Personal statement re Insulin Pump therapy for:
NICE technology appraisal review, Insulin pump therapy (TA057)

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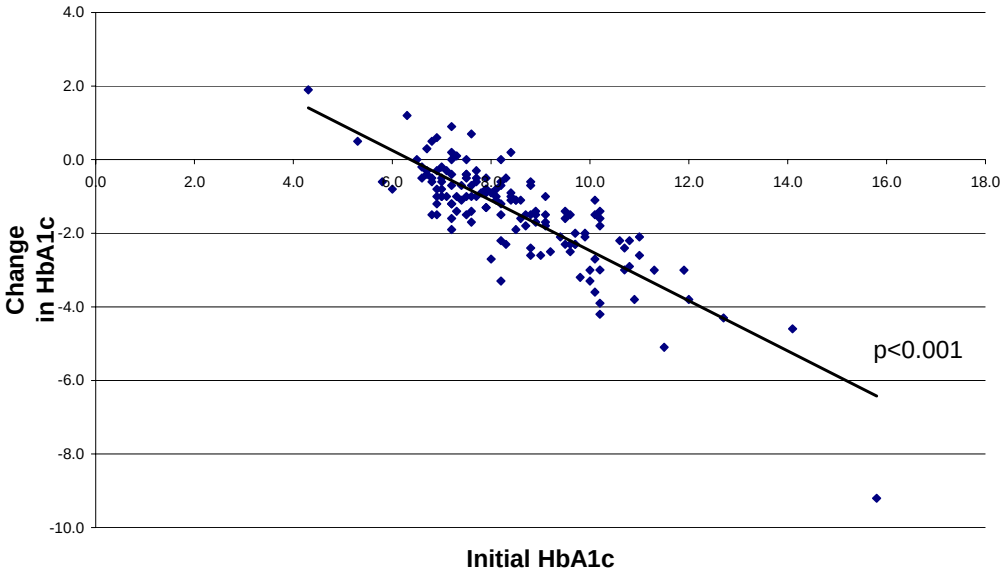
We started to use insulin pump therapy (continuous subcutaneous insulin infusion, CSII) in Harrogate in 1998. At this time it was a widely used technology in the USA and continental Europe but was still distrusted in the UK following a number of serious adverse incidents attributed to pump therapy when it was first introduced in the 1980s. By the time we started to use pump therapy the technology was vastly different to these early prototypes and safety concerns no longer appeared to be a major concern. Our experience with pump therapy was considerably enhanced by participation in the Five Nations study, a randomized crossover trial comparing CSII with isophane-based MDI (multiple daily injections), which demonstrated improved glycaemic control with reduced frequency of severe hypoglycaemia, and better quality of life in certain domains. We recruited the largest number of patients, with 58 participants. We have initiated pump therapy in over 125 patients, ages ranging from 4 to 84. We have trained teams in a number of other centres to use pump therapy, and run a 3 day training course 3 times per year.

There is little doubt that the original NICE appraisal of insulin pump therapy changed attitudes to pump therapy in the UK. It is now an accepted means of insulin delivery, at least for those patients fulfilling the NICE criteria, although there is clear geographical variation in provision of pump therapy as a result of a number of factors:

- Primary care trusts attitude to commissioning pump therapy services and over-reliance on the indicative target population from the NICE guidance of 1-2% of those with type 1 diabetes
- Continued distrust of pump therapy by some health care professionals, particularly consultant diabetologists
- Disparity between paediatric and adult services, such that one or other group are disadvantaged

The existing NICE guidance is a fair reflection of the evidence from randomized controlled trials which predated that appraisal. The updated technology assessment report concludes that there is little new evidence from RCTs, although there is further evidence of reductions in hypoglycaemia frequency with use of CSII and possible benefits in terms of quality of life. There is no RCT evidence to indicate superiority of CSII over analogue-based MDI regimens, using insulin glargine as the long-acting analogue, in terms of glycaemic control or severity of hypoglycaemia. There are however an increasing number of observational studies which do indicate superiority of CSII over glargine-based regimens, and also show that the higher the HbA1c at initiation of pump therapy

the greater the reduction achieved. This is our experience and was confirmed when we analysed data from 150 patients started on pumps in Harrogate, Bournemouth and Liverpool who had been using the pump for at least 12 months (see figure below).



These observational data and our personal experience would indicate that the current NICE criteria for initiation of pump therapy are too narrow; in particular depriving those motivated patients who have done all they can to optimise glycaemic control with MDI but failed to achieve an HbA1c < 7.5%, of the opportunity to try pump therapy.

I would support broadening access to pump therapy by using the following criteria for selecting patients with type 1 diabetes for pump therapy:

- Those who are able to achieve target HbA1c (<7.5% without complications, < 6.5% with complications) but only at the expense of frequent hypoglycaemia which has an adverse effect on quality of life (in line with existing NICE criteria)
- Those who have made significant efforts to optimise control but have a high HbA1c as a result of marked fluctuation in blood glucose levels and for whom further reduction in levels will result in unacceptable hypoglycaemia

It is expected that adults will be self-monitoring at least 4 times per day and are competent at dosage adjustment for meals, physical activity and other lifestyle issues, although this may not be the case in exceptional circumstances.

In significantly increasing access to pump therapy for those with type 1 diabetes it is important to provide guidance as to what to expect from pump therapy. Initiation of pump therapy should in the first instance be regarded as a treatment trial, which should be discontinued if the expected gains are not realised. These gains will depend on the specific indication for pump therapy, but, in the absence of well-defined quality of life indicators, are likely to be based on measurable parameters of glycaemic control, either improvement in HbA1c or reduction in frequency of severe hypoglycaemia. Whilst any reduction in severe hypoglycaemia is likely to be perceived as beneficial, it is more difficult to assign an expected reduction in HbA1c. A fall in HbA1c of 0.5% is likely to be of clinical significance, whilst the technology assessment report suggests a fall of 1.4% is likely to result in an acceptable cost per QALY. If guidance is to be given as to expected HbA1c response to pump therapy, it would seem reasonable to accept a response related to the starting HbA1c, possibly a 10% reduction.

In addition to the broad recommendations considered above there are additional factors which need to be considered.

There is an increasing evidence base for the efficacy of pump therapy in children and adolescents, and it may be necessary to consider modifying the guidance for this particular group. There was support within the DoH insulin pump therapy working group, for offering the choice of insulin pump therapy or MDI as an initial method of intensifying insulin therapy, as MDI can be particularly difficult to use successfully in school-age children. It would also be more reasonable to expect self-monitoring in this group to be according to need and ability.

There are some circumstances where insulin pump therapy may be beneficial, and there are case reports and series to back this up, but there will never be large clinical trials in these patient groups because the problems experienced are uncommon. In our practice these have included:

- Acute painful neuropathy or significant symptoms related to autonomic neuropathy, such as postural hypotension or gastroparesis, in whom conventional treatment has failed. In these conditions blood glucose fluctuations may play a significant role in the severity of symptoms.
- Hypoglycaemia unawareness, where pump therapy offers an option for maintaining stably higher blood glucose levels without excessively compromising overall glycaemic control.
- Allergy to subcutaneous insulin, where there are now a number of published cases successfully using CSII.

There are also two areas where a better evidence base is needed, and the technology assessment report has highlighted these and encouraged further research in these areas:

- Pregnancy – we have considerable expertise in use of pump therapy for diabetic pregnancy, having managed 40 women on pumps through pregnancy. Our observational data show benefits compared to a

comparable cohort of women using MDI, in terms of glycaemic control (HbA1c) preconceptually, in the first trimester, intra-partum and post-partum, with improved intra-partum control resulting in reduced frequency of neonatal hypoglycaemia; reduced frequency of maternal hypoglycaemia; and less maternal weight gain. However we have not seen significant differences in fetal growth between the two cohorts.

- Type 2 diabetes – we have successfully used insulin pump therapy in two patients with severe insulin resistance and unacceptable metabolic control, and there have been a number of similar case reports. Clinical trials to date have either recruited unselected patients with type 2 diabetes, or those suffering from morbid obesity, and have not shown a benefit of pump therapy. A clinical trial targeted at those with severe insulin resistance would seem more likely to be of value.

In summary:

- The existing NICE guidance has been very successful in promoting use of insulin pump therapy, but there is a need to broaden access to pump therapy and to more precisely define the expected health gains from using the technology.
- It would be helpful not to suggest an arbitrary percentage of those with type 1 diabetes who might be expected to need an insulin pump as this has been used as a ceiling by commissioners.
- There needs to be recognition that there are a number of uncommon indications for pump therapy which cannot be defined on the basis of clinical trial results, but the number of people with these indications is very small.
- Further research is needed to establish the place of pump therapy in diabetic pregnancy and type 2 diabetes.