ABCD submission, NICE technology appraisal review, Insulin pump therapy (TA057)

Prepared on behalf of ABCD by:

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1. What is the place of the technology in current practice?

There is a widespread variation in the use of insulin pump therapy even within the criteria established by the original NICE technology appraisal. However the consensus reached by ABCD, and one applied in most large UK adult or paediatric pump centres, is that:

Insulin pump therapy is an option for intensified insulin therapy in those with type 1 diabetes. It will usually be initiated following a period of MDI, including use of long-acting analogues, and a course of structured education. It is of particular benefit for:

- Those who are able to achieve target HbA1c (< 7.0%) but only at the expense of frequent hypoglycaemia which has an adverse effect on quality of life
- Those who have made significant efforts to optimize 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 hypoglcyaemia

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 cases.

Children and adolescents should be offered the choice of insulin pump therapy or MDI as an initial method of intensifying insulin therapy, and will be expected to self-monitor according to need and ability.

Specific indications

Women contemplating pregnancy should be considered for insulin pump therapy pre-conceptually if they fail to achieve their target HbA1c, given that any improvement in control could have significant benefits for fetal and maternal outcome. Women who conceive on MDI should be offered insulin pump therapy during pregnancy if targets for glycaemic control are not achieved (HbA1c < 7.0%; blood glucose 4.4-6.1 mmol/l before meals, < 8.6 mmol/l 2 hours after

meals) or problematic hypoglycaemia occurs. The decision as to whether to continue pump therapy post-partum should be made on an individual basis.

A trial of pump therapy should be considered for people with diabetes suffering from acute painful neuropathy or significant symptoms related to autonomic neuropathy in whom conventional treatment has failed. In these conditions blood glucose fluctuations may play a significant role in the severity of symptoms.

In those with hypoglycaemia unawareness pump therapy offers an option for maintaining stably higher blood glucose levels without excessively compromising overall glycaemic control.

In the rare situation of extreme insulin sensitivity pump therapy may be the only way of achieving blood glucose control without frequent hypoglycaemia.

When needle phobia is associated with adverse metabolic consequences pump therapy may offer a solution for improving concordance and hence control.

In those with type 2 diabetes CSII may be considered when there is severe insulin resistance with unacceptable metabolic control.

There may be specific quality of life issues which could be successfully addressed by switching to pump therapy (table 1). The criteria for success of CSII in these individual situations should be comprehensively defined in advance to allow objective assessment.

Excessive number of injections for optimised control
Unacceptable number of sick days
Pathological fear of hypoglycaemia
Marked glycaemic excursions/dawn phenomenon
Impaired exercise capacity
Abnormal eating behaviour
Shift work
Frequent travel across time zones
Suboptimal school performance
Exclusion from aspects of a full school life
Behavioural problems eg meal times
Adverse impact on family dynamics

Table 1: Specific quality of life issues for CSII

2. Any additional sources of evidence?

In this section we will focus on individual centre experience with insulin pumps, both a general consideration of improvement in glycaemic control and its sustainability, and its use in subsets of patients who do not necessarily fulfill the current NICE criteria.

a) Cohort study from Harrogate, Bournemouth and Liverpool

We analysed glycaemic control in 145 pump users with at least 12 months experience from three large pump centres. The improvements in the mean of the HbA1c over time are very similar in each centre: 8.5% immediately pre-pump; 7.7% after 3 months on pump therapy; 7.0% the lowest on pump therapy ($p<0.0001$ vs pre-pump, one way ANOVA) after an average 17.5 months therapy; 7.8% the latest ($p<0.0001$ vs pre-pump) after an average of 38.5 months on pump therapy (range 12-84 months). 69.5% of pump users have a better HbA1c now than before starting pump therapy, with 53.5% having an HbA1c at least 0.5% lower. HbA1c levels during pregnancy were excluded.
In keeping with a number of recent published cohort studies the worse the pre-pump HbA1c the greater the improvement in HbA1c (figure 1).

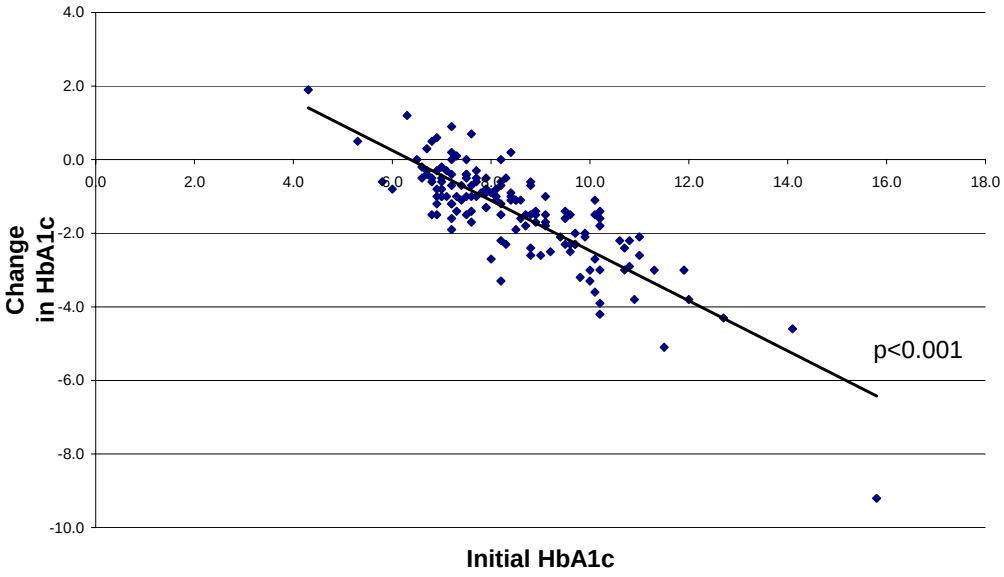

Figure 1: Change in HbA1c (best) vs Pre-pump HbA1c

b) Use of CSII in pregnancy

Since 1998 in Harrogate we have offered an insulin pump to all women wishing to conceive or presenting pregnant. We have managed 72 women with type 1 diabetes, 35 of whom used pump therapy during pregnancy. 25 women used

CSII pre-conceptually, 5 commenced pump therapy during the first trimester and the remaining 5 by 18 weeks gestation.

Women using the pump pre-conceptually had a significantly better HbA1c immediately pre-conception (7.2 ± 1.2 vs 7.9 ± 1.8%, $p < 0.05$ 2 sample t-test). During the first trimester there was a tendency to an improved HbA1c in the women using pump therapy (6.9 ± 1.1 vs 7.5 ± 1.7%, $p = 0.05$ 2 sample t-test) but levels were very similar in the two groups in the remainder of the pregnancy (2^{nd} trimester 6.4 vs 6.5%, 3^{rd} trimester 6.7 vs 6.5%). Mothers who remained on CSII post-partum had a trend towards better control after 3 months (7.6 ± 1.1 vs 8.3 ± 2.0%).

There was a significant reduction in reported hypoglycaemia severity in the women using pumps (figure 2).

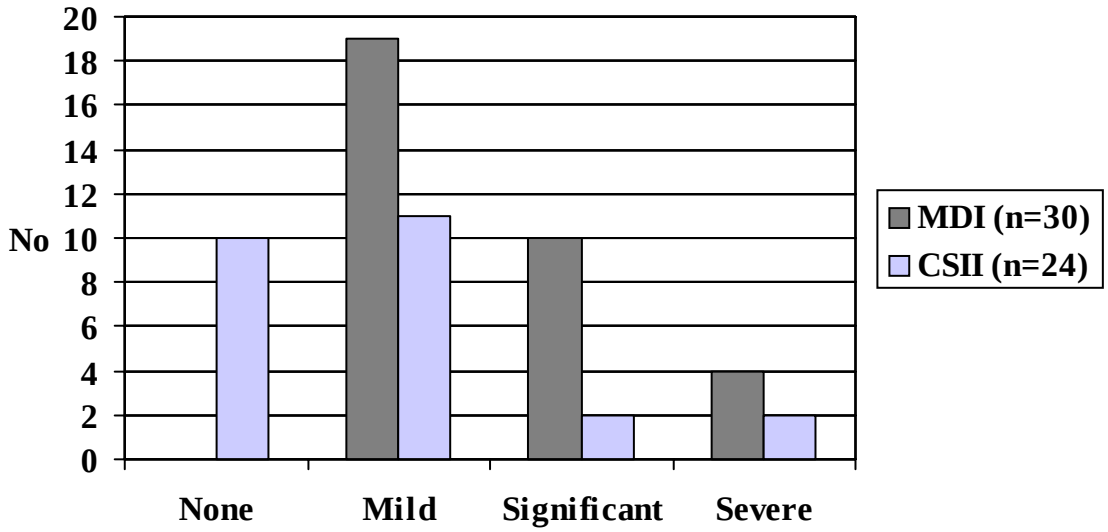

Figure 2: Reported severity of hypoglycaemia in pregnant diabetic women

There was no difference in fetal growth velocity between the two cohorts, perhaps unsurprisingly given the similar HbA1c in second and third trimesters. However average birth weight was marginally lower in the term babies whose mother's had used pump therapy (3.77 vs 3.98 kg**,** NS).

There was a significantly lower rate of neonatal hypoglycaemia amongst babies born to pump users, and average glucose at 1 hour was significantly higher (2.5 ± 0.8 vs 1.9 ± 1.1 mmol/l, $p < 0.05$ 2 sample t-test). This reflects better intra-partum control of maternal glucose in those women using pumps, all of whom continued using the pump during delivery. Average blood glucose within 1 hour of delivery was 5.4 ± 2.1 vs 6.9 ± 2.4 mmol/l (CSII vs MDI, $p < 0.01$ 2 sample t-test). There was a trend towards a reduced severity of jaundice in the pump users' babies, but other neonatal outcomes, including anomaly rates, did not differ between the cohorts.

Mothers using pumps required significantly less insulin at term and gained less weight (11.7 ± 4.5 vs 15.5 ± 4.4 kg, $p < 0.01$ 2 sample t-test).

c) Use of CSII in children with special educational needs (report provided by John Davies, consultant paediatrician, Warwick)

Case histories are presented of 5 children/young people with Type 1 diabetes and special educational needs managed by CSII.

3 children attending the same special school have Down's Syndrome, diabetes and additional problems.

Child A had been diabetic for 3 years, insulin requirements were increasing, control was erratic and gastrointestinal symptoms (bloating, abdominal pain and episodic diarrhea) began to be troublesome. A high titre of gliadin antibodies and positive tissue transglutaminase antibodies indicated coeliac disease. Biopsy was not done. The combination of Down's, diabetes and a gluten free diet rendered control with biphasic Insulin impossible. Multidose Insulin was out of the question. The school staff would not administer Insulin.

CSII using a pump with a 'locked sequence' which accounts for the CHO load in a standardized packed lunch proved very successful. School staff did agree to manage blood sugars using a fixed protocol for boluses after several training sessions. The child's parents quickly found that control at home was much more stable on CSII 'dramatically' changing the child's behaviour, we presume by eliminating previous 'wild' swings in blood sugar. The mother says simply 'the pump gave me my child back'.

Child B had been diabetic for 7 years, has significant 'communication' problems, poor control with onset of puberty and a needle phobia. CSII using a 'locked' pump again led to much improved control and eventually a much less stressful home environment. At first we had problems siting the cannula. The child would only let one particular member of our staff site the cannula in the abdomen, necessitating regular revisits to the ward and some 'ad hoc' to replace 'blocked' cannulae but with patience the child gradually came to accept mother and then father siting cannulae at first on the ward and eventually at home. Child B's parents found the change to CSII difficult but in their own words 'it was worth it, it is so much easier for T……. now'.

Child C had been diabetic for 2 years and also is hypothyroid on Thyroxine replacement. This child's' parents were obviously well aware of what we had done for A & B and not unnaturally asked for the same for their child, which we agreed to after discussion with our PCT. We cannot demonstrate significant improvement in control which was already reasonable on b.d. biphasic insulin but the parents are adamant that this has been a significant benefit to the child's quality of life. The child is only 6 years.

2 other children (children D & E) with 'special educational needs' and at primary schools have been managed with CSII.

Child D presented age 3 in DKA. It was quickly apparent that he had a significant 'language' delay and was hyperactive (all subsequently confirmed at CDC assessment). He had a single young unsupported mother who also had had 'special educational' help when at school. It required 2 nurses to hold Child D to give his insulin, an impossible situation to manage at home. While we had exactly the same problem siting the 'pump cannulae' at least they lasted a couple of days. After 10 days of CSII on the ward he went home running a 'locked sequence' pump but returning frequently for the cannulae to be resited. Eventually and after many training sessions we succeeded in training his single parent how to administer bolus doses appropriately and change the cannulae. He has been on a pump now for 3 years. There are still frequent ad hoc visits to the ward for minor problems but he has had only 3 overnight admissions, all with intercurrent illness. The child attends a normal primary school where by chance one of his year teachers, herself a diabetic, has taken a particular interest and volunteered to be trained to run his pump. We (the diabetic team) have no doubt that without a pump almost certainly we would have been looking to social services for 'fostering arrangements' and probably against his mother's wishes.

Child E has significant learning problems, attends a mainstream primary school but with special provisions and also has a single unsupported mother. Additionally the child has a growth hormone deficiency (delayed bone age, short stature << 0.4^{th} centile) and the local tertiary centre have recommended GH therapy but his mother remains equivocal because he also has a needle phobia. His diabetic control on b.d. injected Insulin was problematic. The doses were small and he was prone to hypoglycaemia. CSII again running with a locked sequence during the day and 'standardized' packed lunch has solved the problem, not the least because we can accurately use small doses of Insulin.

These case reports highlight what can be achieved with pump therapy, both in improving blood glucose control, and, as importantly, in enhancing quality of life, an issue of equal relevance to adult users.

d) Other special situations

Patients with Coeliac disease and Type 1 diabetes have benefited from pump therapy. They often cannot manage their swings in blood sugar with simply a better diet and multiple dose insulin, whilst with pump therapy they are able to reduce fluctuations in glycaemic control and return to a normal active life.
Similarly there are a number of cases of diabetic gastroparesis where CSII has allowed glycaemic control to be markedly improved. This is particularly the case when such patients require nasogastric feeding, with the glucose excursions associated with high calorie feeds difficult to manage with insulin injections. In

some cases the improvement in HbA1c on pump therapy has caused the gastroparesis to improve and allowed patients to return to normal eating.

There are now a number of cases, some published, where CSII has been successfully used in people suffering from allergy to subcutaneous insulin.

There are also a number of anecdotal reports of improvements in intractable painful peripheral neuropathy or symptomatic autonomic neuropathy, usually with intractable postural hypotension, attributed to the use of CSII.

Whilst randomized controlled trials published since the last NICE guidance support the position that pump therapy should not be routinely used for those with type 2 diabetes, there may be small subgroups of those requiring insulin in whom CSII is beneficial. In particular there have been a number of cases of people with severe insulin resistance, where insulin requirements may be in excess of 500 units per day, in whom pump therapy using either conventional rapid-acting analogues or U500 insulin have resulted in dramatic improvements in glycaemic control, sometimes with considerable reductions in total daily insulin dose, presumably because the much smaller subcutaneous insulin depot is much more effectively absorbed.

3. Implementation issues

NICE estimated the cost of insulin pump therapy at £1100-1400 per patient per year, depending on the pump used and consumable costs[1]. This may be offset by around £200 for the reduced insulin requirement and pen needles no longer required. It is possible that a national purchasing agreement could reduce costs further, and VAT costs can be defrayed by patients receiving consumables directly from the pump companies. These issues need consideration when entering into commissioning discussions with PCTs.

Currently there are a few diabetes centres in the UK with significant pump experience caring for at least 50 pump users, a few centres with rapidly increasing numbers of pump users, and many centres with a handful of pump users. The remaining centres refer to local specialist centres or do not consider pump therapy as an option. The latter approach is clearly contrary to NICE guidance and cannot be sustained, whilst an expansion in pump user numbers towards 15% of those with diabetes will determine that provision of pump services should as far as possible be local. There will clearly be a period of transition where new pump services will need to rely on established centres for support, both in training healthcare professionals and possibly patients.

NICE have detailed the personnel needed to run a pump service, a minimum of a physician, diabetes nurse specialist and dietitian with an interest in pump therapy. It would be expected that all these personnel would have attended an accredited training course, and that a minimum of 5 patients per year should be initiated on pump therapy for a diabetes centre to be recognized as a centre for

pump therapy. There is a need for a national system of recognition for these pump centres.

If NICE guidance is to be broadened there is a need for transparent audit to ensure that those who commence pump therapy fulfill the relevant criteria and that they benefit from pump therapy. Assessment of benefit will depend on the indication, but for the main indication should include at least one of:

- Improvement in HbA1c
- Reduction in frequency of severe hypoglycaemia
- Objective evidence of improvement in quality of life

Evidence of benefit should be evident by 6 months and re-evaluated on a regular basis.

For the specific indications for pump therapy it should be defined in advance what benefit should be anticipated. Increasingly pump centres are using contracts for pump users to define criteria for success and facilitate withdrawal of pump therapy if these criteria are not fulfilled.

The evidence base for the effectiveness of pump therapy would be enhanced if pump centres were to contribute anonymised data regarding control and complications to a central database. A number of centres are currently contributing to such a database which has been established by the paediatric epidemiology group at the University of Leeds.

Areas where specific research would be of value in establishing the role of pump therapy would include whether there are subgroups of those with type 2 diabetes who do benefit from pump therapy rather than MDI, and whether pump therapy has any advantages over MDI in the management of diabetic pregnancy. There is little likelihood of an RCT being performed to establish whether pump therapy is better than MDI at reducing the risk of complications, but it may be possible to determine how effective pump therapy is in alleviating the symptoms of peripheral sensorimotor and autonomic neuropathy.