**TITLE**: **Continuous Subcutaneous Insulin Infusion for Type 1 Diabetes: Clinical Effectiveness, Cost-Effectiveness, and Guidelines**

**DATE:** 06 April 2015

## RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of continuous subcutaneous insulin infusion versus intermittent subcutaneous insulin injections for adults with type 1 diabetes?

2. What is the comparative clinical effectiveness of continuous subcutaneous insulin infusion versus intermittent subcutaneous insulin injections for children with type 1 diabetes?

3. What is the cost-effectiveness of continuous subcutaneous insulin infusion in adults versus children with type 1 diabetes?

4. What are the evidence-based guidelines for insulin delivery in patients with type 1 diabetes?

## KEY FINDINGS

Two health technology assessment reports, six systematic reviews (including five meta-analyses), and seven randomized controlled trials were identified regarding the comparative clinical effectiveness of continuous subcutaneous insulin infusion versus intermittent subcutaneous insulin injections for adults or children with type 1 diabetes. Three evidence based guidelines were identified regarding insulin delivery in patients with type 1 diabetes.

## METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2015, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic studies and guidelines. Where possible, retrieval was limited to the human population. The

Disclaimer: The Rapid Response Service is an information service for those involved in planning and providing health care in Canada. Rapid responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. Rapid responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

Copyright: This report contains CADTH copyright material and may contain material in which a third party owns copyright. **This report may be used for the purposes of research or private study only**. It may not be copied, posted on a web site, redistributed by email or stored on an electronic system without the prior written permission of CADTH or applicable copyright owner.

Links: This report may contain links to other information available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners' own terms and conditions.

search was also limited to English language documents published between January 1, 2010 and March 30, 2015. Internet links were provided, where available.

## SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

| | |
|---|---|
| **Population** | Q1: Adults with type 1 diabetes (subgroups of interest: ≥ 25 years of age and < 25 years of age)<br>Q2: Children with type 1 diabetes<br>Q3 & 4: Patients with type 1 diabetes |
| **Intervention** | Q1 & 2: Continuous subcutaneous insulin infusion via insulin pump<br>Q3: Continuous subcutaneous insulin infusion via insulin pump in adults<br>Q4: Continuous subcutaneous insulin infusion via insulin pump; intermittent subcutaneous insulin injections |
| **Comparator** | Q1 & 2: Intermittent subcutaneous insulin injections<br>Q3: Continuous subcutaneous insulin infusion via insulin pump in children<br>Q4: No comparator necessary |
| **Outcomes** | Q1 & 2: Clinical benefits and harms (e.g., control of blood glucose levels [A1C], hypoglycemic events, complications related to diabetes)<br>Q3: Cost-effectiveness<br>Q4: Guidelines |
| **Study Designs** | Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic evaluations, evidence-based guidelines |

## RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, economic evaluations, and evidence-based guidelines.

Two health technology assessment reports, six systematic reviews (including five meta-analyses), and seven randomized controlled trials were identified regarding the comparative clinical effectiveness of continuous subcutaneous insulin infusion versus intermittent subcutaneous insulin injections for adults or children with type 1 diabetes. Three evidence based guidelines were identified regarding insulin delivery in patients with type 1 diabetes. No economic evaluations were identified regarding the cost-effectiveness of continuous subcutaneous insulin infusion in adults versus children with type 1 diabetes.

Additional references of potential interest, including non-randomized studies, are provided in the appendix.

## Health Technology Assessments

*Pediatric Populations, Adults, and Pregnant Women*

1. Institute of Health Economics. Insulin pump therapy for type 1 diabetes [Internet]. Edmonton: IHE; 2012 Mar. [cited 2015 Apr 2]. (Alberta STE Report). Available from: http://www.ihe.ca/publications/insulin-pump-therapy-for-type-1-diabetes
*See: Evidence on safety, page 64*
*Evidence on efficacy, page 70*

2. Cummins E, Royle P, Snaith A, Greene A, Robertson L, McIntyre L, et al. Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. Health Technol Assess [Internet]. 2010 Feb [cited 2015 Apr 2];14(11). Available from: http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0017/65222/FullReport-hta14110.pdf
PubMed: PM20223123

## Systematic Reviews and Meta-analyses

*Pregnant Women*

3. Ranasinghe PD, Maruthur NM, Nicholson WK, Yeh HC, Brown T, Suh Y, et al. Comparative effectiveness of continuous subcutaneous insulin infusion using insulin analogs and multiple daily injections in pregnant women with diabetes mellitus: a systematic review and meta-analysis. J Womens Health (Larchmt). 2015 Mar;24(3):237-49.
PubMed: PM25713996

*Mixed Populations*

4. Yeh HC, Brown TT, Maruthur N, Ranasinghe P, Berger Z, Suh YD, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. Ann Intern Med. 2012 Sep 4;157(5):336-47.
PubMed: PM22777524

5. Golden SH, Brown T, Yeh HC, Maruthur N, Ranasinghe P, Berger Z, et al. Methods for insulin delivery and glucose monitoring: comparative effectiveness [Internet]. Rockville (MD): Agency for Healthcare Research and Quality; 2012 Jul [cited 2015 Apr 2]. (AHRQ Comparative Effectiveness Reviews). Available from: http://www.effectivehealthcare.ahrq.gov/ehc/products/242/749/CER57_Insulin-Delivery_FinalReport_20120703.pdf
*See: Comparative Effectiveness of CSII Versus MDI in:*
*Children and Adolescents with Type 1 Diabetes, page 17*
*Adults with Type 1 Diabetes, page 34*
*Pregnant Women with Pre-existing Type 1 Diabetes, page 61*
*Comparative Effectiveness of CSII Versus MDI, page 101*

.

6. Leelarathna L, Guzder R, Muralidhara K, Evans ML. Diabetes: glycaemic control in type 1. BMJ Clin Evid [Internet]. 2011 May 9 [cited 2015 Apr 2];2011:0607. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3217825
PubMed: PM21549022

7. Monami M, Lamanna C, Marchionni N, Mannucci E. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 1 diabetes: a meta-analysis. Acta Diabetol. 2010 Dec;47 Suppl 1:77-81.
PubMed: PM19504039

8. Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2010;(1):CD005103.
PubMed: PM20091571

**Randomized Controlled Trials**

*Adults*

9. Little SA, Leelarathna L, Walkinshaw E, Tan HK, Chapple O, Lubina-Solomon A, et al. Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2 x 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS). Diabetes Care. 2014 Aug;37(8):2114-22.
PubMed: PM24854041

10. Hermanides J, Norgaard K, Bruttomesso D, Mathieu C, Frid A, Dayan CM, et al. Sensor-augmented pump therapy lowers HbA(1c) in suboptimally controlled Type 1 diabetes; a randomized controlled trial. Diabet Med. 2011 Oct;28(10):1158-67.
PubMed: PM21294770

*Pediatric Populations*

11. Slover RH, Welsh JB, Criego A, Weinzimer SA, Willi SM, Wood MA, et al. Effectiveness of sensor-augmented pump therapy in children and adolescents with type 1 diabetes in the STAR 3 study. Pediatr Diabetes. 2012 Feb;13(1):6-11.
PubMed: PM21722284

12. Thrailkill KM, Moreau CS, Swearingen C, Rettiganti M, Edwards K, Morales AE, et al. Insulin pump therapy started at the time of diagnosis: effects on glycemic control and pancreatic beta-cell function in type 1 diabetes. Diabetes Technol Ther. 2011 Oct;13(10):1023-30.
PubMed: PM21718094

*Mixed Populations or Unclear Age*

13. Rubin RR, Peyrot M, STAR 3 Study Group. Health-related quality of life and treatment satisfaction in the Sensor-Augmented Pump Therapy for A1C Reduction 3 (STAR 3) trial. Diabetes Technol Ther. 2012 Feb;14(2):143-51.
PubMed: PM22133037

14. Bergenstal RM, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. N Engl J Med. 2010 Jul 22;363(4):311-20.
PubMed: PM20587585

15. Logtenberg SJ, Kleefstra N, Houweling ST, Groenier KH, Gans RO, Bilo HJ. Health-related quality of life, treatment satisfaction, and costs associated with intraperitoneal versus subcutaneous insulin administration in type 1 diabetes: a randomized controlled trial. Diabetes Care [Internet]. 2010 Jun [cited 2015 Apr 2];33(6):1169-72. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2875417
PubMed: PM20185731

**Economic Evaluations**
No literature identified

**Guidelines and Recommendations**

16. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of Diabetes in Canada. Can J Diabetes [Internet]. 2013 [cited 2015 Apr 2];37(suppl 1):S1-S212. Available from:
http://guidelines.diabetes.ca/App_Themes/CDACPG/resources/cpg_2013_full_en.pdf
*See: Pharmacotherapy in Type 1 Diabetes, pages S56 to S60*

17. Department of Veteran Affairs, Department of Defense. VA/DoD clinical practice guideline for the management of diabetes mellitus [Internet]. Washington (DC): Department of Veteran Affairs, Department of Defense; 2010 Aug [cited 2015 Apr 2]. 146 p. Available from: http://www.healthquality.va.gov/guidelines/CD/diabetes/DM2010_FUL-v4e.pdf
Summary available from the U.S. National Guideline Clearinghouse:
http://www.guideline.gov/content.aspx?id=24192&search=insulin+pump

*See: Continuous Subcutaneous Insulin Infusion, pages 64 to 67*

18. Scottish Intercollegiate Guidelines Network. Management of diabetes: a national clinical guideline [Internet]. Edinburgh: SIGN; 2010 Mar [cited 2015 Apr 2]. Available from:
http://www.sign.ac.uk/pdf/sign116.pdf
*See: Management of Type 1 Diabetes, page 6*
*CSII Therapy, pages 33 to 34*

**PREPARED BY:**
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

## APPENDIX – FURTHER INFORMATION:

### Systematic Reviews – Unclear Outcomes

19. Reutrakul S, Wroblewski K, Brown RL. Clinical use of U-500 regular insulin: review and meta-analysis. J Diabetes Sci Technol. 2012 Mar;6(2):412-20. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3380787
PubMed: PM22538155

### Randomized Controlled Trials – Alternate Outcome

20. Peyrot M, Rubin RR, STAR 3 Study Group. Treatment satisfaction in the sensor-augmented pump therapy for A1C reduction 3 (STAR 3) trial. Diabet Med. 2013 Apr;30(4):464-7.
PubMed: PM23496302

### Non-Randomized Studies

*Pregnant Women*

21. Mello G, Biagioni S, Ottanelli S, Nardini C, Tredici Z, Serena C, et al. Continuous subcutaneous insulin infusion (CSII) versus multiple daily injections (MDI) of rapid-acting insulin analogues and detemir in type 1 diabetic (T1D) pregnant women. J Matern Fetal Neonatal Med. 2015 Feb;28(3):276-80.
PubMed: PM24724804

22. Mathiesen JM, Secher AL, Ringholm L, Norgaard K, Hommel E, Andersen HU, et al. Changes in basal rates and bolus calculator settings in insulin pumps during pregnancy in women with type 1 diabetes. J Matern Fetal Neonatal Med. 2014 May;27(7):724-8.
PubMed: PM23981186.

23. Talaviya PA, Saboo BD, Joshi SR, Padhiyar JN, Chandarana HK, Shah SJ, et al. Pregnancy outcome and glycemic control in women with type 1 diabetes: a retrospective comparison between CSII and MDI treatment. Diabetes Metab Syndr. 2013 Apr;7(2):68-71.
PubMed: PM23680243

24. Wender-Ozegowska E, Zawiejska A, Ozegowska K, Wroblewska-Seniuk K, Iciek R, Mantaj U, et al. Multiple daily injections of insulin versus continuous subcutaneous insulin infusion for pregnant women with type 1 diabetes. Aust N Z J Obstet Gynaecol. 2013 Apr;53(2):130-5.
PubMed: PM23316799

25. Gonzalez-Romero S, Gonzalez-Molero I, Fernandez-Abellan M, Dominguez-Lopez ME, Ruiz-de-Adana S, Olveira G, et al. Continuous subcutaneous insulin infusion versus multiple daily injections in pregnant women with type 1 diabetes. Diabetes Technol Ther. 2010 Apr;12(4):263-9.
PubMed: PM20210564

*Pediatric Populations*

26. Lukacs A, Kiss-Toth E, Varga B, Soos A, Takac P, Barkai L. Benefits of continuous subcutaneous insulin infusion on quality of life. Int J Technol Assess Health Care. 2013 Jan;29(1):48-52.
PubMed: PM23270655

*Unclear Age*

27. Zheng H, Nathan DM, Schoenfeld DA. Using a multi-level B-spline model to analyze and compare patient glucose profiles based on continuous monitoring data. Diabetes Technol Ther. 2011 Jun;13(6):675-82. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3101946
PubMed: PM21488799

**Economic Evaluations – No Age Comparison**

28. Kamble S, Weinfurt KP, Schulman KA, Reed SD. Patient time costs associated with sensor-augmented insulin pump therapy for type 1 diabetes: results from the STAR 3 randomized trial. Med Decis Making. 2013 Feb;33(2):215-24.
PubMed: PM23128579

29. Kamble S, Schulman KA, Reed SD. Cost-effectiveness of sensor-augmented pump therapy in adults with type 1 diabetes in the United States. Value Health. 2012 Jul;15(5):632-8.
PubMed: PM22867771

**Clinical Practice Guidelines – Methodology Unclear**

30. American Diabetes Association. Standards of medical care in diabetes--2012. Diabetes Care. 2012 Jan;35 Suppl 1:S11-S63. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3632172
PubMed: PM22187469
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3632172/pdf/S11.pdf
*See: D. Pharmacologic and overall approaches to treatment, page S21*

**Review Articles**

31. Pickup JC. Management of diabetes mellitus: is the pump mightier than the pen? Nat Rev Endocrinol. 2012 Jul;8(7):425-33.
PubMed: PM22371161

32. Kaiserman K, Rodriguez H, Stephenson A, Wolka L, Fahrbach JL. Continuous subcutaneous infusion of insulin lispro in children and adolescents with type 1 diabetes mellitus. Endocr Pract. 2012 May;18(3):418-24.
PubMed: PM22297055.

33. Fuld K, Conrad B, Buckingham B, Wilson DM. Insulin pumps in young children. Diabetes Technol Ther. 2010 Jun;12 Suppl 1:S67-S71.
PubMed: PM20515310

**Additional References**

34. The Economic Benefit of Public Funding for Insulin Pumps. Canadian Diabetes Association. http://www.diabetes.ca/publications-newsletters/advocacy-reports/the-economic-benefit-of-public-funding-for-insulin#sthash.ilT5RDcy.dpuf
Newfoundland and Labrador: http://www.diabetes.ca/CDA/media/documents/publications-and-newsletters/advocacy-reports/economic-benefit-of-expanding-public-funding-for-insulin-pumps-in-newfoundland-labrador.pdf