Continuous or Intermittent Monitoring of Glucose in Interstitial Fluid - CAM 10120

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Description

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

Objective

The objective of this evidence review is to determine whether continuous glucose monitoring improves the net health outcome in patients with Type 1, Type 2, or gestational diabetes.

Background

Blood Glucose Control

The advent of blood glucose monitors for use by patients in the home revolutionized the management of diabetes. Using fingersticks, patients can monitor their blood glucose levels both to determine the adequacy of hyperglycemia control and to evaluate hypoglycemic episodes. Tight glucose control, defined as a strategy involving frequent glucose checks and a target hemoglobin A1C (HbA1C) level in the range of 7%, is now considered the standard of care for diabetic patients. Randomized controlled trials assessing tight control have demonstrated benefits for patients with Type 1 diabetes in decreasing microvascular complications. The impact of tight control on Type 1 diabetes and 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 a 25% decrease in risk for progression of renal disease.[1]

Due to an increase in turnover of red blood cells during pregnancy, HbA1C levels are 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 levels should range between 6.0% to 6.5%; an A1C level less than 6% may be optimal as the pregnancy progresses.[2]

Tight glucose control requires multiple daily measurements of blood glucose (i.e., before meals and at bedtime), a commitment that some patients may find difficult to meet. 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. While patients with insulin-treated Type 2 diabetes may also experience severe hypoglycemic episodes, there is a lower relative likelihood of severe hypoglycemia compared with patients who had Type 1 diabetes.[3,4] An additional limitation of periodic self-measurements of blood glucose is that glucose levels are seen in isolation, and trends in glucose levels are undetected. For example, while a diabetic patient's fasting blood glucose level might be within normal values, hyperglycemia might be undetected postprandially, leading to elevated HbA1C levels.

Management

Measurements of glucose in the interstitial fluid have been developed as a technique to measure glucose values automatically throughout the day, producing data that show the trends in glucose levels. Although devices measure glucose in the 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 2 designs; real-time CGM (rtCGM) provides 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.

Approved devices now include devices indicated for pediatric use and those with more advanced software, more frequent measurements of glucose levels, or more sophisticated alarm systems. Devices initially measured interstitial glucose every five to 10 minutes and stored data for download and retrospective evaluation by a clinician. With currently available devices, the intervals at which interstitial glucose is measured range from every 1 to 2 minutes to 5 minutes, and most provide measurements in real-time directly to patients. While CGM potentially eliminates or decreases the number of required daily fingersticks, it should be noted that, according to the U.S. Food and Drug Administration (FDA) labeling, some marketed monitors are not intended as an alternative to traditional self-monitoring of blood glucose levels but rather as adjuncts to monitoring, supplying additional information on glucose trends not available from self-monitoring. The devices must be calibrated twice daily with blood glucose measurements from fingersticks, and are less reliable when used after exercise or post-prandial. Devices may be used intermittently (i.e., for periods of 72 hours) or continuously (i.e., on a long-term basis).

Regulatory Status

Multiple CGM systems have been approved by the FDA through the premarket approval process (see Table 1). FDA product codes: QCD, MDS

CGM devices labeled as "Pro" for specific professional use with customized software and transmission to health care professionals are not enumerated in this list. The Flash glucose monitors (e.g., FreeStyle Libre, Abbott) use intermittent scanning and do not have continuous or real-time alerts.

Table 1. CGM Systems Approved by the U.S. 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.

Related Policies
10130 Artificial Pancreas Device Systems

Policy
Short-Term Use (up to three days)
Short-term use of CGMS can be beneficial in patients with diabetes to detect nocturnal hypoglycemia, the dawn phenomenon, and postprandial hyperglycemia and to assist in the management of hypoglycemic unawareness and when significant changes are made to their diabetes regimen (such as instituting new insulin or to pump therapy) as follows:

Continuous glucose monitoring **may be considered MEDICALLY NECESSARY** when used for up to 72 hours as a diagnostic test is covered without prior authorization for Type 1 and Type 2 patients on insulin.

Long-Term Use
Long-term use of CGMS in the treatment of Type 1 and Type 2 diabetes or gestational diabetes who require insulin **may be considered MEDICALLY NECESSARY** for those who meet all of the following criteria:

- Patient is 4 years old or older (Freestyle Libre) or Patient is 2 years of age or older (Dexcom Sensor)
- Patient has completed a comprehensive diabetic education program (a primary caregiver may complete this program for pediatric patients

- One of the following:
  - Patient is currently using insulin therapy
  - Patient is using non-insulin anti-diabetic medication and has frequent recurring episodes of hypoglycemia (less than 70 mg/dL) despite appropriate modifications to medication, hypoglycemia unawareness, episodes of ketoacidosis, or hospitalization for uncontrolled glucose levels
  - For continuation of care consideration, must provide documentation of having used a Freestyle/Dexcom Continuous Glucose Monitor over the past 6 months (Documentation can include paid receipts/clinical notes/physician attestation as proof of patient filling supplies under their pharmacy or medical benefit)
  - Pregnant female with Type I or Type II or one that has developed gestational diabetes that requires insulin therapy

A certificate of medical necessity (CMN) may be substituted for medical record documentation if it addresses all of the criteria noted above and is signed in attestation by the treating physician.

Eversense CGM must meet criteria above AND medical necessity documentation is required with a rationale as to why the “standard” preferred formulary CGMs are not appropriate (ie. FreeStyle Libre and Dexcom).

Other uses of continuous monitoring of glucose levels in interstitial fluid as a technique of diabetic monitoring are considered investigational and/or unproven and therefore considered **NOT MEDICALLY NECESSARY.**

Policy Guidelines

This policy only evaluates continuous (real-time or intermittent) intersititial glucose monitors and does not evaluate insulin pumps. Insulin pump systems with a built-in continuous glucose monitor and a low-glucose suspend feature are addressed in evidence review 10130 (artificial pancreas device systems).

Short-term intermittent monitoring is generally conducted over 72-hour periods. It may be repeated subsequently depending on the patient’s level of diabetes control.

Best practices in diabetes control include compliance with a self-monitoring blood glucose regimen of 4 or more fingersticks each day and use of an insulin pump or multiple daily injections of insulin. During pregnancy, three or more insulin injections daily could also be considered best practice for patients not on an insulin pump prior to the pregnancy. Prior short-term (72-hour) use of an intermittent glucose monitor would be considered a part of best practices for those considering long-term use of a continuous glucose monitor.

Significant hypoglycemia may include recurrent, unexplained, severe (generally blood glucose levels < 50 mg/dL) hypoglycemia or impaired awareness of hypoglycemia that puts the patient or others at risk.

Women with Type 1 diabetes taking insulin who are pregnant or about to become pregnant with poorly controlled diabetes are another subset of patients to whom the policy statement on intermittent monitoring may apply.

The strongest evidence exists for use of continuous glucose monitoring devices in patients age 25 and older. However, age may be a proxy for motivation and good control of disease, so it is also reasonable to select patients based on their ability to self-manage their disease, rather than their age. Multiple CGM devices have FDA labeling related to age.

Providers board-certified in endocrinology and/or providers with a focus on the practice of diabetes care may be considered qualified to evaluate and oversee individuals for continuous (i.e., long-term) monitoring. Maternal Fetal Medicine and high risk obstetric providers are also considered qualified to evaluate and oversee pregnant individuals with gestational diabetes.

See the Codes table for details

Rationale

This evidence review was created in August 2000 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through Nov. 8, 2021.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and 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 technology, two domains are examined: the relevance, and 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 additional information on glucose levels leads to improved glucose control, or to reduce the morbidity and 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, RCTs are important to isolate the contribution of interstitial glucose measurements to overall diabetes management.

For the evaluation of the clinical utility of 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, QOL and measures of disease progression. Hemoglobin A1C (HbA1C) has commonly been accepted as a marker of glucose control; more recent studies have also reported time in hyperglycemia, time in hypoglycemia, and time in range as intermediate outcome measures.

Continuous Glucose Monitoring Devices for Long-Term Use in Type 1 Diabetes

In some parts of the analysis of Type 1 diabetes, does combined discussion of long-term and short-term glucose monitoring because several systematic reviews and RCTs provided information relevant to both indications.

Clinical Context and Therapy Purpose

The purpose of long-term 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 long-term use of a CGM device improve the net health outcome for individuals with Type 1 diabetes?

The following PICO was used to select literature to inform this review.

Populations

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 test 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 HbA1C levels, time spent in hypoglycemia and hyperglycemia, time in range (generally glucose of 70 to 180 mg/dl), 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.

Study Selection

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Reviews

A number of systematic reviews and meta-analyses have assessed RCTs evaluating CGM for long-term, daily use in treating Type 1 diabetes.[6,7,8,9,10,11] These systematic reviews have focused on slightly different populations, and some did not separate long-term CGM from intermittent glucose monitoring.[9]

The only analysis to use individual patient data was published by Benkhadra et al. (2017).[12] The meta-analysis evaluated data from 11 RCTs that enrolled patients with Type 1 diabetes and compared real-time CGM with 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 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 a significantly greater change in HbA1C levels among individuals 15 years and older, but not among the younger age groups. There were no significant differences between groups in the time spent in hypoglycemia or the incidence of hypoglycemic events. Key findings are shown in Table 2.

Table 2. Individual Patient Data Meta-Analytic Outcomes for Real-Time CGM in Type 1 Diabetes

No. of Trials	N	Group	Point Estimate	95% Confidence Intervals	p
Change in HbA1C levels, %					
8	1371	Overall	-0.258	0.464 to -0.052	.014
7	902	Age > 15 y	-0.356	0.551 to -0.160	< .001
7	178	Age 13 – 15 y	-0.039	-0.320 to 0.242	.787
7	291	Age ≤ 12 y	-0.047	0.217 to 0.124	.592
Time spent in hypoglycemia < 60 mg/dL, min					
4	706	Overall	-8.549	-31.083 to 13 985	.457
4	467	Age > 15 y	-8.095	-32.615 to 16.425	.518
3	109	Age 13 – 15 y	-13.966	31.782 to 3.852	.124
3	130	Age ≤ 12 y	-9.366	19.898 to 1.167	.081
Incidence of hypoglycemic events < 70 mg/dL, mean no. events					
3	351	Overall	0.051	-0.314 to 0.416	.785
3	277	Age > 15 y	-0.074	-0.517 to 0.368	.742
2	47	Age 13 – 15 y	0.536	0.243 to 1.316	.177
2	27	Age ≤ 12 y	0.392	0.070 to 0.854	.097

Adapted from Benkhadra et al. (2017).[12]
CGM: continuous glucose monitoring: HbA1C: hemoglobin A1C

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 Cochrane review by Langendam et al. (2012) assessed CGM in Type 1 diabetes in adults and children included RCTs; it compared CGM with conventional SMBG.[8] 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], -0.2%; 95% confidence interval [CI], -0.4% to -0.1%), but there was no difference in the decline in HbA1C levels at 12 months (1 study, n = 154 patients; MD, 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 CI for the relative risk was wide (relative risk, 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 the longer-term changes 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 systematic review by Wojciechowski et al. (2011) evaluating CGM included RCTs conducted in adults and children with Type 1 diabetes.[10] Reviewers selected studies having a minimum of 12 weeks of follow-up and requiring patients to be on intensive insulin regimens. Studies compared CGM with SMBG; there was no restriction on the type of CGM device but CGM readings had to be used to adjust insulin dose or modify diet. Fourteen RCTs met the eligibility criteria. Study durations ranged from 3 to 6 months. Baseline mean HbA1C levels ranged from 6.4% to 10%. Five included studies found a statistically significant decrease in HbA1C levels favoring CGM, while 9 did not. In a pooled analysis, there was a statistically significant reduction in HbA1C levels with CGM compared with SMBG (weighted mean difference [WMD], -0.26%; 95% CI, -0.34% to -0.19%). For the subgroup of 7 studies that reported on long-term CGM, this difference was statistically significant (WMD = -0.26; 95% CI, -0.34 to -0.18). In a subgroup analysis by age, there were significant reductions in HbA1C levels with CGM in 5 studies of adults (WMD= -0.33; 95% CI, -0.46 to -0.20) and in 8 studies with children and/or adolescents (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 for CGM versus SMBG (standardized mean difference, -0.32; 95% CI, -0.52 to -0.13). In 5 studies reporting the percentage of patients with severe hypoglycemic episodes, there were no differences in the percentages of patients with severe hypoglycemic episodes using CGM and SMBG.

Randomized Controlled Trials
Recent RCTs not included in the meta-analyses above are described next and in Tables 3 and 4. HbA1C, blood glucose, event rates, and patient reported outcomes were assessed at 6 months. None of the studies were blinded. The studies had a large number of pre-specified secondary endpoints, and analyses took into consideration the statistical impact of multiple comparisons.

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, » 8.5%).[13] 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 endpoint 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 (MD = -0.4%; p < .01). Treatment satisfaction (measured by the Diabetes Treatment Satisfaction Questionnaire) was significantly higher in the CGM phase than in the conventional treatment phase (p < .001). 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 usual care (n = 53).[14] 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 < .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 = .01). Prespecified secondary outcomes related to hypoglycemia also differed significantly between groups, favoring the CGM group. 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 = .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 = .03).[15] Quality of life measures assessing overall well-being (World Health Organization Well-Being Index), health status (EQ-5D-5L), diabetes distress (Diabetes Distress Scale), hypoglycemic fear (worry subscale of the Hypoglycemia Fear Survey), and hypoglycemic confidence (Hypoglycemic Confidence Scale) have also been reported.[16] 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 = .01) and a greater decrease in diabetes distress (p = .01) than the usual care group.

Two RCTs were published in 2020 that assessed CGM with a Dexcom G5 in adolescents and young adults (Laffel et al., 2020),[17] and in older adults (Pratley et al., 2020)[18] Both studies found modest but statistically significant differences in HbA1C between patients who used the CGM devices compared to the control arm at follow-up. Secondary measures of HbA1C and blood glucose were mostly better in the CGM arm. Patient-reported outcome measures were not significantly different between the groups, except that glucose monitoring satisfaction was higher in the adolescents and young adults who used CGM. With the newer technology, patients were able to use a smartphone app to monitor glucose levels.

Table 3. Summary of Key RCT Characteristics in Patients With Type 1 Diabetes

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					CGM	SMBG
Beck et al. (2017)[14] DIAMOND				Adults aged 25 or older with baseline HbA1C levels between 7.5% and 10%	Dexcom G4 (n = 105)	Usual care (n = 53)
Laffel et al. (2020)[17]	U.S.	14	2018 – 2019	Adolescents and young adults age 14 to 24 years with HbA1C 7.5% to 10.9% with multiple daily insulin injections or an insulin pump	Dexcom G5, with training on use and a smartphone app and 2 calibration BG per day (n = 74)	Fingerstick blood glucose meter checks at least 4 times daily (n = 79)

Pratley et al. (2020)[18](WISDM)	U.S.	22	1993 – 2012	Older adults > 60 years of age with HbA1C < 10.0% with multiple daily insulin injections or an insulin pump	Dexcom G5 with training on use and 2 calibration BG per day(n = 103)	Fingerstick blood glucose meter checks at least 4 times daily (n = 100)

BG: blood glucose; CGM: continuous glucose monitoring; HbA1C: hemoglobin A1C; RCT: randomized controlled trial; SMBG: self-monitored blood glucose; WISDM: Wireless Innovation for Seniors With Diabetes Mellitus.

Table 4. Summary of Key RCT Results

Study	HbA1C	HbA1C	Blood Glucose (SD) mg/dL	Hypoglycemic Episodes	Patient Reported Outcomes	
Beck et al. (2017)[14] DIAMOND	**Change from Baseline**	**Proportion < 7.0%**		**Minutes per day < 70 mg/dL**		
CGM	1.0%	18 (18%)		43		
SMBG	0.4%	2 (4%)		80		
Diff (95% CI)	0.6%					
P	< .001	.01		0.002		
Laffel et al. (2020)[17]	**Change from Baseline**	**Percent with Reduction of 0.5%**	**Mean (SD)**	**Per Week**	**PAD-PS Survey**	**Glucose Monitoring Satisfaction**
CGM	-0.4 (1.0)	44%	199 (36)	1.4 (0.4 to 2.6)		
SMBG	0.1 (0.8)	21%	217 (35)	1.7 (1.0 to 3.1)		
Diff (95% CI)	-0.37 (-0.66 to -0.08)	23% (7% to 37%)	-14.3 (-23.6 to -5.1)	-0.3 (-0.7 to 0.1)	-0.1 (-3.0, 4.0)	0.27 (0.06, 0.54)
P	.01	.005	.003	.11	.73	.003
Pratley et al. (2020)[18] (WISDM)	**At follow-up**	**Percentage of time glucose values < 70 mg/dL**		**Per week**	**Quality of life**	**Hypoglycemia Awareness**
CGM	7.2 (0.9)	2.7%	162 (23)	0.8 (0.3 to 2.2)		
SMBG	7.4 (0.9)	4.9%	171 (30)	1.8 (0.7 to 4.0)		
Diff (95% CI)	-0.3 (-0.4 to -0.1)	-1.9% (-2,8 to -1.1)	-7.7 (-13.1 to -2.4)	-0.9 (-1.3 to -0.5)		
P		<.001	.005	< .001	NS	NS
Summary[2]	Range					

CI: confidence interval; CGM: continuous glucose monitor; HbA1C: hemoglobin A1c; NS: not significant; PAD-PS; Problem Areas in Diabetes-Pediatric Survey; RCT: randomized controlled trial; SD: standard deviation; SMBG: self monitored blood glucose; WISDM: Wireless Innovation for Seniors With Diabetes Mellitus

Pregnant Women

One trial of real-time CGM in pregnant women with Type 1 diabetes has been reported. Study characteristics, results, and gaps are summarized here and in Tables 5 to 8. 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.[19] 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 to 6.8 d/wk) 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 = .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 = .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 = .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 = .02), fewer incidences of neonatal hypoglycemia requiring treatment with intravenous dextrose (OR = 0.45, 0.22 to 0.89; p = .025), and reduced total hospital length stay (3.1 days vs 4.0 days; p = .0091). Skin reactions occurred in 49 (48%) of 103 CGM participants and 8 (8%) of 104 control participants.

Table 5. 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);[19] 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 HbA1C levels between 6.5% and 10.0% (mean, 6.9%); mean age, 31 y	CGM (real-time) (n = 108)	SMBG (n = 107)

CGM: continuous glucose monitoring: HbA1C: hemoglobin A_{1c}; NCT: national clinical trial; RCT: randomized controlled trial; SMBG: self-monitored blood glucose.

Table 6. 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**	**HbA1C Levels: Change From Baseline to 34 Wk of Gestation**	**Severe Hypoglycemia**
Feig et al. (2017)[19]						
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	.02	.50	.025	.18	.02	1.0

Values are n or n (%) or as otherwise indicated.
CI: confidence interval; CGM: continuous glucose monitoring; HbA1C: hemoglobin A_{1c}; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; TE: treatment effect.

The purpose of the limitations tables (see Tables 7 and 8) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 7. Study Relevance Limitations of RCTs for Real-Time CGM in Pregnant Women With Type 1 Diabetes

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Feig et al. (2017)[19]	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		

The study 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.

Table 8. Study Design and Conduct Limitations of RCTs for Real-Time CGM in Pregnant Women With Type 1 Diabetes

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Feig et al. (2017)[19]		1. Not blinded; chance of bias in clinical management				3, 4. Treatment effects and confidence intervals not calculated for some outcomes

The study 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] 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.

Continuous Glucose Monitoring 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 to 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 for use in adults (ages 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.

Data from 3 nonrandomized prospective studies (PRECISE, PRECISE II, AND PRECISION) were provided to the U.S. Food and Drug Administration (FDA) for the initial approval of Eversense as an adjunctive device.[20,21] 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.[22] 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 had 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 the FDA considered a reasonable assurance of safety and effectiveness of the device for the 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 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.[22] The study design is a non-blinded, prospective, multi-center, single-arm longitudinal cohort study. 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 the 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.

Three post-marketing registry studies of the Eversense device have been published (Tables 9 and 10). Sanchez et al. (2019) reported glucometric and safety data on the first 205 patients in the U.S. to use the Eversense device for at least 90 days.[23] Of the 205 patients, 62.9% reported having Type 1 diabetes, 8.8% Type 2 diabetes , and 28.3% were unreported; results were not reported separately by diabetes type. Diess et al. (2019) reported safety outcomes for 3023 patients from 534 sites in Europe and South Africa who had used the device for 6 months or longer.[24] There were no serious adverse events, and the most commonly reported adverse events were sensor site infection and skin irritation. Tweden et al. (2019) reported accuracy and safety data from 945 patients in Europe and South Africa who used either the 90-day or 180 day Eversense system for 4 insertion-removal cycles.[25] The percentage of patients using the 180-day system increased from cycle 1 to 4 as the device became more widely available (9%, 39%, 68% and 88% in cycles 1 to 4). There was no evidence of degradation of performance of the device over repeated insertion/removal cycles. Adverse events were not otherwise reported.

Table 9. Summary of Key Nonrandomized Trials: Implanted CGM Study Characteristics

Study	Study Type	Country	Dates	Participants	Test/Treatment	Follow-Up
Deiss et al. (2019)[24]	Prospective Single-arm UnbInded Postmarketing registry	Europe and South Africa	2016 – 2018	Adults (≥ 18 years) with T1D or T2D (% not reported) Consecutive patients who reached 4 sensor insertion/removal cycles Total n = 3023; 6 months of use (n = 969), 1 year of use (n = 173)	Implanted CGM Single sensor (90-day or 180 days)	Up to 1 year
Sanchez et al. (2019)[23]	Prospective Single-arm UnbInded Postmarketing registry	United States	2018 – 2019	Consecutive patients who reached a 90-day wear period of the device (62.9% T1D, 8.8% T2D, 28.3% unreported) (n = 205)	Implanted CGM	90 days
Tweden et al. (2019)[25]	Prospective Single-arm UnbInded Postmarketing registry	Europe and South Africa	2016 – 2019	Adult patients with T1D or T2D (% not known) for whom the Eversense CGM System was prescribed and inserted by their health care provider across approximately 1000 centers in Europe and South Africa (n = 945)	Implanted CGM 90 day system or 180 day system	4 insertion-removal cycles

CGM: continuous glucose monitoring; T1D: Type 1 diabetes; T2D: Type 2 diabetes.

Table 10. Summary of Key Nonrandomized Trials: Implanted CGM Study Results

Study Efficacy Outcomes	Efficacy Results	Adverse Events
Deiss et al. (2019)[24]		n = 3023
	NR (safety only)	133 adverse events (85 procedure-related, 22 device-related, 6 drug-related, 4 device/procedure related; 16 not related) No related serious adverse events through 4 insertion/removal cycles. infection (n = 29 patients); adhesive patch irritation (n = 20 patients); unsuccessful first removal attempt (n = 23 patients)
Sanchez et al. (2019)[23]	n = 205	n = 205

MARD (glucose range 40 – 400 mg/dl)	11.2% (SD 11.3%, median 8.2%).	10 (5%) transient skin irritation, redness, and/or swelling. 4 (2%) mild infection, 3 (1.5%) hypoglycemia that was self-treated, 4 (2%) failure to remove the sensor on the first attempt, and 5 (2.5%) skin irritation due to the adhesive
Mean SG (mg/dL)	161.8 Median 157.2 (IQR 138.4 to 178.9)	
% SG values in hypoglycemia (< 54 mg/dL), 24-hour period	1.2% (18.0 minutes)	
% SG values in hypoglycemia (< 54 mg/dL), nighttime	1.7%	
TIR, 24-hour period	62.3% (~15 hours)	
TIR, nighttime	61.8%	
Time in mild hyperglycemia, 24-hour period	21.9%	
Time in mild hyperglycemia, nighttime	21.5%	
Time in significant hyperglycemia, 24-hour period	11.6%	
Time in significant hyperglycemia, nighttime	12.1%	
Tweden et al. (2019)[25]		No evidence of degradation of performance from the repeated insertion and removal procedures occurring in approximately the same subcutaneous tissue of the body. Adverse events otherwise not reported.
MARD (glucose range 40 – 400 mg/dl)	Mean 11.5% to 11.9% during each sensor cycle	
Mean SG (mg/dL)	156.5 to 158.2 mg/dL across 4 sensor cycles	
% SG values in significant hypoglycemia (< 54 mg/dL), 24-hour period	1.1% to 1.3% (16 to 19 minutes)	
% SG values in significant hypoglycemia (< 70 mg/dL), 24-hour period	4.6% to 5.0% (66 to 72 minutes)	
TIR, 24-hour period	63.2% to 64.5% (910 to 929 minutes)	
Time in hyperglycemia (> 180-250 mg/dL), 24-hour period	22.8% to 23.2% (328 to 334 minutes)	
Time in significant hyperglycemia (> 250 mg/dL), 24-hour period	8.1% to 8.8% (117 to 127 minutes)	

CGM: continuous glucose monitoring; CI: confidence interval; IQR: interquartile range; MARD: mean absolute relative difference; NR: not reported; SD: standard deviation; SG: sensor glucose; TIR: time in range

Section Summary: Continuous Glucose Monitoring 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 reductions in HbA1C levels were 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 at 6 months in the CGM group 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 were significantly lower 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 hospital length of stay was shorter by almost 1 day in the CGM group.

Three nonrandomized prospective studies and 3 postmarketing registry studies assessed the accuracy and safety of an implanted glucose monitoring system that provides continuous glucose monitoring for up to 4 insertion/removal cycles 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 for Type 1 diabetes versus 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 the FDA considered a reasonable assurance of safety and effectiveness of the device for the replacement of fingerstick blood glucose monitoring for diabetes treatment decisions. As a condition of approval, the sponsor is required to conduct an additional post-approval-study.

Continuous Glucose Monitoring Devices for Short-Term Use in Type 1 Diabetes

Clinical Context and Therapy Purpose

The purpose of the 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 the short-term use of a CGM device improve the net health outcome for individuals with Type 1 diabetes?

The following PICO was used to select literature to inform this review.

Populations

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. 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 to 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 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 time in range (generally glucose of 70 to 180 mg/dl), 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.

Study Selection

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Reviews

Meta-analyses of glucose monitoring devices for Type 1 diabetes tend to combine studies of short-term glucose monitoring with studies of long-term CGM. For this body of evidence, there is variability in the definitions of intermittent monitoring and the specific monitoring protocols used. Also, many of the trials of short-term monitoring have included additional interventions to optimize glucose control (e.g., education, lifestyle modifications).

Two meta-analyses were identified that reported separate subgroup analyses for intermittent monitoring. In a Cochrane review by Langendam et al. (2012), 4 studies (total n = 216 patients) compared real-time intermittent glucose monitoring systems with SMBG, and the pooled effect estimate for change in HbA1C levels at 3 months was not statistically significant (MD change, -0.18; 95% CI, -0.42 to 0.05).[8] The meta-analysis by Wojciechowski et al. (2011), which assessed RCTs on CGM (described previously), also included a separate analysis of 8 RCTs of intermittent monitoring.[10] On pooled analysis, there was a statistically significant reduction in HbA1C levels with intermittent glucose monitoring compared with SMBG (WMD = -0.26; 95% CI, -0.45 to -0.06).

Randomized Controlled Trials

The largest RCT was the Management of Insulin-Treated Diabetes Mellitus (MITRE) trial, published by Newman et al. (2009); it evaluated whether the use of the additional information provided by minimally invasive glucose monitors improved glucose control in patients with poorly controlled insulin-requiring diabetes.[26] This 4-arm RCT was conducted at secondary care diabetes clinics in 4 hospitals in England. This trial enrolled 404 people over the age of 18 years, with insulin-treated diabetes (types 1 or 2) for at least 6 months, who were receiving 2 or more injections of insulin daily. Most (57%) participants had Type 1 diabetes (41% had Type 2 diabetes, 2% were classified as “other”). Participants had to have 2 HbA1C values of at least 7.5% in the 15 months before trial 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 glucose monitoring was used (i.e., monitoring was performed over several days at various points in the trial). 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). Changes in HbA1C levels from baseline to 3, 6, 12, and 18 months were the primary indicator of short- to long-term efficacy. At 18 months, all groups demonstrated a decline in HbA1C levels from baseline. Mean percentage changes in HbA1C levels 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 intention-to-treat analysis, no significant differences were found between any groups at any assessment times. There was no evidence that the additional information provided by the devices changed the number or nature of treatment recommendations offered by the nurses. Use and acceptability indicated a decline for 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 trial of unselected patients, glucose monitoring (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.[27] 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 did 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 to 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 11 to 14 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.

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).[28] 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 = .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.

Murphy et al. (2008) in the U.K. randomized 71 pregnant women with Type 1 (n = 46) and Type 2 (n = 25) diabetes to CGMor usual care.[29] The intervention consisted of up to 7 days of CGM at intervals of 4 to 6 weeks between 8 weeks and 32 weeks of 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 7 times a day. Baseline HbA1C levels were 7.2% in the CGM group and 7.4% 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 weeks and 32 weeks of gestation, mean HbA1C levels were 6.1% in the CGM group and 6.4% in the usual care group (p = .10). The prevalence of large-for-gestational-age infants (at least 90th percentile) was a secondary outcome. Thirteen (35%) of 37 infants in the CGM group were large-for-gestational age compared with 18 (60%) of 30 in the usual care group. The odds for reduced risk of a large-for-gestational-age infant with CGM was 0.36 (95% CI, 0.13 to 0.98; p = .05).

Table 11. RCT Characteristics for Short-Term Continuous Glucose Monitoring in Pregnant Women With Type 1 Diabetes

Study; Registration	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Secher et al. (2013);[28] NCT00994357	Denmark	1	2009 – 2011	Pregnant women with Type 1 (80%) or Type 2 (20%) diabetes; mean gestational age, < 14 wk); median HbA1C level, 6.7%; median age, 32 y	CGM (for 6 d before each study visits; encouraged to used continuously) plus SOC (n = 79)	SOC (n = 75)

Murphy et al. (2008);[29] ISRCTN84461581	U.K.	2	2003 – 2006	Pregnant women with Type 1 (65%) or Type 2 (35%) diabetes; mean gestational age, 9.2 wk; mean HbA1C 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)

CGM: continuous glucose monitoring; HbA1C: hemoglobin A1C; NCT: national clinical trial; RCT: randomized controlled trial; SOC: standard of care.

Table 12. RCT Results for Short-Term Continuous Glucose Monitoring in Pregnant Women With Type 1 Diabetes

Study	Infant				Maternal	
	Large-for-Gestational Age	Gestational Age at Delivery	Severe Hypoglycemia	Caesarean Section	HbA1C Levels at 36 Weeks of Gestation[a]	Severe Hypoglycemia
		Days				
Secher et al. (2013)[28]						
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	.19	.14	.88	.30	.63	.91
		Weeks				
Murphy et al. (2008)[29]						
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	.05	.80	.50	.40	.007	

Values are n or n (%) or as otherwise indicated.

CGM: continuous glucose monitoring; CI: confidence interval; HbA1C: hemoglobin A_{1c}; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; TE: treatment effect.

[a] N inconsistently reported for HbA1C outcome.

In summary, 2 trials of intermittent glucose monitoring conducted in Europe included pregnant women with Type 1 or 2 diabetes, with most having Type 1 diabetes. Secher et al. (2013) included intermittent, real-time monitoring;[28] Murphy et al. (2008)[29] included intermittent, retrospective monitoring with CGM. The intervention started in early pregnancy in these studies; the mean age was in the early-30s 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 et al. (2016); the difference in HbA1C levels at 36 weeks was about 0.6% (p = .007) in Murphy et al. (2008). Secher et al. (2013) 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 et al. (2013) although not statistically significantly higher; the difference in large for gestational age was statistically significantly lower for CGM in Murphy et al. (2008). 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 trial.

Tables 13 and 14 display notable limitations identified in each study.

Table 13. Study Relevance Limitations of RCTs of Intermittent CGM in Pregnant Women With Type 1 Diabetes

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Secher et al. (2013)[28]	4. Study population had relatively low HbA1C levels	4. Only 64% of the participants used devices per protocol			
Murphy et al. (2008)[29]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CGM: continuous glucose monitoring; HbA1C: hemoglobin A_{1c}; 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 14. Study Design and Conduct Limitations of RCTs of Short-Term CGM Glucose Monitoring in Pregnant Women With Type 1 Diabetes

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Secher et al. (2013)[28]		1. Not blinded; chance of bias in clinical management				3, 4. Treatment effects and confidence intervals not calculated
Murphy et al. (2008)[29]		1. Not blinded; chance of bias in clinical management				3, 4. Treatment effects and confidence intervals not calculated for some outcomes

The study 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] 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 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 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.

Continuous Glucose Monitoring Devices for Use in Type 2 Diabetes
There is limited ability to distinguish between long-term and short-term glucose monitoring in the analysis of the data for Type 2 diabetes, consistent with the literature.

Clinical Context and Therapy Purpose
The purpose of long-term and short-term CGM 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 devices improve the net health outcome for individuals with Type 2 diabetes?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is 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 change in HbA1C 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 HbA1C levels, a minimum follow-up of 8 to 12 weeks 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 6 months to 1 year would be appropriate.

Study Selection

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Reviews

Trials of Type 2 diabetes included in the systematic reviews and meta-analyses is shown in Table 15.

Table 15. CGM Trials for Type 2 Diabetes Included in Systematic Reviews

Primary Study	Ida et al. (2019)[30]
Ehrhardt et al. (2011)[31,a]	●
Cosson et al. (2009)[32,b]	●
Allen et al. (2008)[33,b]	●
Yoo et al. (2008)[34,a]	●
Beck et al. (2017)[14,a]	●
Ajjan et al. (2016)[35,b]	●
Haak et al. ((2017)[36,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 review is shown in Table 16. Results are described in Table 17.

Table 16. Systematic Review Characteristics for CGM in Type 2 Diabetes

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Ida et al. (2019)[30]	1960 – 2018	7	Adults with T2D	669 (25 – 224)	RCT	At least 8 wk

CGM: continuous glucose monitoring; RCT: randomized controlled trial; T2D: Type 2 diabetes.

Table 17. 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)[30]				
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	.004	.0006		
I2	64%	0%		

CGM: continuous glucose monitoring; CI: confidence interval; HbA1C: hemoglobin $A1_c$; NR: not reported; PE: pooled effect.

Randomized Controlled Trials

Key RCTs of CGM in adults with Type 2 diabetes are summarized in Tables 18 to 21. The largest and most recent studies are also briefly summarized in the following paragraphs. Baseline HbA1C levels were between 7.0% and 12.0% in the RCTs, with participants having a mean baseline age range in the mid-50s and early-60s. 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. No studies reported on follow-up beyond 14 months; thus the effect of CGM on outcomes related to diabetic complications is unknown.

An RCT, Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND), was reported by Beck et al. (2017).[37] DIAMOND was performed at 25 endocrinology practices in North America (22 in the U.S., 3 in Canada) and enrolled adults with Type 2 diabetes receiving multiple daily injections of insulin. One-hundred fifty-eight patients were randomized in 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 the clinic was performed using intention-to-treat analysis with missing data handling by multiple imputations. 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 = .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 = .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 QOL measures.

Ehrhardt and colleagues published 2 reports (2011, 2012) from an RCT evaluating 100 patients.[38,31] The trial evaluated the intermittent use of a CGM device in adults with Type 2 diabetes treated with diet/exercise and/or glycemia-lowering medications but not prandial insulin who had an initial HbA1C level of at least 7% but not more than 12%. The trial compared real-time CGM with the Dexcom device used for 4, 2 week cycles (2 weeks on and 1 week off) with SMBG. The primary efficacy outcome was a mean change in HbA1C levels. Mean HbA1C levels in the CGM group were 8.4% at baseline, 7.4% at 12 weeks, 7.3% at 24 weeks, and 7.7% at 52 weeks. In the SMBG group, these values were 8.2% at baseline, 7.7% at 12 weeks, 7.6% at 24 weeks, and 7.9% at 52 weeks. During the trial, the reduction in HbA1C levels was significantly greater in the CGM group than in the SMBG group (p = .04). After adjusting for potential confounders (e.g., age, sex, baseline therapy, whether the individual started taking insulin during the study), the difference between groups over time remained statistically significant (p < .001). The investigators also evaluated SMBG results for both groups. The mean proportions of SMBG tests less than 70 mg/dL were 3.6% in the CGM group and 2.5% in the SMBG group (p = .06).

Martens et al. (2021) reported results of an RCT comparing real-time CGM with SMBG in 176 patients with poorly controlled Type 2 diabetes (HbA1C levels 7.8% to 11.5%) treated with basal insulin without prandial insulin. At 8 months, there was a statistically significantly greater decrease in mean HbA1C in the CGM group (adjusted difference -0.4%; 95% CI -0.8% to -0.1%; p = .02), with 1 hypoglycemic event in each group. Aleppo et al. (2021) reported a 6-month follow-up study of 163 patients who had been randomized in this same trial (93.1%). Patients originally randomized to SMBG continued to use SMBG for another 6 months, and the CGM group was randomly reassigned either to continue CGM or discontinue CGM and resume SMBG. In the group that discontinued CGM, mean HbA1C increased from 7.9% at 8 months to 8.2% at 14 months, whereas in the group that continued CGM, mean HbA1C decreased from 8.2% to 8.1%.

Table 18. Key RCT Characteristics for Continuous Glucose Monitoring in Type 2 Diabetes

Study; Registration	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Beck et al. (2017) (DIAMOND);[37] NCT02282397	U.S., Canada	25	2014 – 2016	Adults with T2D using multiple daily injections of insulin with HbA1C levels 7.5% – 10.0% (baseline mean, 8.5%); mean age, 60 y	Real-time CGM (n = 79)	SMBG (n = 79)
Ehrhardt et al. (2011)[31]	U.S.	1	NR	Adults with T2D using oral antidiabetic agents without prandial insulin with HbA1C levels 7.0% – 12.0% (baseline mean, 8.3%), mean age, 58 y	Real-time CGM for 4 cycles of 3 wk (n = 50)	SMBG (n = 50)
Martens et al. (2021)[39,]	U.S.	15	2018 – 2019	Adults with T2D treated with basal insulin without prandial insulin. HbA1C levels 7.8% – 11.5% (baseline mean, 9.1%); mean age, 57 y	Real-time CGM (n = 116)	SMBG (n = 59)

CGM: continuous glucose monitoring; HbA1C: hemoglobin A1C ; NCT: national clinical trial;NR: not reported; RCT: randomized controlled trial; SMBG: self-monitored blood glucose; T2D: Type 2 diabetes.

Table 19. Key RCT Outcomes for Glucose Monitoring in Type 2 Diabetes

Study	Reduction in HbA1C Levels (Mean Range), %	HbA1C Level < 7.0%, n (%)	Relative Reduction in HbA1C 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
Beck et al. (2017)[37]						
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

Study	Reduction in HbA1C Levels (Mean Range), %	HbA1C Level < 7.0%, n (%)	Relative Reduction in HbA1C Level ≥ 10%, n (%)	Hypoglycemic or Ketoacidosis Events	Diabetes Complications (retinopathy, nephropathy, neuropathy, diabetic foot)	Health-Related Quality of Life
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 14%)	22% (0% to 42%)			0.22 (0.08 to 0.36)
p	.022	.88	.028			.009
	Baseline to 12 Wk					
Ehrhardt et al. (2011)[31]						
N	100	NR	NR	NR	NR	NR
CGM	8.4 to 7.4					
Control	8.2 to 7.7					
TE (95% CI)	NR					
p	.006					
	Baseline to 8 months	at 8 months				
Martens et al. (2021)[39] NCT03566693						
N	156	156	156	175	NR	NR
CGM	9.1% to 8.0%	20 (19%)	66 (63%)	1 hyopglycemic event, 1 ketoacidosis event		
Control	9.0% to 8.4%	5 (10%)	21 (41%)	1 hypoglycemic event		
TE (95% CI)	-0.4% (-0.8% to -0.1%)	11.8 (0.6 to 24.5)	22.4 (12.0 to 32.0)			
p	.02	.04	< .001			

CGM: continuous glucose monitoring; CI: confidence interval; DDS: Diabetes Distress Scale; DTSQ: Diabetes Treatment Satisfaction; HbA1C: hemoglobin A1C ; NCT: national clinical trial;NR: not reported; RCT: randomized controlled trial; TE: treatment effect.
[a] serious hypoglycemic event defined as requiring third-party assistance.

Tables 20 and 21 display notable limitations identified in each study.

Table 20. Study Relevance Limitations of RCTs for Glucose Monitoring in Type 2 Diabetes

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
					1. Follow-up not sufficient to determine effects on diabetic complications
Beck et al. (2017);[37] DIAMOND				1. Did not include outcomes on diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications
Ehrhardt et al. (2011)[31]				1. Focused on HbA1C; did not include outcomes on adverse events, QOL, or diabetic complications6. 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.

Martens et al. (2021)[39]				1. Did not include outcomes on QOL or diabetic complications 24 participants could not complete clinic visits due to COVID-19 restrictions; fingerstick used instead of capillary blood draw in these cases.	1. Follow-up not 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 gaps assessment.
COVID-19: coronavirus disease 2019; HbA1C: hemoglobin A1C; 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 21. 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]
						3, 4. Treatment effects and CIs not calculated
Beck et al. (2017);[37] DIAMOND		1. Not blinded; chance of bias in clinical management				
Ehrhardt et al. (2011)[31]		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
Martens et al. (2021)[39]		1. Not blinded; chance of bias in clinical management				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps 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.

Pregnant Women

As discussed in the section on CGM in pregnant women, 2 RCTs have evaluated short-term 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)[29] and 31 (20%) with Type 2 diabetes in Secher et al. (2013).[28] Results for women with Type 2 diabetes were not reported in Murphy et al. (2008). Secher et al. (2013) reported that 5 (17%) women with Type 2 diabetes experienced 15 severe hypoglycemic events, with no difference between groups; other analyses were not stratified by diabetes type.

Only 2 RCTs used blinded CGM; in 1, there was no difference in reduction in HbA1C levels between CGM and control.

Section Summary: Continuous Glucose Monitoring 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 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 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 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. 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.

Use of Long-Term Continuous Glucose Monitoring 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 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 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 PICO was used to select literature to inform this review.

Populations

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 weeks is appropriate. To assess long-term outcomes follow-up of 6 months to 1 year would be appropriate.

Study Selection

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Reviews

Meta-analytic results for long-term CGM in Type 2 diabetes are summarized in Table 17. The largest and most recently published systematic review of RCTs (Ida et al. [2019][30]) reported 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 = .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 Haak et al. (2017), which was included in the meta-analysis by Ida et al. (2019).[40] Hypoglycemia was analyzed using 3 different glucose level thresholds (< 70 mg/dl, < 55 mg/dl, and < 45 mg/dl). At all 3 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 < .0001); -56.5% (glucose < 55 mg/dl, p < .0001); -61.7% (glucose < 45 mg/dl, p = .0001).

Section Summary: Use of Continuous Glucose Monitoring 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.

Continuous Glucose Monitoring Use in Pregnant Women With Gestational Diabetes

Clinical Context and Therapy Purpose

The purpose of long-term CGM and short-term (intermittent) glucose monitoring devices is to provide a treatment option that is an alternative to or an improvement on existing therapies in women with gestational diabetes.

The question addressed in this evidence review is: Do the use of long-term CGM and short-term (intermittent) glucose monitoring devices improve the net health outcome for women with gestational diabetes?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are women with gestational diabetes.

Interventions
The testing being considered are devices that provide continuous, long-term glucose levels to the patient to direct insulin regimens and intermittent (i.e., 72 hours), short-term monitoring of glucose levels 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 for self-monitoring.

Outcomes
The general outcomes of interest are a change in 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, time spent in hypoglycemia, the incidence of hypoglycemic events and, complications of hypoglycemia, a minimum follow-up of 8 to 12 weeks is appropriate. To assess long-term outcomes such as QOL and maternal and infant outcomes, follow-up of 24 to 36 weeks would be appropriate.

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

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

Review of Evidence
Randomized Controlled Trials
One trial of glucose monitoring in women with gestational diabetes has been published. Trial characteristics, results, and limitations are shown in Tables 22 to 25. In the RCT, Wei et al. (2016) evaluated the use of CGM in 120 women with gestational diabetes at 24 to 28 weeks.[41] Patients were randomized 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 endpoints and did not specify primary outcomes; a significance level of p less than.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 22. Key RCT Characteristics for CGM in Pregnant Women With Gestational Diabetes

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Wei et al. (2016)[41]	China	1	2011 – 2012	Pregnant women with gestational diabetes diagnosed between 24 and 28 wk of gestation; mean HbA1C level, 5.8%; mean age, 30 y	CGM (48 – 721 on weekdays) (n = 51)	SMBG (n = 55)

CGM: continuous glucose monitoring; HbA1C: hemoglobin A_{1c} ; RCT: randomized controlled trial; SMBG: self-monitored blood glucose.

Table 23. RCT Outcomes for CGM in Pregnant Women With Gestational Diabetes

Study	Infant				Maternal	
	Large-for-Gestational Age, n (%)	Gestational Age at Delivery, wk	Severe Hypoglycemia, n (%)	Caesarean Section, n (%)	HbA1C Levels at 36 Wk of Gestation[a]	Severe Hypoglycemia
Wei et al. (2016)[41]						
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	.07	.92	.41	.37	.09	

Values are n (%) or as otherwise indicated.
CGM: continuous glucose monitoring; CI: confidence interval; HbA1C: hemoglobin A1C ; NR: not reported; RCT: randomized controlled trial; TE: treatment effect.
[a] N inconsistently reported for HbA1C outcome.

Tables 24 and 25 display notable limitations identified in each study.

Table 24. Study Relevance Limitations of RCTs for CGM in Pregnant Women With Gestational Diabetes

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]

Wei et al. (2016)[41]	4. Study population had relatively low HbA1C level	4. Compliance with CGM not reported			

The study limitations 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 25. Study Design and Conduct Limitations of RCTs for CGM in Pregnant Women With Gestational Diabetes

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Wei et al. (2016)[41]	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 study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
CGM: continuous glucose monitoring; 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.

Section Summary: Continuous Glucose Monitoring Use in Pregnant Women With Gestational Diabetes
The RCT in women with gestational diabetes was conducted in China with the intervention starting in the second or third 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.

Continuous Glucose Monitoring Using Intermittently Scanned (Flash) Devices
Clinical Context and Therapy Purpose
The purpose of CGM using intermittently scanned (flash) devices is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with Type 1 or Type 2 diabetes.

The question addressed in this evidence review is: Does the use of intermittently scanned (flash) continous glucose monitors improve the net health outcome in individuals with Type 1 or Type 2 diabetes?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with Type 1 or Type 2 diabetes.

Interventions
The testing being considered is intermittently scanned (flash) continuous glucose monitors. Flash glucose monitors measure glucose levels continuously but only display glucose values when scanned by a reader or a smartphone. A sensor inserted on the upper arm allows high frequency monitoring of interstial fluid for up to 14 days.

Comparators
The comparator is capillary blood sampling (finger stick) for blood glucose meters for self-monitoring.

Outcomes

The general outcomes of interest are a change in 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, time spent in hypoglycemia, the incidence of hypoglycemic events and, complications of hypoglycemia, a minimum follow-up of 8 to 12 weeks is appropriate. To assess long-term outcomes such as QOL and maternal and infant outcomes, follow-up of 24 to 36 weeks would be appropriate.

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

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

Review of Evidence

Randomized Controlled Trials

Randomized controlled trials comparing flash glucose monitors to usual care (SMBG) are summarized in Tables 26 and 27. Two RCTs were conducted in individuals with Type 1 diabetes and 2 in individuals with Type 2 diabetes. The studies varied in their populations, primary outcome measures, and duration; further limitations are highlighted in Tables 28 and 29.

Table 26. RCTs of Flash Glucose Monitoring in Type 1 and Type 2 Diabetes

Study; Registration	Countries	Sites	Dates	Participants	Interventions	
Bolinder et al. (2016)[42]	Multiple European	23	2014 – 2015	Adults with Type 1 diabetes, well controlled (HbA1C < 7.5%) and on current insulin regimen for at least 3 months	Flash glucose monitoring with FreeStyle Libre device n = 120	SMBG n = 121
Secher et al. (2021)[43] NCT03682237	Denmark	5	2018 – 2020	Adults with Type 1 diabetes, multiple daily insulin injections and HbA1C > 7.0%	Flash glucose montitoring with FreeStyle Libre device n = 48 Automated bolus calculation n = 41 Automated bolus calculation plus flash monitoring n = 39	Usual care n = 42
Haak et al. (2017)[36] NCT02082184	Multiple European	26	2014 – 2015	Adults with Type 2 diabetes treated with insulin for at least 6 months and on their current regimen for 3 months or more, HbA1C 7.5 to 12.0%.	Flash glucose montitoring with FreeStyle Libre device n = 149	SMBG n = 75
Yaron et al. (2019)[44]	Israel	2	2016 – 2017	Adults with Type 2 diabetes on multiple daily insulin injections for at least 1 year.	Flash glucose montitoring with FreeStyle Libre device n = 53	SMBG n = 48
Furler et al. (2020)[45] NCT02082184	Australia	25	2016 – 2017	Adults with Type 2 diabetes for at least 1 year and HbA1C at least 0.5% above their target desptie being prescribed 2 non-insulin glucose-lowering drugs, insulin, or both.	Flash glucose montitoring with FreeStyle Libre Pro device (hand-held reader retained by the health professional, n = 149	SMBG n = 150

CGM: continuous glucose monitoring; HbA1C: hemoglobin A1C ; NCT: national clinical trial; RCT: randomized controlled trial; SMBG: self-monitored blood glucose.

Table 27. Key RCT Outcomes for Glucose Monitoring in Type 2 Diabetes

Study	Main Results — Primary Outcome Intervention vs Control	Main Results — Secondary Outcomes
Bolinder et al. (2016)[42]	Mean time in hypoglycemia, change from baseline to 6 months: -1.39 hours/day vs -0.14 hours/day Between-group difference: -1.24 (SE 0.239; p < .0001)	5 serious adverse events in each group
Secher et al. (2021)[43]	Time in range (3.9 to 10 mmol/l), change from baseline to 26 weeks: Between-group difference: 3.9% (95% CI -12% to -23%); p = .660	
Haak et al. (2017)[36] NCT02082184	HbA1C change from baseline to 6 months: -3.1 (SE 0.75) mmol/L (-0.29% ± 0.07%) vs -3.4 (SE 1.04 [-0.31 ± 0.09%]) p = .8222	Time in hypoglycemia: < 3.9 mmol/L: reduced by mean 0.47 (SE 0.13) hours/day; p = .0006 < 3.1 mmol/L reduced by 0.22 ± 0.07 hours/day; p = .0014

Study	Main Results — Primary Outcome Intervention vs Control	Main Results — Secondary Outcomes
Yaron et al. (2019)[44]	Treatment satisfaction (DTSQc) at 10 weeks: 2.47 (0.77) vs. 2.18 (0.83); p = .053	The changes in HbA1C were -0.82% (9 mmol/mol) vs. -0.33% (3.6 mmol/mol) in the intervention and control group, respectively (P = 0.005);
Furler et al. (2020)[45]	Change from baseline in mean HbA1C at 12 months: 8.2% (95% CI 8.0 to 8.4) vs 8.5% (8.3 to 8.7] Between-group difference –0·3% (95% CI, –0·5 to 0·01) 66 mmol/ml (95% CI 64 to 68) vs 69 mmol/ml (67 to 72) Between-group difference –3·0 (95% CI, –5·0 to 0·1]; p =.059	At 6 months, HbA1C was lower in the flash glucose monitoring group than in the usual care group\ Between-group difference –0·5% (95% CI, –0·8% to –0·3%); p = .0001 Clinically significant hypoglycaemia increased in both groups during the trial, but no episodes of severe hypoglycaemia or other adverse events reported in either group.

CGM: continuous glucose monitoring; CI: confidence interval; RCT: randomized controlled trial; SE: standard error.

Table 28. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Bolinder et al. (2016)[42]				1. Did not include outcomes on diabetic complications	
Secher et al. (2021)[43]				1. Did not include outcomes on diabetic complications	
Haak et al. (2017)[36]				1. Did not include outcomes on diabetic complications	1. Follow-up not sufficient to determine effects on diabetic complications
Yaron et al. (2019)[44]				1. Did not include outcomes on diabetic complications; orimary outcome was treatment satisfaction	1. Followup 10 weeks- not sufficient to determine effects on diabetic complications
Furler et al. (2020)[45]		5. Used pro system; not currently available in the U.S.		1. Did not include outcomes on diabetic complications	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 29. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Bolinder et al. (2016)[42]		Open label				
Secher et al. (2021)[43]		Open label				

Haak et al. (2017)[36]		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
Yaron et al. (2019)[44]		Open label		primary outcome assessed for 86.8% of intervention gorup and 75% of control group		
Furler et al. (2020)[45]		Open label				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[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); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[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; 5. Other.

Section Summary: Continuous Glucose Monitoring Using Intermittently Scanned (Flash) Devices
Two RCTs using the Freestyle Libre device in patients with Type 1 diabetes have been published. One RCT reported decreased time in hypoglycemia for patients with well-controlled diabetes who used flash monitors compared to SMBG (between-group difference: -1.24 hours/day (standard error, 0.239; P < .0001). The other study found no difference in time in range (3.9 to 10 mmol/L) for patients who used flash monitoring compared to usual care.

Three RCTs using flash glucose-sensing technology as a replacement for SMBG for the management of insulin-dependent treated Type 2 diabetes have been published; 1 of these used a professional device where the healthcare professional maintained the handheld device. One RCT found no improvement on the primary outcome of A1c at 12 months or diabetes-specific distress compared to usual care and clinically significant hypoglycemia increased in both groups. However, A1c was improved at 6 months and time in target was improved at 12 months in the flash monitor group compared to usual care. A second RCT found no difference in A1c change at 6 and 12 months between flash monitor and usual care groups, but severe hypoglycemia (< 45mg/dL) was reduced for intervention participants. In a third trial, the primary outcome of patient satisfaction at 10 weeks was increased with flash monitors compared to usual care. No studies were of sufficient duration to assess diabetes complications.

The limited number of RCTs and differences across these trials in the patient populations, interventions, and outcomes, along with inconsistent results on intermediate measures, preclude drawing conclusions about the effectiveness of flash glucose monitors compared to SMBG in individuals with Type 1 or Type 2 diabetes.

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. 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 in HbA1C 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 2 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 HbA1C levels, 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 to determine that the technology results in an improvement in the net health outcome.

For individuals with Type 1 diabetes who receive short-term continuous glucose monitoring, the evidence includes RCTs and systematic reviews. 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 of glycemic control is mixed, and there was no consistency in HbA1C levels. Some trials have reported improvements in glucose control for the intermittent short-term 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with Type 1 diabetes who receive continuous glucose monitoring using an intermittently scanned (flash) device, the evidence includes RCTs. 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. Two RCTs using the Freestyle Libre device have been published. One RCT reported decreased time in hypoglycemia for patients with well-controlled diabetes who used flash monitors compared to SMBG (between-group difference: -1.24 hours/day [standard error, 0.239; P < .0001]). The other study found no difference in time in range (3.9 to 10 mmol/L) for patients who used flash monitoring compared to usual care. The limited number of RCTs and differences in their populations, primary outcomes, and comparators preclude drawing conclusions about the use of flash monitoring in patients with Type 1 diabetes.

Type 2 Diabetes

For individuals with Type 2 diabetes who receive long-term CGM, the evidence includes RCTs. Relevant outcomes are symptoms, morbid events, QOL, and treatment-related morbidity. Most RCTs of CGM in patients with Type 2 diabetes 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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. 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. 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. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with Type 2 diabetes who receive short-term CGM monitoring, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, morbid events, QOL, 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 that the technology results in an improvement in the net health outcome.

For individuals with Type 2 diabetes who receive short-term continuous glucose monitoring, the evidence includes RCTs and systematic reviews. 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 of glycemic control is mixed, and there was no consistency in HbA1C levels. Some trials have reported improvements in glucose control for the intermittent short-term 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with Type 2 diabetes who receive continuous glucose monitoring using an intermittently scanned (flash) device, the evidence includes RCTs. 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. Three RCTs using flash glucose-sensing technology as a replacement for SMBG for the management of insulin-dependent treated Type 2 diabetes have been published; 1 of these used a professional device where the healthcare professional maintained the handheld device. One RCT found no improvement on the primary outcome of A1c at 12 months or diabetes-specific distress compared to usual care and clinically significant hypoglycemia increased in both groups. However, A1c was improved at 6 months and time in target was improved at 12 months in the flash monitor group compared to usual care. A second RCT found no difference in A1c change at 6 and 12 months between flash monitor and usual care groups, but severe hypoglycemia (< 45mg/dL) was reduced for intervention participants. In a third trial, the primary outcome of patient satisfaction at 10 weeks was increased with flash monitors compared to usual care. No studies were of sufficient duration to assess diabetes complications. Differences across these trials in the patient populations, interventions, and outcomes, along with inconsistent results on intermediate measures, preclude drawing conclusions about the effectiveness of flash glucose monitors compared to SMBG.

Gestational Diabetes

For individuals who are pregnant with gestational diabetes who receive long-term CGM or short-term (intermittent) glucose monitoring, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, QOL, and treatment-related morbidity. In the RCT, the type of glucose monitoring was unclear. Trial reporting was incomplete; however, there was no difference between the groups for most reported outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2019 Input

Clinical input was sought to help determine whether the use of continuous or intermittent monitoring of glucose in the interstitial fluid would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 3 respondents, including 3 physician-level responses identified through 1 specialty society, including 2 physicians with academic medical center affiliations.

Type 1 Diabetes

For individuals who have Type 1 diabetes who receive short-term glucose monitoring, 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 Type 1 diabetes despite the use of best practices and to help determine basal insulin levels prior to insulin pump initiation.

Type 2 Diabetes

For individuals who have Type 2 diabetes who do not require insulin who receive long-term continuous glucose monitoring (CGM), clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice.

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, clinical input supports that this use provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice.

For individuals with Type 2 diabetes who require multiple daily doses of insulin who receive short-term CGM, 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 use of best practices and to help determine basal insulin levels prior to insulin pump initiation.

Further details from clinical input are included in the Appendix.

2008

In response to requests, input was received from 1 physician specialty society and 4 academic medical centers while this policy was under review in 2008. Input concurred that continuous glucose monitoring, particularly intermittent glucose monitoring, was helpful in a subset of patients with diabetes. Reviewers commented that this monitoring can improve diabetes care by reducing glucose levels (and improving hemoglobin A1C levels) and/or by reducing episodes of hypoglycemia. Reviewers argued that there is persuasive data from case reports to demonstrate the positive impact of intermittent glucose monitoring.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in Supplemental Information if they were issued by, or jointly by, a U.S. professional society, an international society with U.S. representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Association of Clinical Endocrinologists and the American College of Endocrinology

In 2020, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) 2015 Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan was supplemented by an AACE/ACE Consensus Statement on Comprehensive Type 2 Diabetes Management. It is recommended that therapy be evaluated regularly including the results of hemoglobin A1C, self-monitoring of blood glucose (SMBG) records (fasting and postprandial) or continuous glucose monitoring tracings. 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 an insulin pump), for those with a 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." [46]

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (2016) updated its guidance on the diagnosis and management of Type 1 diabetes in adults.[47] 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:

> "... 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 optimised 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 (hemoglobin A1C) 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 53 mmol/mol (7%) and/or there has been a fall in HbA1C of 27 mmol/mol (2.5%) or more."

American Diabetes Association

The American Diabetes Association (2021) “Standards of Medical Care in Diabetes"[48] included the following statement in the chapter on glycemic targets:

"Continuous glucose monitoring (CGM) also has an important role in assessing the effectiveness and safety of treatment in many patients with Type 1 diabetes, and limited data suggest it may also be helpful in selected patients with Type 2 diabetes, such as those on intensive insulin regimens."

The standards also state that the technology has evolved rapidly in both accuracy and affordability and that data provided by CGM "will allow the provider to determine time in range (TIR) and to assess hypoglycemia, hyperglycemia, and glycemic variability", noting that there is a strong correlation between TIR and an A1C.

Recommendations (**level of evidence**) related to CGM devices include the following:

- "When prescribing continuous glucose monitoring (CGM) devices, robust diabetes education, training, and support are required for optimal CGM device implementation and ongoing use. People using CGM devices need to have the ability to perform self-monitoring of blood glucose in order to calibrate their monitor and/or verify readings if discordant from their symptoms. **(B)**
- When used properly, real-time continuous glucose monitors in conjunction with multiple daily injections and continuous subcutaneous insulin infusion **(A)** and other forms of insulin therapy **(C)** are a useful tool to lower and/or maintain A1C levels and/or reduce hypoglycemia in adults and youth with diabetes.
- When used properly, intermittently scanned continuous glucose monitors in conjunction with multiple daily injections and continuous subcutaneous insulin infusion **(B)** and other forms of insulin therapy **(C)** can be useful and may lower A1C levels and/or reduce hypoglycemia in adults and youth with diabetes to replace self-monitoring of blood glucose.
- In patients on multiple daily injections and continuous subcutaneous insulin infusion, real-time continuous glucose monitoring (CGM) devices should be used as close to daily as possible for maximal benefit. **(A)** Intermittently scanned CGM devices should be scanned frequently, at a minimum once every 8 h.
- When used as an adjunct to pre- and postprandial self-monitoring of blood glucose, continuous glucose monitoring can help to achieve A1C targets in diabetes and pregnancy. **(B)**
- Use of professional continuous glucose monitoring (CGM) and/or intermittent real-time or intermittently scanned CGM can be helpful in identifying and correcting patterns of hyper- and hypoglycemia and improving A1C levels in people with diabetes on noninsulin as well as basal insulin regimens. **(C)**
- Skin reactions, either due to irritation or allergy, should be assessed and addressed to aid in successful use of devices. **(E)**
- People who have been using continuous glucose monitors should have continued access across third-party payers. **(E)"**

Endocrine Society

The Endocrine Society (2016) published clinical practice guidelines that included the following recommendations on CGM:[49]

6. "Real-time continuous glucose monitors in adult outpatients
   - 6.1 We recommend real-time continuous glucose monitoring (RT-CGM) devices for adult patients with T1DM [Type 1 diabetes mellitus] who have A1C levels above target and who are willing and able to use these devices on a nearly daily basis.
   - 6.2 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 (T2DM)
   - 6.3 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."

International Consensus on Time in Range

In 2019, consensus recommendations on clinical targets for CGM data interpretation were published and endorsed by the American Diabetes Association, American Association of Diabetes Educators, European Association for the Study of Diabetes, Foundation of European Nurses in Diabetes, International Society for Pediatric and Adolescent Diabetes, JDRF, and Pediatric Endocrine Society.[50]

U.S. Preventive Services Task Force Recommendations

Not applicable

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 30.

Table 30. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03981328	The Effectiveness of Real Time Continuous Glucose Monitoring to Improve Glycemic Control and Pregnancy Outcome in Patients With Gestational Diabetes Mellitus	372	Oct 2021 (last update June 2019, not yet recruiting)
NCT03908125[a]	A Post-Approval Study to Evaluate the Long-term Safety and Effectiveness of the Eversense® Continuous Glucose Monitoring (CGM) System	400	Mar 2023
NCT04269655[a]	Scripps Digital Diabetes: Cloud-Based Continuous Glucose Monitoring (CB CGM)	300	Feb 2024
NCT04535830	The Effectiveness of Flash Glucose Monitoring System on Glycemic Control in Patients With New-onset Type 2 Diabetes#A Randomized Controlled Trial	200	Sep 2021
NCT03522870	Effects of Novel Flash Glucose Monitoring System on Glycemic Control in Adult Patients With Type 1 Diabetes Mellitus	104	Dec 2021
Unpublished			
NCT03808376[a]	PROMISE Study: A Prospective, Multicenter Evaluation of Accuracy and Safety of an Implantable Continuous Glucose Sensor Lasting up to 180 Days	181	May 2020 (actual)
NCT03445065[a]	Benefits of a Long Term Implantable Continuous Glucose Monitoring System for Adults With Diabetes - France Randomized Clinical Trial	239	Aug 2020

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

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Coding Section

Codes	Number	Description
CPT	95250	Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; sensor placement, hook-up, calibration of monitor, patient training, removal of sensor, and printout of recording

	95249	; same as 95250 patient owned equipment (effective 01/01/18)
	95251	; physician interpretation and report
	0446T	Creation of subcutaneous pocket with insertion of implantable interstitial glucose sensor, including system activation and patient training
	0447T	Removal of implantable interstitial glucose sensor from subcutaneous pocket via incision
	0448T	Removal of implantable interstitial glucose sensor with creation of subcutaneous pocket at different anatomic site and insertion of new implantable sensor, including system activation
HCPCS	A4238	Supply allowance for adjunctive, non-implanted continuous glucose monitor (cgm), includes all supplies and accessories, 1 month supply=1 unit of service.
	A4239	Supply allowance for non-adjunctive, non-implanted continuous glucose monitor (cgm), includes all supplies and accessories, 1 month supply = 1 unit of service
	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
	E2103	Non-adjunctive, non-implanted continuous glucose monitor or receiver.
	E2102	Adjunctive, non-implanted continuous glucose monitor or receiver.
	S1030	Continuous non-invasive glucose monitoring device, purchase (for physician interpretation of data, use CPT code)
	S1031	Continuous non-invasive glucose monitoring device, rental, including sensor, sensor replacement, and download to monitor (for physician interpretation of data, use CPT code)
ICD-10-CM	E10.10-E13.9	Diabetes mellitus code range
ICD-10-PCS		ICD-10-PCS codes are only used for inpatient services. There is no specific ICD-10- PCS code for this monitoring.
Type of Service	Medicine	
Place of Service	Outpatient	

Procedure and diagnosis codes on Medical Policy documents are included only as a general reference tool for each policy. **They may not be all-inclusive.**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, and other nonaffiliated technology evaluation centers, reference to federal regulations, other plan medical policies and accredited national guidelines.

History From 2013 Forward

03/12/2025 Interim review, removing investigational stance for CGM devices from policy criteria.
02/18/2025 Annual review updating criteria for CGMS and criteria regarding use of Eversense CGM.
02/26/2024 Annual review, no change to policy intent.
11/14/2023 Interim review, adding HCPCS codes E2103, E2102, and A4238, removed HPCS codes K0553 and K0554. No other changes made.
08/14/2023 Interim review, changing category from DME to prescription medicine. No other changes.
02/22/2023 Adding code A4239 to coding section. No other changes.
02/01/2023 Annual review, updating policy and guidelines to address care gestational diabetes. No other changes made.
03/15/2022 Removing erroneous policy statement regarding the use of intermittent scanning devices.
02/08/2022 Annual review, no change to policy intent. Updating description, background, regulatory status, rationale and references.
02/01/2021 Annual review, no change to policy intent. Updating description, regulatory status, rationale and references.
02/03/2020 Annual review, no change to policy intent.
01/06/2020 Interim review to remove requirement that this device be ordered by an endocrinologist. No other changes made.
12/18/2019 Interim review to add language regarding implantable CGM devices. Also updating description, guidelines, rationale and references.
02/12/2019 Annual review, no change to policy intent. Updating description, background, regulatory status, rationale, references and coding.
03/13/2018 Annual review, no change to policy intent. Updating background, description, regulatory status, HCPCS coding in guidelines, rationale and references.
12/19/2017 Interim review, correcting typo and doing minor editing in description and rationale related to Type 2 diabetes. No change in policy intent.
12/12/2017 Interim review, updating policy verbiage significantly to include reformatted medical necessity criteria and criteria to allow for coverage for Type II diabetes.
05/15/2017 Interim Review. Updated Policy statement and Policy guidelines.
02/01/2017 Annual Review, increasing the glucose level for hypoglycemia from 50 to 70 in policy statement. Also updating background, description, rationale and references.
02/10/2016 Annual review, no change to policy intent.
2/05/2015 Interim update. Removing verbiage related to artificial pancreas as a new policy, CAM 10130 has been created to address that issue. Updated background, description, related policy, regulatory status, rationale, references and coding.
11/10/2014 Annual review, no change to policy intent. Added coding section. Updated regulatory status, policy guidelines, rationale and references.
11/11/2013 Updated Description and Rationale.