New York State Department of Health

Dossier Review

Topic: Real-Time Continuous Glucose Monitors

April 2017

Center for Evidence-based Policy
Oregon Health & Science University
3030 SW Moody, Suite 250
Portland, OR 97201
Phone: 503.494.2182
Fax: 503.494.3807
www.ohsu.edu/policycenter

Table of Contents

Dossier Submission

Dexcom, Inc. submitted a dossier on G4™ PLATINUM Continuous Glucose Monitoring and G5™ Mobile CGM on September 8, 2016. The dossier was completed in accordance with the New York State Department of Health's instructions and included 23 articles for review published between 2006 and 2015. Of the submitted articles, 20 were rated by the submitter as having good methodological quality and three were rated as being of fair methodological quality. The submitted articles provided comparative outcomes on real-time continuous glucose monitoring (rt-CGM) in comparison to self-monitoring of blood glucose (SMBG) for type 1 and type 2 diabetes in children and adults.

Dossier Review Process

The Center for Evidence-based Policy (Center) reviewed the submitted dossier. Two Center researchers independently assessed submitted articles for inclusion, methodological quality, and reported results. Literature searches of the MEDLINE® (Ovid) database and the Center's core sources[1] (a select group of resources considered high quality because authors are independent and use systematic methods) were conducted to identify any additional relevant studies.

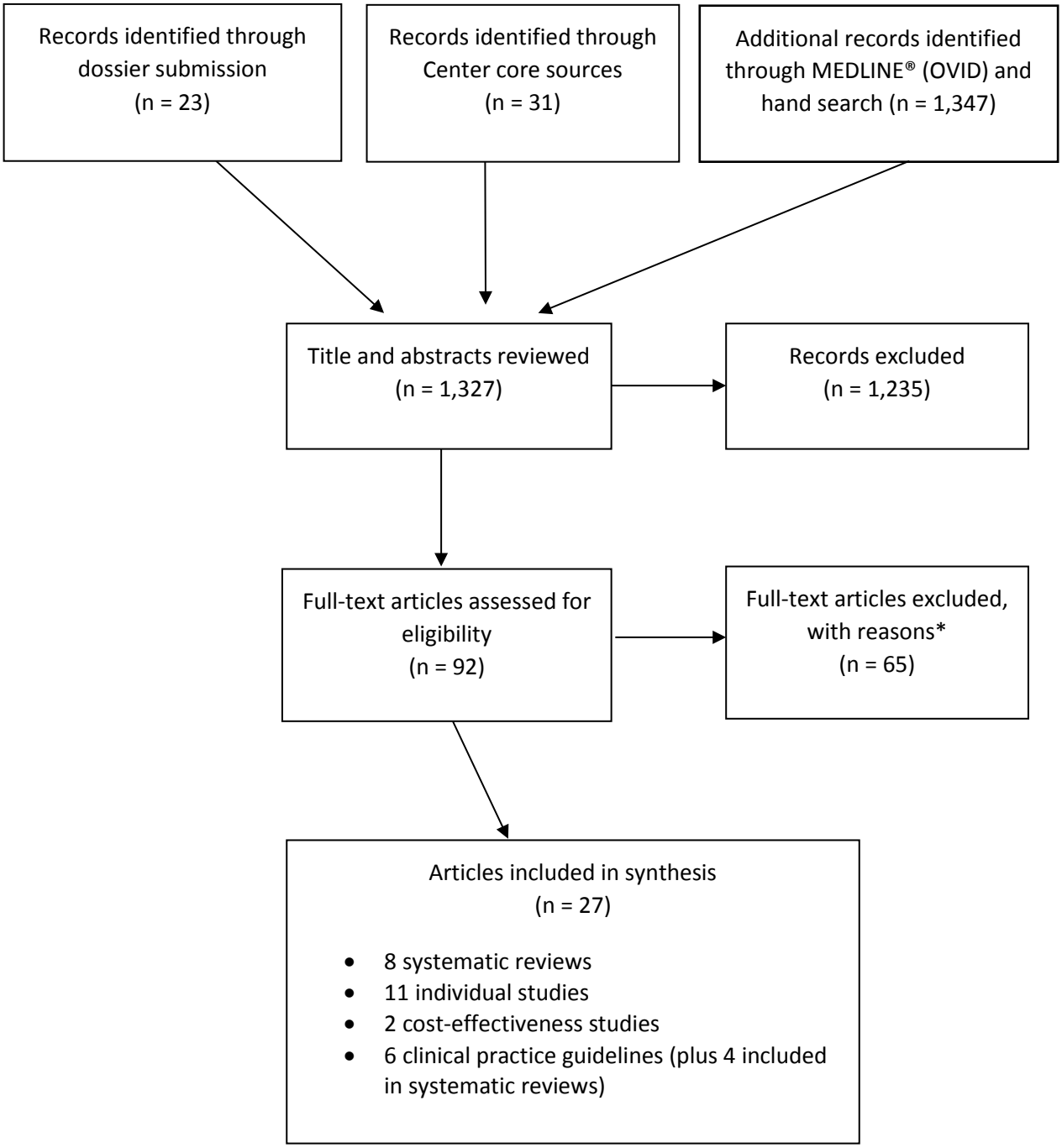
In separate searches, Center researchers identified eight systematic reviews and meta-analyses, 12 individual studies published after the last search dates of the included reviews, two cost-effectiveness studies, and 10 clinical practice guidelines that compared rt-CGM with SMBG and were eligible for this report. Figure 1 outlines the number of articles identified by each source and the total number of studies included in the evidence synthesis. The search strategy and list of studies reviewed in full with the reasons for exclusion are in Appendices A and B, respectively.

Review of the included dossier materials resulted in the exclusion of 20 of the 23 submitted articles (see Appendix B for further description of exclusion rationale). Sixteen of the submitted articles were included in the summarized systematic reviews, and thus not reviewed for individual results nor assessed for methodological quality by Center researchers. Individual publications of these articles were reviewed only to clarify study details. One of the 23 submitted articles was excluded based on study design (Bronstone & Graham, 2016), and a second article (Tildesley et al., 2013) because it had been withdrawn by study authors (Tildesley et al., 2016). Two of the articles (Wojciechowski, Rys, Lipowska, Gaweska, & Malecki, 2011; Yeh et al., 2012) submitted were systematic reviews that were excluded because the results were superseded by more recently published systematic reviews. Of the remaining three studies that were included

[1] Center core sources searched include the Cochrane Library (Wiley Interscience), the United Kingdom National Institute for Health and Care Excellence (NICE), the Blue Cross/Blue Shield Health Technology Assessment (HTA) program, the Veterans Administration Technology Assessment Program (VATAP), *BMJ Clinical Evidence*, the Canadian Agency for Drugs and Technologies in Health (CADTH), the Washington State Health Technology Assessment Program, the United States Preventive Services Task Force (USPSTF), and the Agency for Healthcare Research and Quality (AHRQ).

in this review, two were also identified in the Center's search (Battelino et al., 2015; New, Ajjan, Pfeiffer, & Freckmann, 2015).

Figure 1. Search Results[+]



*Note: †Some duplication of articles between Center core source search results and MEDLINE® (Ovid) search results. *Exclusion rationale provided in Appendix B.*

Brief Overview of the Topic

- Diabetes mellitus is a metabolic disorder that results in elevated blood sugar (glucose) levels caused by the body's inability to make insulin or effectively use insulin that is made within the body. Insulin is a hormone that facilitates getting glucose into cells (Centers for Disease Control and Prevention, 2015).

- Diabetes is the seventh leading cause of death in the U.S. and is associated with significant morbidity including heart disease, stroke, blindness, kidney failure, nerve damage, dental disease, and lower-extremity amputation (American Diabetes Association, 2016b; Centers for Disease Control and Prevention, 2015; National Institute of Diabetes and Digestive and Kidney Diseases, 2016).

- There are three main types of diabetes: type 1, type 2, and gestational diabetes (GDM). In type 1 diabetes (T1DM), also called insulin-dependent or juvenile onset diabetes, the body does not make insulin and daily insulin injections are required for survival. With type 2 diabetes (T2DM), also called non-insulin dependent or adult-onset diabetes, the body cannot use or make insulin effectively (National Institute of Diabetes and Digestive and Kidney Diseases, 2016). GDM occurs in 2% to 10% of pregnancies and can cause significant health issues for mothers and babies (Centers for Disease Control and Prevention, 2015).

- T1DM affects about 5% of the population and is treated through diet, exercise and insulin injections (American Diabetes Association, 2016b; Centers for Disease Control and Prevention, 2015). T2DM, mainly affecting adults, is the predominant type of diabetes in the U.S. and can be treated through diet, exercise, and monitoring of blood glucose levels (Centers for Disease Control and Prevention, 2015). Some individuals with T2DM are also treated with oral medication and/or insulin to control blood glucose levels (Centers for Disease Control and Prevention, 2015). GDM is treated with a similar approach as T2DM (National Institute of Diabetes and Digestive and Kidney Diseases, 2016).

- Diabetes requires daily monitoring and management of blood glucose levels and regular management of blood pressure and cholesterol to prevent diabetes-related health problems (National Institute of Diabetes and Digestive and Kidney Diseases, 2016). Blood glucose testing, also called serum or plasma testing, can indicate potentially serious events such as low or high blood sugar levels (hypoglycemia and hyperglycemia, respectively) (National Institute of Diabetes and Digestive and Kidney Diseases, 2016). Hemoglobin A1c (HbA1c), also called glycated hemoglobin, testing is commonly used to monitor blood glucose levels as it provides an average estimate of blood glucose levels over several weeks or months (National Institute of Diabetes and Digestive and Kidney Diseases, 2016).

- There are several methods to test HbA1c such as SMBG (finger prick for blood sample) and CGM (implanted sensor takes multiple interstitial fluid glucose readings per hour) (National Institute of Diabetes and Digestive and Kidney Diseases, 2016). CGM can be used for retrospective analysis and is often used as a diagnostic tool to determine periods of hypoglycemia or hyperglycemia (National Institute of Diabetes and Digestive and Kidney Diseases, 2016). Rt-CGMs can be used long-term to help an individual with daily glucose level management. CGM (retrospective or real-time) requires an individual to calibrate the device two to four times per day using SMBG (National Clinical Guideline Centre, 2015a). The target blood glucose level for many adults is 7% (National Institute of Diabetes and Digestive and Kidney Diseases, 2016).

- Individuals requiring insulin injections have the option to use multiple daily injections or use an insulin pump that provides continuous subcutaneous insulin infusion (CSII) (National Clinical Guideline Centre, 2015a).

Prevalence

- Nationwide, 1.4 million adults (age 20 years or older) are diagnosed with diabetes each year (American Diabetes Association, 2016b).

- In 2014, approximately 10% of adults (1.6 million) in New York had been diagnosed with diabetes (New York State Department of Health, 2014). In New York, diabetes prevalence is higher among non-Hispanic black and Hispanic adults (14.2% and 11.2, respectively) than white, non-Hispanic adults (8.4%). Adults who are obese also have a higher rate of diabetes (19.8%) than those who are overweight (9.0%) or neither overweight nor obese (4.6%) (New York State Department of Health, 2014). These prevalence rates mirror U.S. national diabetes trends: American Indians and Alaska Natives have the highest diagnosis rates of diabetes (15.9%), followed by non-Hispanic blacks (13.2%) and Hispanics (12.8%) (American Diabetes Association, 2016b).

Methods

Center researchers searched Center core sources and MEDLINE® (Ovid) for systematic reviews (with or without meta-analysis) and technology assessments on rt-CGMs published within the last 10 years. To ensure that the most recent data were included, Center researchers also searched MEDLINE® (Ovid) through March 2016 for individual studies on rt-CGMs published after the search dates of the most recent included systematic reviews. Center researchers evaluated the methodological quality of systematic reviews and individual studies in this report using the quality assessment tools within the dossier submission form (available on the New York State Department of Health website).

Center researchers excluded systematic reviews if all of the included studies were also summarized by a more comprehensive systematic review, a systematic review of a higher

methodological quality, and/or a more recently published systematic review. Center researchers only considered comparative studies for evaluation of efficacy and case series for evaluation of harms. In addition, only patient important outcomes have relevance for the New York State Department of Health. The rationale for study inclusion can be found in the New York State Department of Health Dossier Methods Guidance (New York State Department of Health, 2016). Exclusion criteria were selected before the review of the studies, and study methods were assessed before the review of outcomes to eliminate bias. See Appendix A for a full description of methods.

Studies report on the statistical significance of findings, but it is not always clear how relevant a statistically significant finding is in clinical practice. This report uses the clinical significance threshold as reported in the NICE systematic reviews and meta-analyses in which 0.5 percentage point in HbA1c change is considered a minimally important difference (National Clinical Guideline Centre, 2015a). For women with GDM, this value is slightly variable with a minimally important difference ranging from 0.36 (HbA1c at 28 to 36 weeks) to 0.45 (mean glucose level) percentage points (National Clinical Guideline Centre, 2015b).

The dossier submitter identified outcomes evaluating the effectiveness (i.e., decrease in HbA1c, percentage achieving target HbA1c, relationship between sensor compliance and HbA1c reduction); harms (i.e., frequency of hypoglycemic events); and cost-effectiveness (i.e., incremental cost-effectiveness) of rt-CGMs compared to SMBG. Center researchers reviewed the outcomes submitted in the dossier and additional outcomes identified in the literature with respect to patient importance. Through this review, Center researchers excluded the outcome on the relationship between sensor compliance and HbA1c compliance and included the additional outcomes of adverse events, maternal outcomes (for diabetes in pregnancy), and neonatal outcomes (for diabetes in pregnancy).

Evidence Review

Findings

Using the Center's core sources and materials submitted through the dossier process, Center researchers identified eight systematic reviews and 11 individual studies relevant to the effectiveness and/or harms of rt-CGMs that met inclusion criteria.

Overview of Evidence Sources

Center researchers summarized the evidence as reported by the included systematic reviews. Center researchers did not review the individual studies included in the systematic reviews unless necessary for clarification of information reported in the systematic review. References for studies included in the systematic reviews are provided so that readers can easily identify the primary source of the data. There was substantial overlap in study inclusion across the systematic reviews and meta-analyses. Appendix C provides a comparison of individual studies included across systematic reviews and a reference list of primary studies included by the

reviews. Tables 1 to 4 provide an overview of findings from the included systematic reviews and individual studies.

Systematic Reviews

Langendam, M., Luijf, Y. M., Hooft, L., DeVries, J. H., Mudde, A. H., & Scholten, R. J. P. M. (2012). Continuous glucose monitoring systems for type 1 diabetes mellitus. *Cochrane Database of Systematic Reviews,* Issue 1.

Langendam et al. (2012) conducted a systematic review and meta-analysis that Center researchers assessed as having good methodological quality. The review includes randomized controlled trials (RCTs) published before June 8, 2011 of individuals with T1DM across multiple age groups or populations: children (0 to 14 years), adolescents (15 to 23 years), adults, and pregnant women. Analyses clearly delineate rt-CGM from retrospective CGM for several outcomes (i.e., change in HbA1c, improvement greater than 0.5% in HbA1c, severe hypoglycemia, ketoacidosis, quality of life, CGM-derived hypoglycemia, CGM-derived hyperglycemia). Secondary outcomes included complications and adverse effects. The authors used an extensive search strategy (e.g., multiple databases searched, comprehensive search strategy used, few to no limits on study publication date), to identify three RCTs investigating rt-CGM in children, two RCTs in adolescents, and nine RCTs in adults. Langendam et al. (2012) reported that there was industry funding for all of the CGM studies.

Moy, F. M., Ray, A., & Buckley, B. S. (2014). Techniques of monitoring blood glucose during pregnancy for women with pre-existing diabetes. *Cochrane Database of Systematic Reviews*, Issue 4.

Moy, Ray, and Buckley (2014) conducted a systematic review and meta-analysis that Center researchers assessed as having good methodological quality. The review includes RCTs published through August 2013 involving individuals with preexisting diabetes in pregnancy. Primary outcomes included maternal glycemic control, infant birthweight, and macrosomia. None of the included studies involved women with gestational diabetes. Authors used an extensive search strategy to identify nine studies eligible for inclusion; however, only two RCTs investigated rt-CGM versus SMBG in pregnant women.

National Institute for Health and Care Excellence. (2015a). *Diabetes (type 1 and type 2) in children and young people: Diagnosis and management*. London: NICE. Retrieved from https://www.nice.org.uk/guidance/ng18/evidence/full-guideline-435396352

National Clinical Guideline Centre (2015a) conducted a systematic review and meta-analysis to inform guidelines for the diagnosis and management of diabetes (T1DM and T2DM) in children and young persons. The review includes systematic reviews, RCTs, and observational studies published through August 2014. Primary outcomes included estimates of glycemic control, adherence, quality of life, and satisfaction. The authors used an extensive search strategy to

identify three studies published in the search interval: one systematic review and two RCTs. Center researchers assessed the review as having good methodological quality.

National Institute for Health and Care Excellence. (2015b). *Diabetes in pregnancy: Management of diabetes and its complications from preconception to the postnatal period*. London: NICE. Retrieved from https://www.nice.org.uk/guidance/ng3/evidence/full-guideline-3784285

National Clinical Guideline Centre (2015b) conducted a systematic review to inform guidelines for the diagnosis and management of diabetes in pregnant women. The review includes systematic reviews, RCTs, and observational studies published through June 2014. Primary outcomes included estimates of maternal glycemic control (e.g., HbA1c, fasting glucose), maternal obstetric outcomes (e.g., rates of assisted vaginal births, cesarean section), neonatal outcomes (e.g., hypoglycemia, neonatal intensive care unit [NICU] admission, miscarriage, neonatal death, hypoglycemia, NICU transfer). Authors used an extensive search strategy to identify five studies: three RCTs and two within-participant comparisons. Only one of the five studies directly compared rt-CGM with SMBG; the remaining four studies reported on the retrospective use of CGMs. Center researchers assessed the review as having good methodological quality.

National Institute for Health and Care Excellence. (2015c). *Type 1 diabetes in adults: Diagnosis and management*. London: NICE. Retrieved from https://www.nice.org.uk/guidance/ng17/evidence/full-guideline-435400241

National Clinical Guideline Centre (2015c) conducted a systematic review and meta-analysis to inform guidelines for the diagnosis and management of T1DM in adults. The review includes RCTs published through August 2014. Primary outcomes included estimates of glycemic control (e.g., HbA1c, fasting glucose), quality of life, adverse events, and adherence. The authors used an extensive search strategy to identify nine studies comparing rt-CGM to SMBG in adults with T1DM. Center researchers assessed the review as having good methodological quality.

National Institute for Health and Care Excellence. (2015d). *Type 2 diabetes in adults: Management*. London: NICE. Retrieved from https://www.nice.org.uk/guidance/ng28/evidence/full-guideline-78671532569

National Clinical Guideline Centre (2015d) conducted a systematic review and meta-analysis to inform guidelines for the diagnosis and management of T2DM in adults. The review includes RCTs published through June 2014. Primary outcomes included estimates of glycemic control (e.g., HbA1c, fasting glucose), quality of life, adverse events, and adherence. Authors used an extensive search strategy to identify two studies comparing rt-CGM to SMBG in adults with T2DM. Center researchers assessed the review as having good methodological quality.

Poolsup, N., Suksomboon, N., & Kyaw, A. M. (2013). Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. *Diabetology and Metabolic Syndrome, 5,* 39.

Poolsup, Suksomboon, and Kyaw (2013) conducted a systematic review and meta-analysis investing the impact of CGM compared to SMBG on glucose control in two populations: 1) pediatric patients with T1DM and 2) adults with T2DM. The authors included RCTs published through May 2013, with at least eight weeks of follow-up data. Studies involving pregnant women were excluded. The authors identified five studies on rt-CGM in pediatric patients with T1DM and five studies in adults with T2DM. Center researchers assessed the review as having good methodological quality.

Skelly, A. C., Kisser, J. M. S., Mayfield, J. A., Olson, C. M., & Ecker, E. D. (2011). *Glucose monitoring: Self-monitoring in individuals with insulin dependent diabetes, 18 years of age or under*. Olympia, WA: Washington Health Technology Assessment Program. Retrieved from http://www.hca.wa.gov/assets/program/glucose_monitoring_final[1].pdf

Skelly, Kisser, Mayfield, Olson, and Ecker (2011) conducted a systematic review for the Washington State Health Care Authority, which Center researchers assessed as having good methodological quality. The authors investigated self-monitoring options for pediatric patients (18 years of age or under) with T1DM. They utilized studies on CGM that allowed for patient real-time use of data. Primary outcomes included achieving or maintaining target HbA1c levels, ketoacidosis, hyperglycemia, hypoglycemia, reduction in microvascular complications, mortality, impact on medication or nutritional management, and quality of life. The authors included RCTs and cohort studies with controls, crossover studies (i.e., participants received different interventions during different study periods), and longitudinal studies with long term clinical outcomes. The authors identified three studies on the relationship between CGM and HbA1c. Two of the identified studies used different treatments (e.g., insulin pumps, subcutaneous injections), limiting the ability to assess the direct impact of rt-CGM.

Individual Studies

Battelino, T., Liebat, S., Veeze, H. J., Castandena, J., Arrieta, A., & Cohen, O. (2015). Routine use of continuous glucose monitoring in 10,501 people with diabetes mellitus. *Diabetic Medicine, 32*(12), 1568-74.

Battelino et al. (2015) conducted a retrospective cohort study using administrative data from the Medtronic CareLink™ database on 10,695 individuals with T1DM and T2DM using insulin pump therapy. The authors did not obtain consent to use demographic or other clinical data; thus, the primary outcome was glycemic control based on self-monitor device readings uploaded to the database and stratified by actual time compared to expected time using the Medtronic CGM sensor. Center researchers assessed the review as having poor methodological quality.

Beck, R. W., Riddlesworth, T., Ruedy, K., Ahmann, A., Bergenstal, R., Haller, S., . . . Price, D. (2017). Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: The DIAMOND randomized clinical trial. *JAMA, 317*(4), 371-378. doi: 10.1001/jama.2016.19975

Beck et al. (2017) conducted an RCT (known as the DIAMOND trial) comparing the use of rt-CGM monitoring versus conventional care with SMBG for people with TIDM using multiple daily injections of insulin. The study randomized 158 adults at 24 endocrinology practices in the U.S. Participants completed a two week pre-randomization phase to confirm that they could wear the CGM on at least 85% of days, calibrate the monitor at least twice per day, and perform SMGB at least three times per day. Participants were randomized in a 2:1 ratio to CGM or control groups that were stratified by HbA1c level less than 8.5% or greater than or equal to 8.5%. The primary outcome was change in HbA1c at 12 and 24 weeks. Secondary outcomes included the proportion of participants with HbA1c less than 7%, duration of hypoglycemia, and frequency of SMBG testing. Center researchers assessed the review as having good methodological quality.

Lind, M., Polonsky, W., Hirsch, I. B., Heise, T., Bolinder, J., Dahlqvist, S., . . . Hellman, J. (2017). Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: The GOLD randomized clinical trial. *JAMA, 317*(4), 379-387. doi: 10.1001/jama.2016.19976

Lind et al. (2017) conducted a crossover RCT (known as the GOLD trial) comparing the use of rt-CGM versus SMBG for adults with T1DM using multiple daily insulin injections. The study randomized 161 people at 15 outpatient diabetes clinics in Sweden after a six-week masked CGM run-in period. Enrollees were not randomized if they did not believe they could wear the CGM for more than 80% of the time or did not perform at least 12 calibration checks in seven days. Participants were randomized to begin the trial with either CGM use or conventional SMBG for 26 weeks, followed by a washout period of 17 weeks, and then groups crossed over to the other treatment and were followed for another 26 weeks. The primary outcome was HbA1c at the end of each 26-week active treatment period. Secondary outcomes included severe hypoglycemia, amount of time spent in hypoglycemia, and number of SMBG checks. Center researchers assessed the review as having fair methodological quality.

McQueen, R. B., Ellis, S. L., Maahs, D. M., Anderson, H. D., Nair, K. V., & Campbell, J. D. (2014). Frequency of continuous glucose monitoring use and change in hemoglobin A1c for adults with type 1 diabetes in a clinical practice setting. *Endocrine Practice, 20*(10), 1007-15.

McQueen et al. (2014) conducted a retrospective cohort study evaluating the effectiveness of CGM in adults with T1DM. The study enrolled 133 adults with T1DM from a single center in Arizona. The authors obtained self-reported estimates of CGM use over the past 12 months

from 66 individuals and compared HbA1c changes to 67 individuals using SMBG for a similar time period. Center researchers assessed the review as having poor methodological quality.

New, J. P., Aijan, R., Pfeiffer, A. F., & Freckmann, G. (2015). Continuous glucose monitoring in people with diabetes: The randomized controlled Glucose Level Awareness in Diabetes Study (GLADIS). *Diabetic Medicine, 32*(5), 609-17.

New et al. (2015) conducted an RCT on the effectiveness of CGM in adults with diabetes that Center researchers assessed as having poor methodological quality. The study enrolled 160 adults with either T1DM or T2DM from clinics in the United Kingdom and Germany. The authors investigated the impact of CGM, with and without the alarm feature, on glycemic control compared to SMBG in a 100-day period. Although the impact of the alarm feature is outside the scope of this review, the authors included comparisons of CGM without an alarm and SMBG; these findings are in Table 3.

Rachmiel, M., Landau, Z., Boaz, M., Mazor Aronovitch, K., Loewenthal, N., Ben-Ami, M., … Pinhas-Hamil, O. (2015). The use of continuous glucose monitoring systems in a pediatric population with type 1 diabetes mellitus in real-life settings: the AWeSoMe Study Group experience. *Acta Diabetologica, 52*(2), 323-9.

Rachmiel et al. (2015) conducted a cohort study evaluating the effectiveness of CGM in a pediatric population with T1DM, which Center researchers assessed as having poor methodological quality. The authors enrolled pediatric patients with T1DM (83 individuals using rt-CGM and 66 using SMBG). All enrollees received care in an Israeli pediatric diabetes center and were followed for 12 months. The authors compared the groups across outcomes of glycemic control (e.g., HbA1c, 14-day mean and standard deviation of SMBG). In Israel, rt-CGM and supplies are covered by national insurance, eliminating cost burdens for patients and families. Typical clinical practice is to offer CGM to any individual who experiences two episodes of hypoglycemia (below 70 mg/dL for children under eight years), unawareness of hypoglycemia, or a severe hypoglycemic event for more than six months.

Riveline, J.-P., Schaepelynck, P., Chaillous, L., Renard, E., Sola-Gazagnes, A., Penfornis, A., … Hanaire, H., EVADIAC Sensor Study Group. (2012). Assessment of patient-led or physician-driven continuous glucose monitoring in patients with poorly controlled type 1 diabetes using basal-bolus insulin regimens. *Diabetes Care, 35*(5), 965-71.

Riveline et al. (2012) conducted an RCT evaluating the effectiveness of CGM in individuals with poorly controlled T1DM, which Center researchers assessed as having poor methodological quality. The study randomized 197 individuals with T1DM, aged 8 to 60 years, with a primary goal of investigating the role of CGM (either real-time patient-led or retrospective physician-led) compared to SBMG in glycemic control in individuals aged 8 to 60 years with over 12 months of

experience with T1DM. Enrollees were followed for 12 months. All enrollees were required to complete a 10-day trial period with the CGM before inclusion in the final data set.

Soupal, J., Petruzelkova, L., Flekac, M., Pelci, T., Matoulek, M., Dankova, M., … Pranzny, M. (2016). Comparison of different treatment modalities for type 1 diabetes, including sensor-augmented insulin regimens, in 52 weeks of follow-up: A COMISAIR study. *Diabetes Technology & Therapeutics, 18*(9), 532-8.

Soupal et al. (2016) conducted a prospective cohort study from the Czech Republic evaluating effectiveness of various CGM treatment modalities in patients with T1DM. The study enrolled 65 patients with T1DM and followed them for 12 months. Enrollees were stratified by use of CGM or SMBG and treatment type (CSII or multiple daily injections). The authors reported comparisons of CGM to SMBG (across both treatment types) and comparisons by treatment type (i.e., CGM with CSII compared to SMBG with CSII). Center researchers assessed the review as having fair methodological quality.

Tang, T. S., Digby, E. M., Wright, A. M., Chan, J. H., Mazanderani, A. B., Ross, S. A. … Tildesley, H. D. (2014). Real-time continuous glucose monitoring versus internet-based blood glucose monitoring in adults with type 2 diabetes: A study of treatment satisfaction. *Diabetes Research & Clinical Practice, 106*(3), 481-6.

Tang et al. (2014) conducted an RCT in Canada evaluating the effectiveness of rt-CGM with internet-based SMBG in adults with T2DM. The study enrolled 40 patients and randomized them to rt-CGM or SMBG with an internet-based monitoring assistance program. The primary outcome was patient treatment satisfaction using the Diabetes Treatment Satisfaction Questionnaire. Center researchers assessed the review as having fair methodological quality.

Tumminia, A., Crimi, S., Sciacca, L., Buscema, M., Frittitta, L., Squatrito, … Tomaselli, L. (2015). Efficacy of real-time continuous glucose monitoring on glycaemic control and glucose variability in type 1 diabetic patients treated with either insulin pumps or multiple insulin injection therapy: A randomized controlled crossover trial. *Diabetes/Metabolism Research Reviews, 31*(1), 61-8.

Tumminia et al. (2015) conducted crossover RCT in Italy evaluating the effectiveness of rt-CGM in individuals with T1DM. The study compared rt-CGM to SMBG for HbA1c reduction. The authors only reported outcomes for 14 individuals with the highest level of sensor use, omitting data on six individuals. Center researchers assessed the review as having poor methodological quality.

van Beers, C. A., DeVries, J. H., Kleijer, S. J., Smits, M. M., Geelhoed-Duijvestjin, P. H., Kramer, M. H., … Serne, E. H. (2016). Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycemia (IN CONTROL): A randomised, open-label, crossover trial. *The Lancet Diabetes & Endocrinology, 4*(11), 893-902.

van Beers et al. (2016) conducted a crossover RCT in the Netherlands evaluating the effectiveness of CGM in patients with T1DM and impaired awareness of hypoglycemia. The study enrolled 52 individuals aged 18 to 75 years with T1DM and hypoglycemia unawareness (as defined by a Gold score of at least four). All participants completed a six-week run-in with CGM, then were randomized to either CGM or SMBG for 16 weeks, followed by a 12-week washout, then 16 weeks of the other monitoring system. The primary outcome of the study was the percentage of time spent in normoglycemic (70 to 180 mg/dL) range, with secondary outcomes including severe hypoglycemic event frequency and time spent in hypoglycemic or hyperglycemic range. Center researchers assessed the review as having good methodological quality.

Quality and Limitations

Center researchers rated all eight of the systematic reviews as having good methodological quality (Langendam et al., 2012; Moy et al., 2014; National Clinical Guideline Centre, 2015a, 2015b, 2015c, 2015d; Poolsup et al., 2013; Skelly et al., 2011). Center researchers assessed the methodological quality of included systematic reviews and meta-analyses and not the individual studies within them. References to individual study quality are taken directly from the systematic reviews, and are not assessments made by Center researchers.

Center researchers assessed the methodological quality of studies not included in the systematic reviews using standard quality assessment methods (see Appendix A for further details). Of the 11 additional included studies, Center researchers rated two as good (Beck et al., 2017; van Beers et al., 2016), three as fair (Lind et al., 2017; Soupal et al., 2016; Tang et al., 2014), and six as poor-methodological quality (Battelino et al., 2015; McQueen et al., 2014; New et al., 2015; Rachmiel et al., 2015; Riveline et al., 2012; Tumminia et al., 2015).

There are several common methodological biases across the included studies. The majority of individual studies have limited internal validity; small sample sizes; and extensive industry involvement; in addition, the studies recruited younger, healthier individuals with diabetes. Adverse events were infrequently reported and studies were often underpowered to detect significant differences in clinically relevant harms (e.g., severe hypoglycemia, diabetic ketoacidosis). None of the identified studies included clinically relevant long-term outcomes related to diabetes (e.g., cardiovascular disease, kidney disease, stroke, diabetic foot infections, amputations, mortality). Although results from many of the included studies are biased toward showing an effect in favor of rt-CGM, they often observed no significant differences between rt-

CGM and SMBG. In addition, many of the studies were conducted outside the U.S., limiting the external validity of the results in the U.S. health care system.

Summary of the Evidence

Evidence is summarized by outcomes of effectiveness and harms. Individual study quality discussed in the context of included systematic reviews is taken directly from review authors and is not the Center's original assessment of the work. Tables 1 to 4 provide a high-level summary of the evidence listed by systematic review and included studies. There was significant overlap of included studies across the systematic reviews and meta-analyses.

Evidence for effectiveness is divided by type of diabetes (i.e., T1DM and T2DM), then population (i.e., adults, adolescents, and children). Two systematic reviews addressed preexisting diabetes in pregnancy (Moy et al., 2014; National Clinical Guideline Centre, 2015b). There is scant evidence on the use of rt-CGM in women with gestational diabetes: only a single study met inclusion criteria for the NICE systematic review.

Table 1. Overview of Included Studies: T1DM

Citation, Study Details	# of Studies (k)/ Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
T1DM: Meta-analyses			
Langendam et al. (2012) Search Dates 2003 to June 2011 Included Study Designs RCTs Population Children or adults with T1DM Methodological Quality Good	k = 8 (meta-analysis), 22 (systematic review) Total n = 2,681 *Systematic review authors' quality assessment of individual studies:* Fair to Good	Comparators Rt-CGM vs. SMBG Change in HbA1c *All Ages* (at 6 months, 8 studies, total n = 963) Weighted mean difference: -0.23%; 95% CI, -0.36 to -0.09% Severe hypoglycemia *All Ages* (at 6 months, 6 studies, total n = 689) Risk ratio (RR): 1.05 (95% CI, 0.63 to 1.77)	No studies on GDM were identified. Quality of life assessed using different tools across different age groups; thus, unable to provide single estimate of impact. Authors reported similar findings across CGM users vs. SMBG when using similar tools (e.g., adult physical or mental health QOL). Available evidence does not provide estimates on patient satisfaction, diabetes complications, death, or costs. Limited evidence from single studies on proportion of patients experiencing 0.5% change in HbA1c, quality of life, harms (severe hypoglycemia, ketoacidosis) for age groups (i.e., children, adolescents, adults). Pediatric studies from this systematic review are incorporated in NICE (National Clinical Guideline Centre, 2015a) (see below).

Citation, Study Details	# of Studies (k)/ Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
			Significant statistical heterogeneity was detected between studies included in the all ages meta-analysis (Chi-square, 15.6; p = .03; I^2 = 55%).
National Clinical Guideline Centre (2015a) Search Dates Through August 2014 Included Study Designs Systematic reviews, RCTs, and observational studies Population Children and adolescents with T1DM Methodological Quality Good	k = 3 (T1DM, CGM vs. SMBG) Total n = 298 (CGM vs. SMBG) Patients with T1DM under age 18 *Systematic review authors' quality assessment of individual studies:* Poor	Comparators Rt-CGM vs. SMBG Change in HbA1c *Children or Young Adults* No statistically significant change in HbA1c at 6 months between rt-CGM and SMBG Severe Hypoglycemia Episodes *Children or Young Adults* No statistically significant change episodes of severe hypoglycemia at 12 months	Only change in HbA1c specifies real-time CGM. Severe hypoglycemia not differentiated between real time or retrospective. High strength of evidence of the estimate of effect for change in HbA1c, low strength for severe hypoglycemic episodes. The authors also reported findings from a single RCT on parental satisfaction demonstrating increased satisfaction at 6 months for *rt-CGM vs. SMBG (1 RCT, n = 137)* with a mean difference of 0.3 (95% CI, 0.21 to 0.39).

Citation, Study Details	# of Studies (k)/ Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
National Clinical Guideline Centre (2015c) Search Dates Through August 2014 Included Study Designs RCTs Population Adults with T1DM Methodological Quality Good	k = 12 (CGMS vs. SMBG) Total n = 1,636 (CGM vs. SMBG) *Systematic review authors' quality assessment of individual studies:* Poor to Fair	Comparators Rt-CGM vs. SMBG Change in HbA1c *Adults* Mean difference: -0.30 (95% CI -0.47 to -0.12) Severe Hypoglycemia Episodes *Adults* No statistically significant differences for rt-CGM vs. SMBG	Very low quality of the estimate of the effect. Authors also reported no statistically significant differences in quality of life or adverse events.
Poolsup et al. (2013) Search Dates Through May 2013 Included Study Designs RCTs Population Children with T1DM, Methodological Quality Good	k = 10 Total n = 817 *Systematic review authors' quality assessment of individual studies:* Poor, Good	Comparators Rt-CGM vs. SMBG Change in HbA1c *Aged 18 or under* Pooled mean difference: -0.18% (95% CI, -0.35% to -0.02%)	Only 5 of 10 studies used rt-CGM Use of rt-CGM ranged from daily to 3 days every 3-6 weeks Follow-up ranged from 3-12 months 8 weeks to 3 months of follow-up Excluded pregnant women Various insulin regimens

Citation, Study Details	# of Studies (k)/ Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
T1DM: Systematic Reviews			
Skelly et al. (2011) Search Dates Through June 2010 Included Study Designs RCTs, comparative studies Population Children with T1DM or T2DM Methodological Quality Good	k = 4 (rt-CGM) Total n = 464 *Systematic review authors' quality assessment of individual studies:* Fair	Comparators Rt-CGM vs. SMBG Change in HbA1c *Children* None of the identified studies demonstrated a clinically significant change in HbA1c (0.5% threshold) for rt-CGM vs. SMBG Severe Hypoglycemia *Children* 7% vs. 10%, no further analysis Rate of Severe Hypoglycemic Episodes *Children* 17.9 per 100,000 person years vs. 24.4 per 100,000 (Rate ratio calculated by Center researchers: 0.73)	Estimate of effect on change in HbA1c based on low strength of evidence No data on children with T2DM Data frequently not stratified by age 26 to 52 weeks of follow-up Two of three included studies used different treatments (e.g., pumps, injections), limiting ability to determine direct impact of rt-CGM alone No studies including pregnant teens identified No studies provided data on microvascular outcomes or mortality Episodes of diabetic ketoacidosis were rare Only a single study looked at quality of life; no differences between groups

Citation, Study Details	# of Studies (k)/ Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
T1DM: Randomized Controlled Trials			
Beck et al. (2017) Study Design RCT Location U.S. Methodological Quality Good	n = 158 adults with T1DM using multiple daily insulin injections and HbA1c of 7.5% to 9.9% Mean HbA1c: 8.6 in both groups	Comparators Rt-CGM vs. SMBG Mean HbA1c levels at 24 weeks 7.7% vs. 8.2% HbA1c change from baseline difference between groups, adjusted for baseline HbA1c and site -0.6 (95% CI -0.8 to -0.3) Severe hypoglycemia events 2 in each group (p = 0.67) Minutes of hypoglycemia (<70 mg/dL) per day, median (IQR) (12- and 24-week data pooled) 43 (27 to 69) vs. 80 (36 to 111), p = 0.002	16% dropout rate in rt-CGM group vs. 7.6% in SMBG controls Neither participants nor clinicians were masked to group assignment Multiple authors with industry research funding, including from sponsor of trial (manufacturer of the rt-CGM device.) One co-author was sponsor employee and sat on steering committee. Two authors hold stock in company. Highly controlled study population that may not represent average users of CGM devices.
Lind et al. (2017) Study Design Cross-over RCT Location Sweden	n = 161 Age 46.7 vs. 42.6 years, mean HbA1c, 8.49% vs. 8.45%	Comparators Rt-CGM first vs. Conventional treatment SMBG first Mean HbA1c levels during pooled 26-week treatment periods	Open label crossover design 11.8% dropouts/lost to follow-up

Citation, Study Details	# of Studies (k)/ Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
Methodological Quality Fair		7.92% vs. 8.35, least square mean difference -0.43 (-0.57 to -0.29), p<0.001 Percentage of time in hypoglycemia (<70 mg/dL) (12- and 24-week data pooled) 2.97% vs. 4.79%, no significance testing provided Severe hypoglycemic events, number (event rate per 1000 patient-years) 1 (0.04) vs. 5 (0.19), no significance testing provided Adverse events (total) 77 patients with 137 events vs. 67 patients with 122 events, with " . . . no obvious numerical differences for any adverse event between the treatments." 1 person in CGM group discontinued trial because of allergic reaction to CGM sensor	Last observation carried forward method used to impute some missing data. Multiple authors with industry research funding, including from trial funder. Trial sponsored by hospital system with financial support and devices from the manufacturer.
Riveline et al. (2012) Study Design RCT Location France	n = 257 with T1DM Ages 8 to 60	Comparators Rt-CGM vs. SMBG Change in HbA1c from baseline at 12 months *All ages* -0.5% (95% CI, -0.7 to -0.29) vs. 0.02% (95% CI, -0.18 to 0.23), p = 0.0006	Last observation carried forward 19 enrollees provided no HbA1c data, unclear how many LOCF CSII or MDI for treatment

Citation, Study Details	# of Studies (k)/ Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
Methodological Quality Poor		Proportion patients with HbA1c<7.5% *All ages* 9.7% vs. 1.6%, p = 0.025	No difference in non-severe hypoglycemia Rare diabetic ketoacidosis events Quality of life estimates combined real-time and retrospective CGM users
Tumminia et al. (2015) Study Design RCT Location Italy Methodological Quality Poor	n = 20 adults with T1DM and poor glycemic control (HbA1c >8.0%)	Comparators Rt-CGM vs. SMBG Reported analysis of those most likely to experience the greatest change in HbA1c, those using device >40% of time. Mean HbA1c levels *Individuals with higher utilization of CGM (>40% of time)* 7.76% ± 0.4 vs. 8.54% ± 0.4, p < 0.05 (no further analysis provided) *Individuals with lower utilization rates* 8.53% ± 0.5 vs. 8.22% ± 0.6	Small sample size Outcomes provided by convenience sample of those with highest utilization (>40%) In subgroup of 14 individuals with higher utilization, average HbA1c was lower during time with rt-CGM than SMBG, but values overlap In the 6 individuals with lower utilization, HbA1c ranges overlap Comparison of MDI and CSII as well CGM alarms turned on in study as well Despite enrolling individuals with elevated HbA1c, excluded individuals

Citation, Study Details	# of Studies (k)/ Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
			with poor compliance to diet, insulin therapy, and or/glucose monitoring
van Beers et al. (2016) Study Design Netherlands Location Italy Methodological Quality Good	n = 52 individuals aged 18 to 75 with T1DM and impaired awareness of hypoglycemia	Comparators Rt-CGM vs. SMBG Number severe hypoglycemic events 14 vs. 34, p = 0.03	7/52 (13%) of enrollees did not meet inclusion criteria of impaired hypoglycemia awareness 6 patients withdrew from study, 2 because of issues with the CGM device, 1 because of poor adherence to CGM Both MDI and CSII users included
T1DM: Observational Studies			
McQueen et al. (2014) Study Design Retrospective cohort Location United States Methodological Quality Poor	n = 133 Age >18 with T1DM, non-pregnant	Comparators Rt-CGM vs. SMBG HbA1c Mean Difference No statistically significant difference in change in HbA1c (-0.11%, 95% CI, -0.38 to 0.16)	Enrollees self-reported sensor use in past 12 months Differences in baseline characteristics may have biased results in favor of rt-CGM (e.g., longer time with diabetes, older age) Change in HbA1c is not at set time period, but at lowest experienced during overall study period 36% discontinued CGM within first 12 months, reporting costs, alarm

Citation, Study Details	# of Studies (k)/ Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
			frequency, accuracy concerns, and discomfort as reasons. Half of patients used the sensor less than 21 days per month
Rachmiel et al. (2015) Study Design Prospective cohort Location Israel Methodological Quality Poor	n = 149 pediatric individuals with T1DM	Comparators Rt-CGM vs. SMBG Glycemic control *Children* Average HbA1c levels and mean glucose values in past 14 days did not differ across groups at 3, 6, 9, or 12 months Subgroup analysis by age strata (<8 vs. >8; <11, 11–13, vs. >13) and without any difference Hypoglycemia *Children* 18.1 per 100 patient year episodes severe hypoglycemia in rt-CGM group compared to 10.6 per 100 in control group (Rate ratio calculated by Center researchers = 1.71)	By 12 months, only 32 patients (38% of rt-CGM group) were consistently using their device (>75% of the time) CSII or MDI treatment By 6 months, half of CGM group discontinued use; by 12 months discontinuation increased to nearly two-thirds Clinical practice in Israel is to offer CGM to individuals with severe hypoglycemia or ketoacidosis

Citation, Study Details	# of Studies (k)/ Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
Soupal et al. (2016) Study Design Cohort Location Czech Republic Methodological Quality Fair	n = 65 Adults >18 years of age with T1DM	Comparators Rt-CGM vs. SMBG Average HbA1c at 12 months 7.1% ± 0.8% vs. 8.3% ± 0.9%; p < 0.0001 Proportion of patients with HbA1c <7% 48% vs. 34% (no further statistical analysis provided)	Comparison of multiple insulin treatments and sensor combinations Small sample sizes in each subgroup Rare adverse event reporting Average A1c prior to initiating trial 8.2–8.5% for rt-CGM users vs. 8.3% to 8.4% for SMBG group

Abbreviations: CGM: continuous glucose monitor; CI: confidence interval; CSII: continuous subcutaneous insulin infusion; HbA1c: glycated hemoglobin; MDI: multiple daily injections; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; RR: relative risk; RCT: randomized controlled trial; rt-CGM: real-time continuous glucose monitoring; SMBG: self-monitoring blood glucose: IQR: interquartile range.

Table 2. Overview of Included Studies: T2DM

Citation, Study Details	# of Studies (k)/ Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
T2DM: Meta-analyses			
National Clinical Guideline Centre (2015d) Search Dates Through June 2014 Included Study Designs RCTs Population Adults with T2DM Methodological Quality Good	k = 2 (SMBG+ CGM vs. SMBG) Total n = 165 (SMBG + CGM vs SMBG) *Systematic review authors' quality assessment of individual studies:* Fair to Good	Comparators Rt-CGM vs. SMBG Change in HbA1c at 12 months -0.46 (-0.87 to -0.06) No statistically significant differences for rt-CGM vs. SMBG for fasting blood glucose or postprandial blood glucose	Low to very low strength of evidence
Poolsup et al. (2013) Search Dates Through May 2013 Included Study Designs RCTs Population Children with T1DM Methodological Quality Good	k = 10 Total n = 817 *Systematic review authors' quality assessment of individual studies:* Poor, Good	Comparators Rt-CGM vs. SMBG Change in HbA1c -0.18% (95% CI, -0.35% to -0.02%)	Only 5 of 10 studies used rt-CGM Use of rt-CGM ranged from daily to 3 days every 3 to 6 weeks Follow-up ranged from 3 to 12 months (T1DM); 8 weeks to 3 months of follow-up (T2DM) Excluded pregnant women Various insulin regimens

Citation, Study Details	# of Studies (k)/ Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
T2DM: Randomized Controlled Trials			
Tang et al. (2014) Study Design RCT Location Canada Methodological Quality Fair	n = 57 adults with T2DM on insulin therapy	Comparators Rt-CGM vs. SMBG Change in HbA1c Although both groups improved their glucose control, no between-group differences Adverse events 12/32 (37.5%) of those randomized to rt-CGM dropped out; 7 refused to wear the device, 5 because of discomfort and inconvenience of device 5/25 (25%) of those randomized to SMBG/internet monitoring dropped out, all for personal reasons not related to study protocol	Primary outcome of study was patient satisfaction with either rt-CGM or an internet-based blood glucose monitoring support system using SMBG data

Abbreviations: CGM: continuous glucose monitor; CI: confidence interval; HbA1c: glycated hemoglobin; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; RCT: randomized controlled trial; rt-CGM: real-time continuous glucose monitoring; SMBG: self-monitoring blood glucose

Table 3. Overview of Included Studies: T1DM or T2DM

Citation, Study Details	# of Studies (k)/ Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
T1DM or T2DM: Randomized Controlled Trials			
New et al. (2015) Study Design RCT Location United Kingdom, Germany Methodological Quality Poor	n = 160 Adults aged 18 to 65 years with T1DM or T2DM	Comparators Rt-CGM vs. SMBG Change in HbA1c No statistically significant differences observed in glucose control for rt-CGM *without alarms* vs. SMBG Adverse events 157 underwent CGM placement, 13 adverse events reported: 26% erythema, 21% bleeding, 15% itching. No information provided on whether adverse events led to sensor discontinuation.	Study focused on use of CGM alarm feature for hypo- or hyperglycemia 20 day wash-in phase excluded 15 individuals
T1DM or T2DM: Observational Studies			
Battelino et al. (2015) Study Design Retrospective cohort Location Residents of Western Europe, Israel, Canada	n = 10,501 individuals with T1DM or T2DM using CGM sensor augmented pump therapy (≥ 6 months downloadable data from CareLink™ data [Medtronic])	Comparators Non-CGM users vs. <25%, 25–49%, 50–74%, ≥75% of time Outcomes*** *Mean Blood Glucose Measures From Self-Monitoring* 167 mg/dL for all groups except highest sensor use, 163 mg/dL ($p < 0.0001$)	Statistically different but unclear clinical significance Baseline characteristics of groups not provided All participants used pump therapy

Citation, Study Details	# of Studies (k)/ Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
Methodological Quality Poor		*Estimated Change in HbA1c* Highest sensor group compared to non-users experienced 0.2% decrease based on estimates from mean blood glucose levels (no additional quantitative information provided) *Proportion of Patients With Mean <155 mg/dL* 39.7% for >75% sensor time compared to 30.5–32.1% for other groups (p < 0.0001) *Incidence Rate Ratio: Hypoglycemia (<70 mg/dL)* Compared to >75% of time users; non-users and <25% experienced increased risk of having hypoglycemic events Non-users: 1.36 (95% CI, 1.28 to 1.45) <25%: 1.27 (95% CI, 1.19 to 1.35) 25–49%: 1.12 (95% CI, 1.04 to 1.21) 50–74%: 1.04 (95% CI, 0.96 to 1.12) ***Data provided in mmol/L converted to mg/dL for U.S. consistency	Medtronic employees as authors with unclear role of industry in manuscript development

Abbreviations: CGM: continuous glucose monitor; CI: confidence interval; HbA1c: glycated hemoglobin; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; RCT: randomized controlled trial; rt-CGM: real-time continuous glucose monitoring; SMBG: self-monitoring blood glucose

Table 4. Overview of Included Studies: Diabetes in Pregnant Women

Citation, Study Details	# of Studies (k)/ Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
Diabetes (preexisting or gestational) in pregnant women: Meta-analyses			
Moy et al. (2014) Search Dates Through August 2013 Included Study Designs RCTs Population Pregnant women with preexisting diabetes (T1DM or T2DM) Methodological Quality Good	k = 9 (meta-analysis), 15 (systematic review) Total n = 506 *Systematic review authors' quality assessment of individual studies:* Fair	Comparators Rt-CGM vs. SMBG No statistically significant differences between CGM and SMBG in change in HbA1c, infant birthweight, cesarean section rates, gestational age at delivery, neonatal hypoglycemia, major anomalies, preterm births, death, miscarriage, NICU admissions	Only 2 studies investigated CGM in women with preexisting diabetes Significant heterogeneity of included studies
National Clinical Guideline Centre (2015b) Search Dates Through June 2014 Included Study Designs Systematic reviews, RCTs, and observational studies	k = 5 (CGMS vs. SMBG) Total n = 452 (CGM vs. SMBG) *Systematic review authors' quality assessment of individual studies:* Poor	Comparators Rt-CGM vs. SMBG No statistically significant differences between CGM and SMBG for pregnancy-related outcomes (e.g., assisted vaginal birth, cesarean section, preterm birth, gestational age at birth)	Does not distinguish retrospective from real-time in analysis but only 1 of the included studies was real-time (4 retrospective)

Citation, Study Details	# of Studies (k)/ Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
Population Pregnant women with preexisting diabetes (T1DM or T2DM) or gestational diabetes (GDM) Methodological Quality Good		No statistically significant differences between CGM and SMBG for maternal glucose control outcomes (e.g., HbA1c across gestation) No statistically significant differences between CGM and SMBG for neonatal outcomes (e.g., miscarriage, early neonatal death, large for gestational age) One RCT of women with GDM reported shorter duration of time in the NICU for women with CGM vs. SMBG (RR: 0.8; 95% CI, -1.6 to -0.1).	

Abbreviations: CGM: continuous glucose monitor; CI: confidence interval; HbA1c: glycated hemoglobin; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; RCT: randomized controlled trial; rt-CGM: real-time continuous glucose monitoring; SMBG: self-monitoring blood glucose

T1DM Effectiveness (Change in HbA1c)

Systematic Reviews and Meta-analyses

Good methodological quality systematic reviews and meta-analyses reported consistent statistically significant, but small, decreases in HbA1c from 0.23% to 0.30% for adults with T1DM (Langendam et al., 2012; National Clinical Guideline Centre, 2015c). Although statistically significant, a clinically relevant change is generally accepted to be at least a 0.5% reduction in HbA1c (National Clinical Guideline Centre, 2015c). Table 5 provides an overview of the mean difference in HbA1c findings across systematic reviews.

Table 5. Meta-analyses and Systematic Review Findings: Change in HbA1c in T1DM

Citation (Population)	Mean Difference in HbA1c (%) (95% CI)
Langendam et al. (2012) (T1DM, all ages)	-0.23 (-0.36 to -0.09)
National Clinical Guideline Centre (2015c) (T1DM)	-0.30 (-0.47 to -0.12)

Abbreviations: CI: confidence interval; HbA1c: glycated hemoglobin; T1DM: type 1 diabetes mellitus

In the most recent good methodological quality systematic review and meta-analyses, the authors evaluated the impact of CGM on glucose control in children and young adults with T1DM and found no statistically significant changes in HbA1c for pediatric rt-CGM versus SMBG users (National Clinical Guideline Centre, 2015a). Older systematic reviews (Poolsup et al., 2013) observed a significant but small improvement in HbA1c (-0.18%; 95% CI, -0.35 to -0.02) or no clinically meaningful difference between groups (Skelly et al., 2011).

Individual Studies

Lower methodological quality studies did not observe significant mean differences between rt-CGM users and SMBG (Lind et al., 2017; McQueen et al., 2014)nor did comparisons of mean changes within groups reveal statistically significant changes (Battelino et al., 2015; New et al., 2015; Rachmiel et al., 2015; Riveline et al., 2012; Soupal et al., 2016; Tumminia et al., 2015). One exception is the RCT by Beck and colleagues, which found a mean HbA1c difference of -0.6 (95% CI, -0.8 to -0.3) at 24 weeks, adjusted for baseline HbA1c and study site (Beck et al., 2017).

T2DM Effectiveness (Change in HbA1c)

Systematic Reviews and Meta-analyses

Good-methodological quality systematic reviews and meta-analyses reported consistent statistically significant decreases in HbA1c for adults with T2DM from 0.31% to 0.46% (National Clinical Guideline Centre, 2015d; Poolsup et al., 2013). Although statistically significant, a clinically relevant change is generally accepted to be at least a 0.5% reduction in HbA1c (National Clinical Guideline Centre, 2015c). Table 6 provides an overview of the mean difference in HbA1c findings across systematic reviews.

Table 6. Findings from Systematic Reviews and Meta-analyses: Change in HbA1c in T2DM

Citation (Population)	Mean Difference in HbA1c (%) (95% CI)
National Clinical Guideline Centre (2015d) (T2DM)	-0.46 (-0.87 to -0.06)
Poolsup et al. (2013) (T2DM)	-0.31 (-0.6 to -0.02)

Abbreviations: CI: confidence interval; HbA1c: glycated hemoglobin; T2DM: type 2 diabetes mellitus

Individual Studies

No statistically significant differences in glucose control were observed for users of CGM compared to SMBG (Tang et al., 2014).

Diabetes in Pregnancy Effectiveness (Maternal or Neonatal Outcomes)

Systematic Reviews

Two good methodological quality systematic reviews did not identify any statistically significant maternal or neonatal outcomes for women with preexisting or gestational diabetes (Moy et al., 2014; National Clinical Guideline Centre, 2015b).

Individual Studies

No individual studies addressing maternal or neonatal outcomes were identified.

Harms: Severe Hypoglycemia

Systematic Reviews

Good methodological quality systematic reviews did not identify a difference in risk of severe hypoglycemia between rt-CGM and SMBG users in adult or pediatric populations (Langendam et al., 2012; National Clinical Guideline Centre, 2015a, 2015c, 2015d).

In children with T1DM, Skelly et al. (2011) reported proportions without statistical analyses (7% for CGM vs. 10% for SMBG with rates of 17.9 vs. 24.4 per 100,000 person-years; risk ratio of 0.73 as calculated by Center researchers).

Individual Studies

Rachmiel et al. (2015) conducted a poor methodological quality cohort study in which they observed greater rates of hypoglycemia for rt-CGM users compared to SMBG (18.1 vs. 10.6 per 100 patient years). The fair methodological quality crossover RCT by Lind et al. (2017) reported that the rate of severe hypoglycemic events (expressed as an event rate per 1,000 patient-years) was 0.04 in the rt-CGM group versus 0.19 in the conventional treatment control group (no statistical testing provided). The good methodological quality RCT by Beck and colleagues reported that severe events were uncommon (two in each group), and were not different between groups ($p = 0.67$) (Beck et al., 2017).

Harms: Adverse Events

Systematic Reviews

No statistically significant changes between rt-CGM and SMBG were observed in recent good methodological quality systematic reviews (National Clinical Guideline Centre, 2015c, 2015d).

Individual Studies

New et al. (2015) conducted a poor methodological quality RCT that reported increased adverse events with CGM placement including erythema, bleeding, and itching. A fair methodological quality RCT by Tang et al. (2014) observed that 37.5% of participants discontinued participation because of adverse events with the sensor (seven refused to wear an rt-CGM device, and five reported discomfort or inconvenience from wearing an rt-CGM device). One patient in the fair methodological quality crossover RCT by Lind et al. (2017) discontinued the trial because of an allergic reaction to the sensor. However, this trial reported more generally that there were "no obvious numerical differences for any adverse event between the treatments" (Lind et al., 2017).

Cost-Effectiveness

Estimates of the cost-effectiveness of rt-CGM are based on a single good methodological quality systematic review (National Clinical Guideline Centre, 2015c), one good methodological quality individual study (a separate analysis conducted for the National Clinical Guideline Centre (2015c) review) and two fair methodological quality individual studies (Fonda et al., 2016; Roze et al., 2015). All identified studies evaluated costs for individuals with T1DM with the exception of the Fonda et al. (2016) study of the Dexcom® SEVEN in individuals with T2DM. Table 7 provides a summary of findings across identified studies.

Study settings include the UK (National Clinical Guideline Centre, 2015c), Sweden (Roze et al., 2015), and the U.S. (Fonda et al., 2016). Because the health systems of the UK and Sweden are different from the U.S. system, the generalizability of costs and outcomes to the U.S. population is limited. Estimates of outcomes in individual studies are based on previous patient-level meta-analyses (Roze et al., 2015) or a single RCT (Fonda et al., 2016), which could have inherent limitations or biases that affect the estimates from the economic analyses.

The National Clinical Guideline Centre (2015c) systematic review found that CGM was not cost-effective compared to SMBG for adults with T1DM using a £20,000 per quality-adjusted life-year (QALY) threshold. The Monte-Carlo simulation by Roze et al. (2015) found that the use of CGM with CSII resulted in a 0.42 year difference in discounted life expectancy and approximately €24,367 versus €23,352 (2011 Euros) (USD $26,060 vs. $24,975,[2] respectively) in combined costs (direct and indirect) per QALY compared to SMBG with CSII. The widely accepted cost-effectiveness ratio in the U.S. is $50,000 to $100,000 per QALY.

[2] www.x-rates.com used for currency conversion, with June 1, 2011 as conversion date (0.935 Euros = $1 USD).

For T2DM, Fonda et al. (2016) provided a single cost-effectiveness analysis using a model of 100 individuals with T2DM based on data from a single RCT. The RCT was not assessed for methodological quality by Fonda et al. (2016). Fonda et al. (2016) reported the incremental cost-effectiveness ratio of rt-CGM for individuals with T2DM not on prandial insulin to be $13,030 per QALY. There is some concern for bias in this estimate since the study was funded by industry and two of the authors were employed by Dexcom, Inc.

Table 7. Economic Studies

Citation, Study Details	Population (n)	Study Summary and Findings	Comments
Systematic Reviews			
National Clinical Guideline Centre (2015c) Search Dates Through August 2014 Included Study Designs All economic studies Population Adults with T1DM Methodological Quality Good	k = 3 *Systematic review authors' quality assessment of individual studies:* Fair	Comparators Rt-CGM vs. SMBG Outcomes *Incremental Cost* £15,193 to £47,692 *Incremental Effects (QALYs)* -0.293 to 0.60 *Cost-effectiveness (£ per QALY gained)* £29,029 to £63,828 (Huang et al., 2010; McQueen et al., 2011) NICE (2015c) original cost-effectiveness analysis determined rt-CGM was not cost-effective at a £20,000 per QALY threshold when compared to SMBG	Study authors also performed original cost-effectiveness evaluation of rt-CGM vs. SMBG (see details below) One study demonstrated that rt-CGM has a 48% probability of being cost-effective (McQueen et al., 2011). The other study demonstrated considerable uncertainty, with the incremental cost confidence interval spanning both rt-CGM and SMBG (Huang et al., 2010)
Individual Studies			
Fonda et al. (2016) Study Details Cost-effectiveness analysis, Core Diabetes Model, third-party payer perspective	n = 100 adults with T2DM	Comparators Rt-CGM vs. SMBG Two analyses *Baseline:* 4 episodes of 2 week use in a 12-week time period in Year 1 only *Refresher:* Same as above but repeated in Year 2; estimates based on above evidence, not real world findings	Model based on findings from a single RCT (Englert et al., 2014; Vigersky, Fonda, Chellappa, Walker, & Ehrhardt, 2012) Costs of providers training patients in CGM and diabetes management not included

Citation, Study Details	Population (n)	Study Summary and Findings	Comments
Methodological Quality Fair		Outcomes *Incremental quality-adjusted life expectancy* Baseline: 1.25 months greater for rt-CGM compared to SMBG Refresher: 1.69 months greater for rt-CGM compared to SMBG *Incremental total costs* $653 greater (baseline) $1,312 (refresher) per patient cost ICER per QALY gained: $8,898 (baseline) $13,030 (refresher)	Estimates from refresher are based on original impact of the baseline rt-CGM use, not documented evidence of a refresher Limitations of the original RCT forming the basis of these estimates are not taken into account SMBG not standardized in original RCT Study sponsored by manufacturer, authors are funded as well
National Clinical Guideline Centre (2015c) NCGC Model Study Details Independent economic analysis conducted to inform 2015 guideline Methodological Quality Good	IMS Core Diabetes Model T1DM, 80-year time horizon	Comparator Rt-CGM vs. SMBG Incremental cost: £47,692 QALY: -0.293 Pound per QALY gained: CGM is dominated	Willingness to pay threshold: £20,000 per QALY SMBG remained cost-effective even in models accounting for increasing daily SMBG to 10x per day (vs. 8 per day), 30% decrease in cost of rt-CGM; dramatic improvements in HbA1c (<6%); costs and outcomes discounted by factor of 1.5%; hypoglycemic events estimated at zero compared to 660 per 100-patient years in those using SMBG Subgroup estimation of those with hypoglycemia unawareness, CGM did not demonstrate cost-effectiveness
Roze et al. (2015) Study Details Cost-effectiveness analysis, Core	n = 1000 (Monte-Carlo simulation using adults with T1DM)	Comparators Sensor-augmented pump vs. SMBG plus CSII Outcomes	Based on Pickup (2011) meta-analysis CGM used 5.5 days/week is greater than many previous studies

Citation, Study Details	Population (n)	Study Summary and Findings	Comments
Diabetes Model, societal payer perspective Methodological Quality Fair		Incremental QALY: 0.76 QALY: 13.05 ± 0.12 (sensor/pump) vs. 12.29 ± 0.12 (SMBG/CSII) ICER per QALY: 367,571 Swedish Krona	Swedish health care system perspective Willingness to pay threshold of 500,000 Swedish Krona

Abbreviations: CGM continuous glucose monitor; CSII: continuous subcutaneous insulin infusion; HbA1c: glycated hemoglobin; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year; RCT: randomized controlled trial; rt-CGM: real-time continuous glucose monitoring; SMBG: self-monitoring of blood glucose; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus

Clinical Practice Guidelines

Center researchers identified 10 clinical practice guidelines that addressed the use of CGM for individuals with diabetes mellitus. Six of the guidelines were rated as having poor methodological quality and four of the guidelines (National Clinical Guideline Centre, 2015a, 2015b, 2015c, 2015d) were rated as having good methodological quality. Table 8 provides a summary of recommendations across the included guidelines. The strength of underlying evidence noted in the table for guideline recommendations is an assessment by guideline authors and not Center researchers.

The guideline authors' recommendations vary by population and disease type (e.g., T1DM, T2DM), but CGM is recommended for certain situations such as hypoglycemia unawareness and frequent hypoglycemic episodes, across populations and disease types. The majority of guidelines on CGM focus on T1DM in adults and children. For T2DM, several guidelines referred to ongoing studies and an inability to make a recommendation given insufficient evidence for the use of CGMs in T2DM.

In general, the guideline recommendations on CGM use surpass what is supported by findings from the evidence review. This could be explained through different guideline development processes that often take into account other considerations (e.g., patients' values and preferences, clinical practice standards, and economic impact) when developing a recommendation statement. However, it is important to note that several of the identified guidelines are not based on a transparent systematic review of the evidence.

Table 8. Summary of Clinical Practice Guidelines Recommendations for CGM

Citation, Methodological Quality	Recommendation (Evidence Rating)
General Recommendations	
American Diabetes Association (2016a) (p. 46) Poor	CGM could be a supplemental tool to SMBG in individuals with hypoglycemia unawareness and/or frequent hypoglycemic episodes (C level of evidence)* Given variable adherence to CGM, assess individual readiness for continuing CGM use prior to prescribing (E level of evidence)*
Fonseca et al. (2016) (p. 1006) [AACE and ACE] Poor	Extensive data from randomized controlled and other trials support the use of CGM in children and adults with T1DM. CGM may have similar benefits in insulin-using patients with T2DM and pregnant women with diabetes.
Rewers et al. (2014) (p. 103) [ISPAD] Poor	CGM devices are becoming available that could particularly benefit individuals with hypoglycemic unawareness because the devices trigger an alarm when glucose is below a specified range or glucose decreases rapidly (A level of evidence)±

Citation, Methodological Quality	Recommendation (Evidence Rating)
Children	
American Diabetes Association (2016a) (p. 46) Poor	Although the evidence for A1C reduction is less strong in children, teens, and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device (B level of evidence)*
Bailey et al. (2016b) (p. 239) [AACE and ACE] Poor	T1DM: CGM recommended, particularly for patients with history of severe hypoglycemia or hypoglycemia unawareness and to assist in the correction of hyperglycemia in patients not at goal. CGM users must know basics of sensor insertion, calibration, and real-time data interpretation. More in-depth training and more frequent follow-up is recommended to enable children to adopt the technology more successfully.
National Clinical Guideline Centre (2015a) (p. 203) Good	Offer ongoing rt-CGM with alarms to children and young people with T1DM who have: • Frequent severe hypoglycemia or • Impaired awareness of hypoglycemia associated with adverse consequences (e.g., seizures or anxiety) or • Inability to recognize or communicate about symptoms of hypoglycemia (e.g., because of cognitive or neurological disabilities) Consider ongoing rt-CGM for: • Neonates, infants and preschool children • Children and young people who undertake high levels of physical activity (for example, sports at a regional, national, or international level) • Children and young people who have comorbidities (e.g., anorexia nervosa) or who are receiving treatments (e.g., corticosteroids) that can make blood glucose control difficult Consider intermittent (real-time or retrospective) CGM to help improve blood glucose control in children and young people who continue to have hyperglycemia despite insulin adjustment and additional support
Adults: T1DM	
American Diabetes Association (2016a) (p. 46) Poor	When used properly, CGM in conjunction with intensive insulin regimes is a useful tool to lower A1c in selected adults (≥ 25 years) with T1DM (A level of evidence)*

Citation, Methodological Quality	Recommendation (Evidence Rating)
Bailey et al. (2016b) (p. 239) [AACE and ACE] Poor	CGM recommended, particularly for patients with history of severe hypoglycemia or hypoglycemia unawareness and to assist in the correction of hyperglycemia in patients not at goal. CGM users must know basics of sensor insertion, calibration, and real-time data interpretation.
National Clinical Guideline Centre (2015c) (p. 62) Good	T1DM: Do not offer rt-CGM routinely to adults with type 1 diabetes. Consider rt-CGM for adults with T1DM who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following despite optimized use of insulin therapy and conventional blood glucose monitoring: • >1 episode a year of severe hypoglycemia with no obviously preventable precipitating cause • Complete loss of awareness of hypoglycemia • Frequent (>2 episodes a week) asymptomatic hypoglycemia that is causing problems with daily activities • Extreme fear of hypoglycemia • Hyperglycemia (HbA1c level ≥9%) that persists despite testing ≥10 times a day. Continue rt-CGM only if HbA1c can be sustained ≤7%) and/or there has been a fall in HbA1c of 2.5% or more. For adults with T1DM who are having rt-CGM, use the principles of flexible insulin therapy with either an MDI insulin regimen or CSII therapy. Rt-CGM should be provided by a center with expertise in its use, as part of strategies to optimize a person's HbA1c levels and reduce the frequency of hypoglycemic episodes.
Peters et al. (2016) (p. 3923) [Endocrine Society] Poor	Rt-CGM devices recommended for adult patients with T1DM who have A1c levels above target and who are willing and able to use these devices on a nearly daily basis (high strength of evidence)[†] Rt-CGM devices recommended for adult patients with well-controlled T1DM who are willing and able to use these devices on a nearly daily basis (high strength of evidence)[†]
Adults: T2DM	
Bailey et al. (2016b) [AACE and ACE] Poor	No recommendation, ongoing studies

Citation, Methodological Quality	Recommendation (Evidence Rating)
National Clinical Guideline Centre (2015d) (p. 157-158) Good	*Guideline recommendations are not specific to CGM. National Clinical Guideline Centre (2015d) provides general recommendation statements regarding the use of SMBG in adults with T2DM.*
Peters et al. (2016) (p. 3923) [Endocrine Society] Good	Short-term, intermittent rt-CGM suggested use in adults with T2DM (not on prandial insulin) who have A1C levels ≥7% and are willing and able to use the device (low strength of evidence) †
Pregnancy	
Bailey et al. (2016b) (p. 239) [AACE and ACE] Poor	Unclear benefits in pregnant females with preexisting diabetes; ongoing studies. CGM during pregnancy can be used as a teaching tool, to evaluate glucose patterns, and to fine-tune insulin dosing. CGM in pregnancy can supplement blood glucose monitoring, in particular for monitoring nocturnal hypoglycemia or hyperglycemia and postprandial hyperglycemia
Blumer et al. (2013) (p. 11) [Endocrine Society] Poor	CGM suggested to be used during pregnancy in women with overt or GDM when SMBG levels (or, in the case of the woman with overt diabetes, HbA1c values) are not sufficient to assess glycemic control (including both hyperglycemia and hypoglycemia) (low strength of evidence) †
National Clinical Guideline Centre (2015b) (p. 397) Good	Do not offer CGM routinely to pregnant women with diabetes. Consider CGM for pregnant women on insulin therapy: • Who have problematic severe hypoglycemia (with or without impaired awareness of hypoglycemia) or • Who have unstable blood glucose levels (to minimize variability) or • To gain information about variability in blood glucose levels Ensure that support is available for pregnant women who are using CGM from a member of the joint diabetes and antenatal care team with expertise in its use
Education	
American Diabetes Association (2016a) (p. 46) Poor	When prescribing CGM, robust diabetes education, training, and support are required for optimal CGM implementation and ongoing use (E level of evidence)*
Peters et al. (2016) (p. 3923)	Adults with T1DM and T2DM who use CSII and CGM should receive education, training, and ongoing support to help achieve and

Citation, Methodological Quality	Recommendation (Evidence Rating)
[Endocrine Society] Poor	maintain individualized glycemic goals (Ungraded Good Practice Statement)[†]

*Abbreviations: AACE: American Association of Clinical Endocrinologists; ACE: American College of Endocrinology; GDM: gestational diabetes; HbA1c: glycated hemoglobin; ISPAD: International Society for Pediatric and Adolescent Diabetes; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus. Notes: *Determined by guideline authors. A: Clear evidence from well-conducted, generalizable RCTs that are adequately powered; B: Supportive evidence from well-conducted cohort studies; C: Supportive evidence from poorly controlled or uncontrolled studies; E: Expert consensus or clinical experience.[†] Determined by guideline authors*

Payer Policies

Center researchers searched for policies on the coverage of CGM from Aetna, Blue Shield of Northeastern New York, Capital District Physician's Health Plan, Centers for Medicare & Medicaid Services (CMS), Cigna, Emblem Health, Empire Blue Cross Blue Shield, Excellus Blue Cross Blue Shield, Tufts Health Plan, and UnitedHealthcare. Researchers searched for coverage decisions by the Oregon Health Evidence Review Commission (HERC) and Washington Health Technology Assessment Program (WA HTA) Clinical Committee.

Of the 12 payers searched, Center researchers identified policies from all sources except the Capital District Physician's Health Plan. The majority of payers reviewed do not differentiate coverage between retrospective and rt-CGM; however, there are coverage differences for short-term (diagnostic) and long-term CGM use. Blue Shield of Northeastern New York, Excellus Blue Cross Blue Shield, and the Oregon HERC provide coverage details for rt-CGM.

Under Local Coverage Decision L33822 (and associated policy article A52464), which applies to all 50 states and Washington D.C., CGMs are considered precautionary and are not covered under the Medicare durable medical equipment (DME) benefit. In a recent CMS ruling, CGM devices designed to replace SMBG were classified as therapeutic CGMs and will be covered by Medicare under the DME benefit. Under the ruling, CGM devices that are considered to complement, but not replace, SMBG will continue to be considered adjunctive to SMBG and therefore not covered under the Medicare DME benefit. The Dexcom G5 Mobile Continuous Glucose Monitoring System is the first device to receive U.S. Food and Drug Administration (FDA) approval as a therapeutic CGM (FDA, 2016). This device continues to require a minimum of two SMBG measurements per day for device calibration.

Of the private payers reviewed, six provide coverage of CGM, as outlined in Table 9. Excellus Blue Cross Blue Shield explicitly considers rt-CGMs investigational and does not provide coverage. UnitedHealthcare follows Medicare coverage policy, as described above. No policy was identified for the Capital District Physician's Health Plan.

Of the private payers reviewed that provide coverage of CGM, coverage criteria differentiates between short- and long-term uses of CGM. Short-term CGM use, commonly defined as 72 hours, is predominately covered for diagnostic purposes and often used retrospectively. Thus, the coverage criteria for short-term use of CGMs from the private payers reviewed is not included in this report. For long-term use, there is significant variability between payers on populations covered (e.g., T1DM, T2DM, women who are pregnant, age limitation) and clinical criteria required for CGM coverage. Severe hypoglycemia (defined as blood glucose less than 50 mg/dL), hypoglycemia unawareness, and poorly controlled HbA1c are common required criteria for long-term CGM use across private payers reviewed. Table 9 provides hyperlinks to policies and further coverage criteria details.

HERC and WA HTA both approved coverage of CGMs. The HERC's 2013 decision limited coverage[3] to individuals with T1DM for whom insulin pump management is being considered, initiated, or utilized and have poorly controlled HbA1c (greater than 8.0%) or have a history of recurrent hypoglycemia. The WA HTA Clinical Committee approved coverage of CGM for individuals with diabetes under 19 years of age who are experiencing at least one severe episode of hypoglycemia or are enrolled in an institutional review board-approved trial.

[3] This coverage determination is currently undergoing re-review by the Oregon HERC. An updated guidance is expected in Summer 2017.

Table 9. Payer Coverage of Long-Term Use of CGMs

Payer	Long-Term Use of CGMs
Federal Payer	
Medicare *(effective 1/2017)*	CMS Ruling CMS-1682-R (January 12, 2017) does not directly establish coverage requirement for therapeutic CGM devices, but instructs DME MAC contractors to make claim-by-claim payment determinations based on whether beneficiary has DM; has been using home SMBG at least 4 times per day; requires insulin via MDI or continuous subcutaneous infusion pump; AND insulin regimen requires frequent adjustment based on therapeutic CGM testing results. LCD L33822 and Policy Article A52464 (apply to all 50 states and Washington D.C.): (non-therapeutic) CGM considered precautionary and not covered under the DME benefit.
Private Payers	
Aetna *(last review 6/2016)*	√ As adjunct for SMBG for adults ≥25 yrs with T1DM and younger persons with T1DM who have had recurrent episodes (≥2 episodes in a 30-day period) of severe hypoglycemia*
Blue Shield of NE NY *(last review 3/2016, due to be reviewed 3/1/17, but no update posted as of 4/24/17)*	√ (including rt-CGM) Patients with T1DM who have recurrent, unexplained, severe hypoglycemia* for whom hypoglycemia puts the patient or others at risk √ Patients with T1DM who are pregnant whose diabetes is poorly controlled
Capital District Physician's Health Plan	*No policy identified.*
Cigna *(last review 4/2017)*	√ T1DM or T2DM, and either history of diabetic ketoacidosis; positive islet cell cytoplasmic autoantibodies [ICA] test; fasting C-peptide level ≤110% of the lower limit of normal lab measurement method AND concurrently obtained fasting glucose ≤225 mg/dL; or renal insufficiency with a creatinine clearance ≤50 ml/minute AND fasting C-peptide level ≤200% of lower limit of normal of the lab measurement method

Payer	Long-Term Use of CGMs
Emblem Health *(last review 8/2016)*	√ Severe recurrent hypoglycemia* or evidence of hypoglycemia unawareness
Empire Blue Cross Blue Shield *(last review 8/2016)*	√ Adults ≥25 yrs with T1DM: Inadequate glycemic control [HbA1c between 7.0% to 10.0% AND insulin injections are required ≥3 times per day or an insulin pump is used for blood sugar control maintenance √ Individuals with T1DM: recurring episodes of severe hypoglycemia* AND inadequate glycemic control AND insulin injections are required ≥3 times per day or an insulin pump is used for blood sugar control maintenance √ Individuals with T1DM who are pregnant: inadequate glycemic control AND insulin injections are required ≥3 times per day or an insulin pump is used for blood sugar control maintenance Not covered for individuals with T2DM.
Excellus Blue Cross Blue Shield *(last review 12/2016)*	Real-time CGM considered investigational and not covered
Tufts Health Plan *(last review 10/2016)*	√ Individuals with T1DM: hypoglycemic unawareness; OR recurrent episode of severe hypoglycemia; OR unable to achieve HbA1c of ≤7% for two consecutive readings within the last 12 months or unable to achieve HbA1c of ≤7% for two consecutive readings within the last 12 months, or unable to achieve HbA1c of ≤8% for two consecutive readings within the last 12 months and shows evidence of cardiovascular, oncologic, neurologic, or metabolic comorbidities, or macrovascular or microvascular diabetic complications Not covered for individuals with T2DM or who are pregnant have GDM or T2DM
UnitedHealthcare *(last review 4/2017)*	√ Individuals with T1DM: as a supplement to SMBG for patients who have demonstrated adherence to a physician ordered diabetic treatment plan.

Payer	Long-Term Use of CGMs
	Individuals with T2DM or gestational diabetes: personal use at home is unproven and not medically necessary
State HTA Programs	
Oregon HERC (*last review in 2013; topic under routine re-review in 2017 with any update decision expected in summer of 2017*)	√ (retrospective or rt-CGM) Individuals with T1DM for whom insulin pump management is being considered, initiated, or utilized: HbA1c >8.0% despite compliance with therapy OR history of recurrent hypoglycemia CGMs (real-time or retrospective) not covered for individuals with T2DM
Washington HTA (*last review in 2011*)	√ Individuals with DM <19 years: suffering from ≥1 severe episode of hypoglycemia OR enrolled in an IRB-approved trial

Abbreviations: CGM: continuous glucose monitor; dL: deciliter; GDM: gestational diabetes mellitus; HbA1c: glycated hemoglobin; HTA: health technology assessment program; IRB: institutional review board; LCD: local coverage determination; rt-CGM: real-time continuous glucose monitors; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus
*Notes: √ CGM is covered for long-term use; * Defined as blood glucose <50 mg/dL*

Conclusion

The available clinical evidence demonstrates a consistent statistically significant benefit of rt-CGM on improving glucose control in adults with T1DM or T2DM, as reflected by changes in HbA1c of 0.2% to 0.4%, with the exception of one individual RCT that demonstrated a statistically significant mean-adjusted difference of 0.6% among a study population of adults with T1DM (Beck et al., 2017). Yet, the scale of the improvement shown across the other studies is not clinically meaningful by accepted diabetes care benchmarks (National Clinical Guideline Centre, 2015c). Estimates of the effect of rt-CGM on glucose control in pediatric populations or pregnant women do not demonstrate a difference between rt-CGM and SMBG. Good methodological quality evidence on the impact of rt-CGM on episodes of hypoglycemia does not demonstrate a significant or clinically meaningful difference in adults or children.

Limitations of the available evidence affect the interpretation of these findings. The duration of use of rt-CGM varied across studies, as did the insulin regimen (multiple daily injections versus CSII) of enrollees. The population enrolled in clinical studies might not be generalizable to the overall Medicaid population. The available evidence informing the systematic reviews on rt-CGM consists of studies with small sample sizes, industry funding, and high attrition in the rt-CGM groups. In addition, many of the studies were conducted outside the U.S. setting, limiting the external validity of the results to the U.S. health care system. None of the identified studies included long-term data on diabetes-related complications (e.g., cardiovascular disease, stroke, kidney disease, infections, amputations).

Although not a primary outcome for this review, adverse event reporting in the available evidence, while rare, generally demonstrated increased adverse events in rt-CGM users compared to SMBG, often leading to discontinuation of use. Events included irritation of the skin, bleeding, erythema, frustration with the alarm, negative effects on physical activity, and sleep disruption. The role of the alarm function of these devices was outside the scope of this review.

In general, clinical practice guidelines identified in this review rely on expert opinion over available evidence with the exception of the (National Clinical Guideline Centre, 2015a, 2015b, 2015c, 2015d) guidelines. However, the NICE guideline on pediatric patients with T1DM or T2DM (National Clinical Guideline Centre, 2015a) used the GRADE integration of the values and preferences of parents and patients. Through this process, the guideline development committee endorsed CGM coverage in specific situations despite a lack of evidence of clinical benefit but strong stakeholder interest in rt-CGM, particularly for the very young or those with hypoglycemia unawareness. For other guidelines included, recommendations varied by population and disease type (T1DM, T2DM, GDM). Despite variability in specific recommendations, several of the guidelines recommended the use of CGM in cases of hypoglycemia unawareness and/or frequent hypoglycemic events.

Similar to clinical practice guideline recommendations, coverage across the private and public payers reviewed varied by population and disease type (T1DM, T2DM, GDM). Payers rarely differentiated between retrospective and rt-CGM, but did provide differing coverage related to short-term (e.g., 72 hours) or long-term use of a CGM device. Almost all the payers reviewed cover short-term use; eight of the 11 payers reviewed provide some type of coverage for long-term use.

Many of the available studies on rt-CGM reported findings on older devices, and newer devices are currently entering the market. Future efforts in CGM will likely involve direct integration with insulin pumps and potentially an autonomous artificial pancreas that senses, interprets, and responds to trends in glucose levels for individuals with diabetes.

Strength of Evidence

The Center uses the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group approach to enhance consistency in grading the strength of evidence. RCTs are initially categorized as having high strength of evidence and observational studies are categorized as having low strength of evidence. The strength rating is downgraded based on limitations including inconsistency of results, uncertainty of directness of measurement or population, imprecise or sparse data, and high probability of reporting bias. The grade is increased from low for evidence from observational studies if there is a strong association,[4] a very strong association,[5] or a dose-response gradient. The rating is also increased if all plausible confounders would have reduced the effect (Atkins et al., 2004). Table 10 provides an overview of the strength of evidence by outcome and associated rationale for the strength of evidence rating.

[4] Significant relative risk of >2 or <0.5 with no plausible confounders in two or more observational studies.

[5] Significant relative risk of >5 or <0.2 based on direct evidence with no major threats to validity.

Table 10. Strength of Evidence for rt-CGM: Effectiveness, Harms, and Cost-Effectiveness

Outcome	Strength of Evidence Assessment		Rationale
	Submitter	Center	
Effectiveness			
Change in HbA1c	High	Moderate	Downgraded based on risk of bias, indirectness, publication bias.
Percent Achieving Target HbA1c	High	Very low	A single systematic review reported this outcome and did not demonstrate a difference. None of the other identified systematic reviews reported this outcome.
Maternal Outcomes	*Not submitted in dossier*	Very low	Limited evidence addressing use of rt-CGM in the population did not identify a difference.
Neonatal Outcomes	*Not submitted in dossier*	Very low	There is very limited evidence addressing these outcomes.
Harms			
Severe Hypoglycemia	Moderate	Low	Downgraded for risk of bias, imprecision.
Adverse Events	*Not submitted in dossier*	Low	Despite inconsistent reporting, there was a greater frequency of adverse events for rt-CGM users compared to SMBG.
Cost-effectiveness			
Incremental cost-effectiveness	Moderate	Low	Limited available evidence, inconsistency across cost-effectiveness estimates, significant potential for conflict of interest and funding bias, limited applicability to US setting.

References

American Diabetes Association. (2016). Standards of medical care in diabetes-2016. *Diabetes Care, 39 Suppl 1*, S1-S112.

American Diabetes Association. (2016). *Statistics about diabetes*. Retrieved from http://www.diabetes.org/diabetes-basics/statistics/

Atkins, D., Best, D., Briss, P. A., Eccles, M., Falck-Ytter, Y., Flottorp, S., . . . Zaza, S. (2004). Grading quality of evidence and strength of recommendations. *British Medical Journal (Clinical Research Edition), 328*(7454), 1490. doi: 10.1136/bmj.328.7454.1490

Bailey, T. S., Grunberger, G., Bode, B. W., Handelsman, Y., Hirsch, I. B., Jovanovic, L., . . . Walsh, J. (2016). American Association of Clinical Endocrinologists and American College of Endocrinology 2016 outpatient glucose monitoring consensus statement. *Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, 22*(2), 231-261. doi: 10.4158/ep151124.cs

Battelino, T., Liabat, S., Veeze, H. J., Castaneda, J., Arrieta, A., & Cohen, O. (2015). Routine use of continuous glucose monitoring in 10,501 people with diabetes mellitus. *Diabetic Medicine: A Journal of the British Diabetic Association, 32*(12), 1568-1574. doi: 10.1111/dme.12825

Beck, R. W., Riddlesworth, T., Ruedy, K., Ahmann, A., Bergenstal, R., Haller, S., . . . Price, D. (2017). Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: The DIAMOND randomized clinical trial. *JAMA, 317*(4), 371-378. doi: 10.1001/jama.2016.19975

Blumer, I., Hadar, E., Hadden, D. R., Jovanovic, L., Mestman, J. H., Murad, M. H., & Yogev, Y. (2013). Diabetes and pregnancy: An endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism, 98*(11), 4227-4249. doi: 10.1210/jc.2013-2465

Bronstone, A., & Graham, C. (2016). The potential cost implications of averting severe hypoglycemic events requiring hospitalization in high-risk adults with type 1 diabetes using real-time continuous glucose monitoring. *Journal of Diabetes Science and Technology, 10*(4), 905-913. doi: 10.1177/1932296816633233

Campbell Collaboration. (2017). *For reseachers*. Retrieved from https://www.campbellcollaboration.org/research-resources.html

Centers for Disease Control and Prevention. (2015). *Basics about diabetes*. Retrieved from https://www.cdc.gov/diabetes/basics/diabetes.html

Englert, K., Ruedy, K., Coffey, J., Caswell, K., Steffen, A., & Levandoski, L. (2014). Skin and adhesive issues with continuous glucose monitors: A sticky situation. *Journal of Diabetes Science and Technology, 8*(4), 745-751. doi: 10.1177/1932296814529893

Fonda, S. J., Graham, C., Munakata, J., Powers, J. M., Price, D., & Vigersky, R. A. (2016). The cost-effectiveness of real-time continuous glucose monitoring (RT-CGM) in type 2 diabetes. *Journal of Diabetes Science and Technology, 10*(4), 898-904. doi: 10.1177/1932296816628547

Fonseca, V. A., Grunberger, G., Anhalt, H., Bailey, T. S., Blevins, T., Garg, S. K., . . . Tamborlane, W. (2016). Continuous glucose monitoring: A consensus conference of the American Association of Clinical Endocrinologists and American College of Endocrinology. *Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, 22*(8), 1008-1021. doi: 10.4158/ep161392.cs

Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., & Schunemann, H. J. (2008). GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *British Medical Journal (Clinical Research Edition), 336*(7650), 924-926. doi: 10.1136/bmj.39489.470347.AD

Higgins, J. P. T., & Green, S. (2011). *Cochrane handbook for systematic reviews of interventions: Version 5.1.0*. Retrieved from www.handbook.cochrane.org

Huang, E. S., O'Grady, M., Basu, A., Winn, A., John, P., Lee, J., . . . Wysocki, T. (2010). The cost-effectiveness of continuous glucose monitoring in type 1 diabetes. *Diabetes Care, 33*(6), 1269-1274. doi: 10.2337/dc09-2042

Langendam, M., Luijf, Y. M., Hooft, L., Devries, J. H., Mudde, A. H., & Scholten, R. J. (2012). Continuous glucose monitoring systems for type 1 diabetes mellitus. *The Cochrane Database of Systematic Reviews, 1*, Cd008101. doi: 10.1002/14651858.CD008101.pub2

Lind, M., Polonsky, W., Hirsch, I. B., Heise, T., Bolinder, J., Dahlqvist, S., . . . Hellman, J. (2017). Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: The GOLD randomized clinical trial. *Journal of the American Medical Association, 317*(4), 379-387. doi: 10.1001/jama.2016.19976

McQueen, R. B., Ellis, S. L., Maahs, D. M., Anderson, H. D., Nair, K. V., & Campbell, J. D. (2014). Frequency of continuous glucose monitoring use and change in hemoglobin A1C for adults with Type 1 diabetes in a clinical practice setting. *Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, 20*(10), 1007-1015. doi: 10.4158/ep14027.or

Moy, F. M., Ray, A., & Buckley, B. S. (2014). Techniques of monitoring blood glucose during pregnancy for women with pre-existing diabetes. *Cochrane Database Syst Rev*(4), Cd009613. doi: 10.1002/14651858.CD009613.pub2

National Clinical Guideline Centre. (2015). *Diabetes (type 1 and type 2) in children and young people: Diagnosis and management*. Retrieved from https://www.nice.org.uk/guidance/ng18/evidence/full-guideline-435396352

National Clinical Guideline Centre. (2015). *Diabetes in pregnancy: Management of diabetes and its complications from preconception to the postnatal period*. Retrieved from https://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-from-preconception-to-the-postnatal-period-51038446021

National Clinical Guideline Centre. (2015). *Type 1 diabetes in adults: Diagnosis and management*. Retrieved from https://www.nice.org.uk/guidance/ng17/evidence/full-guideline-435400241

National Clinical Guideline Centre. (2015). *Type 2 diabetes in adults: Management*. Retrieved from https://www.nice.org.uk/guidance/ng28/evidence/full-guideline-78671532569

National Institute for Health and Care Excellence. (2014). *Developing NICE guidelines: The manual*. Retrieved from https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf

National Institute of Diabetes and Digestive and Kidney Diseases. (2016). *Diabetes overview*. Retrieved from https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes

New, J. P., Ajjan, R., Pfeiffer, A. F., & Freckmann, G. (2015). Continuous glucose monitoring in people with diabetes: The randomized controlled Glucose Level Awareness in Diabetes Study (GLADIS). *Diabetic Medicine: A Journal of the British Diabetic Association, 32*(5), 609-617. doi: 10.1111/dme.12713

New York State Department of Health. (2014). *Behavioral Risk Factor Surveillance System (BRFSS) brief*. Retrieved from https://www.health.ny.gov/statistics/brfss/reports/docs/1607_brfss_diabetes.pdf

New York State Department of Health. (2016). *Basic benefit: Evidence-based dossier submission process*. Retrieved from https://www.health.ny.gov/health_care/medicaid/redesign/basic_benefit_ebdsp.htm

Peters, A. L., Ahmann, A. J., Battelino, T., Evert, A., Hirsch, I. B., Murad, M. H., . . . Wolpert, H. (2016). Diabetes technology-continuous subcutaneous insulin infusion therapy

and continuous glucose monitoring in adults: An Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism, 101*(11), 3922-3937. doi: 10.1210/jc.2016-2534

Poolsup, N., Suksomboon, N., & Kyaw, A. M. (2013). Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. *Diabetology & Metabolic Syndrome, 5*, 39. doi: 10.1186/1758-5996-5-39

Rachmiel, M., Landau, Z., Boaz, M., Mazor Aronovitch, K., Loewenthal, N., Ben-Ami, M., . . . Pinhas-Hamiel, O. (2015). The use of continuous glucose monitoring systems in a pediatric population with type 1 diabetes mellitus in real-life settings: The AWeSoMe Study Group experience. *Acta Diabetologica, 52*(2), 323-329. doi: 10.1007/s00592-014-0643-6

Rewers, M. J., Pillay, K., de Beaufort, C., Craig, M. E., Hanas, R., Acerini, C. L., & Maahs, D. M. (2014). ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and monitoring of glycemic control in children and adolescents with diabetes. *Pediatric Diabetes, 15 Suppl 20*, 102-114. doi: 10.1111/pedi.12190

Riveline, J. P., Schaepelynck, P., Chaillous, L., Renard, E., Sola-Gazagnes, A., Penfornis, A., . . . Hanaire, H. (2012). Assessment of patient-led or physician-driven continuous glucose monitoring in patients with poorly controlled type 1 diabetes using basal-bolus insulin regimens: A 1-year multicenter study. *Diabetes Care, 35*(5), 965-971. doi: 10.2337/dc11-2021

Roze, S., Saunders, R., Brandt, A. S., de Portu, S., Papo, N. L., & Jendle, J. (2015). Health-economic analysis of real-time continuous glucose monitoring in people with type 1 diabetes. *Diabetic Medicine: A Journal of the British Diabetic Association, 32*(5), 618-626. doi: 10.1111/dme.12661

Scottish Intercollegiate Guidelines Network. (2009). *Critical appraisal: Notes and checklists*. Retrieved from http://www.sign.ac.uk/methodology/checklists.html

Skelly, A. C., Kisser, J. M. S., Mayfield, J. A., Olson, C. M., & Ecker, E. D. (2011). *Glucose monitoring: Self-monitoring in individuals with insulin dependent diabetes, 18 years of age or under*. Retrieved from https://www.hca.wa.gov/assets/program/glucose_monitoring_final%5b1%5d.pdf

Soupal, J., Petruzelkova, L., Flekac, M., Pelcl, T., Matoulek, M., Dankova, M., . . . Prazny, M. (2016). Comparison of different treatment modalities for type 1 diabetes, including sensor-augmented insulin regimens, in 52 weeks of follow-up: A COMISAIR study. *Diabetes Technology & Therapeutics, 18*(9), 532-538. doi: 10.1089/dia.2016.0171

Tang, T. S., Digby, E. M., Wright, A. M., Chan, J. H., Mazanderani, A. B., Ross, S. A., . . . Tildesley, H. D. (2014). Real-time continuous glucose monitoring versus internet-based blood glucose monitoring in adults with type 2 diabetes: A study of treatment satisfaction. *Diabetes Research and Clinical Practice, 106*(3), 481-486. doi: 10.1016/j.diabres.2014.09.050

The PRISMA Group. (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: PRISMA 2009 Checklist*. Retrieved from http://www.prisma-statement.org/documents/PRISMA%202009%20checklist.pdf

Tildesley, H. D., Wright, A. M., Chan, J. H., Mazanderani, A. B., Ross, S. A., Tildesley, H. G., . . . White, A. S. (2013). A comparison of internet monitoring with continuous glucose monitoring in insulin-requiring type 2 diabetes mellitus. *Canadian Journal of Diabetes, 37*(5), 305-308. doi: 10.1016/j.jcjd.2013.05.006

Tildesley, H. D., Wright, A. M., Chan, J. H., Mazanderani, A. B., Ross, S. A., Tildesley, H. G., . . . White, A. S. (2016). WITHDRAWN: A comparison of internet monitoring with continuous glucose monitoring in insulin-requiring type 2 diabetes mellitus. *Can J Diabetes, 40 Suppl 1*, 24-27. doi: 10.1016/j.jcjd.2016.04.003

Tumminia, A., Crimi, S., Sciacca, L., Buscema, M., Frittitta, L., Squatrito, S., . . . Tomaselli, L. (2015). Efficacy of real-time continuous glucose monitoring on glycaemic control and glucose variability in type 1 diabetic patients treated with either insulin pumps or multiple insulin injection therapy: A randomized controlled crossover trial. *Diabetes/Metabolism Research and Reviews, 31*(1), 61-68. doi: 10.1002/dmrr.2557

U.S. Food and Drug Administration. (2016). *Dexcom G5 mobile continuous glucose monitoring system - P120005/S041*. Retrieved from https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm533969.htm

van Beers, C. A., DeVries, J. H., Kleijer, S. J., Smits, M. M., Geelhoed-Duijvestijn, P. H., Kramer, M. H., . . . Serne, E. H. (2016). Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): A randomised, open-label, crossover trial. *The Lancet Diabetes & Endocrinology, 4*(11), 893-902. doi: 10.1016/s2213-8587(16)30193-0

Vigersky, R. A., Fonda, S. J., Chellappa, M., Walker, M. S., & Ehrhardt, N. M. (2012). Short- and long-term effects of real-time continuous glucose monitoring in patients with type 2 diabetes. *Diabetes Care, 35*(1), 32-38. doi: 10.2337/dc11-1438

Wojciechowski, P., Rys, P., Lipowska, A., Gaweska, M., & Malecki, M. T. (2011). Efficacy and safety comparison of continuous glucose monitoring and self-monitoring of

blood glucose in type 1 diabetes: Systematic review and meta-analysis. *Polish Archives of Internal Medicine, 121*(10), 333-343.

Yeh, H. C., Brown, T. T., Maruthur, N., Ranasinghe, P., Berger, Z., Suh, Y. D., . . . Golden, S. H. (2012). Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: A systematic review and meta-analysis. *Annals of Internal Medicine, 157*(5), 336-347. doi: 10.7326/0003-4819-157-5-201209040-00508

Appendix A. Methods

General Search Strategy

Evidence

A full search of the Center's core clinical evidence primary sources was conducted to identify systematic reviews and meta-analyses and technology assessments. Searches of core sources were limited to citations published after 2005. Center researchers also searched the MEDLINE® (Ovid) database for relevant systematic reviews and meta-analyses or technology assessments, and for individual studies published after the search dates of the identified systematic reviews. MEDLINE searches were updated to April 10 (adults) and 11 (children/adolescents), 2017.

The core sources searched included:

Agency for Healthcare Research and Quality (AHRQ)

BMJ Clinical Evidence

Cochrane Library (Wiley Interscience)

National Institute for Health and Care Excellence (NICE)

PubMed Health

Veterans Administration Evidence-based Synthesis Program (ESP)

Washington State Health Technology Assessment Program (WA HTA)

Clinical Practice Guidelines

Center researchers conducted a full search of Center clinical practice guidelines primary sources to identify clinical practice guidelines using the terms "glucose monitor," "continuous glucose," and "real-time or real time glucose." Searches were limited to citations published within the last five years.

The guideline sources included the following:

American Association of Clinical Endocrinologists

American Diabetes Association

Australian Government National Health and Medical Research Council (NHMRC)

Centers for Disease Control and Prevention (CDC), Community Preventive Services

Endocrine Society

Institute for Clinical Systems Improvement (ICSI)

National Guidelines Clearinghouse

NICE

New Zealand Guidelines Group

Scottish Intercollegiate Guidelines Network (SIGN)

Society for Endocrinology

United States Preventive Services Task Force (USPSTF)

Veterans Administration/Department of Defense (VA/DOD)

Coverage Policies

Center researchers also searched for current coverage policies on CGM from the following payers: Aetna, Blue Shield of Northeastern New York, Capital District Physician's Health Plan, Centers for Medicare and Medicaid Services, Cigna, Emblem Health, Empire Blue Cross Blue Shield, Excellus Blue Cross Blue Shield, Tufts Health Plan, and UnitedHealthcare. A review of coverage decisions by the Oregon Health Evidence Review Commission and WA HTA Clinical Committee are also searched when applicable.

General Exclusion Criteria

Two Center researchers reviewed all searches and excluded studies that were not systematic reviews or technology assessments, or individual studies (as applicable by topic) that were published before 2006, or were published in a language other than English.

Quality Assessment

Center researchers assessed the methodological quality of the included studies using standard instruments developed and adapted by the Center that are modifications of the systems in use by the Campbell Collaboration, Cochrane, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), NICE, and SIGN (Campbell Collaboration, 2017; Guyatt et al., 2008; Higgins & Green, 2011; National Institute for Health and Care Excellence, 2014; Scottish Intercollegiate Guidelines Network, 2009; The PRISMA Group, 2009). Two Center researchers independently rated all studies. In cases in which there was not agreement about the quality of a study, consensus was reached through discussion.

Each rater assigned the study a rating of good, fair, or poor, based on its adherence to recommended methods and potential for biases. In brief, good-quality systematic reviews include a clearly focused question, a literature search sufficiently rigorous to identify all relevant studies, criteria used to select studies for inclusion (e.g., RCTs) and assess study quality, and assessments of heterogeneity to determine whether a meta-analysis would be appropriate. Good-quality RCTs include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Good-quality systematic reviews and RCTs also have low potential for bias from conflicts of interest and funding source(s). Fair-quality systematic reviews and RCTs have incomplete information about methods that might mask

important limitations. Poor-quality systematic reviews and RCTs have clear flaws that could introduce significant bias.

Specific Search Details

The full MEDLINE (Ovid) search strategies are listed below. The search terms, "glucose monitor," "continuous glucose," and "real-time or real time glucose" were used in the remaining core source searches.

Inclusion Criteria

Population: Individuals with diabetes (type 1, type 2, or gestational)

Intervention: Real-time continuous glucose monitors

Comparator: Self-monitoring blood glucose

Outcomes: Change in glycated hemoglobin (HbA1c), maternal outcomes, neonatal outcomes, cost-effectiveness, adverse events

Exclusion Criteria

Study exclusion criteria included:

- Studies that did not stratify outcomes by rt-CGM compared to SMBG
- Non-comparative studies (except for case-series for harms)
- Duplicate information from a research study published in more than one source (only the highest quality, most recent publication with outcome of interest was included)
- Systematic reviews that included only studies that were summarized by more comprehensive SRs or SRs of higher quality and/or that were more recently published
- Studies identified that were included in a summarized SR or technology assessment (TA)
- Archived government reports
- Systematic reviews, meta-analyses and health technology assessments of poor methodologic quality
- Publication before 2007 (2002 for guidelines)
- Non-English publication

MEDLINE® (Ovid) Search

The *MEDLINE®* Search Strategy was adapted from the NICE (National Clinical Guideline Centre, 2015a, 2015b, 2015c, 2015d) systematic reviews. Studies published after the NICE (National Clinical Guideline Centre, 2015a, 2015b, 2015c, 2015d) reviews were included to update the existing systematic reviews.

Adults

Database: Ovid MEDLINE(R) <1946 to December Week 1 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <April 10, 2017>

Search Strategy:

1 diabetes mellitus, type 1/
2 diabetes mellitus, type 2/
3 diabetic ketoacidosis/
4 ((diabet* or dm) adj4 (type 1 or type1 or type i or type one)).ti,ab.
5 ((diabet* or dm) adj4 (type 2 or type2 or type iI or type two)).ti,ab.
6 (diabet* adj2 (autoimmun* or auto immun*)).ti,ab.
7 lada.ti,ab.
8 (diabet* adj2 (brittle or labile)).ti,ab.
9 (diabet* adj2 (sudden onset or juvenile or childhood)).ti,ab.
10 (diabet* adj3 (keto* or acido* or gastropare*)).ti,ab.
11 (dm1 or iddm or t1d* or dka).ti,ab.
12 (dm2 or iddm or t2d* or dka).ti,ab.
13 ((diabet* adj2 (insulin depend* or insulin deficien*)) or non insulin depend*).ti,ab.
14 diabetes mellitus.ti.
15 (diabet* adj3 (type 2 or type ii)).ti.
16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17 ((children or adolescen* or school* or infant* or teenage* or paediatric* or pediatric*) not (adult* or onset)).ti.
18 16 not 17
19 letter/
20 editorial/
21 news/
22 exp historical article/
23 anecdotes as topic/
24 comment/
25 case report/
26 (letter or comment*).ti.
27 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28 18 not 27
29 animals/ not humans/
30 exp animals, laboratory/
31 exp rodentia/ (3339268)
32 (rat or rats or mouse or mice).ti.
33 exp animal experimentation/
34 29 or 30 or 31 or 32 or 33
35 28 not 34
36 limit 35 to english language

37 limit 36 to yr="2014 -Current"
38 blood glucose self-monitoring/
39 ((glucose or continuous or real time or intermittent or retrospective) and monitor*).ti.
40 ((glucose or continuous or real time or intermittent or retrospective) adj5 (monitor* or measure*)).ab.
41 (cgm* or bgm* or smbg*).ti,ab.
42 *hemoglobin a, glycosylated/ and monitor*.ti,ab.
43 38 or 39 or 40 or 41 or 42
44 37 and 43
45 remove duplicates from 44
46 45 not (34 or 27)
47 limit 39 to yr="2014 -Current"

Children

Database : Ovid MEDLINE(R) <1946 to December Week 1 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <April 11, 2017>

Search Strategy:

1 adolescent/ or minors/
2 (adolescen$ or teen$ or youth$ or young or juvenile? or minors or highschool$).ti,ab,jw.
3 exp CHILD/
4 (child$ or schoolchild$ or "school age" or "school aged" or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab,jw.
5 exp INFANT/
6 (infan$ or neonat$ or newborn$ or baby or babies).ti,ab,jw.
7 exp PEDIATRICS/ or exp PUBERTY/
8 (p?ediatric$ or pubert$ or prepubert$ or pubescen$ or prepubescen$).ti,ab,jw.
9 or/1-8
10 exp DIABETES MELLITUS, TYPE 1/
11 (diabet$ adj5 ("type one" or "type 1" or "type I" or T1 or TI or insulin depend$ or juvenile or child$ or earl$ or labile or brittle or sudden onset or auto immun$ or auto?immun$)).ti,ab.
12 (IDDM or T1D or TID or DM1 or DMI).ti,ab.
13 or/10-12
14 and/9,13
15 BLOOD GLUCOSE SELF-MONITORING/
16 ((glucose or blood sugar$ or insulin$) adj3 (meter$ or monitor$ or sensor$ or capillary)).ti,ab.

17 (HBGM or SMBG or BGM or CGM or CGMS or glucometer or glucosemeter$ or (glucose adj meter$)).ti,ab.
18 (finger prick or finger-prick or fingerstick or finger-stick or "finger stick").ti,ab.
19 or/15-18
20 and/14,19
21 limit 20 to english language
22 LETTER/
23 EDITORIAL/
24 NEWS/
25 exp HISTORICAL ARTICLE/
26 ANECDOTES AS TOPIC/
27 COMMENT/
28 CASE REPORT/
29 (letter or comment* or abstracts).ti.
30 or/22-29
31 ANIMALS/ not HUMANS/
32 exp ANIMALS, LABORATORY/
33 exp ANIMAL EXPERIMENTATION/
34 exp MODELS, ANIMAL/
35 exp RODENTIA/
36 (rat or rats or mouse or mice).ti.
37 31 or 32 or 33 or 34 or 35 or 36
38 21 not (30 or 37)
39 remove duplicates from 38
40 limit 39 to yr="2014 -Current"

Appendix B. Articles Selected for Full Text Review Inclusion/Exclusion Rationale

Table B1. Articles Selected for Full Text Review

Citation	Inclusion/Exclusion Rationale
Dossier Submission	
Battelino et al. (2011)	Exclude: Included in Langendam et al. (2012)
Battelino et al. (2012)	Exclude: Included in National Clinical Guideline Centre (2015c)
Battelino et al. (2015)	Include
Beck et al. (2009b)	Exclude: Included in Skelly et al. (2011)
Bode et al. (2009)	Exclude: Included in Langendam et al. (2012)
Bronstone and Graham (2016)	Exclude: Study design (narrative review)
Chase et al. (2010)	Exclude: Included in Skelly et al. (2011)
Deiss et al. (2006)	Exclude: Included in Langendam et al. (2012)
Hirsch et al. (2008)	Exclude: Included in Langendam et al. (2012)
Huang et al. (2010)	Exclude: Included in National Clinical Guideline Centre (2015c)
Kordonouri et al. (2010)	Exclude: Included in Langendam et al. (2012)
Mauras et al. (2012)	Exclude: Included in National Clinical Guideline Centre (2015a)
McQueen, Ellis, Campbell, Nair, and Sullivan (2011)	Exclude: Included in National Clinical Guideline Centre (2015c)
New et al. (2015)	Include
O'Connell et al. (2009)	Exclude: Included in Langendam et al. (2012)
Raccah et al. (2009)	Exclude: Included in Langendam et al. (2012)
Radermecker, Saint Remy, Scheen, Bringer, and Renard (2010)	Exclude: Included in National Clinical Guideline Centre (2015c)
Riveline et al. (2012)	Include
Tamborlane et al. (2008)	Exclude: Included in National Clinical Guideline Centre (2015c)
Tildesley et al. (2013)	Exclude: Article withdrawn by study authors
Weinzimer et al. (2010)	Exclude: Included in Skelly et al. (2011)
Wojciechowski et al. (2011)	Exclude: Superseded by included systematic reviews
Yeh et al. (2012)	Exclude: Superseded by included systematic reviews

Citation	Inclusion/Exclusion Rationale
Center Search	
Agency for Healthcare Research and Quality Surveillance Program (2016)	Exclude: Study design
American Diabetes Association (2016a)	Include
Bailey, Bode, Christiansen, Klaff, and Alva (2015)	Exclude: Population
Bailey et al. (2016b)	Exclude: Intervention
Bailey, Little, and Jung (2016a)	Include
Battelino et al. (2015)	Include
Beck et al. (2017)	Include
Benkhadra et al. (2017)	Exclude: Comparator
Blumer et al. (2013)	Include
Bronstone and Graham (2016)	Exclude: Study design (narrative review)
Chamberlain, Dopita, Gilgen, and Neuman (2015)	Exclude: Comparator
Chamberlain, Rhinehart, Shaefer, and Neuman (2016)	Exclude: Study design
Chetty, Almulla, Odueyungbo, and Thabane (2008)	Exclude: Superseded by included systematic reviews
Craig et al. (2011)	Exclude: Superseded by included systematic reviews
Damiano et al. (2014)	Exclude: Comparator
Day, Bidwell, and Weir (2006)	Exclude: Superseded by included systematic reviews
Englert et al. (2014)	Exclude: Study design
Floyd et al. (2012)	Exclude: Superseded by included systematic reviews
Fonda et al. (2016)	Include
Fonseca et al. (2016)	Include
Gandhi et al. (2011)	Exclude: Superseded by included systematic reviews
Golden et al. (2012)	Exclude: Superseded by included systematic reviews
Golicki, Golicka, Groele, and Pankowska (2008)	Exclude: Superseded by included systematic reviews
Hoeks, Greven, and de Valk (2011)	Exclude: Superseded by included systematic reviews
Hommel et al. (2014)	Exclude: Comparator
Huang et al. (2010)	Exclude: Included in National Clinical Guideline Centre (2015c)
Jamiolkowska et al. (2016)	Exclude: Comparator

Citation	Inclusion/Exclusion Rationale
Kesavadev et al. (2014)	Exclude: Setting
Kovatchev, Patek, Ortiz, and Breton (2015)	Exclude: Outcomes
Langendam et al. (2012)	Include
Leelarathna, Guzder, Muralidhara, and Evans (2011)	Exclude: Superseded by included systematic reviews
Lewis, McCrone, Deiriggi, and Bendre (2017)	Exclude: Comparator
Lim et al. (2016)	Exclude: Intervention
Lind et al. (2017)	Include
Little et al. (2014)	Exclude: Included in National Clinical Guideline Centre (2015c)
Matsuda and Brennan (2012)	Exclude: Superseded by included systematic reviews
McGrath et al. (2016)	Exclude: Intervention
McQueen et al. (2011)	Exclude: Included in National Clinical Guideline Centre (2015c)
McQueen et al. (2014)	Include
Medical Advisory Secretariat (2011)	Exclude: Superseded by included systematic reviews
Moy et al. (2014)	Include
Nakamura and Balo (2015)	Exclude: Outcome, comparator
New et al. (2015)	Include
National Clinical Guideline Centre (2015a)	Include
National Clinical Guideline Centre (2015b)	Include
National Clinical Guideline Centre (2015c)	Include
National Clinical Guideline Centre (2015d)	Include
Olry de Labry Lima, Moya Garrido, and Espin Balbino (2014)	Exclude: Intervention
Pazos-Couselo et al. (2015)	Exclude: Outcomes
Peters et al. (2016)	Include
Pickup, Freeman, and Sutton (2011)	Exclude: Superseded by included systematic reviews
Polonsky, Peters, and Hessler (2016)	Exclude: Comparator

Citation	Inclusion/Exclusion Rationale
Poolsup et al. (2013)	Include
Purins and Hiller (2009)	Exclude: Study design
Rachmiel et al. (2015)	Include
Rewers et al. (2014)	Include
Riemsma et al. (2016)	Exclude: Superseded by included systematic reviews
Roze et al. (2015)	Include
Secher et al. (2014)	Exclude: Included in National Clinical Guideline Centre (2015b)
Senior et al. (2015)	Exclude: Outcomes
Skelly et al. (2011)	Include
Soupal et al. (2016)	Include
Szypowska, Ramotowska, Dzygalo, and Golicki (2012)	Exclude: Superseded by included systematic reviews
Tang et al. (2014)	Include
Telo, Volkening, Butler, and Laffel (2015)	Exclude: Outcome
Thabit et al. (2015)	Exclude: Outcome
Tildesley et al. (2016)	Exclude: Study withdrawal notification
Tumminia et al. (2015)	Include
van Beers et al. (2016)	Include
Wang, Ioacara, and DeHennis (2015)	Exclude: Outcome
Wei et al. (2016)	Exclude: Intervention
Wojciechowski et al. (2011)	Exclude: Superseded by included systematic reviews
Yeh et al. (2012)	Exclude: Superseded by included systematic reviews
Yeoh, Choudhary, Nwokolo, Ayis, and Amiel (2015)	Exclude: Comparator
Yu et al. (2014)	Exclude: Intervention

References Excluded (on Full Text Review)

Agency for Healthcare Research and Quality Surveillance Program. (2016). *Methods for insulin delivery and glucose monitoring: Comparative effectiveness*. Retrieved from https://www.effectivehealthcare.ahrq.gov/ehc/products/242/2182/insulin-blood-sugar-surveillance-160215.pdf

Bailey, T., Bode, B. W., Christiansen, M. P., Klaff, L. J., & Alva, S. (2015). The performance and usability of a factory-calibrated flash glucose monitoring system. *Diabetes Technology & Therapeutics, 17*(11), 787-794. doi: 10.1089/dia.2014.0378

Bailey, T. S., Grunberger, G., Bode, B. W., Handelsman, Y., Hirsch, I. B., Jovanovic, L., . . . Walsh, J. (2016). American Association of Clinical Endocrinologists and American College of Endocrinology 2016 outpatient glucose monitoring consensus statement. *Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, 22*(2), 231-261. doi: 10.4158/ep151124.cs

Battelino, T., Conget, I., Olsen, B., Schutz-Fuhrmann, I., Hommel, E., Hoogma, R., . . . Bolinder, J. (2012). The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: A randomised controlled trial. *Diabetologia, 55*(12), 3155-3162. doi: 10.1007/s00125-012-2708-9

Battelino, T., Phillip, M., Bratina, N., Nimri, R., Oskarsson, P., & Bolinder, J. (2011). Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. *Diabetes Care, 34*(4), 795-800. doi: 10.2337/dc10-1989

Beck, R. W., Hirsch, I. B., Laffel, L., Tamborlane, W. V., Bode, B. W., Buckingham, B., . . . Xing, D. (2009). The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care, 32*(8), 1378-1383. doi: 10.2337/dc09-0108

Benkhadra, K., Alahdab, F., Tamhane, S., Wang, Z., Prokop, L. J., Hirsch, I. B., . . . Murad, M. H. (2017). Real-time continuous glucose monitoring in type 1 diabetes: A systematic review and individual patient data meta-analysis. *Clinical Endocrinology, 86*(3), 354-360. doi: 10.1111/cen.13290

Bode, B., Beck, R. W., Xing, D., Gilliam, L., Hirsch, I., Kollman, C., . . . Wolpert, H. (2009). Sustained benefit of continuous glucose monitoring on A1C, glucose profiles, and hypoglycemia in adults with type 1 diabetes. *Diabetes Care, 32*(11), 2047-2049. doi: 10.2337/dc09-0846

Bronstone, A., & Graham, C. (2016). The potential cost implications of averting severe hypoglycemic events requiring hospitalization in high-risk adults with type 1 diabetes using real-time continuous glucose monitoring. *Journal of Diabetes Science and Technology, 10*(4), 905-913. doi: 10.1177/1932296816633233

Chamberlain, J. J., Dopita, D., Gilgen, E., & Neuman, A. (2015). Impact of frequent and persistent use of continuous glucose monitoring (CGM) on hypoglycemia fear, frequency of emergency medical treatment, and SMBG frequency after one year. *Journal of Diabetes Science and Technology, 10*(2), 383-388. doi: 10.1177/1932296815604633

Chamberlain, J. J., Rhinehart, A. S., Shaefer, C. F., Jr., & Neuman, A. (2016). Diagnosis and management of diabetes: Synopsis of the 2016 American Diabetes Association standards of medical care in diabetes. *Annals of Internal Medicine, 164*(8), 542-552. doi: 10.7326/m15-3016

Chase, H. P., Beck, R. W., Xing, D., Tamborlane, W. V., Coffey, J., Fox, L. A., . . . Ruedy, K. J. (2010). Continuous glucose monitoring in youth with type 1 diabetes: 12-month follow-up of the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. *Diabetes Technology & Therapeutics, 12*(7), 507-515. doi: 10.1089/dia.2010.0021

Chetty, V. T., Almulla, A., Odueyungbo, A., & Thabane, L. (2008). The effect of continuous subcutaneous glucose monitoring (CGMS) versus intermittent whole blood finger-stick glucose monitoring (SBGM) on hemoglobin A1c (HBA1c) levels in Type I diabetic patients: A systematic review. *Diabetes research and clinical practice, 81*(1), 79-87. doi: 10.1016/j.diabres.2008.02.014

Craig, M. E., Twigg, S. M., Donaghue, K. C., Cheung, N. W., Cameron, F. J., Conn, J., . . . Silink, M. (2011). *National evidence-based clinical care guidelines for type 1 diabetes in children, adolescents and adults*. Retrieved from https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/ext004_type1_diabetes_children_adolescents_adults.pdf

Damiano, E. R., McKeon, K., El-Khatib, F. H., Zheng, H., Nathan, D. M., & Russell, S. J. (2014). A comparative effectiveness analysis of three continuous glucose monitors: The Navigator, G4 Platinum, and Enlite. *Journal of Diabetes Science and Technology, 8*(4), 699-708. doi: 10.1177/1932296814532203

Day, P., Bidwell, S., & Weir, R. (2006). *Continuous glucose monitoring devices: Horizon scanning report*. Retrieved from http://nzhta.chmeds.ac.nz/publications/finalcgmd.pdf

Deiss, D., Bolinder, J., Riveline, J. P., Battelino, T., Bosi, E., Tubiana-Rufi, N., . . . Phillip, M. (2006). Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care, 29*(12), 2730-2732. doi: 10.2337/dc06-1134

Englert, K., Ruedy, K., Coffey, J., Caswell, K., Steffen, A., & Levandoski, L. (2014). Skin and adhesive issues with continuous glucose monitors: A sticky situation. *Journal of Diabetes Science and Technology, 8*(4), 745-751. doi: 10.1177/1932296814529893

Floyd, B., Chandra, P., Hall, S., Phillips, C., Alema-Mensah, E., Strayhorn, G., . . . Umpierrez, G. E. (2012). Comparative analysis of the efficacy of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes mellitus. *Journal of Diabetes Science and Technology, 6*(5), 1094-1102. doi: 10.1177/193229681200600513

Gandhi, G. Y., Kovalaske, M., Kudva, Y., Walsh, K., Elamin, M. B., Beers, M., . . . Murad, M. H. (2011). Efficacy of continuous glucose monitoring in improving glycemic control and reducing hypoglycemia: A systematic review and meta-analysis of randomized trials. *Journal of Diabetes Science and Technology, 5*(4), 952-965. doi: 10.1177/193229681100500419

Golden, S. H., Brown, T., Yeh, H. C., Maruthur, N., Ranasinghe, P., Berger, Z., . . . Bass, E. B. (2012). *Methods for insulin delivery and glucose monitoring: Comparative effectiveness*. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from https://effectivehealthcare.ahrq.gov/ehc/products/242/749/CER57_Insulin-Delivery_FinalReport_20120703.pdf.

Golicki, D. T., Golicka, D., Groele, L., & Pankowska, E. (2008). Continuous glucose monitoring system in children with type 1 diabetes mellitus: A systematic review and meta-analysis. *Diabetologia, 51*(2), 233-240. doi: 10.1007/s00125-007-0884-9

Hirsch, I. B., Abelseth, J., Bode, B. W., Fischer, J. S., Kaufman, F. R., Mastrototaro, J., . . . Buckingham, B. A. (2008). Sensor-augmented insulin pump therapy: Results of the first randomized treat-to-target study. *Diabetes Technology & Therapeutics, 10*(5), 377-383. doi: 10.1089/dia.2008.0068

Hoeks, L. B., Greven, W. L., & de Valk, H. W. (2011). Real-time continuous glucose monitoring system for treatment of diabetes: A systematic review. *Diabetic Medicine: A Journal of the British Diabetic Association, 28*(4), 386-394. doi: 10.1111/j.1464-5491.2010.03177.x

Hommel, E., Olsen, B., Battelino, T., Conget, I., Schutz-Fuhrmann, I., Hoogma, R., . . . Bolinder, J. (2014). Impact of continuous glucose monitoring on quality of life, treatment satisfaction, and use of medical care resources: Analyses from the SWITCH study. *Acta Diabetologica, 51*(5), 845-851. doi: 10.1007/s00592-014-0598-7

Huang, E. S., O'Grady, M., Basu, A., Winn, A., John, P., Lee, J., . . . Wysocki, T. (2010). The cost-effectiveness of continuous glucose monitoring in type 1 diabetes. *Diabetes Care, 33*(6), 1269-1274. doi: 10.2337/dc09-2042

Jamiolkowska, M., Jamiolkowska, I., Luczynski, W., Tolwinska, J., Bossowski, A., & Glowinska Olszewska, B. (2016). Impact of real-time continuous glucose monitoring use on glucose variability and endothelial function in adolescents with type 1 diabetes: New technology--new possibility to decrease cardiovascular risk? *Journal of Diabetes Research, 2016*, 4385312. doi: 10.1155/2016/4385312

Kesavadev, J., Sadikot, S., Wangnoo, S., Kannampilly, J., Saboo, B., Aravind, S. R., . . . Vishwanathan, V. (2014). Consensus guidelines for glycemic monitoring in type 1/type 2 & GDM. *Diabetes & Metabolic Syndrome, 8*(3), 187-195. doi: 10.1016/j.dsx.2014.04.030

Kordonouri, O., Pankowska, E., Rami, B., Kapellen, T., Coutant, R., Hartmann, R., . . . Danne, T. (2010). Sensor-augmented pump therapy from the diagnosis of childhood type 1 diabetes: Results of the Paediatric Onset Study (ONSET) after 12 months of treatment. *Diabetologia, 53*(12), 2487-2495. doi: 10.1007/s00125-010-1878-6

Kovatchev, B. P., Patek, S. D., Ortiz, E. A., & Breton, M. D. (2015). Assessing sensor accuracy for non-adjunct use of continuous glucose monitoring. *Diabetes Technology & Therapeutics, 17*(3), 177-186. doi: 10.1089/dia.2014.0272

Leelarathna, L., Guzder, R., Muralidhara, K., & Evans, M. L. (2011). Diabetes: Glycaemic control in type 1. *British Medical Journal Clinical Evidence, 2011*.

Lewis, K. R., McCrone, S., Deiriggi, P., & Bendre, S. (2017). Effectiveness of continuous glucose monitoring in children, adolescents, and young adults with poorly controlled type 1 diabetes. *Journal for Specialists in Pediatric Nursing: JSPN, 22*(1). doi: 10.1111/jspn.12162

Lim, S., Kang, S. M., Kim, K. M., Moon, J. H., Choi, S. H., Hwang, H., . . . Jang, H. C. (2016). Multifactorial intervention in diabetes care using real-time monitoring and tailored feedback in type 2 diabetes. *Acta Diabetologica, 53*(2), 189-198. doi: 10.1007/s00592-015-0754-8

Little, S. A., Leelarathna, L., Walkinshaw, E., Tan, H. K., Chapple, O., Lubina-Solomon, A., . . . Shaw, J. A. (2014). 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, 37*(8), 2114-2122. doi: 10.2337/dc14-0030

Matsuda, E., & Brennan, P. (2012). The effectiveness of continuous subcutaneous insulin pumps with continuous glucose monitoring in outpatient adolescents with type 1 diabetes: A systematic review. *JBI Library of Systematic Reviews, 10*(42 Suppl), 1-10. doi: 10.11124/jbisrir-2012-170

Mauras, N., Beck, R., Xing, D., Ruedy, K., Buckingham, B., Tansey, M., . . . Kollman, C. (2012). A randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to <10 years. *Diabetes Care, 35*(2), 204-210. doi: 10.2337/dc11-1746

McGrath, R. T., Donnelly, V. C., Glastras, S. J., Preda, V. A., Sheriff, N., Ward, P., . . . Fulcher, G. R. (2016). Evaluation of blood glucose meter efficacy in an antenatal diabetes clinic. *Diabetes Technology & Therapeutics, 18*(2), 68-74. doi: 10.1089/dia.2015.0104

McQueen, R. B., Ellis, S. L., Campbell, J. D., Nair, K. V., & Sullivan, P. W. (2011). Cost-effectiveness of continuous glucose monitoring and intensive insulin therapy for type 1 diabetes. *Cost Effectiveness and Resource Allocation, 9*, 13. doi: 10.1186/1478-7547-9-13

Medical Advisory Secretariat. (2011). *Continuous glucose monitoring for patients with diabetes: Ontario health technology assessment series*. Retrieved from http://www.hqontario.ca/Portals/0/Documents/evidence/reports/recommendation-cgm-110630.pdf

Nakamura, K., & Balo, A. (2015). The accuracy and efficacy of the Dexcom G4 Platinum continuous glucose monitoring system. *Journal of Diabetes Science and Technology, 9*(5), 1021-1026. doi: 10.1177/1932296815577812

O'Connell, M. A., Donath, S., O'Neal, D. N., Colman, P. G., Ambler, G. R., Jones, T. W., . . . Cameron, F. J. (2009). Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: A randomised controlled trial. *Diabetologia, 52*(7), 1250-1257. doi: 10.1007/s00125-009-1365-0

Olry de Labry Lima, A., Moya Garrido, M. N., & Espin Balbino, J. (2014). Systematic review of economic evaluation studies and budget impact on ambulatory monitoring of capillary glucose in type 2 diabetics. *Primary Care Diabetes, 8*(1), 13-21. doi: 10.1016/j.pcd.2013.11.005

Pazos-Couselo, M., Garcia-Lopez, J. M., Gonzalez-Rodriguez, M., Gude, F., Mayan-Santos, J. M., Rodriguez-Segade, S., . . . Casanueva, F. (2015). High incidence of hypoglycemia in stable insulin-treated type 2 diabetes mellitus: Continuous glucose monitoring vs. self-monitored blood glucose. Observational prospective

study. *Canadian Journal of Diabetes, 39*(5), 428-433. doi: 10.1016/j.jcjd.2015.05.007

Pickup, J. C., Freeman, S. C., & Sutton, A. J. (2011). Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: Meta-analysis of randomised controlled trials using individual patient data. *British Medical Journal (Clinical Research Edition), 343*, d3805. doi: 10.1136/bmj.d3805

Polonsky, W. H., Peters, A. L., & Hessler, D. (2016). The impact of real-time continuous glucose monitoring in patients 65 years and older. *Journal of Diabetes Science and Technology, 10*(4), 892-897. doi: 10.1177/1932296816643542

Purins, A., & Hiller, J. (2009). *Adelaide health technology assessment: Continuous glucose monitoring in pregnant women with diabetes*. Retrieved from http://www.horizonscanning.gov.au/internet/horizon/publishing.nsf/Content/68B1F63984E68993CA2575AD0080F3E2/$File/PS_Continous%20Glucose%20Monitoring%20in%20Pregnant%20Women%20with%20Diabetes.pdf

Raccah, D., Sulmont, V., Reznik, Y., Guerci, B., Renard, E., Hanaire, H., . . . Nicolino, M. (2009). Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: The RealTrend study. *Diabetes Care, 32*(12), 2245-2250. doi: 10.2337/dc09-0750

Radermecker, R. P., Saint Remy, A., Scheen, A. J., Bringer, J., & Renard, E. (2010). Continuous glucose monitoring reduces both hypoglycaemia and HbA1c in hypoglycaemia-prone type 1 diabetic patients treated with a portable pump. *Diabetes & Metabolism, 36*(5), 409-413. doi: 10.1016/j.diabet.2010.08.001

Riemsma, R., Corro Ramos, I., Birnie, R., Buyukkaramikli, N., Armstrong, N., Ryder, S., . . . Kleijnen, J. (2016). Integrated sensor-augmented pump therapy systems [the MiniMed(R) Paradigm Veo system and the Vibe and G4(R) PLATINUM CGM (continuous glucose monitoring) system] for managing blood glucose levels in type 1 diabetes: A systematic review and economic evaluation. *Health Technology Assessment, 20*(17), v-xxxi, 1-251. doi: 10.3310/hta20170

Secher, A. L., Stage, E., Ringholm, L., Barfred, C., Damm, P., & Mathiesen, E. R. (2014). Real-time continuous glucose monitoring as a tool to prevent severe hypoglycaemia in selected pregnant women with type 1 diabetes - an observational study. *Diabetic Medicine: A Journal of the British Diabetic Association, 31*(3), 352-356. doi: 10.1111/dme.12383

Senior, P. A., Bellin, M. D., Alejandro, R., Yankey, J. W., Clarke, W. R., Qidwai, J. C., . . . Rickels, M. R. (2015). Consistency of quantitative scores of hypoglycemia severity and glycemic lability and comparison with continuous glucose monitoring system

measures in long-standing type 1 diabetes. *Diabetes Technology & Therapeutics, 17*(4), 235-242. doi: 10.1089/dia.2014.0289

Szypowska, A., Ramotowska, A., Dzygalo, K., & Golicki, D. (2012). Beneficial effect of real-time continuous glucose monitoring system on glycemic control in type 1 diabetic patients: Systematic review and meta-analysis of randomized trials. *European Journal of Endocrinology, 166*(4), 567-574. doi: 10.1530/eje-11-0642

Tamborlane, W. V., Beck, R. W., Bode, B. W., Buckingham, B., Chase, H. P., Clemons, R., . . . Xing, D. (2008). Continuous glucose monitoring and intensive treatment of type 1 diabetes. *The New England Journal of Medicine, 359*(14), 1464-1476. doi: 10.1056/NEJMoa0805017

Telo, G. H., Volkening, L. K., Butler, D. A., & Laffel, L. M. (2015). Salient characteristics of youth with type 1 diabetes initiating continuous glucose monitoring. *Diabetes Technology & Therapeutics, 17*(6), 373-378. doi: 10.1089/dia.2014.0290

Thabit, H., Leelarathna, L., Wilinska, M. E., Elleri, D., Allen, J. M., Lubina-Solomon, A., . . . Hovorka, R. (2015). Accuracy of continuous glucose monitoring during three closed-loop home studies under free-living conditions. *Diabetes Technology & Therapeutics, 17*(11), 801-807. doi: 10.1089/dia.2015.0062

Tildesley, H. D., Wright, A. M., Chan, J. H., Mazanderani, A. B., Ross, S. A., Tildesley, H. G., . . . White, A. S. (2013). A comparison of internet monitoring with continuous glucose monitoring in insulin-requiring type 2 diabetes mellitus. *Canadian Journal of Diabetes, 37*(5), 305-308. doi: 10.1016/j.jcjd.2013.05.006

Tildesley, H. D., Wright, A. M., Chan, J. H., Mazanderani, A. B., Ross, S. A., Tildesley, H. G., . . . White, A. S. (2016). WITHDRAWN: A comparison of internet monitoring with continuous glucose monitoring in insulin-requiring type 2 diabetes mellitus. *Can J Diabetes, 40 Suppl 1*, 24-27. doi: 10.1016/j.jcjd.2016.04.003

Wang, X., Ioacara, S., & DeHennis, A. (2015). Long-term home study on nocturnal hypoglycemic alarms using a new fully implantable continuous glucose monitoring system in type 1 diabetes. *Diabetes Technology & Therapeutics, 17*(11), 780-786. doi: 10.1089/dia.2014.0375

Wei, Q., Sun, Z., Yang, Y., Yu, H., Ding, H., & Wang, S. (2016). Effect of a CGMS and SMBG on maternal and neonatal outcomes in gestational diabetes mellitus: A randomized controlled trial. *Scientific Reports, 6*, 19920. doi: 10.1038/srep19920

Weinzimer, S., Miller, K., Beck, R., Xing, D., Fiallo-Scharer, R., Gilliam, L. K., . . . Tsalikian, E. (2010). Effectiveness of continuous glucose monitoring in a clinical care environment: Evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial. *Diabetes Care, 33*(1), 17-22. doi: 10.2337/dc09-1502

Wojciechowski, P., Rys, P., Lipowska, A., Gaweska, M., & Malecki, M. T. (2011). Efficacy and safety comparison of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes: Systematic review and meta-analysis. *Polish Archives of Internal Medicine, 121*(10), 333-343.

Yeh, H. C., Brown, T. T., Maruthur, N., Ranasinghe, P., Berger, Z., Suh, Y. D., . . . Golden, S. H. (2012). Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: A systematic review and meta-analysis. *Annals of Internal Medicine, 157*(5), 336-347. doi: 10.7326/0003-4819-157-5-201209040-00508

Yeoh, E., Choudhary, P., Nwokolo, M., Ayis, S., & Amiel, S. A. (2015). Interventions that restore awareness of hypoglycemia in adults with type 1 diabetes: A systematic review and meta-analysis. *Diabetes Care, 38*(8), 1592-1609. doi: 10.2337/dc15-0102

Yu, F., Lv, L., Liang, Z., Wang, Y., Wen, J., Lin, X., . . . Niu, J. (2014). Continuous glucose monitoring effects on maternal glycemic control and pregnancy outcomes in patients with gestational diabetes mellitus: A prospective cohort study. *The Journal of Clinical Endocrinology and Metabolism, 99*(12), 4674-4682. doi: 10.1210/jc.2013-4332

Appendix C. Primary Studies Included in Systematic Reviews

There is significant overlap in the individual studies included by the reviewed systematic reviews, with over half of the primary studies being included by one or more of the systematic reviews. Table C1 provides a comparison of primary studies across included systematic reviews. Studies that were included by more than one systematic review are highlighted. A full reference list of the primary studies follows Table C1.

Table C1. Comparison of Primary Studies Included in Systematic Reviews

Primary Study Citation	Systematic Reviews							
	Langendam (2012)	Moy (2014)	NICE (2015a)	NICE (2015b)	NICE (2015c)	NICE (2015d)	Poolsup (2013)	Skelly (2011)
Allen, Fain, Braun, and Chipkin (2008)	---	---	---	---	---	---	√	---
Battelino et al. (2011)	√	---	√	---	---	---	---	---
Battelino et al. (2012)	---	---	---	---	√	---	√	---
Bergenstal et al. (2010)	√	---	√	---	---	---	√	√
Cemeroglu et al. (2010)	---	---	---	---	---	---	---	√
Chase et al. (2010)	---	---	---	---	---	---	---	√
Cooke et al. (2009)	√	---	√	---	---	---	---	---
Cosson et al. (2009)	√	---	√	---	---	---	√	---
Deiss et al. (2006)	√	---	√	---	---	---	---	---
Buckingham et al. (2007)	---	---	---	---	---	---	---	√
Ehrhardt, Chellappa, Walker, Fonda, and Vigersky (2011)	---	---	---	---	---	---	√	---
Garg et al. (2006)	---	---	---	---	√	---	---	---
Hermanides et al. (2011)	√	---	√	---	---	---	---	---

Primary Study Citation	Systematic Reviews							
	Langendam (2012)	Moy (2014)	NICE (2015a)	NICE (2015b)	NICE (2015c)	NICE (2015d)	Poolsup (2013)	Skelly (2011)
Hermanns et al. (2009)	√	---	√	---	---	---	---	---
Hirsch et al. (2008)	√	---	√	---	---	---	---	√
Tamborlane et al. (2008)	√	---	√	√	---	---	√	√
Beck et al. (2009a)	---	---	---	---	---	---	---	√
Beck et al. (2009b)	√	---	√	---	---	---	---	√
Beck et al. (2010)	√	---	√	---	√	---	---	√
Weinzimer et al. (2010)	---	---	---	---	---	---	---	√
Kerssen, de Valk, and Visser (2006)	---	---	---	√	---	---	---	---
Kestila, Ekblad, and Ronnemaa (2007)	---	---	---	√	---	---	---	---
Kordonouri et al. (2010)	√	---	√	---	---	---	√	---
Little et al. (2014)	---	---	---	---	√	---	---	---
Logtenberg, Kleefstra, Groenier, Gans, and Bilo (2009)	√	---	√	---	---	---	---	---
Mauras et al. (2012)	---	---	√	---	---	---	√	---
Messer et al. (2009)	---	---	---	---	---	---	---	√
Murphy et al. (2008)	---	√	---	√	---	---	---	---
O'Connell et al. (2009)	√	---	√	---	---	---	---	---
Peyrot and Rubin (2009)	√	---	√	---	---	---	---	---

Primary Study Citation	Systematic Reviews							
	Langendam (2012)	Moy (2014)	NICE (2015a)	NICE (2015b)	NICE (2015c)	NICE (2015d)	Poolsup (2013)	Skelly (2011)
Pickup et al. (2011)	---	---	---	---	√	---	---	---
Raccah et al. (2009)	√	---	√	---	√	---	---	---
Radermecker et al. (2010)	---	---	---	---	√	---	---	---
Secher, Ringholm, Andersen, Damm, and Mathiesen (2013)	---	√	---	√	---	---	---	---
Sequeira et al. (2013)	---	---	---	---	√	---	---	---
Vigersky et al. (2012)	---	---	---	---	---	√	---	---
Yogev et al. (2003)	---	---	---	√	---	---	---	---
Yoo et al. (2008)	---	---	---	---	---	√	√	---

Abbreviations: DRCN: Diabetes Research in Children Network; JDRF: Juvenile Diabetes Research Foundation
Notes: √ Study is included in systematic review; --- Study not included in systematic review's analysis of the effectiveness of rt-CGM compared to SMBG

Primary Studies References

Allen, N. A., Fain, J. A., Braun, B., & Chipkin, S. R. (2008). Continuous glucose monitoring counseling improves physical activity behaviors of individuals with type 2 diabetes: A randomized clinical trial. *Diabetes Research and Clinical Practice, 80*(3), 371-379. doi: 10.1016/j.diabres.2008.01.006

Battelino, T., Conget, I., Olsen, B., Schutz-Fuhrmann, I., Hommel, E., Hoogma, R., . . . Bolinder, J. (2012). The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: A randomised controlled trial. *Diabetologia, 55*(12), 3155-3162. doi: 10.1007/s00125-012-2708-9

Battelino, T., Phillip, M., Bratina, N., Nimri, R., Oskarsson, P., & Bolinder, J. (2011). Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. *Diabetes Care, 34*(4), 795-800. doi: 10.2337/dc10-1989

Beck, R. W., Buckingham, B., Miller, K., Wolpert, H., Xing, D., Block, J. M., . . . Tamborlane, W. V. (2009). Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes. *Diabetes Care, 32*(11), 1947-1953. doi: 10.2337/dc09-0889

Beck, R. W., Hirsch, I. B., Laffel, L., Tamborlane, W. V., Bode, B. W., Buckingham, B., . . . Xing, D. (2009). The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care, 32*(8), 1378-1383. doi: 10.2337/dc09-0108

Beck, R. W., Lawrence, J. M., Laffel, L., Wysocki, T., Xing, D., Huang, E. S., . . . Tamborlane, W. V. (2010). Quality-of-life measures in children and adults with type 1 diabetes: Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. *Diabetes Care, 33*(10), 2175-2177. doi: 10.2337/dc10-0331

Bergenstal, R. M., Tamborlane, W. V., Ahmann, A., Buse, J. B., Dailey, G., Davis, S. N., . . . Wood, M. A. (2010). Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *The New England Journal of Medicine, 363*(4), 311-320. doi: 10.1056/NEJMoa1002853

Buckingham, B., Beck, R. W., Tamborlane, W. V., Xing, D., Kollman, C., Fiallo-Scharer, R., . . . Wysocki, T. (2007). Continuous glucose monitoring in children with type 1 diabetes. *The Journal of Pediatrics, 151*(4), 388-393, 393.e381-382. doi: 10.1016/j.jpeds.2007.03.047

Cemeroglu, A. P., Stone, R., Kleis, L., Racine, M. S., Postellon, D. C., & Wood, M. A. (2010). Use of a real-time continuous glucose monitoring system in children and young adults on insulin pump therapy: Patients' and caregivers' perception of benefit. *Pediatric Diabetes, 11*(3), 182-187. doi: 10.1111/j.1399-5448.2009.00549.x

Chase, H. P., Beck, R. W., Xing, D., Tamborlane, W. V., Coffey, J., Fox, L. A., . . . Ruedy, K. J. (2010). Continuous glucose monitoring in youth with type 1 diabetes: 12-month

follow-up of the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. *Diabetes Technology & Therapeutics, 12*(7), 507-515. doi: 10.1089/dia.2010.0021

Cooke, D., Hurel, S. J., Casbard, A., Steed, L., Walker, S., Meredith, S., . . . Newman, S. P. (2009). Randomized controlled trial to assess the impact of continuous glucose monitoring on HbA(1c) in insulin-treated diabetes (MITRE Study). *Diabetic Medicine: A Journal of the British Diabetic Association, 26*(5), 540-547. doi: 10.1111/j.1464-5491.2009.02723.x

Cosson, E., Hamo-Tchatchouang, E., Dufaitre-Patouraux, L., Attali, J. R., Paries, J., & Schaepelynck-Belicar, P. (2009). Multicentre, randomised, controlled study of the impact of continuous sub-cutaneous glucose monitoring (GlucoDay) on glycaemic control in type 1 and type 2 diabetes patients. *Diabetes & Metabolism, 35*(4), 312-318. doi: 10.1016/j.diabet.2009.02.006

Deiss, D., Bolinder, J., Riveline, J. P., Battelino, T., Bosi, E., Tubiana-Rufi, N., . . . Phillip, M. (2006). Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care, 29*(12), 2730-2732. doi: 10.2337/dc06-1134

Ehrhardt, N. M., Chellappa, M., Walker, M. S., Fonda, S. J., & Vigersky, R. A. (2011). The effect of real-time continuous glucose monitoring on glycemic control in patients with type 2 diabetes mellitus. *Journal of Diabetes Science and Technology, 5*(3), 668-675. doi: 10.1177/193229681100500320

Garg, S., Zisser, H., Schwartz, S., Bailey, T., Kaplan, R., Ellis, S., & Jovanovic, L. (2006). Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: A randomized controlled trial. *Diabetes Care, 29*(1), 44-50.

Hermanides, J., Norgaard, K., Bruttomesso, D., Mathieu, C., Frid, A., Dayan, C. M., . . . DeVries, J. H. (2011). Sensor-augmented pump therapy lowers HbA(1c) in suboptimally controlled type 1 diabetes: A randomized controlled trial. *Diabetic Medicine: A Journal of the British Diabetic Association, 28*(10), 1158-1167. doi: 10.1111/j.1464-5491.2011.03256.x

Hermanns, N., Kulzer, B., Gulde, C., Eberle, H., Pradler, E., Patzelt-Bath, A., & Haak, T. (2009). Short-term effects on patient satisfaction of continuous glucose monitoring with the GlucoDay with real-time and retrospective access to glucose values: A crossover study. *Diabetes Technology & Therapeutics, 11*(5), 275-281. doi: 10.1089/dia.2008.0078

Hirsch, I. B., Abelseth, J., Bode, B. W., Fischer, J. S., Kaufman, F. R., Mastrototaro, J., . . . Buckingham, B. A. (2008). Sensor-augmented insulin pump therapy: Results of the

first randomized treat-to-target study. *Diabetes Technology & Therapeutics, 10*(5), 377-383. doi: 10.1089/dia.2008.0068

Kerssen, A., de Valk, H. W., & Visser, G. H. (2006). Do HbA1c levels and the self-monitoring of blood glucose levels adequately reflect glycaemic control during pregnancy in women with type 1 diabetes mellitus? *Diabetologia, 49*(1), 25-28. doi: 10.1007/s00125-005-0057-7

Kestila, K. K., Ekblad, U. U., & Ronnemaa, T. (2007). Continuous glucose monitoring versus self-monitoring of blood glucose in the treatment of gestational diabetes mellitus. *Diabetes Research and Clinical Practice, 77*(2), 174-179. doi: 10.1016/j.diabres.2006.12.012

Kordonouri, O., Pankowska, E., Rami, B., Kapellen, T., Coutant, R., Hartmann, R., . . . Danne, T. (2010). Sensor-augmented pump therapy from the diagnosis of childhood type 1 diabetes: Results of the Paediatric Onset Study (ONSET) after 12 months of treatment. *Diabetologia, 53*(12), 2487-2495. doi: 10.1007/s00125-010-1878-6

Little, S. A., Leelarathna, L., Walkinshaw, E., Tan, H. K., Chapple, O., Lubina-Solomon, A., . . . Shaw, J. A. (2014). 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, 37*(8), 2114-2122. doi: 10.2337/dc14-0030

Logtenberg, S. J., Kleefstra, N., Groenier, K. H., Gans, R. O., & Bilo, H. J. (2009). Use of short-term real-time continuous glucose monitoring in type 1 diabetes patients on continuous intraperitoneal insulin infusion: A feasibility study. *Diabetes Technology & Therapeutics, 11*(5), 293-299. doi: 10.1089/dia.2008.0088

Mauras, N., Beck, R., Xing, D., Ruedy, K., Buckingham, B., Tansey, M., . . . Kollman, C. (2012). A randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to <10 years. *Diabetes Care, 35*(2), 204-210. doi: 10.2337/dc11-1746

Messer, L., Ruedy, K., Xing, D., Coffey, J., Englert, K., Caswell, K., & Ives, B. (2009). Educating families on real time continuous glucose monitoring: The DirecNet navigator pilot study experience. *The Diabetes Educator, 35*(1), 124-135. doi: 10.1177/0145721708325157

Murphy, H. R., Rayman, G., Lewis, K., Kelly, S., Johal, B., Duffield, K., . . . Temple, R. C. (2008). Effectiveness of continuous glucose monitoring in pregnant women with

diabetes: Randomised clinical trial. *British Medical Journal (Clinical Research Edition), 337*, a1680. doi: 10.1136/bmj.a1680

O'Connell, M. A., Donath, S., O'Neal, D. N., Colman, P. G., Ambler, G. R., Jones, T. W., . . . Cameron, F. J. (2009). Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: A randomised controlled trial. *Diabetologia, 52*(7), 1250-1257. doi: 10.1007/s00125-009-1365-0

Peyrot, M., & Rubin, R. R. (2009). Patient-reported outcomes for an integrated real-time continuous glucose monitoring/insulin pump system. *Diabetes Technology & Therapeutics, 11*(1), 57-62. doi: 10.1089/dia.2008.0002

Pickup, J. C., Freeman, S. C., & Sutton, A. J. (2011). Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: Meta-analysis of randomised controlled trials using individual patient data. *British Medical Journal (Clinical Research Edition), 343*, d3805. doi: 10.1136/bmj.d3805

Raccah, D., Sulmont, V., Reznik, Y., Guerci, B., Renard, E., Hanaire, H., . . . Nicolino, M. (2009). Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: The RealTrend study. *Diabetes Care, 32*(12), 2245-2250. doi: 10.2337/dc09-0750

Radermecker, R. P., Saint Remy, A., Scheen, A. J., Bringer, J., & Renard, E. (2010). Continuous glucose monitoring reduces both hypoglycaemia and HbA1c in hypoglycaemia-prone type 1 diabetic patients treated with a portable pump. *Diabetes & Metabolism, 36*(5), 409-413. doi: 10.1016/j.diabet.2010.08.001

Secher, A. L., Ringholm, L., Andersen, H. U., Damm, P., & Mathiesen, E. R. (2013). The effect of real-time continuous glucose monitoring in pregnant women with diabetes: A randomized controlled trial. *Diabetes Care, 36*(7), 1877-1883. doi: 10.2337/dc12-2360

Sequeira, P. A., Montoya, L., Ruelas, V., Xing, D., Chen, V., Beck, R., & Peters, A. L. (2013). Continuous glucose monitoring pilot in low-income type 1 diabetes patients. *Diabetes Technology & Therapeutics, 15*(10), 855-858. doi: 10.1089/dia.2013.0072

Tamborlane, W. V., Beck, R. W., Bode, B. W., Buckingham, B., Chase, H. P., Clemons, R., . . . Xing, D. (2008). Continuous glucose monitoring and intensive treatment of type 1 diabetes. *The New England Journal of Medicine, 359*(14), 1464-1476. doi: 10.1056/NEJMoa0805017

Vigersky, R. A., Fonda, S. J., Chellappa, M., Walker, M. S., & Ehrhardt, N. M. (2012). Short- and long-term effects of real-time continuous glucose monitoring in patients with type 2 diabetes. *Diabetes Care, 35*(1), 32-38. doi: 10.2337/dc11-1438

Weinzimer, S., Miller, K., Beck, R., Xing, D., Fiallo-Scharer, R., Gilliam, L. K., . . . Tsalikian, E. (2010). Effectiveness of continuous glucose monitoring in a clinical care environment: Evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial. *Diabetes Care, 33*(1), 17-22. doi: 10.2337/dc09-1502

Yogev, Y., Chen, R., Ben-Haroush, A., Phillip, M., Jovanovic, L., & Hod, M. (2003). Continuous glucose monitoring for the evaluation of gravid women with type 1 diabetes mellitus. *Obstetrics and Gynecology, 101*(4), 633-638.

Yoo, H. J., An, H. G., Park, S. Y., Ryu, O. H., Kim, H. Y., Seo, J. A., . . . Baik, S. H. (2008). Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. *Diabetes Research and Clinical Practice, 82*(1), 73-79. doi: 10.1016/j.diabres.2008.06.015

Appendix D: Ongoing or Completed Clinical Trials Registered in Clinicaltrials.gov

The following ongoing or completed but unreported clinical trials are registered in the clinicaltrials.gov database as of April 13, 2017. The PICO and inclusion criteria used for this database is the same as for other databases, with the additional exclusion of trials with published results (would appear in MEDLINE (OVID) Center search) and studies regarding closed loop/"bionic pancreas" devices (not FDA approved).

Search terms used: 1) "continuous glucose monitor"; condition: diabetes. Search **returned 243 results**. Relevant trial listings are in the table below. All are listed as being concluded, but none have associated study results.

Table D1. Clinical Trials

Trial Number	Trial Information
NCT01586065	https://clinicaltrials.gov/ct2/show/NCT01586065?term=continuous+glucose+monitor&cond=diabetes&rank=14 Continuous Glucose Monitoring in Adolescents With Poorly Controlled Type 1 Diabetes Note: This study was concluded in June 2014, but there are no study results or related publications in the trial record.
NCT00529815	https://clinicaltrials.gov/ct2/show/NCT00529815?term=continuous+glucose+monitor&cond=diabetes&rank=33 Continuous Glucose Monitoring in Patients With Type 2 Diabetes (CGM) Note: This study was scheduled to be concluded in September 2010, but there are no study results or related publications in the trial record.
NCT00843609	https://clinicaltrials.gov/ct2/show/study?term=continuous+glucose+monitor&cond=diabetes&rank=50 International Navigator Hypoglycaemia Study Note: This study was concluded in September 2010, but there are no study results or related publications in the trial record.
NCT01578460	https://clinicaltrials.gov/ct2/show/study?term=continuous+glucose+monitor&cond=diabetes&rank=59 Healthy Moms, Healthy Babies (HMHB): A Strategy to Improve the Care and Outcome of Diabetes in Pregnancy in On-Reserve First Nations Women Note: This study was concluded in August 2014, but there are no study results or related publications in the trial record.

Trial Number	Trial Information
NCT00875290	https://clinicaltrials.gov/ct2/show/study?term=continuous+glucose+monitor&cond=diabetes&rank=105 The Effectiveness of Continuous Glucose Monitoring in Diabetes Treatment for Infants and Young Children (Gerber RTSA) Note: This study was estimated to be concluded in November 2014, but there are no study results or related publications in the trial record.
NCT00949221	https://clinicaltrials.gov/ct2/show/study?term=continuous+glucose+monitor&cond=diabetes&rank=133 Study of Insulin Therapy Augmented by Real Time Sensor IN Type 1 Children and Adolescents (START-IN!) (START-IN) Note: This study was estimated to be concluded in July 2012, but there are no study results or related publications in the trial record.
NCT03020069	https://clinicaltrials.gov/ct2/show/study?term=continuous+glucose+monitor&cond=diabetes&rank=137 Use of Continuous Glucose Monitoring System With Intensive Feedback in Adolescents With Poorly Controlled Type 1 Diabetes (NYU School of Medicine. Enrolling participants by invitation only.)

About the Center for Evidence-based Policy

The Center for Evidence-based Policy (Center) is recognized as a national leader in evidence-based decision making and policy design. The Center understands the needs of policymakers and supports public organizations by providing reliable information to guide decisions, maximize existing resources, improve health outcomes, and reduce unnecessary costs. The Center specializes in ensuring diverse and relevant perspectives are considered, and appropriate resources are leveraged to strategically address complex policy issues with high-quality evidence and collaboration. The Center is based at Oregon Health & Science University in Portland, Oregon. Further information about the Center is available at http://centerforevidencebasedpolicy.org/.

Suggested citation: Ray, M., Thielke, A., King, V., & Harrod, C. (2017). *Dossier review: Real-time continuous glucose monitors.* Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University.

Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

Funding/Support: This research was funded by the Center for Evidence-based Policy's Medicaid Evidence-based Decisions project at Oregon Health & Science University.