores (<7 at 5 minutes) not observed. 1 CSII large for age. Respiratory distress in 1 CSII infant. Neonatal hypo (plasma glucose <30 mg/dl) in 1 CSII.	No. preferring: not reported QoL: not reported	Severe hypo: 3 DKA: 3
	MDI + regular	Month: 3 Mean: 6.2% SD: 1.6 Significance: $p > 0.5$ Month: 6 Mean: 6.1% SD: 2.4 Significance: $p > 0.5$ Month: 9 Mean: 6.2% SD: 0.8 Significance: $p > 0.5$	Month: 3 Mean: 36 U/day SD: 24.4 Significance: $p > 0.5$ Month: 6 Mean: 43.7 U/day SD: 35.6 Significance: $p > 0.5$ Month: 9 Mean: 54.7 U/day SD: 39.2 Significance: $p > 0.5$	Mean duration: 38.2 weeks SD: 10 Live births: 93.8% Mean birth weight: 3010 g SD: 1728 No. Caesarean: 7 (43.8%) 1 intrauterine death. 2 MDI small for age. 1 premature MDI birth. Neonatal hypo (plasma glucose <30 mg/dl) in 1 MDI	No. preferring: not reported QoL: not reported	Severe hypo: 1, CSII vs MDI, $p > 0.5$ DKA: 0, CSII vs MDI, $p > 0.1$

Appendix 12

Summary of results: adolescents

Study	Treatment	Glycated Hb	Insulin dose	Patient preference	Adverse events
Schiffrin *et al.*, 1984[97] Randomised crossover Duration: CSII 4 months, MDI 4 months, CSII+MDI 4 months *N*: 24	CSII + soluble	Month: 3 Mean: 8.75% Month: 4 Mean: 8.8% Note: reduction is significant from baseline ($p < 0.001$) CSII vs CSII-ICT, $p < 0.05$ CSII vs ICT, $p < 0.05$	Month: 4 Mean: 44 U/day SD: 12 Note: total insulin/day during treatment – no time point given CSII vs ICT and baseline, $p < 0.001$	No. preferring: 11 100% would recommend CSII to a friend. QoL: not reported	Severe hypo: 1 No different in hypos from other treatments. Mostly mild and averaged one per week per pt. Same pts had severe hypo on CSII and ICT – the latter due to inadvertent administration of extra NPH dose
	MDI + regular	Month: 3 Mean: 9.5% Significant: $p < 0.05$ Month: 4 Mean: 9.6% Significance: $p < 0.05$ Note: reduction is significant from baseline ($p < 0.001$)	Month: 4 Mean: 60 U/day SD: 16 Significance: $p < 0.001$ Note: total insulin/day during treatment – no time point given	No. preferring: 4 66% would recommend ICT to a friend QoL: not reported	Severe hypo: 1 (due to inadvertent administration of extra NPH dose)
	CSII overnight with MDI during day	Month: 3 Mean: 9% Month: 4 Mean: 9.3% Note: reduction significant from baseline ($p < 0.001$) CSII vs CSII–ICT, $p < 0.05$	Month: 4 Mean: 48 U/day SD: 16 Note: during whole study CSII–ICT vs ICT and baseline, $p < 0.001$	No. preferring: 3 70% would recommend CSII–ICT to a friend (2 of 20 completing study reverted to twice daily injections) QoL: not reported	

continued

Study	Treatment	Glycated Hb	Insulin dose	Patient preference	Adverse events
Tamborlane *et al.*, 1989[96] Randomised crossover Duration: CSII 6 months, MDI 6 months *N*: 10	CSII + regular	Month: 6 Mean: 8.5% SD: 1.26	Month: 6 Mean: 1.3 U/day SD: 3.16	No. preferring: not reported QoL: not reported	Episodes of mild hypos were common during each treatment. States that there was only one severe hypo requiring assistance during each 6-month treatment period
	MDI + regular	Month: 6 Mean: 8.7% SD: 1.58 Significance: p = ns HbA_1 significantly reduced compared with baseline during both CSII and MDI, $p < 0.05$	Month: 6 Mean: 1.4 U/day SD: 0.32 Significance: p = ns Month: 0 Mean: 0 U/day Insulin dose (U/day) was increased during both MDI and CSII compared with baseline, $p < 0.05$	No. preferring: not reported QoL: not reported	

Appendix 13

Summary of results: analogue versus soluble insulin

Study	Treatment	Glycated Hb	Insulin dose	Weight	Patient preference	Adverse events
Bode *et al.*, 2002[113] RCT (parallel) Duration: 4 months Lispro: 28 (end of study 27) Regular: 59 (end of study 50) Aspart: 59 (end of study 55)	CSII + lispro	Month: 4 Mean change from baseline: 0.18 (0.84)%	Not reported	Not reported	Not reported	Severe hypo: 0 DKA: 0 Hyperglycaemia (>350 mg/dl): 10 ≤ 3 clogs or blockages: 64% Hypos [episodes, rate (SD)]: All reported: 872, 10.5 (8.1), vs aspart $p = 0.044$ Hypo BG < 50 mg/dl: 359, 4.4 (4.7), vs aspart $p = 0.841$ Nocturnal hypo BG <50 mg/dl: 64, 0.6 (0.61), vs aspart $p = 0.189$
	CSII + buffered regular	Month: 4 Mean change from baseline: 0.15 (0.63)%	Not reported	Not reported	Not reported	Severe hypo: 1 (1.7%) DKA: 0 Hyperglycaemia (>350 mg/dl): 24 ≤ 3 clogs or blockages: 78% Hypos [episodes, rate (SD)]: All reported: 1663, 10.5 (8.9), vs aspart $p = 0.034$ Hypo BG < 50 mg/dl: 770, 4.8 (4.2), vs aspart $p = 0.175$. Nocturnal hypo BG < 50 mg/dl: 207, 0.9 (0.97), vs aspart $p = 0.004$
	CSII + aspart	Month: 4 Mean change from baseline: 0.00 (0.15)% p = ns between groups	Not reported	Not reported	Not reported	Severe hypo: 0 DKA: 0 Hyperglycaemia (>350 mg/dl): 16 (p = ns between all treatments) ≤ 3 clogs or blockages: 75% Herpes zoster = 1 Hypos [episodes, rate (SD)]: All reported: 1126, 6.7 (5.4) Hypo BG<50 mg/dl: 610, 3.7 (3.6) Nocturnal hypo BG <50 mg/dl: 96, 0.5 (0.83)

continued

Study	Treatment	Glycated Hb	Insulin dose	Weight	Patient preference	Adverse events
Melki *et al.*, 1998[116] Randomised crossover Duration: Soluble 3 months, lispro 3 months *N*: 39 End of study: 38	CSII + soluble	Month: 3 Mean: 7.11% SD: 0.92 Note: reduction from baseline: 0.62 (0.8)	Month: 3 Mean: 0.53 U/kg/day SD: 0.12	Month: 3 Mean: 0.04 kg SD: 1.79	No. preferring: 36 (94.7%) Reasons: Control: 89.4% Lifestyle: 84.2% % of favourable responses for lispro varied from 84 to 92% according to the questions QoL: not reported	Catheter obstructions : 9 Severe hypo: 3 (7.9%) DKA: 0 Insulin precipitation in catheter: 1 BG <3.0 mmol/l: 7.03 (5.79) per month BG <2.0 mmol/l: 0.05 (0.31) per month
	CSII + lispro	Month: 3 Mean: 7.88% SD: 0.99 Note: reduction from baseline: 0.09 (0.92) Lispro vs regular, $p = 0.01$	Month: 3 Mean: 0.55 U/kg/day SD: 0.12 Significance: p = ns	Month: 3 Mean: 0.48 kg SD: 1.6 Significance: p = ns	No. preferring: 2 (5.3%) Reasons Control: 5.3% Lifestyle: 5.3% QoL: not reported	Catheter obstructions: 9 Severe hypo: 4 (10.5%) pts, 7 events DKA: 0 Insulin precipitation in catheter: 4 BG <3.0 mmol/l: 7.94 (5.42) per month, p = ns BG <2.0 mmol/l: 0.47 (1.17) per month, $p < 0.05$ 0 resulted in coma or seizures
Raskin *et al.*, 2001[117] Randomised crossover Duration: lispro 3 months, soluble 3 months *N*: 59 End of study: 58	CSII + lispro	Month: 3 Mean: 7.41% SD: 0.97 Note: change from baseline: 0.34 (0.59)	Basal 0.34 U/kg, bolus 0.28 U/kg	Month: 3 Mean: 79.2 kg SD: 17.1 Note: 1 kg gained at end of period 1, vs baseline p = ns	Not reported	Severe hypo: 3 (5.1%) pts (3 episodes) Hyper due to occlusion: 8 pts (16 episodes) Ketosis: 1 Hypo as defined: 7 pts (8 episodes)
	CSII + soluble	Month: 3 Mean: 7.65% SD: 0.85 Significance: $p = 0.004$ Note: change from baseline: 0.09 (0.63), lispro vs regular $p = 0.004$	Basal 0.35 U/kg, bolus 0.30 U/kg	Month: 3 Mean: 78.8 kg SD: 17.3 Significance: $p = 0.78$ Note: 1 kg gained at end of period 1, vs baseline: p = ns	No. preferring: not reported QoL: not reported	Severe hypo: 2 (3.4%) pts (3 episodes) DKA: 0 Note: hyper due to occlusion: 12 pts (23 episodes) Hypo as defined: 7 pts (11 episodes) 1 hospitalised with fever, vomiting, dehydration (38 pts reported 109 episodes of hyper: 39 caused by occlusion, 47 caused by other reasons, 23 no identifiable cause. Groups not specified)

continued

Study	Treatment	Glycated Hb	Insulin dose	Weight	Patient preference	Adverse events
Renner *et al.*, 1999[114] Randomised crossover Duration: lispro 4 months, soluble 4 months *N*: 113	CSII + lispro	Month: 4 Mean: 6.77% SD: 0.88	Month: 4 Mean: 83.1 U/day	Not reported	No. preferring: not reported DTSQ patient satisfaction (max. score of 48 possible): 35.16 (4.25) QoL: not reported	Injection site infection: 4 Serious adverse event not related to drug: 1 Hypo: mean 12.4 (13.9), median 8, episodes/pt. Infection (cold): 19.4% Rhinitis: 15.8% Catheter occlusion: 20 (42 episodes) Ketosis: 5
	CSII + soluble	Month: 4 Mean: 6.9% SD: 0.97 Significance: $p < 0.02$	Month: 4 Mean: 85.4 U/day Significance: p = ns	Not reported	No. preferring: not reported DTSQ patient satisfaction (max. score of 48 possible): 32.36 (5.87), vs lispro $p < 0.001$ QoL: not reported	Injection site infection: 2 Serious adverse event not related to drug : 6 Hypo: mean 11.0 (11.2), median 8, episode/pt, p = ns. Infection (cold): 21.1% Rhinitis: 13.8% Catheter occlusion: 21 (45 episodes), p = ns Ketosis: 4
Schmauss *et al.*, 1998[115] Randomised crossover Duration: lispro 3 months, soluble 3 months *N*: 11	CSII + lispro	Month: 3 Mean: 6% SD: 0.99	Basal 19 (6.6) IU/day Bolus 1.4 (0.3) IU/12 g carbohydrate	Not reported	No. preferring: 11 (100%) Greater flexibility with lispro No significant difference in treatment satisfaction noted QoL: not reported	Severe hypo: 0 DKA: 0 Hypos per 30 days: 4 (2.98) No severe adverse events registered by either treatment
	CSII + soluble	Month: 3 Mean: 6.35% SD: 0.83 Significance: p = ns Note: HbA_{1c} at end of each treatment period not combined in paper	Basal 20 (3.3) IU/day, p = ns Bolus 1.5 (0.3) IU/12 g carbohydrate, p = ns	Not reported	No. preferring: 0 QoL: not reported	Severe hypo: 0 DKA: 0 Hypos per 30 days: 3.2 (2.3), p = ns

continued

Study	Treatment	Glycated Hb	Insulin dose	Weight	Patient preference	Adverse events
Zinman *et al.*, 1997[118] Randomised crossover Duration: lispro 3 months, soluble 3 months *N*: 30	CSII + lispro	Month: 3 Mean: 7.66% SD: 0.71	Month: 3 Mean: 40.4 U/day SD: 9.3	Month: 3 Mean: 72.6 kg SD: 9.9	No. preferring: not reported Quality of life: not reported	Skin reaction: 16 Severe hypo: 0 Discolouration of insulin in reservoir or catheter (did not lead to obstruction or significant hyperglycaemia): 2 Hypos: 8.6 (7.7)/30 days (vs baseline $p = 0.035$) Hypos confirmed by BG: 6.0 (4.9)/30 days (vs baseline $p = 0.03$)
	CSII + soluble	Month: 3 Mean: 8% SD: 0.88 Significance: $p = 0.0041$	Month: 3 Mean: 40.8 U/day SD: 8.8 Significance: p = ns	Month: 3 Mean: 72.8 kg SD: 9.9 Significance: p = ns	No. preferring: not reported QoL: not reported	Skin reaction: 15 Severe hypo: 0 Discolouration of insulin in reservoir or catheter (did not lead to obstruction or significant hyperglycaemia): 2 Hypos: 10.8 (9.9)/30 days (vs baseline and lispro p = ns). Hypos confirmed by BG: 7.6 (7.1)/30 days (vs baseline p = ns, vs lispro p = ns)

Significance is for CSII vs MDI except where stated.

Appendix 14

Calculations for NHS staff costs

Costs/staff	Consultant physician (assuming discretionary point 3 on salary scale)	Diabetes specialist nurse (assuming G grade nurse; top of salary scale, point 5)	Dietitian (assuming senior dietitian, grade 1; top of salary scale, point 6)
Annual salary (£)	76,700	26,056	25,145
Employer's National Insurance (£)	8,119	1,994	1,910
Employer's pension contribution (£)	5,262	1,730	1,675
Overheads[a]	24,320	2,216	2,216
Capital overheads[a]	4,161	2,263	3,606
Total annual costs (£)	118,562	34,259	34,552
Working time	41 weeks × 40 h	42 wks × 37.5 h	42 weeks × 37 h
Cost per hour (£)	72.29	21.75	22.23
Cost per day (£)	578.35	163.14	164.53

[a] Overhead estimates based on data from PSSRU.[138]
Source: Salary scales from Southampton General Hospital Trust (2001–2002).

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

Chair,
Professor Tom Walley,
Director, NHS HTA Programme, Department of Pharmacology & Therapeutics, University of Liverpool

Professor Bruce Campbell, Consultant Vascular & General Surgeon, Royal Devon & Exeter Hospital

Professor Shah Ebrahim, Professor in Epidemiology of Ageing, University of Bristol

Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Radcliffe Hospital, Oxford

Dr Ron Zimmern, Director, Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

HTA Commissioning Board

Members

Programme Director,
Professor Tom Walley,
Director, NHS HTA Programme, Department of Pharmacology & Therapeutics, University of Liverpool

Chair,
Professor Shah Ebrahim,
Professor in Epidemiology of Ageing, Department of Social Medicine, University of Bristol

Deputy Chair,
Professor Jenny Hewison,
Professor of Health Care Psychology, Academic Unit of Psychiatry and Behavioural Sciences, University of Leeds School of Medicine

Dr Jeffrey Aronson
Reader in Clinical Pharmacology, Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford

Professor Ann Bowling, Professor of Health Services Research, Primary Care and Population Studies, University College London

Professor Andrew Bradbury, Professor of Vascular Surgery, Department of Vascular Surgery, Birmingham Heartlands Hospital

Professor John Brazier, Director of Health Economics, Sheffield Health Economics Group, School of Health & Related Research, University of Sheffield

Dr Andrew Briggs, Public Health Career Scientist, Health Economics Research Centre, University of Oxford

Professor Nicky Cullum, Director of Centre for Evidence Based Nursing, Department of Health Sciences, University of York

Dr Andrew Farmer, Senior Lecturer in General Practice, Department of Primary Health Care, University of Oxford

Professor Fiona J Gilbert, Professor of Radiology, Department of Radiology, University of Aberdeen

Professor Adrian Grant, Director, Health Services Research Unit, University of Aberdeen

Professor F D Richard Hobbs, Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Peter Jones, Head of Department, University Department of Psychiatry, University of Cambridge

Professor Sallie Lamb, Research Professor in Physiotherapy/Co-Director, Interdisciplinary Research Centre in Health, Coventry University

Professor Julian Little, Professor of Epidemiology, Department of Medicine and Therapeutics, University of Aberdeen

Professor Stuart Logan, Director of Health & Social Care Research, The Peninsula Medical School, Universities of Exeter & Plymouth

Professor Tim Peters, Professor of Primary Care Health Services Research, Division of Primary Health Care, University of Bristol

Professor Ian Roberts, Professor of Epidemiology & Public Health, Intervention Research Unit, London School of Hygiene and Tropical Medicine

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Professor Mark Sculpher, Professor of Health Economics, Centre for Health Economics, Institute for Research in the Social Services, University of York

Professor Martin Severs, Professor in Elderly Health Care, Portsmouth Institute of Medicine

Dr Jonathan Shapiro, Senior Fellow, Health Services Management Centre, Birmingham

Ms Kate Thomas, Deputy Director, Medical Care Research Unit, University of Sheffield

Professor Simon G Thompson, Director, MRC Biostatistics Unit, Institute of Public Health, Cambridge

Ms Sue Ziebland, Senior Research Fellow, Cancer Research UK, University of Oxford

Current and past membership details of all HTA 'committees' are available from the HTA website (www.ncchta.org)

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Ms Norma Armston, Freelance Consumer Advocate, Bolton

Professor Max Bachmann Professor Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia

Professor Rudy Bilous Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust

Dr Paul Cockcroft, Consultant Medical Microbiologist/Laboratory Director, Public Health Laboratory, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, Addenbrooke's Hospital, Cambridge

Dr David Elliman, Consultant in Community Child Health, London

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales Swansea

Dr John Fielding, Consultant Radiologist, Radiology Department, Royal Shrewsbury Hospital

Dr Karen N Foster, Clinical Lecturer, Dept of General Practice & Primary Care, University of Aberdeen

Professor Antony J Franks, Deputy Medical Director, The Leeds Teaching Hospitals NHS Trust

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Dr Edmund Jessop, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), Department of Health, London

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medical Devices Agency, London

Dr William Rosenberg, Senior Lecturer and Consultant in Medicine, University of Southampton

Dr Susan Schonfield, CPHM Specialised Services Commissioning, Croydon Primary Care Trust

Dr Margaret Somerville, Director of Public Health, Teignbridge Primary Care Trust

Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull

Professor Martin J Whittle, Head of Division of Reproductive & Child Health, University of Birmingham

Dr Dennis Wright, Consultant Biochemist & Clinical Director, Pathology & The Kennedy Galton Centre, Northwick Park & St Mark's Hospitals, Harrow

Pharmaceuticals Panel

Members

Chair,
Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Oxford Radcliffe Hospital

Professor Tony Avery, Professor of Primary Health Care, University of Nottingham

Professor Stirling Bryan, Professor of Health Economics, Health Services Management Centre, University of Birmingham

Mr Peter Cardy, Chief Executive, Macmillan Cancer Relief, London

Dr Christopher Cates, GP and Cochrane Editor, Bushey Health Centre

Professor Imti Choonara, Professor in Child Health, University of Nottingham, Derbyshire Children's Hospital

Mr Charles Dobson, Special Projects Adviser, Department of Health

Dr Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Dr Karen A Fitzgerald, Pharmaceutical Adviser, Bro Taf Health Authority, Cardiff

Mrs Sharon Hart, Managing Editor, *Drug & Therapeutics Bulletin*, London

Dr Christine Hine, Consultant in Public Health Medicine, Bristol South & West Primary Care Trust

Professor Stan Kaye, Professor of Medical Oncology, Consultant in Medical Oncology/Drug Development, The Royal Marsden Hospital

Ms Barbara Meredith, Project Manager Clinical Guidelines, Patient Involvement Unit, NICE

Dr Frances Rotblat, CPMP Delegate, Medicines Control Agency, London

Professor Jan Scott, Professor of Psychological Treatments, Institute of Psychiatry, University of London

Mrs Katrina Simister, New Products Manager, National Prescribing Centre, Liverpool

Dr Richard Tiner, Medical Director, Association of the British Pharmaceutical Industry

Dr Helen Williams, Consultant Microbiologist, Norfolk & Norwich University Hospital NHS Trust

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell,
Consultant Vascular and General Surgeon, Royal Devon & Exeter Hospital

Dr Mahmood Adil, Head of Clinical Support & Health Protection, Directorate of Health and Social Care (North), Department of Health, Manchester

Dr Aileen Clarke, Reader in Health Services Research, Public Health & Policy Research Unit, Barts & the London School of Medicine & Dentistry, Institute of Community Health Sciences, Queen Mary, University of London

Mr Matthew William Cooke, Senior Clinical Lecturer and Honorary Consultant, Emergency Department, University of Warwick, Coventry & Warwickshire NHS Trust, Division of Health in the Community, Centre for Primary Health Care Studies, Coventry

Dr Carl E Counsell, Senior Lecturer in Neurology, University of Aberdeen

Dr Keith Dodd, Consultant Paediatrician, Derbyshire Children's Hospital

Professor Gene Feder, Professor of Primary Care R&D, Barts & the London, Queen Mary's School of Medicine and Dentistry, University of London

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, Department of Orthopaedic Surgery, South Tees Hospital NHS Trust

Ms Bec Hanley, Freelance Consumer Advocate, Hurstpierpoint

Ms Maryann L. Hardy, Lecturer, Division of Radiography, University of Bradford

Professor Alan Horwich, Director of Clinical R&D, The Institute of Cancer Research, London

Dr Phillip Leech, Principal Medical Officer for Primary Care, Department of Health, London

Dr Simon de Lusignan, Senior Lecturer, Primary Care Informatics, Department of Community Health Sciences, St George's Hospital Medical School, London

Dr Mike McGovern, Senior Medical Officer, Heart Team, Department of Health, London

Professor James Neilson, Professor of Obstetrics and Gynaecology, Dept of Obstetrics and Gynaecology, University of Liverpool, Liverpool Women's Hospital

Dr John C Pounsford, Consultant Physician, North Bristol NHS Trust

Dr Vimal Sharma, Consultant Psychiatrist & Hon Snr Lecturer, Mental Health Resource Centre, Victoria Central Hospital, Wirrall

Dr L David Smith, Consultant Cardiologist, Royal Devon & Exeter Hospital

Professor Norman Waugh, Professor of Public Health, University of Aberdeen

Expert Advisory Network

Members

Professor Douglas Altman,
Director of CSM & Cancer Research UK Med Stat Gp, Centre for Statistics in Medicine, University of Oxford, Institute of Health Sciences, Headington, Oxford

Professor John Bond,
Director, Centre for Health Services Research, University of Newcastle upon Tyne, School of Population & Health Sciences, Newcastle upon Tyne

Mr Shaun Brogan,
Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,
Chief Executive, Office of the Chief Executive. Trust Headquarters, Altnagelvin Hospitals Health & Social Services Trust, Altnagelvin Area Hospital, Londonderry

Ms Tracy Bury,
Project Manager, World Confederation for Physical Therapy, London

Mr John A Cairns,
Professor of Health Economics, Health Economics Research Unit, University of Aberdeen

Professor Iain T Cameron,
Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark,
Medical Writer & Consultant Pharmacist, Rossendale

Professor Collette Mary Clifford,
Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham, Edgbaston, Birmingham

Professor Barry Cookson,
Director, Laboratory of Healthcare Associated Infection, Health Protection Agency, London

Professor Howard Stephen Cuckle,
Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Professor Nicky Cullum,
Director of Centre for Evidence Based Nursing, University of York

Dr Katherine Darton,
Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux,
Professor of Paediatric Epidemiology, London

Mr John Dunning,
Consultant Cardiothoracic Surgeon, Cardiothoracic Surgical Unit, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw,
Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles,
Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby,
Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Mr Leonard R Fenwick,
Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Professor David Field,
Professor of Neonatal Medicine, Child Health, The Leicester Royal Infirmary NHS Trust

Mrs Gillian Fletcher,
Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn,
Professor of Medicine, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham

Ms Grace Gibbs,
Deputy Chief Executive, Director for Nursing, Midwifery & Clinical Support Servs, West Middlesex University Hospital, Isleworth

Dr Neville Goodman,
Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Alastair Gray,
Professor of Health Economics, Department of Public Health, University of Oxford

Professor Robert E Hawkins,
CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor F D Richard Hobbs,
Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Allen Hutchinson,
Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Dr Duncan Keeley,
General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping,
Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy,
Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay,
Professor of Psychiatry for the Elderly, University of Leicester, Leicester General Hospital

Professor Rajan Madhok,
Medical Director & Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor David Mant,
Professor of General Practice, Department of Primary Care, University of Oxford

Professor Alexander Markham,
Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Castle Mullen

Professor Alistair McGuire,
Professor of Health Economics, London School of Economics

Dr Peter Moore,
Freelance Science Writer, Ashtead

Dr Andrew Mortimore,
Consultant in Public Health Medicine, Southampton City Primary Care Trust

Dr Sue Moss,
Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Professor Jon Nicholl,
Director of Medical Care Research Unit, School of Health and Related Research, University of Sheffield

Mrs Julietta Patnick,
National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler,
Professor of Liaison Psychiatry, University Mental Health Group, Royal South Hants Hospital, Southampton

Professor Chris Price,
Visiting Chair – Oxford, Clinical Research, Bayer Diagnostics Europe, Cirencester

Ms Marianne Rigge,
Director, College of Health, London

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, Genetics Department, St James's University Hospital, Leeds

Dr Ken Stein,
Senior Clinical Lecturer in Public Health, Director, Peninsula Technology Assessment Group, University of Exeter

Professor Sarah Stewart-Brown,
Director HSRU/Honorary Consultant in PH Medicine, Department of Public Health, University of Oxford

Professor Ala Szczepura,
Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor,
Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster,
Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

ISSN 1366-5278