PROTOCOL

Clinical and cost-effectiveness of continuous subcutaneous insulin infusion therapy in diabetes.

A. This the revised protocol (April 2002)

B. Review team

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C. 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 in whom diabetes control is unsatisfactory, and to consider which groups of patients could benefit most.

D. Clarification of research question and scope

Conventional insulin treatment in people with Type 1 diabetes involves two injections a day, usually giving a mixture of short and longer-acting insulins. (This will be referred to henceforth as conventional treatment or CT for short.) Conventional treatment provides satisfactory control as assessed by glycosylated haemoglobin (HbA1c) 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 HbA1c 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 HbA1c 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 which 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.

Continuous subcutaneous insulin infusion (CSII) is usually used to provide intensive treatment in a different way to MDI, with an 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 multiple daily injections (MDI). The benefits could be better control of blood glucose as reflected in HbA1, or a similar level of control but with other advantages such as fewer problems with hypoglycaemia, or greater flexibility of lifestyle, and hence better quality of life. 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 pre-conceptually 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 diabetic ketoacidosis.

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 3 injections a day.

E. 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 Duesseldorf will be consulted.

Inclusion and exclusion criteria
Exclusions will include: conventional therapy; treatment of newly diagnosed patients; implantable pumps; very short-term studies; hospital in-patient pumps.
Because the key measure of blood glucose control is glycosylated haemoglobin (HbA1c), studies of less than 10 weeks duration on each treatment will be excluded from any HbA1c 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 quality of life 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 diabetic 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, 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 PSS decision-maker.

Data on clinical and quality of life 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. HbA1c, severe hypoglycaemic events, and diabetes-related complications) and additional quality of life 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 hypos, 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 ones such as improved blood glucose control as measured by HbA1c, 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.

F. 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 SHTAC 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.

G. Project management

- Timetable
It is planned to send:
- a final protocol to NCCHTA on 11th March 2002
- an interim progress report on 7th June 2002
- a draft of the report to reviewers on 10 June 2002
  (with response due back 5 July 2002)
- the final report on 12th August 2002.

b) Competing interests
None known.

c) External reviewers and advisory panel
An advisory panel will be assembled which will include:
- people with diabetes and experience of using CSII
- clinical experts with experience in research into CSII
- clinical experts, both nursing and medical, from diabetic medicine and paediatrics
- NHS management, from the Southampton University Hospitals Trust, who will comment on service implications.

It is our standard practice to have some of the experts nominated by external bodies. In this case, these bodies will include the Royal College of Physicians of London; the RCN Paediatric and Adolescent Diabetes Specialist Nurses Group; the Scottish Study Group for the Care of Diabetes in the Young; and INPUT.

BACKGROUND

The number of people with diabetes treated with insulin in the UK has increased in recent decades. This is partly due to increases in the prevalences of both Type 1 (formerly insulin-dependent) diabetes and Type 2 (formerly known as non-insulin dependent) diabetes, and partly because more people with type 2 diabetes are now treated with insulin. However some of the Type 2 patients treated with insulin may have slow onset Type 1 diabetes.

Large studies in both types have shown that intensified management of diabetes, including changes in diet, education, frequency of clinical contact, and changes in insulin regimens aimed at reducing average blood glucose levels, reduces the long-term complications such as eye disease and renal disease. However conventional treatment with twice daily insulin does not give adequate control of blood glucose in most patients. A recent audit of all children with diabetes in Scotland showed that most were not well-controlled. Unpublished data suggested that children on more than 2 injections a day had better control, but this was not from a randomised study, and Danish data show that moving from CT to MDI in the form of meal-time plus basal also fails to provide adequate control in the majority of patients.

There has therefore been a move towards more intensive management, using multiple daily injections, such as a combination of a longer-acting insulin once a day with several injections of short-acting to cover meals. However current longer-acting insulins do tend to have peaks of effect, and these may give rise to hypoglycaemic episodes. Very long-acting insulins such as glargine are becoming available, and are the subject of a separate NICE review.

The purpose of regimens using intensified insulin therapy is to give a steady basal level of insulin provided by the long-acting forms, supplemented by peaks of insulin after meals, provided by the short-acting forms, taken shortly before meals (or in the case of children with unpredictable intake of food, with or just after meals). An alternative is to use insulin pumps to provide CSII, with a steady infusion to provide the basal level, with user-activated short boosts to cover meals. Modern pumps allow the basal infusion rate to be varied during the day.
Pumps were first used in this way in the UK about 25 years ago, but the early models were bulky and less reliable. Insulins have also changed and it is argued that some modern forms may be better suited for use with pumps.

There are about 130,000 pumps users in the USA, and about 800 in the UK. There are different policies about funding pump use amongst different health authorities. Many patients have purchased their own pumps. Different policies also exist for the supply of the expensive disposables used with pumps. It is hoped that guidance from NICE will promote greater equity of provision.