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

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## *Executive summary*

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

**Health Technology Assessment**
**NHS R&D HTA Programme**

# 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.

## Publication

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).

# NHS R&D HTA Programme

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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.

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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.

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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.