NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA151 Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus

This guidance was issued in July 2008
The review date for this guidance is February 2011

Recommendation

- A review of the guidance should be transferred to the 'static guidance list' and this proposal should be subject to consultation. Consideration of options for recommendation:

Options	Comment
A review of the guidance should be planned into the appraisal work programme.	New evidence on continuous subcutaneous insulin infusion (CSII) found whilst preparing the review proposal is unlikely to have a substantive effect on the recommendations of TA151. We therefore believe that a review of TA151 at present would be a poor use of NICE resources
The decision to review the guidance should be deferred [to a specified date].	It is recommended that this appraisal is transferred to the static list, where it can monitored on an ongoing basis
A review of the guidance should be combined with a review of a related technology and conducted at the scheduled time for the review of the related technology.	No suitable reviews of guidance were found
A review of the guidance should be combined with a new appraisal that has recently been referred to the Institute.	There is an appraisal of exenatide (prolonged release) for the treatment of type 2 diabetes, but it would not be suitable to combine this with a review of TA151 because it would conflict with the objective of issuing timely guidance
A review of the guidance should be incorporated into an on-going clinical guideline.	No suitable guidelines were found
A review of the guidance should be updated into an on-going clinical guideline.*[1]	No suitable guidelines were found

[1] See Appendix A on page 4

A review of the guidance should be transferred to the 'static guidance list'.	**New evidence on CSII found whilst preparing the review proposal is unlikely to have a substantive effect on the recommendations of TA151. It is recommended that this appraisal is transferred to the static list, where it can monitored on an ongoing basis**

Original remit(s)

To review and update as necessary guidance to the NHS in England and Wales on the clinical and cost effectiveness of continuous subcutaneous insulin infusion for the treatment of diabetes,[2] which was issued in July 2008[3] and replaced 'NICE technology appraisal guidance 57' issued in February 2003.[4]

The current guidance will remain in place unless and until any new guidance has been issued. The review will consider whether any new evidence that has become available justifies a change in the original guidance.

Current 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

[2] Original remit: To advise on the clinical and cost-effectiveness of insulin pumps in the treatment of Type 1 and Type 2 diabetes; and on the criteria for selecting patients for whom this treatment would be particularly appropriate.
[3] Current guidance: National Institute for Health and Clinical Excellence (2008) Continuous subcutaneous insulin infusion for the treatment of diabetes (review). *NICE technology appraisal guidance no. 151. London: National Institute for Health and Clinical Excellence.*
[4] National Institute for Clinical Excellence (2003) Continuous subcutaneous insulin infusion for diabetes. *NICE technology appraisal guidance* no. 57. London: National Institute for Clinical Excellence.

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 dietitian. 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.

Relevant Institute work

Published

- Liraglutide for the treatment of type 2 diabetes mellitus. Technology Appraisal. TA203. Published: October 2010

- The clinical effectiveness and cost effectiveness of long acting insulin analogues for diabetes. Technology Appraisal. TA53 (The recommendations in this technology appraisal relating to type 2 diabetes have been replaced by recommendations in CG66). Published: December 2002.
- The clinical effectiveness and cost effectiveness of patient education models for diabetes. Technology Appraisal. TA60. (The recommendations in this technology appraisal relating to type 2 diabetes have been replaced by recommendations in CG66). Published: April 2003.

- Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period. Clinical Guideline. CG63. Published: March 2008 (revised reprint July 2008). Review: February 2011.

- Diagnosis and management of type 1 diabetes in children, young people and adults. Clinical Guideline. CG15. Published: July 2004. Review: January 2013.

- Type 2 diabetes: prevention and management of foot problems. Clinical Guideline. CG10. Published: January 2004. Review: February 2011.

- Type 2 Diabetes - newer agents (partial update of CG66). Clinical Guideline. CG87. Published: May 2009. Review: May 2012.

- Type 2 diabetes: the management of type 2 diabetes (update). Clinical Guideline. CG66. Published: May 2008. Review: May 2011.

- Management of type 2 diabetes - management of blood pressure and blood lipids. Clinical Guideline. Guideline H (replaced by CG66). Published: October 2002.

- Management of type 2 diabetes - Managing blood glucose levels. Clinical Guideline. Guideline G (replaced by CG66). Published: September 2002.

- Management of type 2 diabetes - renal disease, prevention and early management. Clinical Guideline. Guideline F (replaced by CG66). Published: February 2002.

- Management of type 2 diabetes – retinopathy Clinical Guideline. Guideline E (replaced by CG66). Published: February 2002.

- Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus. Interventional Procedure. IPG257. Published: April 2008.

- Autologous pancreatic islet cell transplantation for improved glycaemic control after pancreatectomy. Interventional Procedure. IPG274. Published: September 2008.

- Pancreatic islet cell transplantation. Interventional Procedure. IPG13 (replaced by IPG257 and IPG274). Published: October 2003.
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In progress

- Macular oedema (diabetic) - ranibizumab. Technology Appraisal. Expected: TBC.

- Diabetes (type II) – exenatide (prolonged release). Technology Appraisal. Expected: TBC.

- Diabetic foot problems - inpatient management. Clinical Guideline. Expected: 2011.

- Type 2 diabetes - preventing pre-diabetes in adults. Public Health. Expected: June 2011.

- Type 2 diabetes - preventing the progression from pre-diabetes. Public Health. Expected: May 2010.

Suspended/terminated

- Inhaled insulin for the treatment of type 1 and type 2 diabetes. Technology Appraisal. TA113. Published: December 2006.

- New treatments for diabetic foot ulcers. Technology Appraisal.

- Diabetic retinopathy – ruboxistaurin. Technology Appraisal.

In topic selection[5]

[redacted]

Details of new products

Device (manufacturer)	Details
Accu-Chek Aviva Combo (Roche)	The Accu-Chek Combo comprises of a pump that is designed for use with the Accu-Chek Aviva Combo handset, which is an intelligent blood glucose meter, bolus advisor and insulin management system that can remotely control the pump using 'Bluetooth' wireless technology. The handheld device has an integrated bolus advisor, blood glucose monitor and allows the user to manage all the functions of the pump remotely. All pump screens are displayed on the handset meaning there is no requirement for the patient to remove the pump from clothing in order to operate it. This enables discreet and accessible pump therapy.
Dana R insulin pump (Advanced	BOLUS FEATURES

[5] Information held by the NICE Topic Selection Team is treated as being potentially commercially sensitive by default. Details of the topics considered by NICE's Consideration Panels may be available on the NICE website, providing the manufacturers of the technologies under discussion have consented to the release of this information.

Therapeutics UK)	• Dosage increments in 0.05, 0.1, 0.5 or 1.0 units • 1 unit bolus duration: 12, 30 or 60 seconds • Audible notification for each unit delivered • Extended bolus (30 mins - 8 hrs) • Dual pattern bolus • Carbo/Bolus calculation Program • Insulin to carb ratio and correction factor variable by time of day BASAL FEATURES • Number of rates per profile: 24 per day, hourly • Temporary Basal: 1hr - 12hrs, 0% - 200% • Program dosage: 0.01 unit/hr or 0.1 unit/hr • Number of profiles: 4 REMOTE CONTROLLER • Bolus, temporary basal, bolus setting, basal setting and blood glucose measurement and Bolus Calculator INTEGRATED BLOOD GLUCOSE MONITOR IN REMOTE CONTROLLER • Sample: 0.5 µl, capillary whole blood • Time: 5 secs • Range: 1.1 to 33.3mmol/l • Method: Electrochemical • Strip: DANA Blood Glucose Strip
Paradigm Veo (Medtronic)	The Paradigm Veo (554/754) pump systems are indicated for the continuous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. In addition, the pump system is indicated for continuous or periodic monitoring of glucose levels in the fluid under the

	skin, and possible low and high blood glucose episodes. The pump displays continuous glucose values and stores this data so that it can be analysed to track patterns and improve diabetes management. Pump history can be downloaded to a computer for analysis of historical glucose values. The continuous glucose values provided by the Paradigm Veo (554/754) pump systems are not intended to be used directly for making therapy adjustments. Rather, they provide an indication that a confirmation fingerstick measurement may be required. All therapy adjustments should be based on measurements obtained using a home glucose monitor and not based on the value displayed by the pump.

On-going trials

Trial name and contact	Details
NCT00942318 Efficacy of Continuous Subcutaneous Insulin Infusion Versus Basal-bolus Multiple Daily Injections Regimen in Type 2 Diabetes	Recruiting Phase: IV Start date: March 2009 Completion date: November 2011 Primary completion date: February 2011
NCT01182493 OpT2mise Glucose Control in Type 2 Diabetes Mellitus (DM) With Insulin Pump Therapy	Phase IV Not yet recruiting Start date: November 2010 Completion date: June 2013 Primary completion date: December 2010

Proposal for updating the guidance [to be completed by PM]

If the guidance is to be updated as an appraisal, it would be scheduled into the work programme accordingly.

New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline(R) In-Process and Embase. References

from 2007 onwards were reviewed. The results of the literature search are discussed in the 'Appraisals comment' section below.

Trials

Publication title	Details
Effectiveness of Sensor-Augmented Insulin-Pump Therapy in Type 1 Diabetes (2010)	Population: Adults with type 1 diabetes Comparison: CSII vs MDI Outcomes: mean glycated hemoglobin level Results: At 1 year, the baseline mean glycated hemoglobin level (8.3% in the two study groups) had decreased to 7.5% in the pump-therapy group, as compared with 8.1% in the injection-therapy group (P<0.001).
Comparison of a Multiple Daily Insulin Injection Regimen (Basal Once-Daily Glargine Plus Mealtime Lispro) and Continuous Subcutaneous Insulin Infusion (Lispro) in Type 1 Diabetes (2009)	Population: Adults with type 1 diabetes Comparison: CSII or glargine-based MDI (both otherwise using lispro) Outcomes: Total insulin requirement and mean AiC level Results: Total insulin requirement at end point was 36.2 on CSII and 42.6 on MDI. Mean AiC decreased -0.7 in CSII group, compared with -0.6 in MDI group.
Effects of insulin therapy with Continuous Subcutaneous Insulin Infusion (CSII) in diabetic patients: Comparison with Multi-daily Insulin Injections Therapy (MDI) (2009)	Population: Adults with type 1 and 2 Comparison: CSII vs MDI Outcomes: glicemic control Results: At 1 year, the baseline mean HbA1c level, had decreased from 9.2% to 7.6% in CSII group (P<0.0001), and from 9.3% to 8.2% in MDI group (p<0.05). Results were not presented separately for type 1 and type 2 diabetes.
Effects of insulin pump vs. injection treatment on quality of life and impact of disease in children with type 1 diabetes mellitus in a randomized, prospective comparison (2008)	Population: Children with type 1 diabetes Comparison: CSII vs MDI Outcomes: Pediatric Quality of life Inventory (PedsQL) and HbC1a levels Results: PedsQL during randomisation remained stable in MDI group, and increased by 2.5 points on average in CSI group (improved). After randomisation all children were on CSI by preference. At 10.5 month, HbC1a level decreased by 0.22% compared to baseline in CSI group (p=0.02).

Systematic reviews

Publication title	Details
Continuous subcutaneous	Population: type 1 diabetes

insulin infusion versus multiple insulin injections for type 1 diabetes mellitus (Cochrane collaboration review) (2010)	Comparison: CSII vs MDI Results: Meta-analyses of 23 studies. Statistically significant difference in HbA1c favouring CSII of -0.03%.
Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion (2008)	Population: type 1 diabetes Comparison: CSII vs MDI Results: 22 studies. Severe hypoglycaemia was reduced during CSII compared with MDI, with a rate ratio of 2.89. Mean difference in HbA1c was 0.21% in favour of CSII in RCTs
Hypoglycemia with intensive insulin therapy: A systematic review and meta-analyses of randomised trials of continuous subcutaneous insulin infusion versus multiple daily injections (2009)	Population: type 1 and type 2 diabetes Comparison: CSII vs MDI Results: 15 studies. People with type 1 diabetes using CSII had lower HbA1c compared with MDI (-0.2%). HbA1c was not different in people with type 2 diabetes
Use of Continuous Insulin Infusion Pumps in yong children with Type 1 Diabetes: A Systematic Review (2009)	Population: Children with type 1 diabetes Comparison: CSII vs MDI Results: 7 studies. All reported decreases in HbA1c levels after CSII initiation. In the trials that also had MDI groups, all reported lower mean HbA1c levels in the MDI, but not to the extent of those in CSII groups.
Evidence-based insulin treatment in type 1 diabetes mellitus (2009)	Population: type 1 diabetes Comparison: CSII vs conventional insulin injections and multiple insulin injections Results: Meta-analysis of 49 studies. CSII compared with conventional or multiple insulin injections demonstrations a significant reduction in mean HBA1c of 1.2% ($p<0.001$).
Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analyses (2008)	Population: type 1 and type 2 diabetes Comparison: CSII vs MDI Results: Meta-analysis of 22 studies (17 on type 1, 2 on type 2, and 3 on children). In adults with type 1 diabetes, between-treatment difference of -0.4% in HbA1c level in favour of CSII compared with MDI. In people with type 2 diabetes, CSI and MDI showed no statistically significant difference for HbA1c. In adolescents with type 1 diabetes, glycated haemoglobin levels were satistically lower in CSII groups compared with MDI groups.
Continuous subcutaneous insulin infusion vs multiple daily injections in children with type 1 diabetes (2009)	Population: Children with type 1 diabetes Comparison: CSII vs MDI Results: Meta-analysis of 6 studies. Significant reduction in HbA1c level in CSII

	group compared with MDI group (-0.24%).

Implementation

The audit has identified 1812 children (defined as less than 18 years old) and 3855 adults aged 18 years or older currently using an insulin pump (see Appendix 1). The costing report for TA151 estimates a total of 21760 people to be managed with insulin pumps, based on 10% of >12 years old and 25% of under 12 years old to be eligible. Therefore, the actual usage is far lower than what costing predicted. The low uptake was confirmed by a recently published paper which reported results of a survey of English PCTs. The survey reported significant inequity in the provision of insulin pumps across England and a lack of adherence to NICE guidance on pump provision. The report noted that the average pump use is 3.7% which is around a third of the suggested rate (based on 67 PCTs). In some PCTs the uptake is very low, for instance in one PCT, 5 out of up to 1,991 patients have a pump – which represents an uptake of 0.25%.

Equality and diversity issues

No equality issues were raised in TA151.

Appraisals comment:

Current guidance TA151 recommends CSII for the treatment of specific groups of people with type 1 diabetes mellitus. Due to an absence of evidence of improved outcomes, it does not recommend CSII for the treatment of people with type 2 diabetes mellitus. There were no recommendations for future research outlined in TA151.

Review of new evidence – type 1 diabetes

Of the new evidence identified since the publication of TA151 (see 'new evidence section'), four trials and seven systematic reviews compared CSII with insulin analogue-based multiple daily injections (MDI) in people with type 1 diabetes. All reported greater decreases in haemoglobin levels (indicating an improvement in haemoglobin control) in groups receiving CSII compared with groups receiving MDI, however only two trials reported a statistically significant difference. Of the systematic reviews identified, four reported a statistically significant reduction in HbA1c levels in the CSII groups compared with the MDI groups. This new evidence is consistent with the evidence which was considered by the Committee in coming to the recommendation in TA151 for people with type 1 diabetes.

Review of new evidence – type 2 diabetes

One trial included people with type 2 diabetes, however the results were not separated by type of diabetes. The overall outcome was a statistically

significant decrease in HbA1c levels in the group that received CSII compared to group that received MDI. Two systematic reviews presented the outcomes for people with type 2 diabetes. One review reported that there was no difference in HbA1c levels between those receiving treatment with CSII compared with those receiving MDI treatment. The second review reported no statistically significant difference between the treatments in people with type 2 diabetes. This new evidence does not suggest that the guidance should be amended for people with type 2 diabetes.

Changes to CSII therapy since TA151

TA151 does not make recommendations on use of specific CSII models, but rather on the class of CSII devices. Since the publication of TA151 a number of new insulin pump models have come to the market, which combine a blood glucose meter with an insulin pump using wireless technology. The objective of using wireless technology is to enable a discrete bolus injection without accessing the pump. NICE understands that these models have a similar indication, and offer the same level of benefit to the models considered in TA151.

Ongoing or proposed NICE guidance

Since the publication of TA151, the Institute has issued several pieces of guidance for the treatment of people with type 2 diabetes: TA203 on the use of liraglutide, a clinical guideline on the management in primary and secondary care of type 2 diabetes (CG66, 2008) and a clinical guideline on newer agents for the treatment of type 2 diabetes (CG86, 2009). The guidelines do not update or replace TA151. There is one appraisal currently in development on the use of exenatide (prolonged release) for the second- or third-line treatment of type 2 diabetes; however it would be unsuitable for this to be incorporated with a review of TA151 as it would conflict with the objective of issuing timely guidance.

Key issues

Since the publication of TA151 some new evidence has been published and there have been developments in the treatment of diabetes but it is considered that these would be unlikely to result in a change the recommendations of TA151. It is recommended that this appraisal is transferred to the static list, where it can monitored on an ongoing basis.

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Appendix 1

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

IMPLEMENTATION DIRECTORATE

Guidance Executive Review

Technology appraisal 151: Continuous subcutaneous insulin infusion for the treatment of diabetes (review)

1. National data

The NICE implementation programme has not looked at any routinely collected data in order to determine the uptake of this technology appraisal (TA).

2. External literature

2.1 ERNIE

2.1.1 The NHS Information Centre for Health and Social Care (2010) Insulin Pump Audit-Findings for England

The audit has identified 1812 children (defined as less than 18 years old) and 3855 adults aged 18 years or older currently using an insulin pump. There was considerable variation between provider units for the number of patients reported to be using insulin pumps. Of those participating in the audit 42% have less than 20 patients on insulin pumps, 31% between 20 and 39 and 16% of units were providing pump services for more than 60 patients.