"MBG" Members Only: Effective July 1, 2017:
For Codes A9276, A9277, A9278, K0553 and K0554
Refer to LCD 33822 and Article 52464

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Continuous or Intermittent Monitoring of Glucose in the Interstitial Fluid

Policy #: 038
Category: DME

Latest Review Date: August 2019
Policy Grade: B

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Tight glucose control in patients with diabetes has been associated with improved outcomes. Several devices are available to measure glucose levels automatically and frequently (e.g., every 5-10 minutes). The devices measure glucose in the interstitial fluid and are approved as adjuncts to traditional self-monitoring of blood glucose levels. Devices can be used on an intermittent (short-term) basis or a continuous (long-term) basis.

Hypoglycemia affects many aspects of cognitive function, including attention, memory, and psychomotor and spatial ability. Severe hypoglycemia can cause serious morbidity affecting the central nervous system (e.g., coma, seizure, transient ischemic attack, stroke), heart (e.g., cardiac arrhythmia, myocardial ischemia, infarction), eye (e.g., vitreous hemorrhage, worsening of retinopathy), as well as cause hypothermia and accidents that may lead to injury. Fear of hypoglycemia symptoms can also cause decreased motivation to adhere strictly to intensive insulin treatment regimens.

Blood Glucose Control

The advent of blood glucose monitors for use by patients in the home revolutionized the management of diabetes. Using fingersticks, patients could monitor their blood glucose level both to determine the adequacy of hyperglycemia control and to evaluate hypoglycemic episodes. Randomized controlled trials of tight control have demonstrated benefits for type 1 diabetics in decreasing microvascular complications. The impact of tight control on type 1 diabetic patients and on macrovascular complications such as stroke or myocardial infarction is less certain. The Diabetes Control and Complications Trial (2002) demonstrated that a relative HbA1c level reduction of 10% is clinically meaningful and corresponds to approximately a 40% decrease in risk for progression of diabetic retinopathy and 25% decrease in risk for progression of renal disease.

Due to an increase in turnover of red blood cells during pregnancy, HbA1c is slightly lower in women with a normal pregnancy compared with nonpregnant women. The target A1C in women with diabetes is also lower in pregnancy. The American Diabetes Association recommends that, if achievable without significant hypoglycemia, the A1c should range between 6.0 to 6.5%; an A1c less than 6% may be optimal as the pregnancy progresses.

Tight glucose control requires multiple daily measurements of blood glucose each day (i.e., before meals and at bedtime), a commitment that some patients may be unwilling or unable to meet. In addition, the goal of tight glucose control has to be balanced with an associated risk of hypoglycemia. Hypoglycemia is known to be a risk in patients with type 1 diabetes. Studies have also found that approximately 50% of patients with type 2 diabetes may experience hypoglycemic episodes, but the severity of these episodes may vary. An additional limitation of periodic self-measurements of blood glucose is that glucose values are seen in isolation, and trends in glucose levels are undetected. For example, while a diabetic's fasting blood glucose level might be within normal values, hyperglycemia might be undetected postprandially, leading to elevated hemoglobin A1C values.

Management

Recently, measurements of glucose in interstitial fluid have been developed as a technique of automatically measuring glucose values throughout the day, producing data that show the trends in glucose measurements, in contrast to the isolated glucose measurements of the traditional blood glucose measurements. Although devices measure glucose in interstitial fluid on a periodic rather than a continuous basis, this type of monitoring is referred to as continuous glucose monitoring (CGM).

Currently, CGM devices are of two designs; real-time CGM (rtCGM) provide real-time data on glucose level, glucose trends, direction, and rate of change and, intermittently viewed (iCGM) devices that show continuous glucose measurements retrospectively. These devices are also known as flash-glucose monitors (FGM).

Approved devices now include devices indicated for pediatric use and those with more advanced software, more frequent measurements of glucose levels, more sophisticated alarm systems, etc. Devices initially measured interstitial glucose every 5 to 10 minutes and stored data for download and retrospective evaluation by a clinician. With currently available devices, the time intervals at which interstitial glucose is measured ranges from every 1 to 2 minutes to 5 minutes and most provide measurements in real-time directly to patients. While continuous glucose monitors potentially eliminate or decrease the number of required daily fingersticks, it should be noted that, according to the FDA labeling, some marketed monitors are not intended to be an alternative to traditional self-monitoring of blood glucose levels but rather provide adjunct monitoring, supplying additional information on glucose trends that are not available from self-monitoring. In addition, it is important to note that devices may be used intermittently, e.g., time periods of 72 hours, or continuously, i.e., on a long-term basis.

For coverage information regarding Medtronic's MiniMed 530G/630G and 670G, refer to medical policy #636 Artificial Pancreas Device Systems.

Policy:

Effective for dates of service on or after September 26, 2013:

Intermittent Monitoring

Blue Advantage will treat **intermittent monitoring, i.e., 72 hours, of glucose levels in interstitial fluid** as a **covered benefit** in patients with **Type 1 diabetes mellitus whose diabetes is documented in the medical records as *poorly controlled despite current use of **best practices.**

*Poorly controlled Type 1 diabetes mellitus includes the following clinical situations:

- Unexplained hypoglycemic episodes;
- Hypoglycemic unawareness;
- Suspected postprandial hyperglycemia;
- Recurrent diabetic ketoacidosis.

Blue Advantage will treat **intermittent monitoring of glucose levels in interstitial** as a **covered benefit** in patients with Type 1 diabetes **prior to insulin pump initiation to determine basal insulin levels.**

Intermittent monitoring is generally conducted in 72-hour periods. It may be repeated at a subsequent time depending on the patient's level of diabetes control.

Continuous Monitoring
Blue Advantage will treat **continuous, i.e., long-term, monitoring of glucose levels in interstitial fluid, including real-time monitoring, as a technique of diabetic monitoring,** as a **covered benefit** when the following situations are **documented in the medical records** and occur despite use of **best practices:

- Patients with Type I diabetes who have recurrent, unexplained, severe (generally blood glucose levels less than 50 mg/dL) hypoglycemia or impaired awareness for whom hypoglycemia puts the patient or others at risk; or
- Patients with Type I diabetes who are pregnant.

** Best practices in diabetes control for patients with diabetes mellitus include:

- Compliance with a regimen of four **(4)** or more fingersticks each day; or
- Use of insulin pump; or
- Prior use of intermittent (72-hour) glucose.

Blue Advantage will treat **replacement or upgrade of existing, properly functioning equipment, even if warranty has expired,** as a **non-covered benefit**.

Blue Advantage will treat the **glucose sensor and transmitter components** of a continuous glucose monitor used with a combined continuous subcutaneous insulin infusion and blood glucose monitoring devices as a **covered benefit** for coverage when all the above criteria met.

Blue Advantage will treat **other uses of continuous monitoring of glucose levels in interstitial fluid as a technique of diabetic monitoring** as a **non-covered benefit** and as **investigational**.

The **Eversense Continuous Glucose Monitoring System** is considered a **non-covered benefit** and as **investigational**.

Coverage for non-medical items, even when the items may be used to serve a medical purpose, such as smart devices (smart phones, tablets, personal computers, etc.) are non-covered. This includes smart devices used in conjunction with Continuous Glucose Monitors.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most

appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature search was performed through June 20, 2019. Following is a summary of the key literature to date:

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

The evidence review focuses on the clinical utility of continuous glucose monitoring (CGM) systems. That is, their ability to provide either additional information on glucose levels, leading to improved glucose control or to improve the morbidity/mortality associated with clinically significant severe and acute hypoglycemic or hyperglycemic events. Because diabetic control encompasses numerous variables including the diabetic regimen and patient self-management, randomized controlled trials (RCTs) are important to isolate the contribution of interstitial glucose measurements to the overall diabetic management. Data on patients with Type I diabetes and Type II diabetes are discussed separately.

For the evaluation of the clinical utility of continuous glucose monitoring (CGM), studies would need to use the test as either an adjunct or a replacement to current disease status measures to manage treatment decisions in patients with diabetes. Outcomes would include measures of glucose control, quality of life and measures of disease progression.

CGM Devices for Long Term Use in Type I Diabetes

Clinical Context and Therapy Purpose

The purpose of long-term CGM glucose monitoring devices is to provide a testing option that is an alternative to or an improvement on existing testing used in the management of individuals with type 1 diabetes.

The question addressed in this evidence review is: Does long-term use of a CGM device improve the net health outcome for individuals with type 1 diabetes?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with type 1 diabetes. All individuals with type 1 diabetes require engagement in a comprehensive self-management and clinical assessment program that includes assessment of blood glucose control.

Interventions
The testing being considered is the use of a CGM device to assess blood glucose levels as part of optimal diabetes management.

Comparators
The following practice is currently being used to measure glucose levels: capillary blood sampling (finger stick) for self-monitoring of blood glucose (SMBG). Standard treatment for patients with type 1 diabetes includes injection of long-acting basal insulin plus multiple daily injections (MDI) of rapid-acting insulin boluses as required for meal intake. Activity level may require patients need to modify the timing and dose of insulin administration. Individuals with type 1 diabetes may also use an insulin pump either for initial treatment or convert to pump use after a period of MDI. Individuals are required to check their blood glucose before making preprandial insulin calculations, in response to symptoms of hypoglycemia or related to activity-related insulin adjustments.

Outcomes
The general outcomes of interest are change in hemoglobin A1c (HbA1c) levels, time spent in hypoglycemia, the incidence of hypoglycemic events, complications of hypoglycemia, and QOL. To assess short-term outcomes such as HbA1c levels, a minimum follow-up of 8 to 12 weeks is appropriate. Additional intermediate outcomes include time spent in hypoglycemia and hyperglycemia and, the incidence of hypoglycemic events especially nocturnal hypoglycemia. Longer-term include complications of hypoglycemia and hyperglycemia and QOL generally require at least six months to one year of follow-up.

CGM devices and self-glucose monitor devices may be used in the home, outpatient, or inpatient setting and patients are monitored by endocrinologists, diabetologists, internists and primary care physicians and clinicians.

Study Selection
Methodologically credible studies were selected using the following principles:

a) To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b) In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

c) To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

d) Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

A number of systematic reviews and meta-analyses of RCTs evaluating CGM for long-term, daily use in treating type 1 diabetes have been published. These systematic reviews have focused on slightly different populations, and some did not separate long-term CGM from intermittent glucose monitoring. The most recent meta-analysis, which was also the only analysis that used individual patient data, was published by Benkhadra et al in 2017. The meta-analysis evaluated data from 11 RCTs that enrolled patients with type 1 diabetes and compared real-time CGM to a control intervention. Studies in which patients used insulin pumps or received multiple daily insulin injections were included. Reviewers contacted corresponding study authors requesting individual patient data; data were not obtained for 1 trial. Mean baseline hemoglobin A1C (HbA1c) levels were 8.2% in adults and 8.3% in children and adolescents. The overall risk of bias in the studies was judged to be moderate. In pooled analyses, there was a statistically significantly greater decrease in HbA1c levels with real-time CGM versus control conditions. Overall, the degree of difference between groups was 0.26%. In subgroup analyses by age, there was significantly greater change in HbA1c levels among individuals 15 years and older, but not in the younger age groups. There were no significant differences between groups in the time spent in hypoglycemia or in the incidence of hypoglycemic events. Key findings are shown in Table 2.

Table 2. Main Findings from a 2017 Individual Patient Data Meta-Analysis on Real-Time CGM in Type 1 Diabetes

No of Trials	N	Outcomes	Point Value	95% Confidence Interval	p
Change in HbA1C levels, %					
8	1371	Overall	-0.258	0.464 to -0.052	0.014
7	902	Age > 15 y	-0.356	0.551 to -0.160	<0.001
7	178	Age 13-15 y	-0.039	-0.320 to 0.242	0.787
7	291	Age ≤ 12 y	-0.047	0.217 to 0.124	0.592
Time Spent in Hypoglycemia <60mg/dl, min					
4	706	Overall	-8.549	-31.083 to 13.985	0.457
4	467	Age > 15 y	-8.095	-32.615 to 16.425	0.518
3	109	Age 13-15	-13.966	31.782 to 3.852	0.124
3	130	Age ≤12 y	-9.366	19.898-1.167	0.081
Incidence of Hypoglycemic events <70mg/dl, mean no. events					
3	351	Overall	0.051	-0.314 to 0.416	0.785
3	277	Age >15 y	-0.074	-0.517-0.368	0.742
2	47	Age 13-15 y	0.536	0.243 to 1.316	0.177
2	27	Age ≤ 12 y	0.392	0.070 to 0.854	0.097

CGM: continuous glucose monitoring: HbA1C, hemoglobin A1C
Adapted from Benkhadra et al (2017)

Earlier meta-analyses of glucose monitoring devices for type 1 diabetes tended to combine studies of intermittent glucose monitoring with studies of long-term CGM. Several reported separate subgroup analyses for long-term CGM. A 2012 Cochrane review of CGM in type 1 diabetes in adults and children included RCTs comparing CGM with conventional self-monitored blood glucose (SMBG). In pooled analysis (6 studies; n=963 patients) of studies of long-term CGM, the average decline in HbA1c levels 6 months after baseline was statistically significantly larger for CGM users than for SMBG users (mean difference [MD] change, -0.2%; 95% confidence interval [CI], -0.4% to -0.1%), but there was no difference in decline in HbA1c levels at 12 months (1 study, n=154 patients; MD change, 0.1; 95% CI, -0.5 to 0.7). In a meta-analysis of 4 RCTs (n=689 patients), there was no significant difference in the risk of severe hypoglycemia between CGM and SMBG users and the confidence interval for the relative risk (RR) was wide (RR=1.05; 95% CI, 0.63 to 1.77), indicating lack of precision in estimating the effect of CGM on hypoglycemia risk. Reviewers were unable to compare longer term change in HbA1c levels or hypoglycemia outcomes for real-time CGM. Trials reporting results by compliance subgroups found larger treatment effects in highly compliant patients.

A 2011 systemic review of RCTs on CGM included trials conducted in adults and children with Type I diabetes who were on an intensive insulin regimen (studies of Type II diabetes were not included). This meta-analysis required a minimum of 12 weeks of follow-up in the studies (as compared to at least 8 weeks in the Gandhi meta-analysis). Studies compared CGM to SMBG; there was no restriction related to type of CGM device, but the CGM readings had to be used to adjust insulin dose or modify diet. A total of 14 RCTs met eligibility criteria. Study duration ranged from 3 to 6 months. The baseline mean HbA1c ranged from 6.4 to 10. Five of the included studies found a statistically significant decrease in HbA1c in favor of CGM while 9 did not. In a pooled analysis, there was a statistically significant reduction in HbA1c with CGM compared to SMBG, WMD: -0.26%, 95% CI: -0.34 to -0.19%. For the subgroup of 7 studies that reported on continuous long term monitoring, this difference was statistically significant (WMD = -0.26; 95% CI, -0.34, -0.18). In a sub-group analysis by age, there were significant reductions in HbA1c with CGM in studies of adults (n=5), WMD: -0.33 (95% CI: -0.46 to -0.20) and in studies with children and/or adolescents (n=8), WMD: -0.25, 95% CI: -0.43 to -0.08. Four of the studies provided data on the frequency of hypoglycemic episodes. Pooled results showed a significant reduction in hypoglycemic events in CGM versus SMBG (SMD=–0.32; 95% CI,–0.52 to –0.13). Five of the studies reported the percentage of patients with severe hypoglycemic episodes and there were no differences in the percentage of patients with severe hypoglycemic episodes for CGM versus SMBG in any of the 5 studies.

Randomized Controlled Trials

Recent RCTs not included in the meta-analyses are described next.

Van Beers et al (2016) published a crossover RCT comparing CGM with SMBG and focusing on patients with impaired hypoglycemia awareness. Eligible patients were 18 to 75 years old, were treated with insulin infusion pumps or multiple daily insulin injections, undertook at least 3 SMBG measurements per day, and had impaired awareness of hypoglycemia (i.e., Gold score ≥413). The trial used an artificial pancreas device system without using the low glucose suspend feature. After a 6-week run-in phase (during which patients received education about diabetes management), 52 patients received both 16 weeks of CGM and 16 weeks of SMBG, in random

order. There was a 12-week washout period between interventions. All patients were included in the primary intention-to-treat analysis. Six patients withdrew from the study early.

The primary outcome, time spent in normoglycemia (4-10 mmol/L), was significantly higher in the CGM phase than in the SMBG phase. The percentage of time spend in normoglycemia was 65.0% in the CGM phase and 55.4% in the SMBG group (mean difference, 9.6%; p<0.001). The sequence allocation did not have an effect on the primary end point. Most other CGM-derived outcomes (e.g., number and duration of nocturnal hypoglycemia events) also significantly favored the CGM group. The total number of severe hypoglycemic events (i.e., those needing third-party assistance) was 14 in the CGM phase and 34 in the SMBG phase, which differed significantly between groups (p=0.033). The number of patients with 1 or more severe hypoglycemic event during the intervention period, however, did not differ significantly between phases 10 in the CGM phase and 18 in the SMBG phase (p=0.062). HbA1c outcomes did not differ significantly; e.g., change in HbA1c levels from baseline was -0.1% in both phases (p=0.449). In terms of hypoglycemia awareness, one of 4 variables, Gold score at the study end point differed significantly (mean, 4.6 for the CGM phase vs 5.0 for the SMBG phase, p=0.035.); 3 other variables related to hypoglycemia awareness did not differ between groups.

Two 2017 RCTs evaluated long-term CGM in patients with type 1 diabetes treated with multiple daily insulin injections. Both trials used the Dexcom G4 CGM device. Lind et al (2017) reported on a crossover study with 142 adults ages 18 and older who had baseline HbA1c levels of 7.5% or higher (mean baseline HbA1c level, approximately 8.5%). There was a 6-week run-in period using a CGM device with masked data and patients were excluded from further participation if they did not believe they would use the device more than 80% of the time or did not perform an adequate number of calibrations during the run-in period. Enrolled patients underwent 26-week treatment periods with a CGM device and conventional therapy using SMBG, in random order. There was a 17-week washout period between intervention phases. The primary end point was the difference in HbA1c levels at the end of each treatment period. Mean HbA1c levels were 7.9% during CGM use and 8.4% during conventional therapy (mean difference, -0.4%; p<0.01). There were a large number of secondary end points. A portion of them were prespecified and analyses took into consideration the statistical impact of multiple comparisons; the remaining secondary outcomes were considered descriptive and p values were not reported. Among the prespecified secondary outcomes, treatment satisfaction (measured by the Diabetes Treatment Satisfaction Questionnaire [DTSQ]) was significantly higher in the CGM phase than in the conventional treatment phase (p<0.001). Hypoglycemia outcomes were secondary descriptive outcomes. There was 1 (0.7%) severe hypoglycemic event during the CGM phase and 5 (3.5%) events during conventional therapy. The percentage of time with hypoglycemia (<70 mmol/L) was 2.8% during CGM treatment and 4.8% during conventional therapy.

In the second study, Beck et al (2017) randomized 158 patients on a 2:1 basis to 24 weeks of CGM (n=105) or to usual care (n=53). The trial included patients with type 1 diabetes who were ages 25 or older and had baseline HbA1c levels between 7.5% and 10%. Before randomization, patients underwent a 2-week period using a CGM system (without seeing data from the CGM) to ensure compliance. To be eligible, patients had to wear the CGM on at least 85% of days, calibrate the device at least twice daily and perform SMBG at least 3 times daily. The primary outcome (change in HbA1c levels at 24 weeks) was 1.0% in the CGM group and 0.4% in the

usual care group (p<0.001), with a between-group difference of 0.6%. Prespecified secondary outcomes on the proportion of patients below a glycemic threshold at 24 weeks also favored the CGM group. The proportion of patients with HbA1c levels less than 7.0% was 18 (18%) in the CGM group and 2 (4%) in the control group (p=0.01). The proportion of patients with HbA1c levels less than 7.5% was 39 (38%) in the CGM group and 6 (11%) in the control group (p<0.001). Moreover, prespecified secondary outcomes related to hypoglycemia also differed significantly between groups, favoring the CGM group. The time spent in hypoglycemia less than 70 mg/dL was 43 minutes per day in the CGM group and 80 minutes per day in the usual care group (p=0.002). Comparable numbers for time spent at less than 50 mg/dL were 6 minutes per day in the CGM group and 20 minutes per day in the usual care group (p=0.001). The median change in the rate per 24 hours of hypoglycemia events lasting at least 20 minutes at less than 3.0 mmol/L (54 mg/dL) fell by 30% from 0.23 at baseline to 0.16 during follow-up in the CGM group but was practically unchanged (0.31 at baseline and 0.30 at follow-up) in the usual care group (p=0.03). Quality of life measures assessing overall well-being (WHO-5), health status (EQ-5D-5L), diabetes distress (DDS), hypoglycemic fear (worry subscale of the HFS-II), and hypoglycemic confidence (HCS) have also been reported. There were no significant differences between CGM and usual care in changes in well-being, health status, or hypoglycemic fear. The CGM group demonstrated a greater increase in hypoglycemic confidence (p=0.01) and a greater decrease in diabetes distress (p=0.01) than the usual care group.

Pregnant Women

One trial of real-time CGM in pregnant women with type 1 diabetes has been reported. Study design results and gaps are summarized here and in Tables 3 to 6. Feig et al (2017) reported results of 2 multicenter RCTs in women ages 18 to 40 with type 1 diabetes who were receiving intensive insulin therapy and who were either pregnant (≤13 weeks and 6 days of gestation) or planning a pregnancy.The trial enrolling pregnant women is reviewed here. Women were eligible if they had a singleton pregnancy and HbA1c levels between 6.5% and 10.0%. The trial was conducted at 31 hospitals in North America and Europe. Women were randomized to CGM (Guardian REAL-Time or MiniMed Minilink system) plus capillary glucose monitoring or capillary glucose monitoring alone. Women in the CGM group were instructed to use the devices daily. Women in the control group continued their usual method of capillary glucose monitoring. The target glucose range was 3.5 to 7.8 mmol/L and target HbA1c levels were 6.5% or less in both groups. The primary outcome was the difference in change in HbA1c levels from randomization to 34 weeks of gestation. The proportion of completed scheduled study visits was high in both groups; however, participants using CGM had more unscheduled contacts, which were attributed both to sensor issues and to sensor-related diabetes management issues. The median frequency of CGM use was 6.1 days per week (interquartile range, 4.0-6.8) and 70% of pregnant participants used CGM for more than 75% of the time. The between-group difference in the change in HbA1c levels from baseline to 34 weeks of gestation was statistically significant favoring CGM (MD = -0.19%; 95% CI, -0.34 to -0.03; p=0.02). Women in the CGM group spent an increased percentage of time in the recommended glucose control target range at 34 weeks of gestation (68% vs 61%, p=0.003). There were no between-group differences in maternal hypoglycemia, gestational weight gain, or total daily insulin dose. A smaller proportion of infants of mothers in the CGM group were large-for-gestational age (odds ratio [OR], 0.51; 95% CI, 0.28 to 0.90; p=0.02). In addition, for infants of mothers in the CGM group, there were fewer neonatal intensive care admissions lasting more than 24 hours (OR=0.48; 95% CI, 0.26 to 0.86;

p=0.02), fewer incidences of neonatal hypoglycemia requiring treatment with intravenous dextrose (OR=0.45, 0.22 to 0.89; p=0.025), and reduced total length of hospital stay (3.1 days vs 4.0 days; p=0.0091). Skin reactions occurred in 49 (48%) of 103 CGM participants and 8 (8%) of 104 control participants.

Table 3. RCT Characteristics for Real-Time CGM in Pregnant Women with Type 1 Diabetes

Study; Registration	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Feig et al (2017); NCT01788527	Canada, England, Scotland, Spain, Italy, Ireland, U.S.	31	2013-2016	Pregnant women (<14 wk gestation) with type 1 diabetes receiving intensive insulin therapy with HbA_{1c} levels between 6.5% and 10.0% (mean, 6.9%); mean age, 31 y	CGM (real-time, continuous) (n=108)	SMBG (n=107)

CGM: continuous glucose monitoring: HbA1c: hemoglobin A1c; RCT: randomized controlled trial; SMBG: self-monitored blood glucose.

Table 4. RCT Outcomes for Real-Time CGM in Pregnant Women with Type 1 Diabetes

	Infant				Maternal	
Study	**Large-for-Gestational Age**	**Gestational Age at Delivery, wk**	**Severe Hypoglycemia**	**Caesarean Section**	**HbA_{1c} Levels: Change From Baseline to 34 Wk of Gestation**	**Severe Hypoglycemia**
Feig et al (2017)						
n	211	201	200	202	173	214
CGM	53 (53%)	Median, 37.4	15 (15%)	63 (63%)	-0.54	11 (11%)
Control	69 (69%)	Median, 37.3	28 (28%)	74 (73%)	-0.35	12 (12%)
TE (95% CI)	OR=0.51 (0.28 to 0.90)	NR	OR=0.45 (0.22 to 0.89)	NR	-0.19% (-0.34% to -0.03%)	NR
p	0.02	0.50	0.025	0.18	0.02	1.0

Values are n or n (%) or as otherwise indicated.
CI: confidence interval; CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; TE: treatment effect.

Table 5. Relevance Limitations of RCTs for Real-Time CGM in Pregnant Women with Type 1 Diabetes

Study	Population	Intervention	Comparator	Outcomes	Follow-Up
Feig et al (2017)	4. Run-in period requirement may have biased selection to highly compliant participants	3. More unscheduled contacts in CGM group	3. More unscheduled contacts in CGM group	None noted	None noted

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. CGM: continuous glucose monitoring; RCT: randomized controlled trial. a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use. b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest. c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively. d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported. e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

CGM Implanted Device for Long-Term Use

The Eversense Continuous Glucose Monitoring System is implanted in the subcutaneous skin layer and provides continuous glucose measurements over a 40-400 mg/dL range. The system provides real-time glucose values, glucose trends, and alerts for hypoglycemia and hyperglycemia and low glucose through a mobile application installed on a compatible mobile device platform. The Eversense CGM System is a prescription device indicated or use in adults (age 18 and older) with diabetes for up to 90 days. The device was initially approved as an adjunctive glucose monitoring device to complement information obtained from standard home blood glucose monitoring devices. Prescribing providers are required to participate in insertion and removal training certification.

The primary literature on the use of the implanted glucose sensor system is limited to three nonrandomized prospective studies that were intended to evaluate the accuracy and safety of the device in adults. Accuracy measures included the mean absolute relative difference (MARD) between paired samples from the implanted device and a reference standard blood glucose measurement (Yellow Springs Instrument). Device development led to a demonstration of increasing accuracy of the sensors. However, the accuracy tends to be lower in hypoglycemic ranges. Outcomes could not be differentiated for T1D vs T2D. Serious adverse events were primarily limited to skin reactions. Trends in secondary glycemic measures were variably reported but the studies were not designed to acquire clinical outcome data.

Tables 6 and 7 summarize results from the Eversense trials.

Table 6. Summary of Key Nonrandomized Trials: Implanted CGM Study Characteristics

Study	Study Type	Country	Dates	Participants	Test/Treatment	Follow-Up
Kropff (2017) PRECISE	Prospective Single-arm Blinded	Germany, Netherlands, UK	2014-2015	Adults (≥ 18 years) with T1 or T2 diabetes using insulin (N=71)	Implanted CGM	180 days
Christiansen (2018) PRECISE II	Prospective Single-arm Blinded	United States	2016	Adults (≥ 18 years) with T1D (67.8%) T2D (32.2%) Insulin use: Total: (75.6%) T2D: (6.6%)	Implanted CGM Single sensor=75 Bilateral sensor	90 days

				(N=90)	=15	
Christiansen (2019) PRECISION	Prospective Single-arm Unblinded	United States	2017-2018	Adults (≥ 18 years) with T1D (71.4%) T2D (28.6%) Insulin use: Total: (85.7%) T2D: NR (N=35)	Implanted CGM Single sensor=8 Bilateral sensor=27	90 days

CGM: continuous glucose monitoring; NR: not reported; T1D: type 1 diabetes; T2D: type 2 diabetes.

Table 7. Summary of Key Nonrandomized Trials: Implanted CGM Study Results

Study	MARD (glucose range 40-400mg/dl)	Adverse Events
Kropff (2017) PRECISE	N=71	N=71
	11.1% (glucose >75mg/dl)	14 device/ procedure-related nonsevere adverse events 11 participants (total number of 147 sensors implanted, used, and removed)
Christianen (2018) PRECISE II	N=90	N=90
	8.8% 95% CI: 8.1%-	14 device/ procedure-related nonsevere adverse events in 7 participants (total number of 106 sensors implanted, used, and removed)

	9.3%	
Christiansen (2019) PRECISION	N=35	N=35
	9.6% 95% CI: 8.9%-10.4%	8 device/ procedure-related nonsevere adverse events in 5 participants (total number of 62 sensors implanted, used, and removed)

CI: confidence interval; MARD: mean absolute relative difference.

The study information provided in Tables 6 and 7 reflects the data provided to the FDA for the initial approval of Eversense as an adjunctive device. Expanded approval was granted in June 2019 and Eversense is now approved as a device to replace fingerstick blood glucose measurements for diabetes treatment decisions. Historical data from the system can be interpreted to aid in providing therapy adjustments. No new clinical studies were conducted to support the change in the indications for the device. The sponsor previously performed clinical studies to establish the clinical measurement performance characteristics of the device, including accuracy across the claimed measuring range (40 to 400 mg/dL glucose), precision, claimed calibration frequency (every 12 hours), the wear period for the sensor (90 days), and performance of the alerts and notifications. This same clinical study information was used to support what FDA considered a reasonable assurance of safety and effectiveness of the device for replacement of fingerstick blood glucose monitoring for diabetes treatment decisions. As a condition of approval, the sponsor is required to conduct a post-approval-study. The study design is a non-blinded, prospective, multi-center, single arm longitudinal cohort study intended to evaluate the safety and effectiveness of diabetes management with the Eversense CGM System non-adjunctively compared to self-monitoring of blood glucose using a blood glucose meter in participants with either Type 1 or Type 2 diabetes. Subjects will serve as their own control, with baseline SMBG use to manage their diabetes for the first 6 months of the study followed by use of the CGM nonadjunctively for the next 6 months. Total follow-up duration is 12 months. Approximately 925 subjects will be screened to achieve an enrollment such that approximately 740 subjects will be available for analysis at the end of the study. The investigation will include both clinic visits and home use of the device.

Section Summary: CGM Devices for Long-Term Use in Type 1 Diabetes

Numerous RCTs and several systematic reviews of RCTs have evaluated CGM in patients with type 1 diabetes. A 2017 individual patient data analysis, using data from 11 RCTs, found that reduction in HbA1c levels was significantly greater with real-time CGM compared with a control intervention. In addition, a 2012 meta-analysis of 6 RCTs found a significantly larger decline in HbA1c levels 6 months in CGM users than the SMBG group. There are few studies beyond 6 months. Two recent RCTs in patients who used multiple daily insulin injections and were highly compliant with CGM devices during run-in phases found that CGM was associated with a larger reduction in HbA1c levels than previous studies. Reductions were 0.4% and 0.6%, respectively, compared with approximately 0.2 to 0.3% in previous analyses. One of the 2 RCTs prespecified hypoglycemia-related outcomes, and time spent in hypoglycemia was significantly less in the CGM group.

One RCT in pregnant women with type 1 diabetes (n=215) has compared CGM with SMBG. Adherence was high in the CGM group. The difference in the change in HbA1c levels from baseline to 34 weeks of gestation was statistically significant favoring CGM, and women in the CGM group spent an increased percentage of time in the recommended glucose control target range at 34 weeks of gestation. There were no between-group differences in maternal hypoglycemia, gestational weight gain, or total daily insulin dose. A smaller proportion of infants of mothers in the CGM group were large for gestational age, had neonatal intensive care admissions lasting more than 24 hours, and had neonatal hypoglycemia requiring treatment. The total length of hospital stay was shorter by almost 1 day in the CGM group.

Three nonrandomized prospective studies assessed accuracy and safety of an implanted glucose monitoring system that provides continuous glucose monitoring for up to 90 days as an adjunct to home glucose monitoring devices. Accuracy measures included the mean absolute relative difference between paired samples from the implanted device and a reference standard blood glucose measurement. The accuracy tended to be lower in hypoglycemic ranges. Limitations on the evidence include lack of differentiation in outcomes type 1 diabetes vs type 2 diabetes and variability in reporting of trends in secondary glycemic measures. The initial approval of the device has been expanded to allow the device to be used for glucose management decision making. The same clinical study information was used to support what FDA considered a reasonable assurance of safety and effectiveness of the device for replacement of fingerstick blood glucose monitoring for diabetes treatment decisions. As a condition of approval, the sponsor is required to conduct a post-approval-study.

CGM Devices for Short Term use in Type 1 Diabetes

The meta-analyses of CGM devices for type 1 diabetes tended to combine studies of intermittent glucose monitoring with studies of continuous long term monitoring. For this body of evidence, there is variability in the definitions of intermittent monitoring and the specific monitoring protocols used. In addition, many of the trials of intermittent monitoring included additional interventions to optimize glucose control such as education and recommendations on lifestyle modifications.

Clinical Context and Therapy Purpose
The purpose of short-term use of CGM devices is to provide a testing option that is an alternative to or an improvement on existing testing used in the management of individuals with type 1 diabetes.

The question addressed in this evidence review is: Does short-term use of a CGM device improve the net health outcome for individuals with type 1 diabetes?
The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with type 1 diabetes. All individuals with type 1 diabetes require engagement in a comprehensive self-management and clinical assessment program that includes assessment of blood glucose control. Individuals with type 1 diabetes may have poorly controlled diabetes, despite current use of best practices, including situations such as unexplained hypoglycemic episodes, hypoglycemic unawareness, suspected postprandial hyperglycemia, and recurrent diabetic ketoacidosis. In addition, individuals with type 1 diabetes may need to determine basal insulin levels prior to insulin pump initiation.

Interventions
The testing being considered is the short-term use of a CGM device to assess blood glucose levels as part of optimal diabetes management. Short-term use is generally for 72 hours. However, reports of use range from 3-30 days.

Comparators
The following practice is currently being used to measure glucose levels: capillary blood sampling (finger stick) for SMBG. Standard treatment for patients with type 1 diabetes includes injection of long-acting basal insulin plus MDI of rapid-acting insulin boluses as required for meal intake. Activity level may require patients need to modify the timing and dose of insulin administration. Individuals with type 1 diabetes may also use an insulin pump either for initial treatment or convert to pump use after a period of MDI. Individuals with type 1 diabetes may also use an insulin pump either for initial treatment or convert to pump use after a period of MDI. Individuals are required to check their blood glucose before making preprandial insulin calculations, in response to symptoms of hypoglycemia or related to activity-related insulin adjustments

Outcomes
For short-term use of CGM, the general outcomes of interest include frequency and time spent in hypoglycemia and, frequency and time spent in hyperglycemia for the duration of the monitoring. Repeat CGM may be necessary to assess the impact of changes in management. CGM devices and self-glucose monitor devices may be used in the home, outpatient, or inpatient setting and patients are monitored by endocrinologists, diabetologists, internists and primary care physicians and clinicians.

Study Selection
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Two meta-analyses were identified that reported separate subgroup analysis for intermittent monitoring. In the 2012 Cochrane review, there were 4 studies (216 patients) comparing real-time intermittent CGM systems to SMBG, and the pooled effect estimate for change in HbA1c at 3 months was not statistically significant (MD change = -0.18; 95% CI, -0.42 to 0.05). The 2011 meta-analysis of RCTs on CGM described previously also included a separate analysis of 8 RCTs of intermittent monitoring. On pooled analysis, there was a statistically significant reduction in HbA1c with CGM compared with SMBG (WMD = -0.26; 95% CI, -0.45 to -0.06).

Randomized Controlled Trials

The largest individual RCT was the MITRE trial, published by Newman and colleagues in 2009, was conducted to evaluate whether the additional information provided by use of minimally invasive glucose monitors resulted in improved glucose control in patients with poorly controlled insulin-requiring diabetes. This was a 4-arm RCT conducted at secondary care diabetes clinics in 4 hospitals in England. In this study, 404 people aged older than 18 years, with insulin-treated diabetes mellitus (Types 1 or 2) for at least 6 months, who were receiving 2 or more injections of insulin daily, were eligible. The majority of participants, 57%, had Type 1 diabetes, 41% had Type 2 diabetes and 2% were classified as "other." Participants had two HbA1c values of at least 7.5% in the 15 months prior to entry and were randomized to 1 of 4 groups. Two groups received minimally invasive glucose monitoring devices (GlucoWatch Biographer or MiniMed Continuous Glucose Monitoring System, CGMS). Intermittent CGM was used (i.e., monitoring was performed over several days at various points in the study). These groups were compared with an attention control group (standard treatment with nurse feedback sessions at the same frequency as those in the device groups) and a standard control group (reflecting common practice in the clinical management of diabetes). Change in HbA1c from baseline to 3, 6, 12, and 18 months was the primary indicator of short- to long-term efficacy in this study. At 18 months, all groups demonstrated a decline in HbA1c levels from baseline. Mean percentage changes in HbA1c were -1.4 for the GlucoWatch group, -4.2 for the CGMS group, -5.1 for the attention control group, and -4.9 for the standard care control group. In the intent-to-treat (ITT) analysis, no significant differences were found between any of the groups at any of the assessment times. There was no evidence that the additional information provided by the devices resulted in any change in the number or nature of treatment recommendations offered by the nurses. Use and acceptability indicated a decline in use of both devices, which was most marked in the GlucoWatch group by 18 months (20% still using GlucoWatch vs. 57% still using the CGMS). In this study of unselected patients, use of continuous glucose monitors (CGMS on an intermittent basis) did not lead to improved clinical outcomes.

Pregnant Women

Systematic Reviews

Voormolen et al (2013) published a systematic review of the literature on CGM during pregnancy. They identified 11 relevant studies (total N=534 women). Two were RCTs, one of which was the largest of the studies (N=154). Seven studies used CGMs that do not have data available in real-time; the remaining 4 studies used real-time CGM. Reviewers did not pool study findings; they concluded that the evidence was limited on the efficacy of CGM during pregnancy. The published RCTs are described next.

Randomized Controlled Trials

Two RCTs of intermittent glucose monitoring in pregnant women with type 1 or type 2 diabetes are summarized in Tables 7 to 10 and the following paragraphs. While both trials included a mix of women with type 1 and type 2 diabetes, most women had type 1 diabetes in both trials, so the trials are reviewed in this section.

In 2008, Murphy et al in the U.K. randomized 71 pregnant women with Type 1 (n=46) or Type 2 (n=25) diabetes to CGM or usual care. The intervention consisted of up to 7 days of CGM at intervals of 4 to 6 weeks between 8 and 32 weeks' gestation. Neither participants nor physicians had access to the measurements during sensor use; data were reviewed at study visits. In addition to CGM, the women were advised to measure blood glucose levels at least seven times a day. Baseline HbA1c was 7.2% (standard deviation [SD] =0.9) in the CGM group and 7.4% (SD=1.5) in the usual care group. The primary study outcome was maternal glycemic control during the second and third trimesters. Eighty percent of women in the CGM group wore the monitor at least once per trimester. Mean HbA1c levels were consistently lower in the intervention arm, but differences between groups were statistically significant only at week 36. For example, between 28 and 32 weeks' gestation, mean HbA1c levels were 6.1% (SD=0.60 in the CGM group and 6.4% (SD=0.8) in the usual care group, p=0.10. The prevalence of large-for-gestational age infants (at least 90th percentile) was a secondary outcome. Thirteen of 37 (35%) infants in the CGM group were large-for-gestational age compared with 18 of 30 (60%) in the usual care group. The odds ratio for reduced risk of a large-for-gestational age infant with CGM was 0.36 (95% CI, 0.13 to 0.98, p=0.05).

Secher et al (2013) randomized 154 women with type 1 (n=123) and type 2 (n=31) diabetes to real-time CGM in addition to routine pregnancy care (n=79) or routine pregnancy care alone (n=75). Patients in the CGM group were instructed to use the CGM device for 6 days before each of 5 study visits and were encouraged to use the devices continuously; 64% of participants used the devices per-protocol. Participants in both groups were instructed to perform 8 daily self-monitored plasma glucose measurements for 6 days before each visit. Baseline mean HbA1c levels were 6.6% in the CGM group and 6.8% in the routine care group. The 154 pregnancies resulted in 149 live births and 5 miscarriages. The prevalence of large-for-gestational age infants (at least 90th percentile), the primary study outcome, was 45% in the CGM group and 34% in the routine care group. The difference between groups was not statistically significant (p=0.19). Also, no statistically significant differences were found between groups for secondary outcomes, including the prevalence of preterm delivery and the prevalence of severe neonatal hypoglycemia. Women in this trial had low baseline HbA1c levels, which might explain the lack of impact of CGM on outcomes. Other factors potentially contributing to the negative findings

included the intensive SMBG routine in both groups and the relatively low compliance rate in the CGM group.

Table 8. Key RCT Characteristics for Intermittent CGM in Pregnant Women with Type 1 Diabetes

					Interventions	
Author; Registration	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
Murphy et al (2008); ISRCTN84461581	U.K.	2	2003-2006	Pregnant women with type 1 (65%) and type 2 (35%) diabetes; mean gestational age, 9.2 wk; mean HbA_{1c} level, 7.3%; mean age, 31 y	CGM (up to 7 d of CGM at intervals of 4-6 wk) plus SOC (n=38)	SOC (n=33)
Secher et al (2013); NCT00994357	Denmark	1	2009-2011	Pregnant women with type 1 (80%) or type 2 (20%) diabetes; mean gestational age, <14 wk); median HbA_{1c} level, 6.7%; median age, 32 y	CGM (for 6 d before each study visits; encouraged to used continuously) plus routine care (n=79)	Routine care (n=75)

CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; RCT: randomized controlled trial; SOC: standard of care.

Table 9. RCT Outcomes of Intermittent CGM in Pregnant Women with Type 1 Diabetes

	Infant				Maternal	
Study	**Large-for-Gestational Age**	**Gestational Age at Delivery**	**Severe Hypoglycemia**	**Caesarean Section**	**HbA_{1c} Levels: At 36 Wk' Gestation[a]**	**Severe Hypoglycemia**
		Weeks				
Murphy et al (2008)						
n	71	71	68	69	71	NR
CGM	13 (35%)	Mean, 37.6	3 (8%)	27 (71%)	Mean, 5.8%	
Control	18 (60%)	Mean, 37.5	5 (17%)	21 (61%)	Mean, 6.4%	
TE (95% CI)	OR=0.36 (0.13 to 0.98)	NR	NR	NR	0.6% (CI NR)	
p	0.05	0.80	0.50	0.40	0.007	
		Days				
Secher et al (2013)						
n	154	154	145	154		154
CGM	34 (45%)	Median, 263	9 (13%)	28 (37%)	Median, 6.0%	16%
Control	25 (34%)	Median, 264	10 (14%)	33 (45%)	Median, 6.1%	16%
TE (95% CI)	NR	NR	NR	NR	NR	NR
p	0.19	0.14	0.88	0.30	0.63	0.91

Values are n or n (%) or as otherwise indicated.
CGM: continuous glucose monitoring; CI: confidence interval; HbA1c: hemoglobin A1c; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; TE: treatment effect.
a N inconsistently reported for HbA1c outcome.

In summary, 2 studies of intermittent glucose monitoring conducted in Europe included pregnant women with type 1 or 2 diabetes, with most having type 1 diabetes. Murphy et al (2008) included intermittent, retrospective monitoring with CGM; Secher et al (2013) included intermittent, real-time monitoring. The intervention started in early pregnancy in these studies; mean age was in the early thirties and mean baseline HbA1c level was greater than 6.5% There was no statistically significant difference between CGM and routine care for maternal HbA1c levels at 36 weeks in Secher; the difference in HbA1c levels at 36 weeks was about 0.6% (p=0.007) in Murphy. Secher also reported no difference in severe maternal hypoglycemia. The proportion of infants that were large for gestational age (>90th percentile) was higher in the CGM group in Secher, although not statistically significantly higher; the difference in large for gestational age was statistically significantly lower for CGM in Murphy. The differences in the proportions of infants born via caesarean section, gestational age at delivery, and infants with severe hypoglycemia were not statistically significant in either trial.

Table 10. Relevance Limitations of RCTs of Intermittent CGM in Pregnant Women with Type 1 Diabetes

Study	Population	Intervention	Comparator	Outcomes	Follow-Up
Murphy et al (2008)	None noted	None noted	None noted	None noted	None noted
Secher et al (2013)	4. Study population had relatively low HbA_{1c}	4. Only 64% of the participants used devices per protocol	None noted	None noted	None noted

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; RCT: randomized controlled trial. a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use. b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest. c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively. d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported. e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 11. Study Design and Conduct Gaps of RCTs of Intermittent Glucose Monitoring in Pregnant Women with Type 1 Diabetes

Study	Allocation	Blinding	Selective Reporting	Follow-Up	Power	Statistical
Murphy et al (2008)	None noted	1. Not blinded; chance of bias in clinical management	None noted	None noted	None noted	3, 4. Treatment effects and confidence intervals not calculated for some outcomes
Secher et al (2013)	None noted	1. Not blinded; chance of bias in clinical management	None noted	None noted	None noted	3, 4. Treatment effects and confidence intervals not calculated

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. CGM: continuous glucose monitoring; RCT: randomized controlled trial. a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias. b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician. c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication. d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials). e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference. f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Glucose Monitoring Devices for Intermittent, Short-Term Use in Type 1 Diabetes

For short-term monitoring of type 1 diabetes, there are few RCTs and systematic reviews. The evidence for short-term monitoring on glycemic control is mixed, and there was no consistent in HbA1c levels. Some trials have reported improvements in glucose control for the intermittent monitoring group but limitations in this body of evidence preclude conclusions. The definitions of control with short-term CGM use, duration of use and the specific monitoring protocols varied. In some studies, short-term monitoring was part of a larger strategy aimed at optimizing glucose control, and the impact of monitoring cannot be separated from the impact of other interventions. Studies have not shown an advantage for intermittent glucose monitoring in reducing severe hypoglycemia events but the number of events reported is generally small and effect estimates imprecise. The limited duration of use may preclude an assessment of any therapeutic effect. Two RCTs of short-term CGM use for monitoring in pregnancy included women with both type 1 and 2 diabetes, with most having type 1 diabetes. One trial reported a difference in HbA1c levels at 36 weeks; the proportion of infants that were large for gestational age (>90th percentile) favored CGM while the second trial did not. The differences in the proportions of infants born via cesarean section, gestational age at delivery, and infants with severe hypoglycemia were not statistically significant in either study. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice when used in specific situations such as poor control of diabetes despite the use of best practices and to help determine basal insulin levels prior to insulin pump initiation.

CGM Devices for Use in Type 2 Diabetes

Clinical Context and Therapy Purpose

The purpose of long-term CGM and short-term glucose monitoring devices is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with type 2 diabetes.

The question addressed in this evidence review is: Does the use of long-term or short-term CGM glucose monitoring devices improve the net health outcome for individuals with type 2 diabetes? The following PICOs were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with type 2 diabetes. All individuals with type 2 diabetes require engagement in a comprehensive self-management and clinical assessment program that includes assessment of blood glucose control. Some individuals with type 2 diabetes may have poorly controlled diabetes, despite current use of best practices, including situations such as unexplained hypoglycemic episodes, hypoglycemic unawareness, and persistent hyperglycemia and A1C levels above target. In addition, some individuals with type 2 diabetes may need to determine basal insulin levels prior to insulin pump initiation.

Interventions
The testing being considered is the use of long-term or short-term CGM devices to assess blood glucose levels as part of optimal diabetes management.

Comparators
The following practice is currently being used to measure glucose levels: SMBG (capillary blood sampling (finger stick) using blood glucose meters) and periodic measurement of HbA1c.

Outcomes
The general outcomes of interest are a change inHbA_{1c} levels, frequency of and time spent in hypoglycemia, frequency and time spent in hyperglycemia, complications of hypoglycemia and hyperglycemia, and QOL. To assess short-term outcomes such as HbA_{1c} levels, a minimum follow-up of 8 to 12 week is appropriate. To assess long-term outcomes such as time spent in hypoglycemia, the incidence of hypoglycemic events, complications of hypoglycemia, and QOL, follow-up of six months to one year would be appropriate. CGM devices and self-glucose monitor devices may be used in the home, outpatient, or inpatient setting and patients are monitored by endocrinologists, diabetologists, internists and primary care physicians and clinicians.

Study Selection
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
Two systematic reviews (previously described) also reported on the efficacy of CGM in patients with type 2 diabetes. A comparison of the trials of type 2 diabetes included in the systematic reviews and meta-analyses in these reviews is shown in Table 12.

Table 12. Comparison of CGM Trials for Type 2 Diabetes Included in Systematic Reviews

Primary Study	Ida et al (2019)	Poolsup et al (2013)	Gandhi et al (2011)
Ehrhardt et al (2011)[a]	●	●	
Cosson et al (2009)[b]	•	●	●

Allen et al (2008)[b]	•	●	●
Yoo et al (2008)[a]	•	●	●
Beck et al (2017) [a]	•		
Ajjan et al (2016) [b]	●		
Haak et al ((2017)[b]	●		

CGM: continuous glucose monitoring
[a] These studies used real-time CGM (RT-CGM) devices compared to SMBG
[b] These studies used retrospective CGM (r-CGM) devices compared to SMBG

A summary of the characteristics of the systematic reviews is shown in Table 13. Results are briefly described in Table 13 and the following. Gandhi et al (2011) discussed above, included studies of Type 1 and Type 2 diabetes. Three RCTs included patients with Type 2 diabetes. One RCT included patients with either type of diabetes. There was a mixture of patients with Type 2 diabetes who did and did not require insulin. Two of the 3 trials evaluated retrospective intermittent CGM of different lengths and durations and the third evaluated real-time intermittent CGM. Patients included in the studies had baseline HbA1c > 8%. In a meta-analysis of the three trials, there was a statistically significant reduction in HbA1C with CGM compared to SMBG in adults with Type 2 diabetes (WMD: -0.70, 95% CI: -1.14 to -0.27). In 2013, Poolsup et al conducted a meta-analysis of four trials using adults with Type 2 diabetes. Three of the trials in Poolsup overlapped with Gandhi; the remaining trial also evaluated real-time CGM but with a longer period of use (2 weeks on and 1 week off for 3 months).In a pooled analysis, CGM had greater efficacy in terms of HbA1c than usual care. The pooled mean difference in HbA1c was -0.31% 95% CI, -0.6 to 0.02, p=0.04). Because of a lack of statistical heterogeneity among studies, subgroup analyses (e.g., by type of CGM device) were not performed.

Table 13 Systematic Review Characteristics for CGM in Type 2 Diabetes

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Ida et al (2019)	1960-2018	7	Adults with T2D	669 (25-224)	RCT	At least 8 wk
Poolsup et al (2013)	To 2013	4	Adults with T2D	228 (25-100)	RCT	At least 8 wk (median, 3 mo)

Gandhi et al (2011)	1996-2010	3	Adult outpatients with T2D; mean baseline HbA_{1c} level >8%	128 (25-57)	RCT	At least 8 wk (median, 3 mo)

CGM: continuous glucose monitoring; HbA_{1c}: hemoglobin A_{1c}; RCT: randomized controlled trial; T2D: type 2 diabetes.

Table 14. Meta-Analytic Results for CGM in Type 2 Diabetes

Study	Reduction in HbA1c Levels (Mean Difference)	Hypoglycemic Events (Mean Difference)	Diabetes Complications (retinopathy, nephropathy, neuropathy, diabetic foot)	Health-Related Quality of Life
Ida et al (2019)				
Total N	660	285		
PE (95% CI)	-0.42 (-0.70 to -0.13)	-0.35 (-0.59 to -0.10)a	NR	Multiple diabetes specific scales used in each study therefore results could not be combined for meta-analyses
p	0.004	0.0006		
I2	64%	0%		
Poolsup et al (2013)				
Total N	228	NR	NR	NR
PE (95% CI)	-0.31 (-0.60 to -0.02)			
p	0.04			
I2	0%			
Gandhi et al (2011)				
Total	128	NR	NR	NR

N				
PE (95% CI)	-0.70 (-1.14 to -0.27)			
p	NR			
I2	0%			

CGM: continuous glucose monitoring; CI: confidence interval; HbA_{1c}: hemoglobin A_{1c}; NR: not reported; PE: pooled effect.

Randomized Controlled Trials

Several RCTs of CGM in adults with type 2 diabetes are summarized in Tables 14 to 17. The largest and most recent studies are also briefly summarized in the following paragraphs. The studies were conducted in North America, Europe, and Asia. Baseline HbA1c levels were between 8.5% and 9.0% in the RCTs, with participants having a mean baseline age range in the mid-50s and early-60s. The RCTs used a mixed of intermittent and continuous, real-time monitoring.

Ehrhardt and colleagues published 2 reports (2011, 2012) from an RCT evaluating the largest sample (N=100) in the Poolsup et al (2013) systematic review (accounting for 45% of the weight in the pooled analysis of HbA1c levels). The trial evaluated intermittent use of a CGM device in adult patients with Type 2 diabetes who were treated with diet/exercise and/or glycemic lowering medications but not prandial insulin and had an initial HbA1C of at least 7% but not more than 12%. The study compared real-time continuous monitoring with the DexCom device used for four 2-week cycles (2 weeks on/ 1 week off) to self-monitoring of blood glucose (SMBG). The primary efficacy outcome was mean change in HbA1c. Mean (SD) HbA1c in the CGM group were 8.4% (1.5%) at baseline, 7.4% (1.0%) at 12 weeks, 7.3% (1.1%) at 24 weeks, and 7.7% (1.1%) at 52 weeks. In the SMBG group, these values (SD) were 8.2% (1.1%) at baseline, 7.7% (1.2%) at 12 weeks, 7.6% (1.3%) at 24 weeks, and 7.9% (1.4%) at 52 weeks. Over the course of the study, the reduction in HbA1c was significantly greater than in the SMBG group (p=0.04). After adjusting for potential confounding variables including age, sex, baseline therapy, and whether the individual started taking insulin during the study, the difference between groups over time remained statistically significant (p<0.0001). The investigators also evaluated SMBG results from both groups. The mean proportion of SMBG tests that were less than 70 mg/dL were 3.6% in the CGM group and 2.5% in the SMBG group (p=0.06).

The RCT by Sato et al (2016), included 34 patients with type 2 diabetes who were at least 20 years old and were on insulin injection therapy, had HbA1c levels between 6.9% and 11.0% during the previous 3 months, with fluctuations of HbA1c within 0.5%. All patients conducted SMBG and used a retrospective CGM device for 4 to 5 days before each of 3 clinic visits, 2 months apart. At the clinic visits, patients' were evaluated and suggestions were made to improve glucose control by lifestyle changes and secondarily by changing medication doses. In

the intervention group, but not the control group, the patients and physicians had access to the CGM data at the clinic visits. The primary endpoint was change in HbA1c and this did not differ significantly between groups at the end of the study, compared with baseline, between the first and second visit or between the second and third visits. HbA1c changed little in either group. In the intervention group, the mean (SD) baseline HbA1c was 8.2% (1.2%) and the mean final HbA1c was also 8.2% (SD: 1.3%). Comparable percentages in the control group were 8.2% (0.9%), and 7.9% (0.8%). In this study, which was conducted in Japan, decisions around medication doses were made only by the physician at clinic visits and practices may differ in other countries.

The largest RCT, Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND), was reported by Beck et al (2017). DIAMOND was performed at 25 endocrinology practices in North America (22 in the United States, 3 in Canada) and enrolled adults with type 2 diabetes receiving multiple daily injections of insulin. One-hundred fifty-eight patients were randomized into 2 groups, CGM and usual care (n=79 in each group). Patients compliant during a run-in period were eligible for randomization. Patients in both groups were given a blood glucose meter. Participants in the CGM group were given a Dexcom G4 Platinum CGM System (Dexcom) and instructions on use. Change in HbA1c level from baseline to 24 weeks was the primary outcome. Analyses were adjusted for baseline HbA1c levels and clinic were performed using intention-to-treat analysis with missing data handling by multiple imputation. At baseline, the mean total daily insulin dose was 1.1 U/kg/d. Week 24 follow-up was completed by 97% of the CGM group and 95% of the control group. Mean CGM use was greater than 6 d/wk at 1 month, 3 months, and 6 months. The adjusted difference in mean change in HbA1c level from baseline to 24 weeks was -0.3% (95% CI, -0.5% to 0.0%; p=0.022) favoring CGM. The adjusted difference in the proportion of patients with a relative reduction in HbA1c level of 10% or more was 22% (95% CI, 0% to 42%; p=0.028) favoring CGM. There were no events of severe hypoglycemia or diabetic ketoacidosis in either group. The treatment groups did not differ in any of the quality of life measures.

Table 15. RCT Characteristics for Glucose Monitoring in Type 2 Diabetes

Study; Registration	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Haak et al (2017)	France, Germany, UK	26	2013-2014	Adults (≥18y) with T2D on intensive insulin therapy (MDI or CSII),HbA1c levels (7.5-12.0%), SMBG >10/week	Flash sensor based glucose monitoring (n=149)	SMBG (n=75)
Beck et al (2017) (DIAMOND); NCT02282397	U.S., Canada	25	2014-2016	Adults with T2D using multiple daily injections of insulin with HbA_{1c}levels 7.5%-10.0% (baseline mean, 8.5%); mean age, 60 y	Real-time CGM (n=79)	SMBG (n=79)
Sato et al (2016); UMIN: 000012034[a]	Japan	1	2012-2014	Adults with T2D using insulin with HbA_{1c} levels 6.9%-11.0% (baseline mean, 8.2%); mean age, 62 y	CGM for 4-5 d every 4 mo; reviewed at study visits (n=17)	"Blinded" CGM (n=17)
Ehrhardt et al (2011)	U.S.	1	NR	Adults with T2D using oral	Real-time CGM	SMBG (n=50)

				antidiabetic agents without prandial insulin with HbA_{1c} levels 7.0%-12.0% (baseline mean, 8.3%), mean age, 58 y	for 4 cycles of 3 wk (n=50)	
Cosson et al (2009)	France	5	NR	Adults with T1D or T2D treated with oral antidiabetic agents with or without insulin with HbA_{1c} levels 8.0%-10.5% (baseline mean, 9.1% in T2D); mean age, 57 y in T2D	CGM for 48 h at baseline and 3 mo; CGM data shared with physician and patient (n=11 with T2D)	"Blinded" CGM (n=14 in T2D)
Allen et al (2008)	U.S.	2	NR	Adults with T2D not receiving insulin with HbA_{1c} levels >7.5% (baseline mean, 8.6%), not participating in physical activity; mean age, 57 y	Diabetes education plus CGM for 3 d (n=27)	Diabetes education (n=25)
Yoo et al (2008)	Korea	4	2007	Adults with T2D using oral antidiabetic	CGM (3 d at a time for 3 mo)	SMBG (n=33)

				agents or insulin with HbA_{1c}levels 8.0%-10.0% (baseline mean, 9%); mean age, 56 y	(n=32)	

CGM: continuous glucose monitoring; CSII: continuous subcutaneous insulin infusion; HbA_{1c}: hemoglobin A_{1c}; NR: not reported; MDI: multiple daily injections; RCT: randomized controlled trial; SMBG: self-monitored blood glucose; T1D: type 1 diabetes; T2D: type 2 diabetes.

Most RCTs used a type of intermittent monitoring; some reported data for patients in real-time while others provided data reviewed only at study visits. Four of the 6 RCTs of CGM in type 2 diabetes reported a statistically significant larger decrease in HbA1c levels with CGM than with control. In Cosson et al (2009), the comparative treatment effect was not reported, but the CGM group had a statistically significant reduction in HbA1c levels from baseline to 3 months. Few other outcomes were reported. Beck et al (2017) reported more patients in CGM with a relative reduction in HbA1c levels of greater than 10% at 24 weeks but no difference in the quality of life measures. No trials reported on follow-up beyond 6 months. Thus the effect of CGM on outcomes related to diabetic complications is unknown. Only 2 RCTs used blinded CGM; in one, there was no difference in reduction in HbA1c levels between CGM and control.

Table 16. RCT Outcomes for Glucose Monitoring in Type 2 Diabetes

Study	Reduction in HbA_{1c} Levels (Mean Range), %	HbA_{1c} Level <7.0%, n (%)	Relative Reduction in HbA_{1c}Level ≥10%, n (%)	Hypoglycemic or Ketoacidosis Events	Diabetes Complications (retinopathy, nephropathy, neuropathy, diabetic foot)	Health-Related Quality of Life
	Baseline to 24 Wk	At 24 Wk	At 24 Wk			DTSQ Overall Mean Score at 24 Wk
Hack et al (2017)						
N	224	NR	NR		NR	224
Flash monitor	8.6 to 8.37			3 serious hypoglycemic events[a]		(mean±SE) 13.1 (0.50)
Control SMBG	8.75 to 8.34			1 serious hypoglycemic events[a]		9.0 (0.72)
TE (95% CI)	NR					NR

Study	Reduction in HbA_{1c} Levels (Mean Range), %	HbA_{1c} Level <7.0%, n (%)	Relative Reduction in HbA_{1c}Level ≥10%, n (%)	Hypoglycemic or Ketoacidosis Events	Diabetes Complications (retinopathy, nephropathy, neuropathy, diabetic foot)	Health-Related Quality of Life
p	0.8222					<0.0001
	Baseline to 24 Wk	At 24 Wk	At 24 Wk			DDS Overall Mean Score at 24 Wk
Beck et al (2017)						
N	158	158	158	158	NR	150
CGM	8.6 to 7.7	11 (14%)	40 (52%)	0		Baseline: 1.78 24 weeks: 1.61
Control	8.6 to 8.2	9 (12%)	24 (32%)	0		Baseline: 1.69 24 weeks: 1.78
TE (95% CI)	-0.3 (-0.5 to 0.0)	3% (-9% to	22% (0% to			0.22 (0.08 to

Study	Reduction in HbA_{1c} Levels (Mean Range), %	HbA_{1c} Level <7.0%, n (%)	Relative Reduction in HbA_{1c}Level ≥10%, n (%)	Hypoglycemic or Ketoacidosis Events	Diabetes Complications (retinopathy, nephropathy, neuropathy, diabetic foot)	Health-Related Quality of Life
		14%)	42%)			0.36)
p	0.022	0.88	0.028			0.009
	Baseline to 8 Mo					
Sato et al (2016)						
N	34	NR	NR	NR	NR	NR
CGM	8.2 to 8.2					
Control	8.2 to 7.9					
TE (95% CI)	NR					
p	>0.05					

Study	Reduction in HbA_{1c} Levels (Mean Range), %	HbA_{1c} Level <7.0%, n (%)	Relative Reduction in HbA_{1c}Level ≥10%, n (%)	Hypoglycemic or Ketoacidosis Events	Diabetes Complications (retinopathy, nephropathy, neuropathy, diabetic foot)	Health-Related Quality of Life
	Baseline to 12 Wk					
Ehrhardt et al (2011)						
N	100	NR	NR	NR	NR	NR
CGM	8.4 to 7.4					
Control	8.2 to 7.7					
TE (95% CI)	NR					
p	0.006					
	Baseline to 3 Mo			Time Spent With Hypoglycemia, min		

Study	Reduction in HbA_{1c} Levels (Mean Range), %	HbA_{1c} Level <7.0%, n (%)	Relative Reduction in HbA_{1c}Level ≥10%, n (%)	Hypoglycemic or Ketoacidosis Events	Diabetes Complications (retinopathy, nephropathy, neuropathy, diabetic foot)	Health-Related Quality of Life
Cosson et al (2009)						
N	25	NR	NR	19	NR	NR
CGM	9.2 to 8.6			18		
Control	9.0 to 8.8			11		
TE (95% CI)	NR			NR		
	Baseline to 8 Wk					
Allen et al (2008)						
N	46	NR	NR	NR	NR	NR
CGM	8.9 to 7.7					

Study	Reduction in HbA_{1c} Levels (Mean Range), %	HbA_{1c} Level <7.0%, n (%)	Relative Reduction in HbA_{1c}Level ≥10%, n (%)	Hypoglycemic or Ketoacidosis Events	Diabetes Complications (retinopathy, nephropathy, neuropathy, diabetic foot)	Health-Related Quality of Life
Control	8.4 to 8.1					
TE (95% CI)	NR					
p	<0.05					
	Baseline to 3 Mo					
Yoo et al (2008)						
N	57	NR	NR	NR	NR	NR
CGM	9.1 to 8.0					
Control	8.7 to 8.3					
TE (95% CI)	NR					

Study	Reduction in HbA_{1c} Levels (Mean Range), %	HbA_{1c} Level <7.0%, n (%)	Relative Reduction in HbA_{1c}Level ≥10%, n (%)	Hypoglycemic or Ketoacidosis Events	Diabetes Complications (retinopathy, nephropathy, neuropathy, diabetic foot)	Health-Related Quality of Life
p	0.004					

CGM: continuous glucose monitoring; CI: confidence interval; DDS: Diabetes Distress Scale; DTSQ: Diabetes Treatment Satisfaction; HbA_{1c}: hemoglobin A_{1c}; NR: not reported; RCT: randomized controlled trial; TE: treatment effect.
[a]serious hypoglycemic event defined as requiring third-party assistance

Tables 17 and 18 display notable limitations identified in each study.

Table 17. Relevance Limitations of RCTs for Glucose Monitoring in Type 2 Diabetes

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Haak et al (2017)				1. Did not include outcomes on diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications
Beck et al (2017); DIAMOND				1. Did not include outcomes on diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications

Sato et al (2016)				1. Focused on HbA_{1c}; did not include outcomes on adverse events, QOL, or diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications
Ehrhardt et al (2011)				1. Focused on HbA_{1c}; did not include outcomes on adverse events, QOL, or diabetic complications 6. No justification for clinically significant difference	1. Follow-up not sufficient to determine effects on diabetic complications; patients reportedly followed for 52 wk but data not reported.
Cosson et al (2009)				1. Focused on HbA_{1c}; did not include outcomes on adverse events, QOL, or diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications
Allen et al (2008)				1. Focused on HbA_{1c}; did not include outcomes on adverse events, QOL, or diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications
Yoo et				1. Focused on HbA_{1c}; did	1. Follow-up not

al (2008)				not include outcomes on adverse events, QOL, or diabetic complications	sufficient to determine effects on diabetic complications

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
HbA_{1c}: hemoglobin A_{1c}; QOL: quality of life; RCT: randomized controlled trial.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 18. Study Design and Conduct Limitations of RCTs for Glucose Monitoring in Type 2 Diabetes

Study; Trial	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Haak et al (2017)		1.Pre-randomization blinded run-in phase for both groups. Control group only blinded for last 2 weeks of study				3, 4. Treatment effects and CIs not calculated
Beck et al (2017);		1. Not blinded; chance of bias in				

Study; Trial	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
DIAMOND		clinical management				
Sato et al (2016)[x]						3, 4. Treatment effects and CIs not calculated
Ehrhardt et al (2011)		1. Not blinded; chance of bias in clinical management	1. Registration not reported		3. No justification for difference used for power calculation	3, 4. Treatment effects and CIs not calculated
Cosson et al (2009)			1. Registration not reported	2. Unclear how missing data were handled in analyses	1.-3. No power calculations	3, 4. Treatment effects and CIs not calculated
Allen et al (2008)		1. Not blinded; chance of bias in clinical	1. Registration not reported		2, 3. Power not calculated a priori;	3, 4. Treatment effects and

Study; Trial	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
		management			convenience sample size	CIs not calculated
Yoo et al (2008)		1. Not blinded; chance of bias in clinical management	1. Registration not reported			3, 4. Treatment effects and CIs not calculated

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
CI: confidence interval; RCT: randomized controlled trial.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.
Haak et al (2017) reported the results of a 12-month open-access extension of the REPLACE RCT comparing flash glucose-sensing technology in individuals with type 2 diabetes treated with intensive insulin therapy. Summaries of the study characteristics and results are provided in Table 19 and 20 respectively.

Generally, the impact on outcomes of reduction in time in hypoglycemia and reduction in nocturnal hypoglycemia was maintained at 12 months. There was no change in time in range (70-180mg/dl). Sensor utilization was maintained at a rate of 83.6% (SD: 13.8%) of daily intended use. Adverse events were reported in five participants in the open-access phase, which lead to withdrawal from the study. Two participants died but death was not judged to be a device or study-related. Three participants experienced sensor site complications severe enough to warrant study discontinuation.

Table 19. Summary of Key Nonrandomized Trial Characteristics

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
Haak (2017a)	Prospective Open Access Extension	France, Germany, UK	2013-2015	Adults (≥18 years) REPLACE trial intervention group participants who completed 6-month treatment phase (N=139)	Flash glucose sensor use for self-management of T2D using insulin (Insulin pen device = 94%)	12 months

Table 20. Summary of Key Nonrandomized Trial Results

Study	Reduction in Time in Hypoglycemia Hours/day (12 months)	Frequency of Hypoglycemic Events/day (12 months)	Reduction in Time in Nocturnal Hypoglycemia Hours per 7 hours (12 months)	Frequency of Nocturnal Hypoglycemia Events per 7 hours (12 months)	Change From Baseline Hypoglycemic Events/day (12 months)
Haak (2017a)	N (108)	N (108)	N (108)	N (108)	N (108)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	(%)

Glucose <70 mg/dl	-0.70 (1.85) p=0.0002	-.0.27 (0.67) p<0.0001	-0.31 (0.84) p=0.0002	-0.1 (0.33) p=0.0021	-40.8 p<0.0001
Glucose <55 mg/dl	-0.40 (1.09 p=0.0002	-0.20 (0.49) p<0.0001	-0.19 (0.57) p=0.0008	-0.9 (0.21) p<0.0001	-56.5 p<0.0001
Glucose <45 mg/dl	-0.23 (0.73) p= 0.0013	-0.13 (0.35) p<0.0002	-0.12 (0.42) p=0.0032	-0.05 (0.15) p=0.0008	-61.7 p=0.0001

SD: standard deviation.

Pregnant Women

As discussed in the section on CGM in pregnant women, 2 RCTs have evaluated short-term CGM glucose monitoring in pregnant women with type 1 and type 2 diabetes. Most women had type 1 diabetes in both trials. There were 25 (35%) women with type 2 diabetes in Murphy et al (2008) and 31 (20%) with type 2 diabetes in Secher et al (2013). Results for women with type 2 diabetes were not reported in Murphy. Secher reported that 5 (17%) women with type 2 diabetes experienced 15 severe hypoglycemic events, with no difference between the groups; other analyses were not stratified by diabetes type.

Section Summary: CGM for Use in Type 2 Diabetes

Most RCTs of CGM in patients with type 2 trials found statistically significant benefits of CGM regarding glycemic control. However, the degree of HbA_{1c} reduction and the difference in HbA_{1c} reduction between groups might not be clinically significant. Moreover, additional evidence would be needed to show what levels of improvements in HbA_{1c} levels over the short-term would be linked to meaningful improvements over the long-term in health outcomes such as diabetes-related morbidity and complications. Also, the variability in entry criteria as well as among interventions makes it difficult to identify an optimal approach to CGM use; the studies used a combination of intermittent and continuous monitoring with a review of data in real-time or at study visits only. Only the DIAMOND trial (n=158) used real-time CGM in type 2 diabetes. Selected patients were highly compliant during a run-in phase. The difference in change in HbA_{1c} levels from baseline to 24 weeks was -0.3% favoring CGM. The difference in the proportion of patients with a relative reduction in HbA_{1c} level by 10% or more was 22% favoring CGM. There were no differences in the proportions of patients with an HbA_{1c} level of less than 7% at week 24. There were no events of severe hypoglycemia or diabetic ketoacidosis in either group. The treatment groups did not differ in any of the QOL measures. RCTs using flash glucose-sensing technology as a replacement for SMBG for the management of insulin-dependent treated type 2 diabetes found no difference in HbA1c change at 6 and 12 months between groups. However, time in severe hypoglycemia (<45mg/dL) was reduced for intervention participants. Two trials of CGM have enrolled pregnant women with type 2 diabetesbut the total number of women with type 2 diabetes included in both trials is only 58. One study reported a difference in HbA_{1c} levels at 36 weeks, and the proportion of infants that were large for gestational age (>90th percentile) favored CGM while the second study did not. Neither trial reported analyses stratified by diabetes type. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input for long-term (continuous) CGM in patients with type 2 diabetes who do not require insulin did not provide strong support of a safety benefit and clinically meaningful improvement in net health outcome. Evidence reported through clinical input for use of short-term CGM in patients with type 2 diabetes who require multiple daily doses of insulin supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice when used in specific situations such as poor control of diabetes despite use of best practices and to help determine basal insulin levels prior to insulin pump initiation.

Use of Long-Term (Continuous) CGM in Individuals with Type 2 Diabetes on Multiple Daily Doses of Insulin with Significant Hypoglycemia in the Setting of Insulin Deficiency
Clinical Context and Therapy Purpose
The purpose of long-term CGM glucose monitoring devices is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with type 2 diabetes(T2DM).
The question addressed in this evidence review is: Does the use of long-term CGM glucose monitoring devices improve the net health outcome for individuals with type 2 diabetes who are on multiple daily doses of insulin with significant hypoglycemia in the setting of insulin deficiency?
The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest is a subgroup of individuals with type 2 diabetes who are willing and able to use the device and have adequate medical supervision and who experience significant hypoglycemia on multiple daily doses of insulin or an insulin pump in the setting of insulin deficiency who receive long-term (continuous) glucose monitoring.

Interventions
The testing being considered is the use of long-term CGM devices to assess blood glucose levels and detect hypoglycemia as part of optimal diabetes management.

Comparators
The following practice is currently being used to measure glucose levels: SMBG (capillary blood sampling (finger stick) using blood glucose meters) and periodic measurement of HbA1c.

Outcomes
The general outcomes of interest are the frequency of and time spent in hypoglycemia, the incidence of hypoglycemic episodes, complications of hypoglycemia, and QOL. To assess short-term outcomes a minimum follow-up of 8 to 12 week is appropriate. To assess long-term outcomes follow-up of 6 months to 1 year would be appropriate. CGM devices and self-glucose monitor devices may be used in the home, outpatient, or inpatient setting and patients are monitored by endocrinologists, diabetologists, internists and primary care physicians and clinicians.

Study Selection
Methodologically credible studies were selected as described above in the section CGM Devices for Use in Type 2 Diabetes

Systematic Reviews
Meta-analytic results for long-term CGM in type 2 diabetes are summarized in Table 14. The largest and most recently published systematic review of RCTs (Ida et al [2019]) reports a statistically significant reduction in hypoglycemic events in 285 subjects for CGM with a mean reduction of -0.35 (mean difference -0.59 to -0.10, p=0.0006).

Key Non-Randomized Trials
Twelve-month open-access, follow-up results for long-term CGM in 108 individuals with type 2 diabetes treated with intensive insulin therapy are summarized in Table 20 (Haak (2017)). Hypoglycemia was analyzed using 3 different glucose level thresholds (<70 mg/dl, **<55 mg/dl,** and <45 mg/dl). At all three glucose level thresholds, there were statistically significant reductions in time in hypoglycemia, frequency of hypoglycemic events, time in nocturnal hypoglycemia, and frequency of nocturnal hypoglycemia. Change for hypoglycemic events per day at 12 months compared to baseline was also significant: -40.8% (glucose <70 mg/dl, p<0.0001); -56.5% (glucose <55 mg/dl, p<0.0001); -61.7% (glucose <45 mg/dl, p=0.0001).

Section Summary: Use of Long-Term (Continuous) CGM in Individuals with Type 2 Diabetes on Multiple Daily Doses of Insulin with Significant Hypoglycemia in the Setting of Insulin Deficiency
A recently published systematic review and 12-month follow-up study using long-term CGM in patients with type 2 diabetes demonstrate that CGM can significantly reduce time in hypoglycemia and frequency of hypoglycemia events both during the day and at night. At 12-month follow-up, hypoglycemic events were reduced by 40.8% to 61.7% with a greater relative reduction in the most severe thresholds of hypoglycemia. The published evidence supports a meaningful improvement in the net health outcome. Evidence reported through clinical input provides additional clinical context and based on both the published evidence and clinical input the following patient selection criteria are associated with a clinically meaningful improvement in net health outcome and are consistent with generally accepted medical practice: selected patients with type 2 diabetes who are (1) willing and able to use the CGM device and have adequate medical supervision and (2) experiencing significant hypoglycemia on multiple daily doses of insulin or an insulin pump in the setting of insulin deficiency.

CGM use in Pregnant Women with Gestational Diabetes
Clinical Context and Therapy Purpose
The purpose of CGM devices is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does use of CGM devices improve the net health outcome for individuals with gestational diabetes?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with gestational diabetes.

Interventions
The therapy being considered are CGM devices that provide continuous, long-term glucose levels to the patient to direct insulin regimens, and intermittent (i.e., 72 hours), short-term monitoring used by the provider to optimize management.

Comparators
The following practice is currently being used to measure glucose levels: capillary blood sampling (finger stick) for blood glucose meters

Outcomes
The general outcomes of interest are change in HbA1c levels, time spent in hypoglycemia, incidence of hypoglycemic events, complications of hypoglycemia and quality of life.

Randomized Controlled Trials
One trial of glucose monitoring in women with gestational diabetes has been published. Trial design, results, and gaps are shown in Tables 21 to 24. In an RCT, Wei et al (2016) evaluated the use of CGM in 120 women with gestational diabetes at 24 to 28 weeks. Patients were allocated to prenatal care plus CGM (n=58) or SMBG (n=62). The CGM sensors were reportedly inserted for 48 to 72 hours on weekdays; it is not clear whether the readings were available in real-time. The investigators assessed a number of end points and did not specify primary outcomes; a significance level of p less than 0.05 was used for all outcomes. The groups did not differ significantly in a change in most outcomes, including a change in maternal HbA1c levels, rates of preterm delivery before the 35th gestational week, cesarean delivery rates, proportions of large-for-gestational age infants, or rates of neonatal hypoglycemia. Women in the CGM group gained significantly less weight than those in the SMBG group.

Table 21. Key RCT Characteristics for CGM in Pregnant Women with Gestational Diabetes

					Interventions	
Author	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
Wei et al (2016)	China	1	2011-2012	Pregnant women with gestational diabetes diagnosed between 24 and 28 wk' gestation; mean HbA_{1c} level, 5.8%; mean age, 30 y	CGM (48- 721 on weekdays) (n=51)	SMBG (n=55)

CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c. RCT: randomized controlled trial; SMBG: self-monitored blood glucose.

Table 22. RCT Outcomes for CGM in Pregnant Women with Gestational Diabetes

	Infant			Maternal		
Study	**Large-for-Gestational Age**	**Gestational Age at Delivery, wk**	**Severe Hypoglycemia**	**Caesarean Section**	**HbA_{1c} Levels at 36 Wk' Gestation[a]**	**Severe Hypoglycemia**
Wei et al (2016)						
N	106	106	106	106		NR
CGM	18 (35%)	Mean, 37.4	4 (8%)	31 (60%)	Mean, 5.5%	
Control	29 (53%)	Mean, 37.5	7 (13%)	38 (69%)	Mean, 5.6%	
TE (95% CI)	NR	NR	NR	NR	NR	
p	0.07	0.92	0.41	0.37	0.09	

Values are n (%) or as otherwise indicated.
CGM: continuous glucose monitoring; CI: confidence interval; HbA1c: hemoglobin A1c; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; TE: treatment effect. a N inconsistently reported for HbA1c outcome.

Table 23. Relevance Limitations of RCTs for CGM in Pregnant Women with Gestational Diabetes

Study	Population	Intervention	Comparator	Outcomes	Follow-Up
Wei et al (2016)	4. Study population had relatively low HbA_{1c} level	4. Compliance with CGM not reported	None noted	None noted	None noted

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. CGM: continuous glucose monitoring; HbA1c: hemoglobin A1c; RCT: randomized controlled trial. a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use. b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest. c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively. d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported. e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms

Table 24. Study Design and Conduct Gaps of RCTs for CGM in Pregnant Women with Gestational Diabetes

Study	Allocation	Blinding	Selective Reporting	Follow-Up	Power	Statistical
Wei et al (2016)	3. Not reported	1. Not blinded; chance of bias in clinical management	1. Registration not reported	5. Exclusions not well justified	1. No power calculations reported; primary outcome not specified	3, 4. Treatment effects and CIs not calculated

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. CGM: continuous glucose monitoring; RCT: randomized controlled trial. a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias. b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician. c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication. d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials). e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference. f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated

Section Summary: CGM use in Pregnant Women With Gestational Diabetes
The RCT in women with gestational diabetes was conducted in China with the intervention starting in the 2nd or 3rd trimester and mean baseline HbA1c level less than 6.0%. The type of CGM monitoring was unclear. Trial reporting was incomplete; however, there were no differences between groups for most reported outcomes.

Summary of Evidence
Type 1 Diabetes
For individuals with type 1 diabetes who are willing and able to use the device, and have adequate medical supervision, who receive long-term CGM, the evidence includes RCTs and systematic reviews. The relevant outcomes are symptoms, morbid events, QOL, and treatment-related morbidity. Systematic reviews have generally found that at least in the short-term, long-term CGM resulted in significantly improved glycemic control for adults and children with type 1 diabetes, particularly highly compliant patients. A 2017 individual patient data analysis, pooling data from 11 RCTs, found that reductions inHbA1c levels were significantly greater with real-time CGM than with a control intervention. Two RCTs in patients who used multiple daily insulin injections and were highly compliant with CGM devices during run-in phases found that CGM was associated with a larger reduction in HbA1c levels than previous studies. One of the two RCTs prespecified hypoglycemia-related outcomes and reported that time spent in hypoglycemia was significantly less in the CGM group. One RCT in pregnant women with type 1 diabetes, which compared real-time CGM with self-monitoring of blood glucose, has also reported a difference in change in HbA1clevels, an increased percentage of time in the recommended glucose control target range, a smaller proportion of infants who were large for gestational age, a smaller proportion of infants who had neonatal intensive care admissions lasting more than 24 hours, a smaller proportion of infants who had neonatal hypoglycemia requiring treatment, and reduced total hospital length of stay all favoring CGM. The evidence is sufficient that the long-term use of CGM provides an improvement in net health outcomes for persons with type 1 diabetes mellitus.

For individuals with type 1 diabetes who receive short-term glucose monitoring, the evidence includes RCTs and systematic reviews. The relevant outcomes are symptoms, morbid events, QOL, and treatment-related morbidity as well as intermediate outcomes related to measures of glucose control such as frequency and time in hypoglycemia and hyperglycemia. The evidence for short-term monitoring on glycemic control is mixed, and there was no consistency in HbA1c levels. Some trials have reported improvements in glucose control for the intermittent monitoring group but limitations in this body of evidence preclude conclusions. The definitions of control with short-term CGM use, duration of use and the specific monitoring protocols varied. In some studies, short-term monitoring was part of a larger strategy aimed at optimizing glucose control, and the impact of monitoring cannot be separated from the impact of other interventions. Studies have not shown an advantage for intermittent glucose monitoring in reducing severe hypoglycemia events but the number of events reported is generally small and effect estimates imprecise. The limited duration of use may preclude an assessment of any therapeutic effect. Two RCTs of short-term CGM use for monitoring in pregnancy included women with both type 1 and 2 diabetes, with most having type 1 diabetes. One trial reported a difference in HbA1c levels at 36 weeks; the proportion of infants that were large for gestational age (>90th percentile) favored CGM while the second trial did not. The differences in the proportions of infants born

via cesarean section, gestational age at delivery, and infants with severe hypoglycemia were not statistically significant in either study. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice when used in specific situations such as poor control of diabetes despite the use of best practices and to help determine basal insulin levels prior to insulin pump initiation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Type 2 Diabetes

For individuals with type 2 diabetes who receive long-term CGM, the evidence includes RCTs. The relevant outcomes are symptoms, morbid events, QOL, and treatment-related morbidity. Most RCTs of CGM in patients with type 2 trials found statistically significant benefits of CGM regarding glycemic control. However, the degree of HbA1c reduction and the difference in HbA1c reduction between groups might not be clinically significant. Moreover, additional evidence would be needed to show what levels of improvements in HbA1c levels over the short-term would be linked to meaningful improvements over the long-term in health outcomes such as diabetes-related morbidity and complications. Also, the variability in entry criteria as well as among interventions makes it difficult to identify an optimal approach to CGM use; the studies used a combination of intermittent and continuous monitoring with a review of data in real-time or at study visits only. Only the DIAMOND RCT (n=158) has used real-time CGM in type 2 diabetes. Selected patients were highly compliant during a run-in phase. The difference in change in HbA1c levels from baseline to 24 weeks was -0.3% favoring CGM. The difference in the proportion of patients with a relative reduction in HbA1c level by 10% or more was 22% favoring CGM. There were no differences in the proportions of patients with an HbA1c level of less than 7% at week 24. There were no events of severe hypoglycemia or diabetic ketoacidosis in either group. The treatment groups did not differ in any of the QOL measures. RCTs using flash glucose-sensing technology as a replacement for SMBG for the management of insulin-dependent treated type 2 diabetes found no difference in HbA1c change at 6 and 12 months between groups. However, time in severe hypoglycemia (<45mg/dL) was reduced for intervention participants. Two trials of CGM have enrolled pregnant women with type 2 diabetes, but the total number of women with type 2 diabetes included in both trials is only 58. One study reported a difference in HbA1c levels at 36 weeks, and the proportion of infants that were large for gestational age (>90th percentile) favored CGM while the second study did not. Neither trial reported analyses stratified by diabetes type. Limitations of the published evidence preclude determining the effects of the technology on net health outcome. Evidence reported through clinical input for long-term (continuous) CGM in patients with type 2 diabetes who do not require insulin did not provide strong support of a safety benefit and clinically meaningful improvement in net health outcome. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with type 2 diabetes who are willing and able to use the device and have adequate medical supervision and who experience significant hypoglycemia on multiple daily doses of insulin or an insulin pump in the setting of insulin deficiency who receive long-term (continuous) glucose monitoring, the evidence includes a systematic review and non-randomized study with 12-month follow-up. The relevant outcomes are the frequency of and time spent in

hypoglycemia, the incidence of hypoglycemic episodes, complications of hypoglycemia, and QOL. The available studies demonstrate that CGM can significantly reduce time in hypoglycemia and frequency of hypoglycemia events both during the day and at night. At 12-month follow-up, hypoglycemic events were reduced by 40.8% to 61.7% with a greater relative reduction in the most severe thresholds of hypoglycemia.

For individuals who have type 2 diabetes who receive short-term, intermittent CGM, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related morbidity. Systematic reviews of 3 to 4 RCTs have found statistically significant benefits from CGM regarding glycemic control. However, the degree of HbA1c reduction and the difference in HbA1c reductions between groups may not be clinically significant. Also, the limited number of RCTs and variability among interventions make it difficult to identify an optimal approach to CGM or a subgroup of type 2 diabetes patients who might benefit. Moreover, studies of CGM in patients with type 2 diabetes have generally not addressed the clinically important issues of severe hypoglycemia and diabetic complications. Very few pregnant women with type 2 diabetes have been included in RCTs. The evidence is insufficient to determine the effects of the technology on health outcomes.

Gestational Diabetes

For individuals who are pregnant with gestational diabetes who receive long-term (continuous) or short-term (intermittent) glucose monitoring, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, quality of life, and treatment-related morbidity. In the RCT, the type of CGM was unclear. Trial reporting was incomplete; however, there was no difference between the groups for the majority of the reported outcomes. The evidence is sufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American Association of Clinical Endocrinologists and American College of Endocrinology

In 2016, the American Association of Clinical Endocrinologists and American College of Endocrinology published a consensus statement on outpatient glucose monitoring. Following are their recommendations on CGM:

- Type 1 diabetes, adults: "CGM recommended, especially for patients with history of severe hypoglycemia, 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."
- Type 1 diabetes, children: Same as adults, except that more training and follow-up is needed.
- Type 2 diabetes receiving insulin, sulfonylureas or glinides: "Data on CGM in T2DM [type 2 diabetes mellitus] are limited at this time. Trials assessing the use of CGM in T2DM are ongoing."

The AACE and ACE (2018) published a consensus statement on a T2D management algorithm. It is recommended that therapy be evaluated regularly including the results of A1C, SMBG records (fasting and postprandial) or continuous glucose monitoring tracings.

In 2019, theAACE) and American College of Endocrinology (ACE) 2015 Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan further supplemented by an AACE/ACE Consensus Statement on Comprehensive Type 2 Diabetes Management. The statement supports consideration of the use of personal CGM devices for those patients who are on intensive insulin therapy (3 to 4 injections/day or on insulin pump), for those with history of hypoglycemia unawareness, or those with recurrent hypoglycemia. Regarding the duration of use the statement reads; "While these devices could be used intermittently in those who appear stable on their therapy, most patients will need to use this technology on a continual basis."

UK National Institute for Health and Care Excellence (NICE)

The National Institute for Health and Care Excellence updated its guidance on diagnosis and management of type 1 diabetes in adults in 2016. The guidance stated that real-time CGM should not be offered routinely to adults with type 1 diabetes but that it can be considered in the following:

- "Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes"
- …"adults with type 1 diabetes 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:
    - More than 1 episode a year of severe hypoglycaemia with no obviously preventable precipitating cause.
    - Complete loss of awareness of hypoglycaemia.
    - Frequent (more than 2 episodes a week) asymptomatic hypoglycaemia that is causing
    - Problems with daily activities.
    - Extreme fear of hypoglycaemia.
    - Hyperglycaemia (HbA1c level of 75 mmol/mol [9%] or higher) that persists despite testing at least 10 times a day. Continue real-time continuous glucose monitoring only if HbA1c can be sustained at or below"

American Diabetes Association

The 2019 American Diabetes Association "Standards of Medical Care in Diabetes: Diabetes Technology" included the following statement:

" SMBG or CGM is especially important for insulin-treated patients to monitor for and prevent hypoglycemia and hyperglycemia. Most patients using intensive insulin regimens (MDI or insulin pump therapy) should assess glucose levels using SMBG or a CGM prior to meals and snacks, at bedtime, occasionally postprandially, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving"

Endocrine Society

In 2016, the Endocrine Society published a clinical practice guideline developed by a task force that included the following recommendations on continuous glucose monitoring:

- "Real-time continuous glucose monitors in adult outpatients

- We recommend real-time continuous glucose monitoring (RT-CGM) devices for adult patients with T1DM [type 1 diabetes mellitus] who have Ab1C levels above target and who are willing and able to use these devices on a nearly daily basis.
- We recommend RT-CGM devices for adult patients with well-controlled T1DM who are willing and able to use these devices on a nearly daily basis.

- Use of continuous glucose monitoring in adults with type 2 diabetes mellitus
  - We suggest short-term, intermittent RT-CGM use in adult patients with T2DM (not on prandial insulin) who have A1C levels ≥7% and are willing and able to use the device."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Key Words:

GlucoWatch®, wrist glucose monitor, Glucose Biographer, AutoSensor, and GlucoWatch® G2™ Biographer, continuous monitoring of glucose in the interstitial fluid, intermittent monitoring of glucose in the interstitial fluid, Continuous Glucose Monitoring System, CGMS, CGMS® System Gold™, Minimed, MiniMed Paradigm 522 or 722 insulin pumps, MiniMed Paradigm Real-Time Insulin Pump and Continuous Glucose Monitoring System, combined continuous subcutaneous insulin infusion and blood glucose monitoring device, DexCom STS Continuous Glucose Monitoring System, CGMS iPro Recorder, Freestyle Navigator® Continuous Glucose Monitoring System, Guardian® REAL-Time Continuous Glucose Monitoring System, CGM, Dexcom G5, Abbott® Freestyle Libre Flash, Dexcom G6

Approved by Governing Bodies:

Multiple continuous glucose monitoring systems have been approved by the FDA through the premarket approval process:

CGM devices labeled as "Pro" for specific professional use with customized software and transmission to health care professionals are not enumerated in this list.

Table 1. CGM Systems Approved by the Food and Drug Administration

Device	Manufacturer	Approval	Indications
Continuous Glucose Monitoring System (CGMS®)	MiniMed	1999	3-d use in physician's office
GlucoWatch G2® Biographer		2001	Not available since 2008
Guardian®-RT (Real-Time) CGMS	MiniMed (now Medtronic)	2005	

Dexcom® STS CGMS system	Dexcom	2006	
Paradigm® REAL-Time System (second-generation called Paradigm Revel System)	MiniMed (now Medtronic)	2006	Integrates CGM with a Paradigm insulin pump
FreeStyle Navigator® CGM System	Abbott	2008	
Dexcom® G4 Platinum	Dexcom	2012	Adults ≥18 y; can be worn for up to 7 d
		2014	Expanded to include patients with diabetes 2-17 y
Dexcom® G5 Mobile CGM	Dexcom	2016[a]	Replacement for fingerstick blood glucose testing in patients ≥2 y. System requires at least 2 daily fingerstick tests for calibration purposes, but additional fingersticks are not necessary because treatment decisions can be made based on device readings[5,]
Dexcom® G6 Continuous Glucose Monitoring System	Dexcom	2018	Indicated for the management of diabetes in persons age ≥2 years. Intended to replace fingerstick blood glucose testing for diabetes treatment decisions. Intended to autonomously communicate with digitally connected devices, including automated insulin dosing (AID) systems. with 10-day wear
Freestyle Libre®Flash Glucose Monitoring System	Abbott	2017	Adults ≥18 y. Indicated for the management of diabetes and can be worn up to 10 days It is designed to replace blood glucose testing for diabetes treatment decisions.
Freestyle Libre® Flash Glucose Monitoring System	Abbott	2018	Adults ≥18 y. Extended duration of use to 14 days
Guardian Connect	Medtronic MiniMed	2018	Adolescents and adults (14-75 years) Continuous or periodic monitoring of interstitial

			glucose levels. Provides real-time glucose values, trends, and alerts through a Guardian Connect app installed on a compatible consumer electronic mobile device
Eversense Continuous Glucose Monitoring System	Senseonics	2018 2019	Adults ≥18 y. Continually measuring glucose levels up to 90 days. Use as an adjunctive device to complement, not replace, information obtained from standard home blood glucose monitoring devices. Adults ≥18 y. Continually measuring glucose levels up to 90 days. Indicated for use to replace fingerstick blood glucose measurements for diabetes treatment decisions. Historical data from the system can be interpreted to aid in providing therapy adjustments.

CGM: continuous glucose monitoring.

[a] As a supplement to the G4 premarketing approval.

Food and Drug Administration product codes: MDS, PQF, QCD

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT codes:

95249 Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; patient-provided equipment, sensor placement, hook-up, calibration of monitor, patient training, and printout of recording **(Effective 01/01/2018)**

95250 Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of **72 hours**; physician or other qualified health care professional (office) provided equipment, sensor placement, hook-up, calibration of monitor, patient training, removal of sensor, and printout of recording

95251 Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of **72 hours**; analysis, interpretation and report

99091 Collection and interpretation of physiologic data (e.g., ECG, blood pressure, glucose monitoring) digitally stored and/or transmitted by the patient and/or caregiver to the physician or other qualified health care professional, qualified by education, training, licensure/regulation (when applicable) requiring a minimum of 30 minutes of time

HCPCS:

A4226 Supplies for maintenance of insulin infusion pump with dosage rate adjustment using therapeutic continuous glucose sensing, per week

A9276 Sensor; invasive (e.g., subcutaneous), disposable, for use with interstitial continuous glucose monitoring system, one unit = 1 day supply

A9277 Transmitter; external, for use with interstitial continuous glucose monitoring system

A9278 Receiver (monitor); external, for use with interstitial continuous glucose monitoring system

A9999 Miscellaneous DME supply, accessory, and/or service component of another HCPCS code

E1399 Durable medical equipment, miscellaneous

K0553 Supply allowance for therapeutic continuous glucose monitor (CGM) system, includes all supplies and accessories, 1 month supply = 1 unit of service.

K0554 Receiver (monitor), dedicated, for use with therapeutic continuous glucose monitor system.

S1030 Continuous noninvasive glucose monitoring device purchase (for physician interpretation of data, use CPT code)

S1031 Continuous noninvasive glucose monitoring device, rental, including sensor, sensor replacement, and download to monitor (for physician interpretation of data, use CPT code)

Continuous glucose monitoring (CGM) systems measure glucose in interstitial fluid, rather than capillary blood. Because they do not measure blood glucose, different HCPCS and CPT coding are used for these systems and supplies (HCPCS codes **A9276-A9278** and **K0553-K0554**).

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This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case by case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.