

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (review of technology appraisal guidance 57)

1 Guidance

1.1 Continuous subcutaneous insulin infusion (CSII or 'insulin pump') therapy is recommended as a treatment option for adults and children 12 years and older with type 1 diabetes mellitus provided that:

- attempts to achieve target haemoglobin A1c (HbA1c) levels with multiple daily injections (MDIs) result in the person experiencing disabling hypoglycaemia. For the purpose of this guidance, disabling hypoglycaemia is defined as the repeated and unpredictable occurrence of hypoglycaemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life

or

- HbA1c levels have remained high (that is, at 8.5% or above) on MDI therapy (including, if appropriate, the use of long-acting insulin analogues) despite a high level of care.

1.2 CSII therapy is recommended as a treatment option for children younger than 12 years with type 1 diabetes mellitus provided that:

- MDI therapy is considered to be impractical or inappropriate, and
- children on insulin pumps would be expected to undergo a trial of MDI therapy between the ages of 12 and 18 years.

- 1.3 It is recommended that CSII therapy be initiated only by a trained specialist team, which should normally comprise a physician with a specialist interest in insulin pump therapy, a diabetes specialist nurse and a dietician. Specialist teams should provide structured education programmes and advice on diet, lifestyle and exercise appropriate for people using CSII.
- 1.4 Following initiation in adults and children 12 years and older, CSII therapy should only be continued if it results in a sustained improvement in glycaemic control, evidenced by a fall in HbA1c levels, or a sustained decrease in the rate of hypoglycaemic episodes. Appropriate targets for such improvements should be set by the responsible physician, in discussion with the person receiving the treatment or their carer.
- 1.5 CSII therapy is not recommended for the treatment of people with type 2 diabetes mellitus.

2 Clinical need and practice

- 2.1 Diabetes mellitus is a chronic metabolic disorder caused by insufficient activity of the hormone insulin and a subsequent loss of control of blood glucose levels. There may be a lack of the hormone itself or resistance to its action. Insulin is produced by the beta cells of the pancreas in response to rising blood glucose levels and mainly regulates the metabolism of carbohydrates, but also of proteins and fats. There are two types of diabetes mellitus. Type 1 diabetes mellitus is caused by the destruction of insulin-producing cells, leading to an absolute lack of the hormone. Type 2 diabetes mellitus is characterised by insulin resistance and is often associated with obesity. In type 2 diabetes mellitus, the pancreas initially responds by increasing insulin production, but over time this excess production cannot be maintained, leading to a decrease in insulin production and a lack of insulin. Both types of diabetes

mellitus are characterised by hyperglycaemia – an elevation of blood glucose levels above normal.

2.2 The onset of type 1 diabetes mellitus usually occurs in children and young adults, with an estimated prevalence in the UK in 2005 of 0.42% (approximately 250,000 people). The incidence has been increasing over time, with the greatest increase in children younger than 5 years. Type 2 diabetes mellitus occurs in adults and usually begins after the age of 45 years. The current prevalence in England is estimated to be 4.3% (approximately 2.5 million people). The incidence is rising and expected to rise further, because of an ageing population and an increasing prevalence of obesity. There is also an increasing incidence of type 2 diabetes mellitus in children.

2.3 Diabetes mellitus can cause short- and long-term complications. Short-term complications are acute metabolic emergencies that can be life-threatening: diabetic ketoacidosis, which is a consequence of high blood glucose levels (hyperglycaemia); and low blood glucose levels (hypoglycaemia) caused by treatment. Mild hypoglycaemia can be corrected by oral intake of sugars. Severe hypoglycaemia is defined by the need for assistance from another person for recovery. Severe hypoglycaemia can cause convulsions, coma and, very occasionally, death. In children, especially those younger than 5 years, severe hypoglycaemia can cause long-term cognitive impairment. Fear of recurrent hypoglycaemia not only decreases quality of life but can also hinder adherence to treatment and the achievement of good glycaemic control. The long-term microvascular and macrovascular complications of chronically elevated blood glucose levels include retinopathy and blindness, nephropathy and renal failure, ischaemic heart disease, stroke, neuropathy, and foot ulceration and amputation. Uncontrolled diabetes in pregnancy is associated with adverse pregnancy outcomes.

- 2.4 Diabetes mellitus is a lifelong condition in which both morbidity and treatment affect quality of life. On conventional (that is, injection) insulin regimens daily life activities need to be arranged around a relatively inflexible structure of meal times and insulin injections. Diabetes is a source of stress for all members of an affected person's family and in the case of children can cause intense parental anxiety. As the length of time with diabetes increases and with the onset of complications, people with diabetes may experience occupational difficulties because of disabilities as well as requiring prolonged and frequent medical attention.
- 2.5 Type 1 diabetes mellitus requires lifelong treatment with insulin. Type 2 diabetes mellitus is initially managed by lifestyle change including diet and weight loss, if necessary. If this is insufficient, oral glucose-lowering drugs are introduced. Over time, many people will need insulin to control their blood glucose levels. There are various types of insulin, distinguished by their rate of onset and duration of action. Insulin requirements change depending on food intake, exercise or intercurrent illness. Insulins with varying times to onset and durations of action are combined in treatment regimens, which are then delivered by multiple injections timed to coincide with insulin requirements. Achieving good control of blood glucose through an intensive regimen reduces the risk of complications. Intensive insulin regimens attempt to reproduce the normal secretion of insulin by the pancreas. However, exogenously administered insulin lacks the feedback mechanism that the pancreas uses to regulate insulin secretion, whereby insulin production decreases as blood glucose levels fall. Therefore, people taking insulin need to check their blood glucose levels regularly by using a monitor (glucometer). Regular measurements enable short-term control of blood glucose levels by adjusting the insulin dose. Long-term monitoring of control is achieved by measuring glycosylated haemoglobin (HbA1c) levels, which reflect

average blood glucose levels over the preceding 3 months. Good control is indicated by a value of less than 7.5% (the normal range for people who do not have diabetes is 4.5–6.1%).

3 The technology

- 3.1 The following insulin pump models are currently available: Animas IR 2020 (Animas, Johnson & Johnson, cost £2600), Paradigm real-Time MMT-522 (Medtronic, cost £2750), Paradigm real-Time MMT-722 (Medtronic, cost £2750), Accu-Chek Spirit (Roche Diagnostics, cost £2375), Accu-Chek D-Tron Plus (Roche Diagnostics, cost £996) and Deltec Cozmo (Smiths Medical, cost £2750).
- 3.2 Continuous subcutaneous insulin infusion (CSII) therapy makes use of an external pump that delivers insulin continuously from a refillable storage reservoir by means of a subcutaneously placed cannula. The pump can be programmed to deliver a basal rate of insulin throughout the day, with higher infusion rates triggered by the push of a button at meal times. This may be a bolus or over a period of time, and it can also deliver different basal rates of insulin at different times of the day and night. It is recommended that the cannula is replaced and repositioned every 3 days. The choice of pump in very young children should take into account the ability to deliver a very low basal rate.
- 3.3 Specific but infrequent complications of CSII therapy include reactions and occasionally infections at the cannula site, tube blockage and pump malfunction.
- 3.4 The pumps usually have a 4-year warranty and in some cases this can be extended by 2 years at an additional cost. CSII therapy also incurs costs for batteries, reservoirs, infusion sets, insulin, lancets, test strips and glucometers for monitoring. The costs of monitoring are common to all forms of insulin therapy. There is also a one-off cost for education of people when starting treatment with a pump,

and there are additional costs for continued medical support during the time that the person is learning to become self-sufficient in the management of their diabetes mellitus.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

4.1.1 From the evidence presented in the NICE appraisal of glargine (NICE technology appraisal guidance 53 [TA53]) and a search for evidence that has emerged since, the Assessment Group concluded that multiple daily injection (MDI) therapy based on long-acting insulin analogues is more efficacious than MDI therapy based on older insulins, such as neutral protamine Hagedorn (NPH, Isophane), in type 1 diabetes mellitus. Therefore, in type 1 diabetes mellitus, analogue-based MDI therapy was used as the comparator for CSII therapy. For type 2 diabetes mellitus, a Cochrane review from 2007 concluded that there was no benefit of long-acting insulin analogues over NPH. Taking TA53 into account, which limited the use of glargine in type 2 diabetes mellitus, the Assessment Group concluded that, in type 2 diabetes mellitus, the advantage of long-acting insulin analogues over NPH was not proven and both remained valid comparators for CSII therapy in this appraisal.

4.1.2 The Assessment Group found four randomised controlled trials (RCTs) in type 1 diabetes mellitus that compared CSII with analogue MDI therapy and four RCTs in type 2 diabetes mellitus that compared CSII with MDI therapy (three NPH-based and one glargine-based). One RCT conducted in children and adolescents with type 1 diabetes mellitus reported a statistically significant greater reduction in HbA1c levels following 16 weeks of CSII

therapy compared with analogue-based MDI therapy (1% decrease versus no change). In the three further studies in type 1 diabetes mellitus and the four studies in people with type 2 diabetes mellitus, there was little evidence of a statistically significant difference between CSII and MDI therapy in terms of HbA1c reduction. There were statistically significant fewer episodes of severe hypoglycaemia with CSII therapy compared with MDI therapy in the study in children and adolescents with type 1 diabetes mellitus. The other studies had too few hypoglycaemic episodes to comment or showed no difference. There was no evidence of a statistically significant difference in insulin dose being administered, mean blood glucose levels, glucose variability or weight between the two groups. There was no statistically significant difference in the quality of life for people with type 1 diabetes mellitus between CSII and MDI therapy in the two studies that reported this outcome. In type 2 diabetes mellitus, one study found no difference in the quality of life and another reported a statistically significant difference in treatment satisfaction favouring CSII therapy. Many of these studies were of brief duration, and improvements in glycaemic control may be gained as the person's expertise with the use of the pump increases with time. Conversely, any improvements in HbA1c levels observed in the short term cannot be assumed to persist in the longer term.

- 4.1.3 The Assessment Group reported a total of 48 observational studies. The majority of the patients in these studies had type 1 diabetes mellitus; only four studies included a small number of people (3–7%) with type 2 diabetes mellitus. It noted that, although these studies carried a greater risk of bias than the RCTs, they were much larger, of longer duration and more representative of people likely to be considered for CSII therapy in routine clinical practice than the populations in the RCTs available. A total of 46 studies reported HbA1c levels before and after CSII therapy. Of

these, all 18 studies in the adult/mixed age group showed a statistically significant decrease in HbA1c levels (in the range 0.2–1.4%) after initiation of CSII therapy. Of the 23 studies in the children/adolescent age group, 20 studies showed a decrease in HbA1c levels after starting CSII therapy (in the range 0.2–1.2%) with the difference reaching statistical significance in 13 studies. Three studies showed an increase in HbA1c levels after starting CSII therapy; however, in two of these studies the increase was not statistically significant, and the third study did not report whether the HbA1c increase of 0.6% was statistically significant. In five studies in young children, the HbA1c decrease after starting CSII therapy was in the range 0.2–1.6%, with the change being statistically significant in four of these studies. Twenty-six observational studies compared the rate of severe hypoglycaemic episodes in people receiving CSII and MDI therapy. Of the 10 studies in the adult/mixed age groups, eight reported statistically significant decreases in the rate of severe hypoglycaemic episodes after starting CSII therapy. The rate ratios were in the range 0.07–0.40. In the remaining two studies, there were no episodes before or after beginning pump use. Of the 11 studies in children and adolescents, one had no severe hypoglycaemic episodes and the other 10 reported decreases in their frequency following initiation of CSII therapy, with rate ratios in the range 0.12–0.80. In four of these studies, the reduction was statistically significant, three did not report significance, and three did not show a statistically significant decrease. In five studies in young children, the rate ratios were in the range 0–0.81, with the difference being statistically significant in three. Observational studies also showed no statistically significant increase in the incidence of diabetic ketoacidosis, some minor weight gain and, in some studies, an overall reduction in daily insulin dose, after initiation of CSII therapy. Of the 22 studies that reported continuation rates, these were in the range of 74–100% at 1–5 years.

- 4.1.4 The Assessment Group also accessed data from the Insulin Pump Clinical Database. This information is collected from a group of centres with considerable experience of using pumps and reflects results with routine care in centres with expertise.
- 4.1.5 The Assessment Group identified six observational studies of CSII therapy in pregnant women with type 1 diabetes mellitus. One study showed statistically significant lower HbA1c levels in women on CSII compared with MDI therapy, although the Assessment Group felt the results should be disregarded because there appeared to be selection bias in the study. Overall, there were no statistically significant differences in either maternal or fetal outcomes of pregnancy between CSII and MDI therapy.
- 4.1.6 The clinical-effectiveness evidence from the manufacturers was based on a so-far unpublished meta-analysis of RCTs and observational studies of people with type 1 diabetes mellitus, comparing CSII therapy with isophane-based or glargine-based MDI therapy. The meta-analysis provided data on the baseline rate of, and the reduction in, severe hypoglycaemic events in the group of people receiving CSII therapy. The greatest reduction occurred in people who had the highest initial hypoglycaemia frequency. Glycaemic control was also significantly better for those people receiving CSII therapy; the greatest reduction was achieved in people who had the highest baseline HbA1c levels when receiving MDI therapy. Detailed results of this study were designated as 'academic in confidence'.
- 4.1.7 The clinical specialists emphasised the robustness of the evidence that allowed the decrease in HbA1c levels to be used as a reliable proxy for avoidance of the long-term complications of diabetes mellitus. The relationship between complications and HbA1c levels is such that, for any particular decrease in HbA1c, the benefits in terms of complications avoided are greater for a higher baseline

HbA1c. In addition, it is also possible that the variability in blood glucose level may also have a role to play in the development of long-term complications, and there is evidence that CSII therapy can reduce this variability. The clinical specialists also reported that, regardless of the mode of treatment, the higher the baseline HbA1c the greater the value of any improvement would be. The paediatric clinical specialist emphasised the difficulty in controlling blood glucose in very young children because of their sensitivity to insulin, small size and irregular lifestyle, and noted the special relevance of insulin pumps to this age group. The time of puberty was also identified as a difficult time to control diabetes because of hormonal and psychosocial reasons. Children also have a greater lifetime risk of complications because these depend on the duration of the disease, and an early onset makes for a potentially longer time lived with diabetes. The patient expert described the stress that being the parent of a child with diabetes entails and the effects of this on a person's social and professional life.

- 4.1.8 In summary, there is little evidence from the RCTs of a significant difference between CSII and MDI therapy in terms of a decrease in HbA1c levels or in the rate of severe hypoglycaemic episodes in people with diabetes mellitus. Observational studies show a much greater improvement (decrease) in HbA1c levels with CSII therapy, as well as statistically significant decreases in the rate of severe hypoglycaemia episodes. There is no clear evidence of any greater benefit of CSII over MDI therapy in pregnancy.

4.2 Cost effectiveness

- 4.2.1 A systematic review of the cost-effectiveness literature for insulin pumps conducted by the Assessment Group found 11 publications. Except for one study which developed a relatively simple Markov model and another in which the model was not reported, all publications used the Centre for Outcomes Research (CORE)

model. Three studies that were performed in the UK and took the health service perspective reported incremental cost-effectiveness ratios (ICERs) for CSII therapy compared with MDI therapy of £11,500, £26,300 and £32,800 per quality-adjusted life year (QALY) gained. In the cost-effectiveness studies, the most common assumed improvement in HbA1c levels with CSII therapy compared with MDI therapy was 1.2%.

4.2.2 The manufacturers provided a joint economic evaluation that was also based on the CORE model. The patient cohort characteristics were based on a UK database of 3000 adults with type 1 diabetes mellitus followed up over a period of 9 years. The average age was 37.8 years. Three values for the decrease in HbA1c levels with CSII therapy were considered: the lower value for the decrease in HbA1c levels was based on the results of the confidential meta-analysis (see section 4.1.6); the upper value for the decrease in HbA1c levels was 1.29%, reflecting the higher baseline HbA1c seen in the UK population; the third value was an intermediate decrease in HbA1c levels, midway between the upper and lower values. The decreases in HbA1c levels were applied to a baseline of 9.4% in each analysis. The rate of severe hypoglycaemic episodes was assumed to be reduced by approximately 75% during treatment with CSII therapy compared with MDI therapy. Health-state utilities were those reported from the United Kingdom Prospective Diabetes Study (UKPDS), which was conducted in people with type 2 diabetes mellitus.

4.2.3 All three analyses showed a gain in QALYs for people receiving CSII compared with MDI therapy at an increased cost. The ICER for CSII compared with MDI therapy was £34,330 per QALY gained for the lower value of decrease in HbA1c levels, £16,842 per QALY gained for the upper value of decrease in HbA1c levels, and £22,897 per QALY gained for the intermediate decrease in HbA1c levels.

- 4.2.4 The Assessment Group commented that the industry submission assumed that the cost of a severe hypoglycaemic episode was £413, which included a hospital stay. As in clinical practice, only a minority of people with severe hypoglycaemia are hospitalised. This would overestimate the average cost of managing an episode of severe hypoglycaemia and underestimate the ICER of CSII compared with MDI therapy. The Assessment Group also noted that the manufacturers' economic model did not consider the benefits associated with the avoidance of the fear of hypoglycaemia, the reduced incidence of depression, or the avoidance of cognitive impairment in children, which could result from improved glycaemic control. The effect of excluding such considerations would be an overestimation of the calculated ICERs.
- 4.2.5 The Assessment Group's economic evaluation was also based on the CORE model. It simulated a cohort of people with type 1 diabetes mellitus with an average age of 40 years. The base-case analysis assumed a baseline HbA1c level of 8.8% before CSII therapy, and a reduction of 0.9% while receiving CSII therapy, based on preliminary data from the Insulin Pump Clinical Database for people aged 20–39 years. Sensitivity analyses for the effect of CSII therapy on the reduction in HbA1c levels from a baseline of 9.0% were also undertaken. A baseline rate for severe hypoglycaemic events of 18.7 per 100 person years was assumed for the base case, as in previous modelling carried out for the development of TA53; the effect of CSII therapy on this rate was investigated using reductions of 50% and 75%. Sensitivity analysis assumed a higher baseline rate of severe hypoglycaemia equal to that in the manufacturers' submission (designated as academic in confidence; see section 4.1.6). Lastly, the Assessment Group modelled a cohort of people who were assumed to have good control with an HbA1c level of 7.5% (in whom further reductions would not occur) but who had a very high rate of severe

hypoglycaemia (134 episodes per 100 person years), with an investigation of reductions of 50% and 75% with CSII therapy.

- 4.2.6 The costs of the pumps were annualised and it was assumed that the associated infusion equipment was changed every 3 days, as recommended. For CSII therapy, the daily requirement of insulin was 0.6 IU per kg – less than the 0.7 IU per kg required for MDI therapy. CSII therapy was assumed to incur a one-off training cost of £240 when a person starts to use the pump. Both CSII and MDI therapy were assumed to incur the same costs for blood glucose testing. The average cost of an episode of severe hypoglycaemia was assumed to be £65.
- 4.2.7 The base-case analysis with a reduction of HbA1c levels of 0.9% and a severe hypoglycaemic event rate of 18.7 episodes per 100 person years reduced by 50%, over a time horizon of 50 years, produced an ICER of £37,712 per QALY gained for CSII compared with MDI therapy. Changing the reduction in the rate of severe hypoglycaemia events to 0% or 75% did not change the ICER significantly. With the higher baseline rate of severe hypoglycaemia assumed in the manufacturers' submission (designated as academic in confidence; see section 4.1.6), a 50% reduction, and baseline HbA1c levels reduced to 7.9% from a baseline of 8.8%, the ICER was £36,587 per QALY gained. When a greater reduction in HbA1c levels of 1.4% was assumed, with no reduction in severe hypoglycaemic event rates, the ICER was £24,720 per QALY gained. In the cohort with good glycaemic control, when there was assumed to be no improvement in HbA1c levels but the severe hypoglycaemic event rate was 134 per 100 person years, the ICER was £273,992 per QALY gained for a 50% reduction and £152,058 per QALY gained for a 75% reduction in severe hypoglycaemia rate. Avoidance of severe hypoglycaemic events can lead to quality of life gains by avoiding the disutility of the event itself and because of the reduced fear of such events. In the scenario with a 0.9%

decrease in HbA1c from a baseline of 8.8% and a 50% reduction in the rate of severe hypoglycaemia events from that in the manufacturers' submission, which was associated with an ICER of £36,587, an assumed annual 0.01 quality of life increment in the CSII arm decreased the ICER to £29,300 per QALY gained. When the assumed quality of life increment was 0.03, the ICER decreased to £21,000 per QALY gained. In the cohort with good glycaemic control, when there was assumed to be no improvement in HbA1c levels, the severe hypoglycaemic event rate was 134 per 100 person years, an annual quality of life increment of 0.05 was assumed and a reduction in the rate of severe hypoglycaemia events by 50%, the ICER was £28,600 per QALY gained. For the same cohort but with a 75% reduction in severe hypoglycaemia events, and an annual quality of life increment of 0.04 the ICER was approximately £31,300 per QALY gained.

4.3 *Consideration of the evidence*

- 4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of CSII for the treatment of diabetes mellitus. It discussed the important outcomes of treatment, including reduced HbA1c levels, reductions in both hypoglycaemia and the fear of recurrent severe hypoglycaemia, and other aspects of quality of life for both adults and children. It weighed up the RCT evidence, the observational evidence and the views expressed by the clinical specialists and patient experts. It considered evidence on the nature of the condition and the value placed on the benefits of CSII by people with diabetes mellitus and those who represent them. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.3.2 The Committee first considered the evidence from the RCTs. The Committee was persuaded that these few, small trials of relatively short duration could not be relied on alone to capture the benefits

of CSII therapy. The Committee noted that the larger quantity of evidence from observational trials showed significant and larger benefits from the initiation of CSII therapy. It was aware of the biases operating in such studies and the need to interpret these results with caution. However, it agreed that people enrolled in observational studies would more closely resemble the population in routine clinical practice that would be considered as likely candidates for CSII therapy. In addition, these studies included a larger number of people and ran over longer periods of time. The Committee concluded that it was appropriate to use evidence from such studies as well as from the RCTs to inform its decisions.

4.3.3 The Committee considered the effect of CSII therapy on quality of life. It was persuaded by the clinical specialists and patient experts that the use of insulin pumps yielded quality of life benefits, such as flexibility, autonomy, and improved sleep and socialisation. In particular, the Committee agreed that decreasing the rate of severe hypoglycaemic episodes would improve the quality of life for those people who experience frequent and disabling episodes and who consequently live with fear of such episodes.

4.3.4 The Committee therefore concluded that CSII therapy had a valuable effect on blood glucose control. HbA1c levels were reduced, particularly when these levels were high at baseline (approximately 9.0%). The Committee noted that the decrease in HbA1c levels after beginning CSII therapy was clearly related to the initial HbA1c level, with more pronounced decreases in HbA1c levels seen in people with higher baseline levels. The Committee also heard that complications increased at more than a linear rate as HbA1c levels increased, leading to the conclusion that decreases in HbA1c from a higher baseline level would result in larger reductions in complications. It was also persuaded that CSII therapy could reduce the rate of hypoglycaemic episodes, and it heard from the patient experts that when hypoglycaemia occurs in

people using CSII therapy, it does so gradually and with sufficient time for the pump user to take remedial action.

4.3.5 The Committee considered the results of both the manufacturers' and the Assessment Group's economic modelling. In both, ICERs for CSII therapy were sensitive to the assumed decrease in HbA1c levels. The Committee noted that only pronounced decreases in HbA1c levels, contingent on a baseline level well above 7.5%, brought the ICERs down to a level usually considered to be acceptable.

4.3.6 The Committee was aware that guidelines for people with diabetes, including those of NICE, recommend a target HbA1c level of 7.5%, or lower in the presence of vascular complications. The Committee endorses these previously recommended target levels for HbA1c. However, the Committee noted that there were several means to this end, including the use of structured education; and it considered that the contribution to be made by insulin pumps had to be restricted to circumstances where the pumps were a cost-effective option. The Committee agreed that at very high baseline HbA1c levels the decrease expected with CSII could make CSII therapy cost effective because of the avoidance of long-term complications. However, at baseline levels of less than 9.0%, CSII would only be cost effective if an additional quality of life benefit was assumed. This benefit could be derived from the avoidance of the fear of hypoglycaemia as well as from other quality of life improvements associated with the use of insulin pumps themselves which were not captured in the base-case economic modelling. The Committee judged that when a plausible small quality of life benefit is assumed, CSII would be cost effective at a baseline HbA1c level of 8.5% or above, and therefore concluded that CSII therapy is recommended as a treatment option for adults with type 1 diabetes mellitus whose HbA1c levels have remained high (that is, at 8.5%

or above) on MDI therapy (including, if appropriate, the use of long-acting insulin analogues) despite a high level of care.

4.3.7 The Committee was aware that lower HbA1c levels are associated with a greater risk of episodes of hypoglycaemia and that attempts to achieve target haemoglobin levels with MDI can result in a greater risk of hypoglycaemic episodes. The Committee considered the economic modelling for people who reach a target HbA1c level of 7.5% on MDI, but who experience the occurrence of disabling hypoglycaemic episodes. The Committee accepted that such episodes can be significantly decreased with CSII therapy. Although this effect did not have a pronounced impact on the ICERs in the Assessment Group's base case, the Committee considered that there would be a greater quality of life benefit due to the avoidance of the fear of hypoglycaemia by the use of CSII. Taking into account the fact that the model excluded any impact of mild and moderate hypoglycaemia episodes on the quality of life, the Committee agreed that CSII therapy could be considered an appropriate use of resources in the NHS for adults with baseline HbA1c levels below 8.5% but who experience disabling hypoglycaemia with further intensification of MDI therapy aimed at decreasing the HbA1c level. Therefore, the Committee concluded that CSII therapy is recommended as a treatment option for adults with type 1 diabetes mellitus when attempts to achieve target HbA1c levels, typically 7.5%, with MDI therapy result in the person experiencing disabling hypoglycaemia. Disabling hypoglycaemia is, for the purpose of this guidance, defined as repeated and unpredictable occurrence of hypoglycaemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life.

4.3.8 The Committee paid special attention to the use of CSII therapy in children. It heard from the clinical specialists about the importance of this treatment in very young children. It was also aware of the

difficulties and delay that a trial of MDI therapy, to prove that such therapy was ineffective, would entail in this young patient group. The Committee was concerned that the CORE model was not validated in children and the data from adults used in the model could not be extrapolated to children. However, the Committee considered that all the factors relevant to favouring CSII therapy for adults in whom MDI therapy had failed to achieve an acceptable HbA1c level, or who experienced disabling hypoglycaemia, applied as least as much to children. In addition, the Committee heard from the clinical specialists that managing the delivery of small insulin doses in very young children and delivering midday doses of insulin to young school children are difficult or impractical, leading to ineffective glycaemic control. The Committee therefore decided that, on balance, CSII therapy should be recommended for children younger than 12 years with type 1 diabetes mellitus as a treatment option without an intensive trial of MDI therapy if such a trial was felt clinically inappropriate or impractical. This recommendation is consistent with NICE clinical guideline 15 (Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults).

- 4.3.9 In developing the recommendations for children, the Committee considered that children 12 years and older would normally be competent to self-inject an afternoon dose of insulin at school which would allow for a proper trial of MDI therapy. The Committee also agreed that because MDI therapy based on long-acting analogues is more efficacious for type 1 diabetes mellitus than MDI therapy based on older insulins, MDI therapy should be judged to be unable to attain the required HbA1c levels only if it is based, if clinically appropriate, on long-acting insulin analogues. The Committee considered its approach for children on insulin pumps who reach the age of 12 years and who, following this guidance, would not have had a trial of MDI. The Committee considered that

the continuation of CSII could not equitably be supported without a trial of MDI after that stage. The Committee was mindful that making such a recommendation too strict could mean a change in insulin regimen for children who had achieved satisfactory control of their blood glucose level. The Committee discussed the implications of undergoing such a trial, especially during a period where children experience many developmental, social and educational changes. It concluded that such a trial of MDI would normally need to be undertaken sometime before a child reached adulthood at the age of 18 years.

4.3.10 The Committee considered the use of CSII therapy in women with type 1 diabetes mellitus who were pregnant or planning a pregnancy. It agreed that such women benefited from the use of insulin pumps but that there was no evidence that the criteria for the use of pumps should differ from those applied to other adults.

4.3.11 The Committee considered the use of CSII therapy in people with type 2 diabetes. There was no evidence placed before the Committee that showed that CSII therapy improved outcomes in this group of individuals. Furthermore, the economic modelling was limited to cohorts with type 1 diabetes mellitus. The Committee was aware that type 2 diabetes mellitus occurred in a much more heterogeneous group of people, including some severely insulin-resistant individuals. The Committee also heard that there would be subgroups of the type 2 diabetic population, such as those with a body mass index below a certain level or those with low levels of C peptides, who would possibly stand to benefit from insulin pumps, but was aware that there was no evidence to support such a recommendation. In conclusion, the Committee decided that, in the absence of evidence of improved outcomes, the use of CSII therapy in people with type 2 diabetes mellitus could not be recommended as a cost-effective use of NHS resources.

- 4.3.12 The Committee noted that adherence to any insulin regimen required a high degree of motivation, commitment and competence from patients and carers to ensure that it was both safe and effective. Insulin therapy requires attention to maintaining personal hygiene, blood glucose testing several times a day, estimating carbohydrate and calorie consumption throughout every day and self-injection. The Committee was aware that structured education of people with diabetes and their carers in flexible insulin therapy can, of itself, improve glycaemic control and improve chances of successful CSII therapy. The Committee agreed that structured education is very important in maintaining and improving glycaemic control and an important adjunct to CSII. The use of CSII should not be considered to replace the need for education.
- 4.3.13 The use of effective insulin pump therapy would require resetting of the cannula every 2–3 days and programming the pump. The Committee was aware that the use of a pump was only likely to be cost effective when it was used appropriately. The Committee therefore considered that all patients potentially eligible for this treatment, and their carers if appropriate, should have the opportunity for an informed discussion with the responsible clinician about the advantages and disadvantages of insulin pumps, including the requirements for using a pump effectively. Insulin pump therapy should only begin where it is agreed that the patient is likely to benefit from the intervention. However, the Committee agreed that most of these requirements were equally applicable to injection therapy and patients who were eligible would have already shown a high level of care of their diabetes, if necessary with the aid of carers. The elements of a high level of care are detailed in NICE's clinical guideline for the management of type 1 diabetes in adults and children (CG15).
- 4.3.14 The recommendations made by the Committee were based on people who switched from MDI to CSII therapy experiencing a

benefit in terms of either improved glycaemic control and decreased HbA1c levels, or a decrease in the rate of hypoglycaemic episodes and the fear resulting from these, and a resulting improvement in their quality of life. However, the Committee was mindful that not all people started on CSII therapy would gain these benefits and the continued use of an expensive therapy in the absence of demonstrable benefits would be an inappropriate use of resources. The Committee therefore felt the need to specify that if such benefits were not gained within a reasonable time period CSII therapy should be withdrawn. The appropriate targets in terms of decrease in HbA1c levels or avoidance of hypoglycaemia, as well as the length of the trial period and the maintenance of improvements beyond that period, would need to be set on an individual basis by the responsible clinician in consultation with the pump user, relevant carers and other healthcare professionals. The Committee also agreed that before withdrawing CSII there should be further efforts at providing support and care for the pump user including further structured education, where necessary.

- 4.3.15 The Committee was aware that the delivery of insulin was just one aspect of the management of diabetes mellitus. The care provided should also include advice on diet, lifestyle, exercise and education. The management of a person's diabetes mellitus when using CSII should involve interaction with a multidisciplinary team specialised in the treatment of diabetes mellitus. Such specialist teams are especially important during the initial period when a new pump user is developing expertise. The Committee was unable to make firm recommendations for the exact composition of specialist teams and considered this a decision for the individual centre. However, the Committee expected that the specialist team would normally include a physician with a specialist interest in insulin pump therapy, a diabetes specialist nurse and a dietician, among

others. The Committee agreed that structured education was a vital component of CSII therapy and would need to be ongoing and intensified before withdrawal of CSII. In addition, education was an important aspect of optimal MDI therapy and inability to achieve targets on MDI would normally require further patient education before switching to CSII.

5 Implementation

- 5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- 5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- 5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website

(www.nice.org.uk/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives which support this locally.
- Audit support for monitoring local practice.

6 Related NICE guidance

- Inhaled insulin for the treatment of diabetes (types 1 and 2). NICE technology appraisal guidance 113 (2006). Available from: www.nice.org.uk/TA113
- Guidance on the use of patient-education models for diabetes. NICE technology appraisal guidance 60 (2003). Available from: www.nice.org.uk/TA60
- Guidance on the use of long-acting insulin analogues for the treatment of diabetes – insulin glargine. NICE technology appraisal guidance 53 (2002). Available from: www.nice.org.uk/TA53
- Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults. NICE clinical guideline 15 (2004). Available from: www.nice.org.uk/CG15
- Type 2 diabetes: prevention and management of foot problems. NICE clinical guideline 10 (2004). Available from: www.nice.org.uk/CG10
- Management of type 2 diabetes: management of blood pressure and blood lipids. Inherited clinical guideline H (2002). Available from: www.nice.org.uk/CGH

- Management of type 2 diabetes: management of blood glucose. Inherited clinical guideline G (2002). Available from: www.nice.org.uk/CGG
- Management of type 2 diabetes: renal disease, prevention and early management. Inherited clinical guideline F (2002). Available from: www.nice.org.uk/CGF
- Management of type 2 diabetes: retinopathy – early management and screening. Inherited clinical guideline E (2002). Available from: www.nice.org.uk/CGE
- Pancreatic islet cell transplantation. NICE interventional procedure guidance 13 (2003). Available from: www.nice.org.uk/IPG13

NICE is developing the following guidance (details available from www.nice.org.uk).

- Type 2 diabetes: the management of type 2 diabetes (update). NICE clinical guideline (publication expected March, 2008).
- Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period. NICE clinical guideline (publication expected March, 2008).

7 Review of guidance

- 7.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.
- 7.2 The guidance on this technology will be considered for review in February 2011. The Institute would particularly welcome comment on this proposed date.

Andrew Stevens
Chair, Appraisal Committee
February 2008

Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice-chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor David Barnett

Professor of Clinical Pharmacology, University of Leicester

Professor Mike Campbell

Professor of Medical Statistics, University of Sheffield

Dr Carol Campbell

Senior Lecturer, University of Teesside

Professor David Chadwick

Professor of Neurology, University of Liverpool

Ms Jude Cohen

Special Projects Consultant, UK Council for Psychotherapy

Dr Mike Davies

Consultant Physician, Manchester Royal Infirmary

Dr Rachel A Elliott

Lord Trent Professor of Medicines and Health, the University of Nottingham

Mrs Eleanor Grey

Lay member

Professor Peter Jones

Pro Vice Chancellor for Research & Enterprise, Keele University

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Richard Alexander Nakielny

Consultant Radiologist, Royal Hallamshire Hospital, Sheffield

Dr Katherine Payne

Health Economics Research Fellow, The University of Manchester

Dr Philip Rutledge

GP and Consultant in Medicines Management, NHS Lothian

Professor Andrew Stevens

Chair of Appraisal Committee C and Professor of Public Health, University of Birmingham

Dr Cathryn Thomas

Senior Lecturer, Department of Primary Care & General Practice, University of Birmingham

Mr William Turner

Consultant Urologist, Addenbrooke's Hospital, Cambridge

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Elangovan Gajraj

Technical Lead

Elisabeth George

Technical Adviser

Chris Feinmann

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by the Aberdeen Health Technology Assessment Group.

- Cummins E, Royle P, Snaith A et al. Clinical and cost-effectiveness of continuous subcutaneous infusion for diabetes: updating review, August 2007

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, assessment report and the appraisal consultation document (ACD). Consultee organisations are provided with the opportunity to appeal against the final appraisal determination.

I Manufacturers/sponsors:

- Animas Corporation/Johnson & Johnson Medical Ltd (Animas IR2020)
- Medtronic Ltd (Paradigm)
- Roche Diagnostics Ltd (Accu-Chek Spirit)
- Smiths Medical International (Deltec Cozmo)
- Starbridge Systems Ltd (Starlet)

II Professional/specialist and patient/carer groups:

- Association of British Clinical Diabetologists
- British Dietetic Association
- Diabetes UK
- INPUT
- Insulin Dependent Diabetes Trust
- Insulin Pumpers UK
- Juvenile Diabetes Research Foundation
- Royal College of Nursing
- Royal College of Paediatrics and Child Health
- Royal College of Physicians
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- Association of British Health-Care Industries (ABHI)
- British National Formulary

- Department of Health, Social Services and Public Safety for Northern Ireland
- Eli Lilly & Co Ltd
- National Collaborating Centre for Chronic Conditions
- National Collaborating Centre for Women's and Children's Health
- NHS Quality Improvement Scotland
- Novo Nordisk Ltd
- Pfizer Ltd
- The Dose Adjustment for Normal Eating (DAFNE) Steering Group

C The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on continuous subcutaneous insulin infusion for the treatment of diabetes mellitus by attending the initial Committee discussion and/or providing written evidence to the Committee. They were invited to comment on the ACD.

- Mr John Davis, National Coordinator (INPUT), nominated by INPUT – patient expert
- Mrs Lesley Jordan, nominated by Insulin Pumpers UK – patient expert
- Mrs Alexandria Moseley, nominated by Juvenile Diabetes Research Foundation – patient expert
- Professor John Pickup, Professor of Diabetes & Metabolism, nominated by INPUT – clinical specialist
- Dr Peter Hammond, Consultant Physician/Endocrinologist, nominated by Association of British Clinical Diabetologists – clinical specialist
- Dr Fiona Campbell, Consultant Paediatrician, nominated by Diabetes UK – clinical specialist