FNATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology Appraisals and Guidance Information Services

Static List Review (SLR)

Title and TA publication number of static topic:	TA151; Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus
Final decision:	The guidance will remain on the 'static guidance list'

1. Publication date:	23 July 2008
2. Date added to static list:	2011
3. Date the last searches were run:	November 2010
4. 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 or HbA1c levels have remained high (that is, at 8.5% [69 mmol/mol] 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.
5. Research recommendations from original guidance:	None
6. Current cost of technology/ technologies:	"Insulin pumps tend to cost between £2,000 and £3,000 and the consumables for an insulin pump, including infusion sets, reservoirs and batteries, can cost around £1,000 to £2,000 a year"**.** Diabetes.co.uk notes that the price of new pumps have "stayed within similar price

	boundaries" as the prices for pumps identified in 2008 for TA151. Source: Getting an Insulin Pump (2016) and Costs of Insulin Pumps (2016) Diabetes.co.uk
7. Cost information from the original TA (if available):	3.1 The following insulin pump models are currently available: Animas 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).
8. Alternative company(ies):	Currently, 10 insulin pumps are available in the UK: Animas Vibe (Animas) Cellnovo (Cellnovo) Minimed 640G (Medtronic) Minimed Paradigm Veo (MMT 554/MMT 754) (Medtronic, Accu-Chek Combo (Roche) Accu-Chek Insight (Roche) Accu-Chek Spirit (Roche) DANA Diabecare R (Sooil) mylife Omnipod Insulin Pump (Ypsomed) Source: Insulin Pumps (2016) Diabetes.co.uk

9. Changes to the original indication:	Unchanged
10. New relevant trials:	Trial NCT01474538: Safety and Efficacy Study of Insulin Lispro Versus Insulin Aspart in Participants With Type 2 Diabetes on Insulin Pump Therapy Phase 3. Completed February 2013, trial has results. Trial NCT00948324: Effect of Intensive Therapy Associated With CSII on β-cell Function With Newly Diagnosed Type 2 Diabetes Phase 4. Study to be completed in December 2018. Trial NCT00942318: Efficacy of Continuous Subcutaneous Insulin Infusion Versus Basal-bolus Multiple Daily Injections Regimen in Type 2 Diabetes Phase 4. Completed February 2013. Trial NCT022823977: Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes Phase 4. Study to be completed in March 2016 Trial NCT01454700: Effect of CSII and CGM on Progression of Late Diabetic Complications Phase 4. Completed December 2014. Trial NCT02561078: An Administration Method Study of Human Regular U-500 Insulin (LY041001) in Participants With Type 2 Diabetes Mellitus Phase 3. Study to be completed in December 2016 Trial NCT01999322: A Trial Evaluating Compatibility and Safety of FIAsp and Insulin Aspart With an External Continuous Subcutaneous Insulin Infusion System in Adult Subjects With Type 1 Diabetes Phase 3. Completed May 2014. Trial NCT01182493: OpT2mise Glucose Control in Type 2 Diabetes Mellitus (DM) With Insulin Pump Therapy Phase 4. Completed August 2014. Trial NCT02685449: Insulin Requierment for Pure-protein Meal in Children With Type 1 Diabetes on Insulin Pumps. Phase 4. Study to be completed in August 2018 Trial NCT02657213: Study of Insulin Pump in Prevention of Low Glucose Events in Adults With

	Type 1 Diabetes at Risk of Severe Hypoglycemia. Phase 3. Study to be completed in December 2017 Trial NCT01550809: New Strategies for Postprandial Glycemic Control Using Insulin Pump Therapy. Phase 3. Completed June 2011, trial has results. Trial NCT01468519: Exploratory CSII Trial on Erectile Dysfunction in T2DM Patients. Phase 4. Completed November 2014 Trial NCT01790308: Effect of Liraglutide Combined With Short-term CSII on Long-term Glycemic Remission and β Cell Function. Phase 4. Completed December 2015 Trial NCT01295788: Timing of Initiation of Continuous Glucose Monitoring in Established Pediatric Diabetes (The CGM TIME Trial). Phase 4. Completed January 2015 Trial NCT01471808: Effects of Different Early Intensive Therapies on Long-term β-cell Function. Phase 4. Study to be completed in December 2021 Trial NCT01678235: Insulin Glulisine and Aspart in Postprandial Glycemic Control After High-GI Meal in Children With Type 1 Diabetes Mellitus. Phase 4. Completed September 2012 Trial NCT01109316: Insulin Lispro 6 Days Versus Insulin Aspart 6 Days in Pump Use. Phase 3. Completed August 2011 Trial NCT02048189: Treatment With Continuous Sub-cutaneous Insulin Infusion Via a Portable Pump Versus Discontinuous Insulin Infusion Via Multiple-injections in Type 2 Diabetes. Phase 4. Completed December 2015 Trial NCT01368978: Pediatric Diabetics Type 1 Using InsuPatch. Phase 3. Completed May 2012 Trial NCT02546401: Comparison of Insulin's Injection Before or After the Meal in Type 1 Diabetic

	Patients Treated With Insulin Pump. Phase 3. Study to be completed in June 2016 Trial NCT02229097: Efficacy of Coordinated Insulin Boluses in Type 1 Diabetic Patients. Phase 4. Completed December 2015 Trial NCT01616784: The REPOSE (Relative Effectiveness of Pumps Over MDI and Structured Education) Trial. Phase 3. Completed November 2015 Trial NCT01776788: Effect of Short-Term Intensive Insulin Sequential Exenatide Therapy in Newly Diagnosed Type 2 Diabetic Patients. Phase 4. Completed February 2015 Trial NCT01134107: Insulin Lispro 6 Days Versus Insulin Aspart 6 Days in Pump Use. Phase 3. Completed December 2011, trial has results. Trial NCT02097316: Feasibility Study of the JewelPump Version 3. Phase 3. Completed September 2014 Trial NCT02276859: Normal Versus Dual Wave Insulin Bolus for High-protein Food. Phase 4. Completed September 2015 Trial NCT02379299: DiaCon Dual-Hormone Closed-Loop Glucose Control. Phase 2/3. Study to be completed in June 2016 Trial NCT01497938: Outpatient Study to Evaluate Safety and Effectiveness of the Low Glucose Suspend Feature. Phase 3. Completed June 2013, trial has results. Trial NCT01712594: Safety and Effectiveness Study of a Closed Loop System Maintaining Patients' Glucose Levels During an Overnight Period. Phase 3. Completed December 2014
11. Relevant NICE guidance (published or in progress):	**Published**

	Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system) (2016) NICE diagnostic assessment guidance 21 MiniMed 640G system with SmartGuard for managing blood glucose levels in people with type 1 diabetes (2016) NICE MedTech innovation briefing 51 Diabetes in adults (2011) NICE quality standard 6 Diabetes (type 1 and type 2) in children and young people: diagnosis and management (2015) NICE guideline 18 Type 1 diabetes in adults: diagnosis and management (2015) NICE guideline 17 Type 2 diabetes in adults: management (2015) NICE guideline 28 Diabetes in pregnancy: management from preconception to the postnatal period (2015) NICE guideline 3 **In Progress** Diabetes in adults QS (update). NICE quality standard. Publication expected August 2016 Diabetes in children and young people. NICE quality standard. Publication expected June 2016

12. Relevant safety issues:	Accu-Chek® Insight insulin pump system, manufactured by Roche Diabetes Care – risk of inappropriate treatment (2016) Medicines and Healthcare products Regulatory Agency All Accu-Chek® Insight insulin pumps - risk of hyperglycaemia from rapid pump battery depletion or unexpected shut down (2015) Medicines and Healthcare products Regulatory Agency Insulin infusion pump - risk of delay in treatment (2014) Medicines and Healthcare products Regulatory Agency Insulin infusion pump - risk of hyperglycaemia or hypoglycaemia (2015) Medicines and Healthcare products Regulatory Agency Ambulatory insulin infusion pumps - software problem (2013) Medicines and Healthcare products Regulatory Agency Paradigm ambulatory insulin infusion pumps - risk of compromised insulin therapy (2013) Medicines and Healthcare products Regulatory Agency Paradigm ambulatory insulin infusion pumps - risk of hypoglycaemia (2014) Medicines and Healthcare products Regulatory Agency Regulator asks those with diabetes to check insulin pumps (2015) Medicines and Healthcare products Regulatory Agency
13. Any other additional relevant information or comments:	Continuous Subcutaneous Insulin Infusion for Type 1 Diabetes (2015) Canadian Agency for Drugs and Technologies in Health - Rapid Review

	Insulin therapy in type 1 diabetes (2016) NICE Clinical Knowledge Summaries Diabetes - type 1 (2015) NICE Clinical Knowledge Summaries Insulin therapy in type 2 diabetes (2015) NICE Clinical Knowledge Summaries
14. Technical Lead comments and recommendation:	New information has been identified for both type 1 and type 2 diabetes, however it is not expected that this new information will affect the existing recommendations. **Review of new evidence – type 1 diabetes** Several clinical trials were identified that included continuous subcutaneous insulin infusion (CSII) in all treatment arms, for example trials focussed on monitoring or administration of treatment for people using CSII; comparing different types of pump, and considering the compatibility of different types of insulin with CSII. This does not provide any comparative evidence for CSII compared with an alternative intervention, and therefore is not expected to affect the positive recommendations for type 1 diabetes. The REPOSE trial and trial NCT01454700 compared CSII with an alternative intervention. Trial NCT01454700 is of limited relevance to TA151. The primary outcome (change in urine albumine excretion) was not designed to test efficacy, and the trial population was small (n=60) and not generalisable to the whole population in TA151 (it included only to those with a history of albuminuria and on stable renin-angiotensin system inhibition). The REPOSE trial compared CSII with multiple daily injections, and both interventions were combined with structured education in self-management. The population in REPOSE is different to the population eligible for treatment in TA151: treatment eligibility in TA151 is restricted only to those with a higher need for control of disease, whereas REPOSE excludes people with a “strong need for pump therapy” (suggesting a comparatively lower need population in REPOSE). Furthermore, in the

	comparatively lower-need population of REPOSE, although both treatment groups experienced an improvement in HbA1c following structured education, and the reduction for pumps after 2 years (-0.84%) was numerically larger than with multiple daily injections (-0.42%), this result was not statistically significant (p=0.121). Several other outcomes also showed no statistically significant differences between the 2 arms. Therefore the findings of REPOSE do not support broadening the recommendations in TA151 to include a lower-need population. In addition to clinical trial evidence, observational evidence is available from several audits considering the effectiveness of CSII in reducing HbA1c. A UK-based audit by Beato-Víbora et al. (2015) presented long-term effectiveness data of CSII over 12 years for 327 patients in a UK specialist referral centre. The study found that HbA1c reduced after starting CSII, and the authors concluded that the benefits for type 1 diabetes can be sustained over several years in clinical practice. Although this does not compare CSII with another intervention, it provides supportive evidence for the effectiveness of CSII for type 1 diabetes. **Review of new evidence – type 2 diabetes** Several clinical trials were identified that included CSII in all arms, therefore although this could provide supporting evidence for the effectiveness of pumps for type 2 diabetes, it does not provide comparative evidence. The OpT2mise trial compared CSII with multiple daily injections for people with type 2 diabetes whose disease is sub optimally controlled with multiple daily injections. For the primary outcome (mean change in HbA1c at 6 months) the trial found that mean HbA1c reduced by -1.1% in the CSII arm, and -0.4% in the multiple daily injection group (a statistically significant difference of -0.7%, 95% confidence interval –0·9 to –0·4; p<0·001). This suggests that CSII could be more effective than multiple daily injections for type 2 diabetes. However, the primary outcome was measured at a relatively short time frame (6 months), which limits the strength of the effectiveness evidence and leaves uncertainty about the long-term effect of both interventions. It is therefore

	expected that longer term evidence would be required before it could be considered sufficiently robust to impact the recommendations in TA151. Two trials were identified that were conducted in France comparing CSII with multiple daily injections for type 2 diabetes, TRICIDIA (n=60), and trial NCT00942318 (n=52). However, the small population size and uncertain generalisability (both conducted in French centres and TRICADIA had an inclusion criterion of a BMI >28.5) reduces the likelihood that this trial evidence will be substantial enough to impact the recommendations in TA151. There are 2 ongoing trials for type 2 diabetes, VIVD and DIAMOND. VIVID compares human regular U-500 insulin (U-500R) administered by CSII or with multiple daily injections in participants with type 2 diabetes. However, the trial results will not be generalisable to the whole population in TA151, because U-500R insulin is for patients with a need for large doses of insulin. Furthermore, because both arms of the trial include higher doses than usual of insulin, it may not be clear from the results what proportion of change in HbA1c can be attributed to the dose of insulin and what proportion to the administration method. DIAMOND is of limited relevance to the recommendations in TA151. The trial is primary designed to consider the effect of glucose monitoring for people using multiple daily injections. Although the trial will include “additional assessments” for the benefits of switching from multiple daily injections to CSII, this will be in the second phase of the trial only, and it may not be clear what proportion of any effectiveness benefit can be attributed to the change in administration method and what proportion is due to the change in monitoring. Furthermore, the trial population includes people with both type 1 and type 2 diabetes which reduces the relevance to type 2 disease. **Summary** The indication for CSII has not changed, and no new safety issues have been identified (there have been several safety alerts, but these have been about individual issues with

	specific devices). In addition, Diabetes.co.uk notes that the "prices of most pumps have stayed within similar price boundaries" as those considered in the original guidance for TA151. New clinical evidence has been identified for both type 1 and 2 disease, but it is not expected that the evidence will affect the existing recommendations in TA151. REPOSE, the main new evidence for type 1 disease, has limited generalisability to the population currently eligible for treatment in TA151, and the generally non-statistically significant findings do not support a broadening of the current recommendation in TA151 to include those with a lower need for control of disease. For type 2 disease, the OpT2mise trial provides some short-term effectiveness evidence, but long term effectiveness of CSII is lacking. Therefore it is the finding of this review that TA151 should remain on the static list.

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Appendix 1 – explanation of options

Options	Consequence	Selected – 'Yes/No'
The guidance will remain on the 'static guidance list'	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes
The decision to review the guidance will be deferred to specify date or trial	NICE will consider whether a review is necessary at the specified date. NICE will actively monitor the evidence available to ascertain when a consideration of a review is more suitable.	No
A full consideration of a review will be carried out through the Review Proposal Process	There is evidence that could warrant a review of the guidance. NICE will schedule a consideration of a review, including a consultation with relevant consultees and commentators.	No
The guidance will be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. NICE will schedule a consideration of a review, including a consultation with relevant consultees and commentators.	No
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be	No

	withdrawn. NICE will schedule a consideration of a review, including a consultation with relevant consultees and commentators.	